SECTION:PIL

IN THE SUPREME COURT OF INDIA
(CIVIL ORIGINAL WRIT JURISDICTION)

WRIT PETITION (CIVIL) NO. _____OF 2021

IN THE MATTER OF:
DR. JACOB PULIYEL .....PETITIONER

VERSUS

UNION OF INDIA & ORS. .....RESPONDENTS

FILING INDEX

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2	ANNEXURE P1 TO P39	1	NIL
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NEW DELHI 110001
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NEW DEHI:
DATED: 12.05.2021

DOL RAJ BHANDARI , REGD. CLERK, I.D. NO. 3745, MOB. NO. 9868255076

IN THE HON'BLE SUPREME COURT OF INDIA

(CIVIL ORGINAL WRIT JURISDICTION)

WRIT PETITION (CIVIL) NO. _____OF 2021

(PUBLIC INTEREST LITIGATION)

IN THE MATTER OF

DR. JACOB PULIYEL .....PETITIONER

VERSUS

THE UNION OF INDIA & ORS. .....RESPONDENTS

PAPER BOOK

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COUNSEL FOR THE PETITIONER: **PRASHANT BHUSHAN**

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SECTION: PIL

PROFORMA FOR FIRST LISTING

The case pertains to (Please tick/check the correct box):

☐	Central Act: (Title)	**CONSTITUTION OF INDIA**
☐	Section	**UNDER ARTICLE 14 AND 21**
☐	Central Rule : (Title)	**-NA-**
☐	Rule No(s):	**- NA -**
☐	State Act: (Title)	**- NA -**
☐	Section :	**- NA -**
☐	State Rule : (Title)	**- NA -**
☐	Rule No(s):	**- NA -**
☐	Impugned Interim Order: (Date)	**- NA -**
☐	Impugned Final Order/Decree: (Date)	**-NA-**
☐	High Court : (Name)	**-NA-**
☐	Names of Judges:	**-NA-**
☐	Tribunal/Authority ; (Name)	**-NA -**
1.	Nature of matter : Civil ☐ ☐ Criminal	
2.	(a) Petitioner/appellant No.1 :	**DR. JACOB PULIYEL**
	(b) e-mail ID:	**JACOB@PULIYEL.COM**
	(c) Mobile Phone Number:	**9868035091**
3.	(a) Respondent No.1:	**UNION OF INDIA & ORS.**
	(b) e-mail ID:	**- NA -**
	(c) Mobile Phone Number:	**- NA -**
4.	(a) Main category classification:	**08 (0812)**
	(b) Sub classification:	**OTHER PIL MATTER**
5.	Not to be listed before:	
6.	(a) Similar disposed of matter with citation, if any & case details:	**NO SIMILAR MATTER IS PENDING**
	(b) Similar Pending matter with case details:	**NO DISPOSED SIMILAR MATTER**

A2

7. **Criminal Matters:**

(a) Whether accused/convict has surrendered: Yes ☐ No ☐

(b) FIR No. **- NA -** Date: **- NA -**

(c) Police Station: **- NA -**

(d) Sentence Awarded: **- NA -**

(e) Period of sentence undergone including period of Detention/ Custody Undergone: **- NA -**

8. Land Acquisition Matters: **- NA -**

(a) Date of Section 4 notification: **- NA -**

(b) Date of Section 6 notification: **- NA -**

© Date of Section 17 notification: **- NA -**

9. Tax Matters: State the tax effect: **- NA -**

10. Special Category (first Petitioner/ appellant only): **- NA -**

☐ Senior citizen > 65 year ☐ SC/ST ☐ Woman/child

☐ Disabled ☐ Legal Aid case ☐ In custody **- NA -**

11. Vehicle Number (in case of Motor Accident Claim matters): **- NA -**

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NEW DELHI
DATED: 12.05.2021

SYNOPSIS

B

The petitioner herein is filing the instant writ petition under Article 32 of the Constitution of India for the enforcement of fundamental rights under Article 14 and 21 of the Constitution of India, seeking a writ directing the respondents to make public the segregated data of the clinical trials for the vaccines that are being administered to the population in India under the Emergency Use Authorisation granted by the Drugs Controller General of India (DCGI). The petitioner is a former member of the National Technical Advisory Group on Immunisation (the government's apex body on immunization). The petitioner avers and wishes to record the evidence in medical literature that, vaccines that have not been adequately tested for safety or efficacy are now licensed under Emergency Use Authorisation without the data being disclosed to the public. This is a clear violation of the basic norms of scientific disclosure and the guidelines with respect to disclosure of clinical trial data, as laid down by the World Health Organisation (WHO) and followed by the Indian Council of Medical Research (ICMR). In India, the manner in which the vaccines have been licensed vitiates and even precludes the possibility that the vaccines can be evaluated objectively in the future. Under these circumstances the petitioner is forced to appeal to this court for public disclosure of trial data and post vaccination data, as required by international medical norms.

The petitioner submits that the importance of disclosure of segregated data of vaccine clinical trials (segregated for each vaccine and for each age group) that have been undertaken with respect to the two vaccines being administered in India, cannot be undermined and must be disclosed through peer reviewed scientific journals. The disclosure of

such information is essential to ascertain whether a certain section of the population is more susceptible to adverse effects, to determine what are the adverse effects in various age groups and on differing populations, etc. So far, the respondents have practiced complete secrecy in the matter and have not disclosed any data from trials for the vaccines that have been developed in India – Covaxin by the Bharatbiotech or for the Covishied manufactured at the Serum Institute, India (SII). The clinical trial information that is available for the COVISHIED vaccine is preliminary data of clinical trials that have been undertaken for the vaccine in other countries.

Besides this, it is important for the respondent authorities to carefully monitor vaccine recipients and publicly record all adverse events. In other countries, this type of observation has helped identify the occurrence of blood clots and strokes in vaccine recipients. Many countries stopped administering the vaccine till they evaluated this occurrence and countries like Denmark have completely banned use of the Astra Zeneca vaccine (branded as Covishield in India). India, with its huge population and numbers vaccinated, should have reported these adverse events first. But due to poor follow-up, poor Adverse Events Following Immunization (AEFI) evaluation and suppression of data, these events have not been put in the public domain – endangering many more to suffer the same fate. Under these circumstances the petitioner has approached this court also seeking that that all AEFI be actively solicited by notification in newspapers, and be made available in publicly accessible data base (Like the VAERS data base in the USA). Currently the website cowin.gov.in only mentions certain numbers of AEFI but details of those cases are not available for scientific scrutiny.

Further the petitioner prays that no coercive mandates for use of these inadequately tested vaccines may be issued and that the courts reiterate that vaccine mandates are repugnant to the right of humans to autonomy and right to self-determine what may be injected into their bodies. In so doing this Hon'ble Court must uphold the rights of individuals to give informed consent as the Delhi High Court did, in the Measles Rubella case. It is submitted that coercing citizens directly or indirectly to get vaccinated is unconstitutional and violates the Right to Life of citizens. While the government has clearly stated in numerous RTIs that Covid vaccines are voluntary, there are many instances from across the country where now various authorities are mandating the vaccines.

The petitioner recognises that Covid is a public health emergency and that such an emergency may require emergency use authorisations of vaccines which may not yet have been adequately tested. However, that should not mean that all information and data of relevance as to the efficacy or side effects of the vaccines which have been given such approval, should not be collected systematically and made publicly available, especially when the vaccines are being used in a universal immunisation programme. Though emergency authorisation of the vaccines may be advisable in the present situation, it does not however mean that these vaccines can be forced upon people, especially without all relevant data being available for independent public and scientific scrutiny. The present petition therefore should not be understood to be a petition challenging the present Covid vaccination programme.

For the first time in history, a universal mass vaccination programme is being undertaken in India and many other countries using vaccines

which have not been fully tested for efficacy and side effects, in the manner in which vaccines are required to be tested normally, usually over a period of three years or so, so that even long term adverse effects can be examined. The problem is further compounded due to the lack of transparency in the vaccine trial data and the manner of granting approvals to the vaccines based on that data which is withheld from disclosure to the public or not available to independent researchers for scientific scrutiny.

History has shown that vaccines can be very useful instruments for fighting disease and epidemics but vaccines can also have serious unintended side effects. That is why before vaccines are approved they need to be properly tested and studied by thorough clinical trials and the test results must be available for scrutiny by independent scientists. While there may be circumstances warranting emergency approvals to vaccines which have not been fully and properly tested, there cannot be any reason whatever for trial data (that has been collected and on the basis for which approvals have been given), to be withheld from public scrutiny. This is what the WHO and ICMR guidelines also require. In such circumstances, coercing people to take the vaccines on pain of losing their jobs or access to essential services, which has begun to happen in many parts of the country, is a violation of the fundamental rights of people, especially in a situation where emergency approvals have been given to vaccines without full and adequate testing and without any transparency of the trial data and post vaccination data.

Hence this writ petition.

F

LIST OF DATES

June 1964	World Medical Association adopts the Declaration of Helsinki, Ethical Principles for Medical Research involving Human Subjects
8.05.2012	The need for greater transparency has been noted by the Parliamentary Standing Committee on Health and Family Welfare, in its 59th Report which called for "increased transparency in decision-making" of the Central Drugs Standard Controls Organisation (CDSCO) and other regulatory authorities.
9.04.2015	World Health Organisation Statement on Public Disclosure of clinical trial results
10.11.2017	In the case of WP(C) 36065 of 2017 between the Parents Teachers Association, Government Higher Secondary School, Kokkur, Kerala and the State of Kerala **(2017 SCC Online Kerala 36408**), the Hon'ble High Court of Kerala had passed order: "If at all any parent has an objection, it has to be necessarily brought before the authorities, and there need not be any vaccination administered to such children whose parents object to the Vaccination. The learned government pleader also submits that no forceeful vaccination is attempted".
22.01.2019	In the case of W.P.(C) 343/2019 & CM Nos.1604-1605/2019 between Master Haridaan Kumar (Minor through Petitioners Anubhav Kumar and Mr. Abhinav Mukherji) Versus Union of India, &W.P.(C) 350/2019 & CM Nos.1642-1644/2019 between Baby Veda Kalaan& Others Versus Director of Education & Others ***the Hon'ble High Court of Delhi had observed that:***

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	"13. Undisputedly, there is an urgent need to disseminate information regarding the MR campaign and the assumption that children could be vaccinated forcibly or without consent is unsustainable. This Court is of the view that all efforts are required to be made to obtain the decision of the parents before proceeding with the MR campaign. In this regard, it would be apposite to ensure that the consent forms/slips are sent to each and every student. Since the time period for implementing the campaign is short, the response period should be reduced and parents / guardians of students must be requested to respond immediately and, in any case, in not more than three working days. ***If the consent forms/slips are not returned by the concerned parent, the class teacher must ensure that the said parents are contacted telephonically and the decision of such parent is taken on phone.***" "14. ***The contention that indication of the side effects and contraindications in the advertisement would discourage parents or guardians from consenting to the MR campaign and, therefore, the same should be avoided, is unmerited.*** The entire object of issuing advertisements is to ensure that necessary information is available to all parents/guardians in order that they can take an informed decision. The respondents are not only required to indicate the

benefits of the MR vaccine but also indicate the side effects or contraindications so that the parents/guardians can take an informed decision whether the vaccine is to be administered to their wards/children."

The Hon'ble High Court of Delhi thus passed the following orders:

"15.4 ***MR vaccines will not be administered to those students whose parents/guardians have declined to give their consent.*** The said vaccination will be administered only to those students whose parents have given their consent either by returning the consent forms or by conforming the same directly to the class teacher/nodal teacher and also to students whose parents/guardians cannot be contacted despite best efforts by the class teacher/nodal teacher and who have otherwise not indicated to the contrary".

Further on the issue of informed consent, the The Hon'ble High Court of Delhi directed that:

"15.1Directorate of Family Welfare shall issue quarter page advisements in various newspapers as indicated by the respondents...The advertisements shall also indicate that the vaccination shall be administered with Auto Disable Syringes to the eligible children by Auxiliary Nurse Midwifery. ***The advertisement shall also clearly indicate the***

	side effects and contraindications as may be finalised by the Department of Preventive Medicine, All India Institute of Medical Sciences"
13.04.2019	Article in Green Medinfo "Anti Vaccination;Pro Science;Pro-Health;Anti-Industry" by Jagannath Chatterjee notes how clinical trials are known to obfuscate troublesome data. The article notes: "In September 2017, a report titled "Infanrix hexa and sudden death: a review of the periodic safety update reports submitted to the European Medicines Agency" published in the Indian Journal of Medical Ethics[35] alleged that GlaxoSmithKline (GSK) apparently excluded certain cases of infant deaths in their official report to the European Medicines Agency. GSK stated that the deaths reported after the vaccine is "coincident" and not related to the vaccine. However analysis by Puliyel and Sathyamala, authors, showed that 83% of the reported deaths occurred within 10 days of vaccination and another 17% occurred in the following ten days. "Glossing over of the deaths after vaccination has potential to result in more, unnecessary deaths which are difficult to justify ethically," they observed in a Press Release. The same vaccine and an MMR vaccine have also been embroiled in serious contamination scandals and the list grows by the day. In yet another shocking incident the Government of India preferred not to release clinical data of an indigenous Rotavirus vaccine that showed a very high incidence of a potentially lethal intestinal obstruction in vaccinated children under the plea that revealing the data would "alarm the public".

17.05.2019	A paper titled, "Revised World Health Organisation assessment of adverse events following immunization – a critique" published by the petitioner, describes how the WHO has recently revised how AEFI are classified. Only reactions that have previously been acknowledged in epidemiological studies to be caused by the vaccine are classified as a vaccine product related reaction. Deaths observed during post-marketing surveillance are not considered as 'consistent with casual association with vaccine', if there was no statistically significant increase in deaths recorded during the small Phase 3 trials that preceded it.
14.03.2020	Vide the letter, dated 14.03.2020, addressed to the Chief Secretaries of all States by the Ministry of Home Affairs (Disaster Management Division), the Central Government notified COVID as disaster under Disaster Management Act, 2005
26.05.2020	CIC order in Prashant Reddy T. v. Central Public Information Officer, Drug Controller General of India & Ministry of Health, made the following observations involving files that went missing from the Office of the Drug Controller General of India (DCGI) "The Commission however expressed its serious concern over the record keeping methodology in the office of DCGI / CDSCO due to the fact that an important report relating to the review of procedures and practices followed by CDSCO for granting approval and clinical trials on certain drugs went missing from their office that had to be procured from the author after receipt of notice of hearing from the Commission. This is despite the fact that the Parliamentary Standing Committee had also taken cognizance of the lapses by the Public

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	Authority. The intent and the conduct of the Public Authority should always be above board in matters relating to grant of approvals through a transparent and objective mechanism. The Commission advises Secretary, M/o Health and Family Welfare, Govt. of India to examine this matter appropriately for further necessary action at its end."
30.06. 2020	The Drugs Controller General of India (DGCI) approved Bharat Biotech application to conduct a Phase I and II clinical trial of Covaxin. The vaccine was being developed with the collaboration of Indian Council of Medical Research ((ICMR).
06.07.2020	An RTI was filed seeking information from the Indian Council of Medical Research, regarding the list of ingredients present in the proposed COVAXIN, the methodology and techniques used in manufacturing the vaccines, the research papers published detailing the reports of pre clinical trial of COVAXIN and details of the agreement between ICMR and Bharat Biotech. . However the ICMR refused to give any information and in its reply stated: *"Since it is the third party information sought, which is under an agreement between the same cannot be shared under PPP ethical code."*
26.08.2020	Serum Institute of India started the clinical trials of Covishield developed by Oxford University and AstraZeneca in pursuance of the approval by The Drugs Controller General of India on 30.07.2020.
20.09.2020	A letter dated was written to the Hon'ble Health Minister by a group of concerned citizens including senior doctors and health specialists, researchers and transparency activists expressing

	concerns about the opacity in clinical trials data. They highlighted that the CTRI (Clinical Trials Registry) database is valuable for doctors and researchers to learn from developments in medical research. Apart from the opacity in the clinical trial, the letter also raised issues regarding the loopholes in the CTRI database. CTRI database allows citizens to monitor the recruiting practices employed by pharma companies during the trials conducted in India. However, the Hon'ble Health Minister didn't respond to the letter.
23.10.2020	The Drugs Controller General of India (DCGI) granted permission for conducting phase-3 clinical trial of COVAXIN. The permission was granted after recommendation of subject expert committee after assessing the data from Phase I & II as well as animal challenge study.
07.12.2020	Bharat Biotech and Serum Institute of India applied to the central drug regulator seeking emergency use authorization for its COVID-19 vaccine i.e. Covaxin and Covishield.
30.12.2020	Subject Expert Committee reviewed the requests of Serum Institute and Bharat Biotech for grant of Emergency approval of their vaccines. M/s Serum Institute of India Pvt. Ltd. (SIIPL), Pune, in light of the earlier recommendations presented safety immunogenicity & efficacy data of phase II/III clinical trials of AstraZeneca vaccine carried out in UK & Brazil & South Africa along with the safety & immunogenicity data from the ongoing Phase II/III clinical trial of COVISHIELD vaccine manufactured by SIIPL in the country. The firm also presented the draft factsheet & prescribing information of the vaccine. The firm also mentioned that AstraZeneca had received Emergency Use Authorization for

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	the vaccine in UK subject to various conditions & restrictions. The committee discussed the safety, efficacy & immunogenicity data, draft factsheet & prescribing information as provided by the firm & decided that clarification/justification on various aspects are still needed. After detailed deliberation, the committee recommended that the firm should submit complete details of the conditions & restrictions under which AstraZeneca was granted Emergency Use Authorization in UK and also present the revised factsheet & prescribing information in Indian context as required by the committee for further consideration. Also the firm was informed during the meeting regarding other requirements including clarification/justification on factsheet & prescribing information. BIO/MA/20/000103 Whole Virion, Inactivated Corona Virus Vaccine (BBV152) (EUA) M/s Bharat Biotech International limited, Hyderabad In light of the earlier recommendations of the committee, the firm presented updated recruitment status & safety data including SAE data of the ongoing Phase III clinical trial in the country. After detailed deliberation, the committee recommended that firm should update & present Immunogenicity, Safety & Efficacy data for further consideration.
01.01.2021	Subject Expert Committee meeting further reviewed the proposals and information submitted by the companies. BIO/MA/20/00010 2 ChAdOx1 nCoV19 Corona Virus Vaccine (Recombinant) (COVISHIELD) M/s Serum Institute of India Pvt Ltd. The minutes detail that in light of the recommendations of the committee in its earlier meeting dated 30.12.2020, the firm

	presented the details of the conditions & restrictions under which AstraZeneca was granted Emergency Use Authorization in UK and the revised factsheet & prescribing information in Indian context as required by the committee for further consideration. The MHRA approval dated 30.12.2020 along with its conditions/restrictions was also reviewed by the committee. The committee noted that the safety & immunogenicity data presented by the firm from the Indian study is comparable with that of the overseas clinical trial data. Considering the serious nature of the COVID-19 pandemic, emergency situation, there is an urgent need of vaccine in the country. After detailed deliberation, the committee recommended for grant of permission for restricted emergency use of the vaccine subject to various regulatory provisions. The committee with respect to Covaxin recorded: "In light of the earlier recommendations of the committee dated 30.12.2020, the firm presented safety & immunogenicity data, GMT, GMFR including SAE data from the Phase I & Phase II clinical trial along with the data from the ongoing Phase III clinical trial in the country. The committee noted that this vaccine is Inactivated Whole Virion, Corona Virus Vaccine having potential to target mutated corona virus strains. The data generated so far demonstrates a strong immune response (both antibody as well as T cell) and invitro viral neutralization. The ongoing clinical trial is a large trial on 25800 Indian subjects in which already 22000 subjects have been enrolled including subjects with comorbid conditions as well which has demonstrated safety till date. **However, efficacy is yet to be demonstrated.**

	After detailed deliberation, the committee recommended that the firm should try to expedite the recruitment and may perform interim efficacy analysis for further consideration of restricted emergency use approval."
02.01.2021	On January 2, however, the committee recommended approval of Covaxin, citing efficacy data from a challenge study on non-human primates. The minutes of the meeting states: "In light of the recommendations of the committee dated 01.01.2021, the firm further presented the updated data, justification and requested for consideration of their proposal in the wake of incidence of new mutated corona virus infection. As already noted by the committee, this vaccine is Inactivated Whole Virion, Corona Virus Vaccine having potential to target mutated corona virus strains. The data generated so far demonstrates a strong immune response (both antibody as well as T cell) and in-vitro viral neutralization. The ongoing clinical trial is a large trial on 25800 Indian subjects in which already 22500 subjects have been enrolled including subjects with comorbid conditions as well which has demonstrated safety till date. Moreover, firm has presented the safety and efficacy data from Non-human primate challenge study where the vaccine has been found to be safe and effective. In view of above, after detailed deliberation, the committee recommended for grant of permission for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode, to have more options for vaccinations, especially in case of infection by mutant strains. Further, the firm shall continue the on-going Phase III clinical trial and submit data emerging from the trial as and when available."

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03.01.2021	Drugs Controller General of India (DCGI) granted emergency approval to two COVID – 19 vaccines i.e Covaxin And Covishield . The press statement by the Drugs Controller General of India (DCGI) on Restricted Emergency approval of COVID – 19 virus vaccine is as follows: "*The Subject Expert Committee (SEC) has reviewed the data on safety and immunogenicity of the vaccine and recommended for grant of permission for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode, to have more options for vaccinations, especially in case of infection by mutant strains. The clinical trial ongoing within the country by the firm will continue.*" Petitioner herein submits that the grant of emergency use license to the vaccines in India foreclosed the Phase III trials, restricting it to a mere 2 months. Subsequently the population in general have been encouraged to be vaccinated, so the control group to study adverse effects and efficacy for the trials has vanished and after that the ability to compare adverse events in the vaccinated and unvaccinated is lost forever. The Emergency Use Authorization by Respondent without disclosing the data for each of the phases of clinical trials is in clear violation of Article 19 and 21 of Constitution of India and the principle of "informed consent" as held by this Hon'ble Court in various judgments. As reported in The Times of India, The Drug Controller General of India stated that the Covid-19 vaccines are "110% safe".
5.01.2021	Deccan Herald report "Covaxin phase-3 trials to end today, average efficacy 60-70%". Covaxin does not have any data from its Phase 3 trial published in a peer reviewed journal. The first

	participant was enrolled in the phase three trial on the 11th of November 2020 and as shown on the Clinical Trials Registry website, the estimated duration of the trial was one year. Yet the company is reported to have ended its phase 3 trial on 5th of January 2021, as reported in the Deccan Herald.
16.01.2021	An order was issued by Civil Surgeon (equivalent to CMO/CMHO) in Koderma, Jharkand, mandating local government health workers to take Covid-19 Vaccine or otherwise their salary will be withheld. The order was subsequently withdrawn.
11.02.2021	The Indian Express reported that, "The Circular from Garudeshwar taluka, falling in the tribal Narmada district, cites a video-conference held by the district primary education officer (DPEO) on February 8, and was issued to two nodal officers in the taluka on February 9. It said, "Teachers of the government primary schools, who have to interact with students and work among the students, have to mandatorily take the Covid-19 vaccine, which must be ensured. If any teacher refuses to take the vaccine or remains absent during the vaccination drive, and if any student thereafter contracts Covid-19 from the teacher, the entire responsibility of the same will be on the teachers." Teachers who refuse to take the vaccine shot will have to submit a certificate in writing, citing reasons for the same the circular added". While the district administration later called it a "draft copy" that was issued "by mistake", officers in

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	charge of the nodal supervision of the vaccination drive for teachers said the decision to make teachers "accountable" was taken because many had refused to take the shot. The same news report, mentions another circular: "the circular issued by the Ahmedabad Municipal Corporation School Board made it compulsory for its teachers and other staffers to get themselves vaccinated. Municipal school teachers told the The Indian Express on conditions of anonymity, they were asked to not sign the muster roll if they did not take the vaccine."
27.02.2021	The WHO holds that the vaccine does not prevent the spread of the disease from person to person and so has little potential of stopping the pandemic or the preservation of public health. Dr Antony Fauci who heads the Center for Disease Control in the USA made the following statement recently as reported in The Atlantic: *"Anthony Fauci said last week on CNN that "it is conceivable, maybe likely," that vaccinated people can get infected with the coronavirus and then spread it to someone else, and that more will be known about this likelihood "in some time, as we do some follow-up studies."*
9.03.2021	RTI reply by the Ministry of Health and Family Welfare stated, "taking the Covid Vaccines was entirely voluntary and there is no relation whatsoever to provision of government facilities, citizenship, job etc to the vaccine".
10.03.2021	The Subject Expert Committee on Vaccines (SEC) in its meeting dated 10.03.2021, recommended for omission of the condition of

	the use of the vaccine in "clinical trial mode". The petitioner submits that this has been done in haste to enable the vaccines acceptability and use despite its phase 3 trial which is still ongoing. It is hereby submitted that despite the phase 3 trials of the Covaxin being underway, the removal of the "clinical trial mode" label attached to the emergency authorisation of the vaccine would mean that the vaccine would now be administered effectively in a phase 3 trials but without seeking informed consent of those to whom the vaccine is being administered. Thereby depriving the participants from right to get compensation in cases of adverse effect of vaccination. The reason Covaxin had been given restricted emergency use authorisation "in clinical trial mode" in the first place was because Bharat Biotech had not completed recruitment of participants for phase 3 trials and thus not been able to submit information regarding the vaccines efficacy. Therefore such recommendation should not be implemented.
13.03.2021	**T**he Government of Maharashtra Department of Revenue and Forest Disaster Management, Relief and Rehabilitation, has issued a governmental order No: *DMU/ 2020 / CR. 92 / Dis M-1, directing:* "*Essential shops owners and person working at all shops to get vaccinated at the earliest, as per criteria of GOI*"
17.03.2021	The Hindu published an article stating that a group of experts in public health, ethics, medicine, law and journalism have written to the Health Minister and the Drug Controller General of India, appealing for a time bound and transparent investigation following deaths and serious adverse effects after Covid-19

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	vaccination. The experts underline that even as the Indian health administration continues to be indifferent to the adverse effects of vaccination, several countries across the world such as Denmark, Iceland, Norway, Italy, France, Bulgaria, Germany, Luxembourg, Estonia, Lithuania, Latvia and Ireland have paused immunisation with Astra Zeneca vaccine pending investigation of a small number of post-vaccination deaths from intravascular clotting/ thromboembolic events. Austria has even suspended the use of certain batches... They have demanded a transparent investigation into each of the adverse incidents and sought details of all serious AEFIs till date, status of their investigation, findings of AEFI probe including cause of death by clinical diagnosis, autopsy findings, causality assessment and the process undertaken by AEFI committees to arrive at their conclusions.
1.04.2021	As reported in The Hindu, the Subject Expert Committee allowed Bharat Biotech to unblind trials participants aged above 45 and offer them the vaccine free of cost. The Committee recommended that the company unblind the participants as "vaccines are already available under the immunization programme, and therefore all the eligible age groups under the immunization programme should be permitted for unblinding for vaccination."
04.04.2021	The Daily Expose reported the statement of Dr Polyakova, who is the Medical Director of a hospital in Kent has said that "the levels of sickness after vaccination is unprecedented" among NHS staff, confirming that some are even suffering neurological symptoms which is having a "huge impact on the health service

	functioning". The doctor, who progressed into medical management of the hospital over the past three years says that she is struggling with the "failure to report" adverse reactions to the Covid vaccines among NHS staff, and clarified that the young and healthy are missing from work for weeks after receiving a dose of either the Pfizer or AstraZeneca experimental vaccine"
09.04.2021	The Hindu reported in an article "180 deaths following vaccination reported in India" that according to a presentation made to the National AEFI Committee during a meeting held on March 31, there have been 617 severe and serious (including deaths) adverse events following immunisation. As on March 29, a total of 180 deaths (29.2%) have been reported following vaccination across the country. Complete documentation is available only for 236 (38.3%) cases. In all, 492 severe and serious AEFI have been classified by the AEFI Secretariat of the Immunisation Technical Support Unit (ITSU) at the Health Ministry. Classification has been completed for 124 deaths, 305 serious events that required hospitalisation, and 63 severe events that did not require hospitalization. Therefore in such case it is necessary that Respondent disclose the post vaccination data regarding adverse events, vacinees who got infected with Covid, those who needed hospitalization and those who died after such infection post vaccination.
18.04.2021	The Lokmat Times reported that "*The Maharasthra government has imposed strict restrictions until May 1 to break the coronavirus chain. After that, the Aurangabad Municipal Corporation (AMC) will not allow unvaccinated traders and general people, aged 45 and above, to step out of home. So citizens eligible for vaccination should get vaccinated as soon as*

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	possible," said AMC administrator Astik Kumar Pandy."
22.04.2021	The Gujarat Technological University, Govt of Gujarat issued a circular regarding Covid-19 Vaccination before Winter -2021 Exam form filling. An excerpt from the circular is below: "All students who have attained age of 18 years as on 1/05/2021 are hereby informed that it is mandatory to get Covid-19 vaccination before filling Winter 2021 exam forms. Along with the prevailing GTU norms, institutes will have to allow only the students who have taken Covid 19 vaccination to fill their Winter – 2021 exam forms"
23.04.2021	In the letter number: G-1/2021/36650 dated 23-04-2021, issued by the Office of the District Education Officer, Tarn, Tarn, it is stated, *"This has reference to the meeting hled by the Deputy Commissioner on 22-04-2021, regarding COVID Vaccination and the instructions were issued and received by this office on the mandatory COVID Vaccination of all the officers/employees. It is clearly stated that if any officer/employee is unwilling or refuses to be vaccinated, the concerned DEOs shall not draw the salary of such officers/employees."*
27.04.2021	The President of the Tamil Nadu Practitioners Association, Dr. CMK Reddy flags his concern about the reported deaths after taking Covid vaccine. The letter states: "Though the Adverse Effects Following Immunisation (AEFI) Committee comforts public and profession by saying they're unrelated to the vaccine, we have to take it with a grain of salt...If they are due to reasons other than vaccination, they should be evenly distributed during every week following

	vaccination, but 75% deaths occurred and 90% were hospitalised during the first 3 days. Hence let us not take it for granted and find out if we can prevent the complications."
29.04.2021	The Administration of Whistling woods International, Goregaon East, Mumbai, sent an office Memo to All, by email titled, "Vaccination against Covid". In that mail it was stated, *"We would like everyone who plans to come to campus post lockdown to be vaccinated, this will help us build a safer work place. Please ensure that you have your dozes of vaccines before end of July 2021 so we can start our operations full force as soon as the restrictions are over. After getting vaccinated, kindly send your vaccination certificate."*
30.04.2021	In the State of Punjab, the Governmental Order No: 7/56/2020/ 2H4/2142 dated 30th April 2021, addressed to all officers of the Police department including Divisional Commissioners, Zonal IGPs, Commissioners of Police, DIGs and SSPs, the Department of Home Affairs and Justice, stated in section 1(xv), *"In Government offices – Health / frontline workers and employees over 45 years who have not got at least one vaccine dose in last 15 days or more, should be encouraged to take leave and stay home until then Employees under 45 years to be allowed only on basis of negative RT-PCR not more than 5 days old or else should take leave and stay home".*

2.05.2021	RTI application to the Ministry of Health and Family welfare dated 21.04.2021, applicant Rakesh Singh requested for the following information; "1. Is corona vaccine (Covid-19 vaccine compulsory? 2. Can private company force its employees to take Covid 19 vaccine? 3. Will I be debarred from public services like Metro rail, Indian railway, bus services, hospital, electricity, internet, food and inter and intra-city movement, if I don't take covid-19 vaccine? 4. what can I do it my senior officer forces me to take Covid-19 vaccine? ... 7. Can a government Health worker be suspended for not taking Covid 19 vaccine? 8. Does government or its any associate body have any reliable data of Covid 19 vaccine research so that citizens can trust the efficacy of vaccines? Vide reply dated 2nd May 2021, from the Ministry of Health and Family Welfare stated: "1. Vaccination for Covid-19 is voluntary. However it is advisable to receive the complete schedule of Covid-19 vaccine for protecting oneself against this disease and also to limit the spread of this disease to the close contacts including family members, friends, relatives and co-workers. 2-8 – in view of the reply as SI. No. 1, these questions have no relevance."

02.05.2021	The Department of Home Affairs and Justice, Government of Punjab stated in section 2(ii), In its order No: 7/56/2020/2H4/2143 stated: *"Nobody to enter the State whether by air, rail or road without either:* *a- Negative Covid report not more than 72 hours old, or* *b- Vaccination certificate (at least one dose) over 2 weeks old."* It is hereby submitted that making Covid Vaccines are experimental treatments. Those agreeing to receive them are agreeing to be participants in an ongoing medical experiment with several unknowns. There is no certainty about issues like long term safety. Coercing citizens to get the vaccines directly or directly violates Article 21 and any order which makes the administration of vaccine mandatory is liable to be set aside.
3.05.2021	Report in The Hindu titled "ICMR to get royalty from Covaxin sale". As reported in The Hindu, the ICMR is to get royalties from the sale of Covaxin and this should disqualify them from sitting on regulatory committees to license this product or similar competing products. Given all these pervasive conflicts of interest, only data transparency and its availability to independent scientists to reassess, can protect the public interest.

10.05.2021	Data released today by the Centers for Disease Control and Prevention (CDC) on the number of injuries and deaths reported to the Vaccine Adverse Event Reporting System (VAERS) following COVID vaccines revealed reports of blood clots and other related blood disorders associated with all three vaccines approved for Emergency Use Authorization in the U.S. — Pfizer, Moderna and Johnson & Johnson (J&J). So far, only the J&J vaccine has been paused because of blood clot concerns. Every Friday, VAERS makes public all vaccine injury reports received through a specified date, usually about a week prior to the release date. Today's data show that between Dec. 14, 2020 and April 30, a total of 157,277 total adverse events were reported to VAERS, including 3837 deaths, including 21623 requiring urgent care, 1132 heart attacks, 213 miscarriages, 7463 severe allergic reactions.
12.05.2021	The act of respondents in maintaining opacity with regard to data of clinical trials of the vaccines administered in India, non disclosure of the detailed minutes of the meetings of the Subject Expert Committee with regard to the vaccine emergency authorisations and the documents and information relied upon for such permissions, the failure to disclose names of the members of the SEC who were present in the meetings where emergency authorisation for the use of vaccines was granted, as well as the lack of post vaccination data regarding recording and reporting adverse events, violates Article 19 and 21 of Constitution of India and the principle of "informed consent" as held by this Hon'ble Court in various judgments. Hence, the present Writ Petition.

IN THE SUPREME COURT OF INDIA

[EXTRAORDINARY ORIGINAL JURISDICTION]

WRIT PETITION (CIVIL) NO._____OF 2021

(PUBLIC INTEREST LITIGATION)

IN THE MATTER OF:-

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...PETITIONER

VERSUS

1. **THE UNION OF INDIA**
   THROUGH IT'S SECRETARY
   MINISTRY OF HEALTH AND FAMILY WELFARE
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   NEW DELHI – 110001

2. **CENTRAL DRUGS STANDARD CONTROL ORGANISATION**
   THROUGH THE DRUGS CONTROLLER
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   AND FAMILY WELFARE
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A WRIT PETITION UNDER ARTICLE 32 OF THE CONSTITUTION SEEKING A WRIT OF MANDAMUS OR ANY OTHER APPROPRIATE WRIT DIRECTING THE RESPONDENTS TO DISCLOSE CLINICAL TRIAL DATA, POST VACCINATION DATA AND ADVERSE EVENTS FOR THE VACCINES BEING ADMINISTERED IN INDIA UNDER THE EMERGENCY AUTHORISATION AND FOR RESTRAINING RESPONDENT NO. 1 FROM MANDATING THE USE OF THESE VACCINES WITHOUT FULL AND INFORMED CONSENT

To,

THE HON'BLE CHIEF JUSTICE OF INDIA AND HIS COMPANION JUDGES OF THE HON'BLE SUPREME COURT OF INDIA

The Humble Petition of the
Petitioner above-named

MOST RESPECTFULLY SHOWETH:-

1. The petitioner herein is filing the instant writ petition under Article 32 of the Constitution of India for the enforcement of fundamental rights under Article 14 and 21 of the Constitution of India, seeking a writ directing the respondents to make public the segregated data of the clinical trials for the vaccines that are being administered to the population in India under the Emergency Use Authorisation granted by the Drugs Controller General of India (DCGI). The petitioner avers and wishes to record the evidence in medical literature that, vaccines that have not been adequately tested for safety or efficacy are now licensed under Emergency Use Authorisation without the data being disclosed to the public. This is a clear violation of the basic norms of scientific disclosure. In India, the manner in which the vaccines have been licensed vitiates and even precludes the possibility that the vaccines can be evaluated objectively in the future. Furthermore, the Government has made illogical claims and resorted to hyperbole in its promotion of these untested vaccines with the DCGI stating that the vaccine is 110% safe which is a logical fallacy. Under these circumstances the petitioner is forced to appeal to this court for public disclosure of trial data and post vaccination data, as required by international medical norms. Further the petitioner prays that no coercive mandates for use of these inadequately tested vaccines may be issued and that the courts reiterate that vaccine mandates are repugnant to the right of humans to autonomy and right to self-determine what may be

injected into their bodies. In so doing this Hon'ble Court must uphold the rights of individuals to give informed consent as the Delhi High Court did, in the Measles Rubella case. Besides this, it is important for the respondent authorities to carefully monitor vaccine recipients and publicly record all adverse events. In other countries, this type of observation has helped identify the occurrence of blood clots and strokes in vaccine recipients. Many countries stopped administering the vaccine till they evaluated this occurrence and countries like Denmark have completely banned use of the Astra Zeneca vaccine (branded as Covishield in India). India, with its huge population and numbers vaccinated, should have reported these adverse events first. But due to poor follow-up, poor Adverse Events Following Immunization (AEFI) evaluation and suppression of data, these events have not been put in the public domain – endangering many more to suffer the same fate. Under these circumstances the petitioner has approached this court also seeking that that all AEFI be actively solicited by notification in newspapers, and be made available in publicly accessible data base (Like the VAERS data base in the USA). Currently the website cowin.gov.in only mentions certain numbers of AEFI but details of those cases are not available for public scrutiny.

The petitioner recognises that Covid is a public health emergency and that such an emergency may require emergency use authorisations of vaccines which may not yet have been adequately tested. However, that should not mean that all

information and data of relevance to the efficacy or side effects of the vaccines which have been given such approval, should not be made publicly available, especially when the vaccines are being used in a universal immunisation programme. Though emergency authorisation of the vaccines may be advisable in the present situation, it does not however mean that these vaccines can be forced upon people, especially without all relevant data being available for independent public and scientific scrutiny. The present petition therefore should not be understood to be a petition challenging the present Covid vaccination programme.

Description of petitioner

1A. Dr. Jacob Puliyel, MD MRCP MPhil, is a paediatrician who has been advising Government of India on vaccines as a member of the National Technical Advisory Group on Immunization (NTAGI) for several years, and who rotated out after over two terms on the committee. He has numerous publications in internationally peer reviewed medical journals and is very widely cited. The petitioner is a peer reviewer for international journals like the British Medical Journal and the Canadian Medical Journal. The petitioners bank account no. is 564010000418, average annual income is 480,000 and Pan no. is AIMPP2310C.

The petitioner has no personal interest, or private/oblique motive in filing the instant petition. There is no civil, criminal, revenue or any litigation involving the petitioner, which has or could have a legal nexus with the issues involved in the PIL.

The petitioner has not made any representations to the respondents in this regard because of the extreme urgency of the matter in issue.

That the instant writ petition is based on the information/documents which are in the public domain.

FACTS OF THE CASE

Adverse consequences for testing vaccine efficacy due to the Emergency Approval of vaccines in India

2. India's drug regulator approved two COVID – 19 vaccines on January 3rd. The press statement by the Drugs Controller General of India (DCGI) on Restricted Emergency approval of COVID – 19 vaccine states:

> "The Subject Expert Committee (SEC) has reviewed the data on safety and immunogenicity of the vaccine and recommended for grant of permission for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode, to have more options for vaccinations, especially in case of infection by mutant strains. The clinical trial ongoing within the country by the firm will continue."

However as shown below the trials have not been allowed to continue.

(A copy of the press statement by the Drugs Controller General of India (DCGI) on Restricted Emergency approval of COVID – 19

virus vaccine, dated 3rd January 2021 is annexed as **Annexure P1 (Page 32 to 33).**

3. On the same day as reported in the Times of India, the Drug Controller General of India stated that the Covid-19 vaccines are "110% safe". The report further quotes the DCGI as below:

"We will never approve anything if there is even slightest safety concern. Vaccines are 100 percent safe. Some side effects like mild fever, pain and allergy are common for every vaccine. It (rumors of impotency) is complete nonsense," VG Somani, Drug Controller General of India said. When asked if people would face side effects after taking the vaccine, the DCGI said, "Yes, minor side effects will be there, including a little like pain in the shoulders, a slight fever, little allergies. This occurs in every vaccine but of course, the vaccine is 110 per cent safe."

(A copy of the Times of India report dated 3.01.2021 is annexed as **Annexure P2 (Page 34 to 35).**

4. With respect to these two vaccines licensed for use in India by the Drug Controller General of India, it is important to highlight that the Covishield (Astra Zeneca) has some (intermediate analysis) efficacy data from phase 3 trials published in peer review journals. The full trial data can only be published after the trial is complete. The second, Covaxin does not have any data from its Phase 3 trial published in a peer reviewed journal. The first participant was enrolled in the phase three trial on the 11th of November 2020 and

as shown on the Clinical Trials Registry website, the estimated duration of the trial was one year. Yet the company is reported to have ended its phase 3 trial on 5th of January 2021, as reported in the Deccan Herald.

(A copy of the Deccan Herald report dated 5th January 2021 "Covaxin phase-3 trials to end today, average efficacy 60-70% is annexed as **Annexure P3 (Page 76 to 77).**
(A copy of the CTRI database regarding the Phase 3 trials details of the Covaxin is annexed as **Annexure P4 (Page 78 to 85).**

4. Given the public panic surrounding the Covid pandemic, Emergency Use Authorization has been given to these 2 vaccines. In effect, because the Covaxin vaccine is now available to the public, many (above 45 years) in the original control group have got antibody levels tested and taken the vaccine, the control trial crucial in Phase 3 has been abandoned. We cannot now evaluate most adverse effects of the vaccine compared against those receiving placebo and we have moved to Phase 4 post marketing surveillance. The disadvantage of diluting Phase 3 prematurely and going on to this Phase 4 data is that there are few controls to compare against and it is usually difficult to say what events are caused by the vaccine and what are coincidental events that can occur in some persons when a large number of people are observed with or without vaccine. But it behooves the authorities to carefully monitor all vaccine recipients and publicly record all adverse events. As reported in The Hindu on

1st April 2021, the Subject Expert Committee allowed Bharat Biotech to unblind trials participants aged above 45 and offer them the vaccine free of cost. The Committee recommended that the company unblind the participants as "vaccines are already available under the immunization programme, and therefore all the eligible age groups under the immunization programme should be permitted for unblinding for vaccination."

(A copy of The Hindu Report dated 1st April 2021 titled, "Covaxin for those who got placebo" is Annexed as **Annexure P5 (Page 86 to 88)**.

5. The petitioner submits that in order to effectively study a vaccine, it must be compared to a placebo (i.e. an inactive substance). Therefore, usually in trials the participants are divided into at least two groups: the group receiving the vaccine (study group) and the group receiving the placebo (control group). The efficacy of the vaccine is seen by looking at how many are protected from getting the disease in the study group compared to controls. Also, the numbers who develop adverse events in the two groups can also be compared. Such trials are conducted over two to five years, so that sustained efficacy and long-term adverse effects can be studied. Thus, effectively the vaccines being administered now are really still part of a gigantic clinical trial on the public at large. Unfortunately, though there is considerable anecdotal evidence and news reports about the adverse events including deaths of people who took the vaccine as well as vaccinated people getting seriously infected,

hospitalized and even dying, no information about these events is being put out on a real time basis.

6. With the emergency roll out of the vaccine, the phase three trials (meant to last for 1 year) have been severely truncated/abandoned, after about 2 months. In fact Covaxin which got approval for emergency use in 'clinical trial mode' is now no longer being administered in Clinical trial mode. Therefore such quick approvals does not inspire any confidence in the decision making process where the vaccine is initially licensed saying "The clinical trial ongoing within the country by the firm will continue" and this is then stopped without fulfilling the protocol registered by the manufacturers to CTRI and especially since the data for such trials has not been released.

7. The WHO holds that the vaccine does not prevent the spread of the disease from person to person and so has little potential of stopping the pandemic or the preservation of public health. Dr Antony Fauci who heads the Center for Disease Control in the USA made the following statement recently as reported in The Atlantic:

> "Anthony Fauci said last week on CNN that "it is conceivable, maybe likely," that vaccinated people can get infected with the coronavirus and then spread it to someone else, and that more will be known about this likelihood "in some time, as we do some follow-up studies."

(A copy of the article in The Atlantic dated 27th February 2021 is annexed as **Annexure P6 (Page 89 to 92)**.

8. While some vaccines have been useful in eradicating/controlling diseases, it is well known and established that vaccines can have serious short term and long term side effects. Quite apart from problems encountered with the Astra Zeneca vaccine administered under the name Covishield in India, such as blood clots, etc which have led to stopping the administration of the vaccine in many European countries, there could be other more serious long term side effects. Therefore it is essential that clinical trials are conducted in a rigorous manner and the results of the trials and all data be disclosed in a transparent manner for scientific scrutiny of independent scientists and researchers.

Need for transparency in publishing segregated clinical trial data of vaccines

9. The petitioner submits that the importance of disclosure of segregated data of vaccine clinical trials (segregated for each vaccine and for each age group) that have been undertaken with respect to the two vaccines being administered in India, cannot be undermined and must be disclosed through peer reviewed scientific journals. The disclosure of such information is essential to ascertain whether a certain section of the population is more susceptible to adverse effects, to determine what are the adverse effects in various age groups and on differing populations, etc. So far, the respondents have practiced complete secrecy in the matter and have not

disclosed any data from trials for the vaccines that have been developed in India – Covaxin by the Bharatbiotech or for the Covishied manufactured at the Serum Institute, India (SII). The clinical trial information that is available for the COVISHIED vaccine is preliminary data of clinical trials that have been undertaken for the vaccine in other countries.

10. It is submitted that the revised version of Declaration of Helsinki, developed after the horrific Nazi medical experiments on prisoners and human subjects without their consent, and the resultant Nuremberg Code for medical ethics in human medical research, and adopted by the ICMR in India, states that

> "Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject." And that "Researchers have a duty to make publicly available the results of their research...Negative and inconclusive as well as positive results must be published or otherwise made publicly available"

(A copy of the relevant section of the revised Declaration of Helsinki is annexed as **Annexure P7 (Page 93 to 96).**

11. The World Health Organisation (WHO) released a strong statement advocating for public disclosure of all clinical trial results. According to the statement, when data is not released it means that doctors, patients and medical regulators cannot make informed decisions

about which treatments are best. Non-disclosure of complete clinical trial results means that hundreds of thousands of patients have volunteered to take part in clinical trials where results have been kept hidden or are only selectively disclosed.

(A copy of the 'WHO statement on Public Disclosure of Clinical Trial Results' released on 14.04.2015 is annexed as **Annexure P8 (Page 97 to 99).**

12. Since trials of vaccines for testing its efficacy for side effects are normally done by the vaccine manufacturing companies themselves (which have a commercial interest in the propagation and use of their vaccines), the rules of most national regulatory institutions require the entire data for the vaccine trials to be put out in the public domain so that independent researchers could examine that data and pick up significant flaws which the vaccine manufacturers may have omitted or tried to hide. Historically there have been many cases of drug manufacturers being caught hiding or manipulating data and concealing side effects or overstating efficacy after the data was examined by independent researchers/scientists. Many drug manufacturers including many who are now involved in the manufacture of Covid vaccine, have been held guilty for manipulating data in the past and have had to pay billions of dollars as fines. An article in GreenMedinfo notes as follows:

> 'Clinical trials are also known to obfuscate troublesome data. In September 2017, a report titled "Infanrix hexa and sudden death: a review of the periodic safety update reports submitted to the European Medicines Agency" published in the Indian Journal of Medical Ethics[35] alleged that

GlaxoSmithKline (GSK) apparently excluded certain cases of infant deaths in their official report to the European Medicines Agency. GSK stated that the deaths reported after the vaccine is "coincident" and not related to the vaccine. However analysis by Puliyel and Sathyamala, authors, showed that 83% of the reported deaths occurred within 10 days of vaccination and only 17% occurred in the following ten days. "Glossing over of the deaths after vaccination has potential to result in more, unnecessary deaths which are difficult to justify ethically," they observed in a Press Release.

The same vaccine and an MMR vaccine have also been embroiled in serious contamination scandals and the list grows by the day. In yet another shocking incident the Government of India preferred not to release clinical data of an indigenous Rotavirus vaccine that showed a very high incidence of a potentially lethal intestinal obstruction in vaccinated children under the plea that revealing the data would "alarm the public".

(A copy of the article dated 13th April 2019 titled, "Anti Vaccination;Pro Science;Pro-Health;Anti-Industry" by Jagannath Chatterjee is Annexed as **Annexure P9 (Page 100 to 110).**

13. In the case of COVID vaccines, many of the standard rules for testing vaccines through clinical trials and transparency in disclosure of clinical trial data have been given a go-by by many regulators because of the panic in the media and population caused by the pandemic. However, the case of the Indian regulator is particularly pathetic and galling in as much as not even the preliminary data of Phase 3 have been put out in peer reviewed literature after all this time. Covisheild vaccine uses new recombinant genetic engineering technologies.

14. Vide RTI application dated 6.07.2020, information was sought from the Indian Council of Medical Research, regarding the list of ingredients present in the proposed COVAXIN, the methodology and techniques used in manufacturing the vaccines, the research papers published detailing the reports of pre clinical trial of COVAXIN and details of the agreement between ICMR and Bharat Biotech.

Maintaining opacity with regard to all of this information, the reply received by the ICMR stated:

"Since it is the third-party information sought, which is under an agreement between the same cannot be shared under PPP ethical code."

(A copy of the RTI application and reply are annexed as **Annexure P10 (Page 111 to 112).**

15. The petitioners are concerned about the lack of transparency in the clinical trials data which raises various concerns regarding the efficacy and safety of these vaccines. Transparency in publishing clinical trials data by the Central Drugs Standard Controls Organisation (CDSCO) that grants final approval for the vaccines by various manufactures to enter the immunization chain, flows from Section 4 of the Right to Information Act, 2005, which requires the government to make proactive disclosures of its records through the internet and other means of communications to the general public. Citizens cannot effectively assert their fundamental right to free speech against the State without access to information about the

internal workings of the State, especially in matter concerning the public health of citizens.

16. While media reports and press statements by Bharat Biotech suggest that the Covaxin has an efficacy rate of 81% based on preliminary data of its phase 3 trials, this is information that is being put out by way of a press statement in the lay press, by the vaccine manufacturer itself. The data on the basis of which the claim is being made has not been disclosed for it to be verified by independent researchers.

Non-disclosure of clinical data

17. The petitioners submit that is imperative that greater transparency of clinical trials be mandated by disclosure of both positive and negative results.

18. In a letter dated 20th September 2020 to the Hon'ble Health Minister, a group of concerned citizens, including senior doctors and health specialists, researchers and transparency activists, wrote expressing concerns about the opacity in clinical trials data. They highlighted that the CTRI database is valuable for doctors and researchers to learn from developments in medical research. Further, the CTRI database allows citizens to monitor the recruiting practices employed by pharma companies during the trials conducted in India. The letter however highlighted the following issues that the CTRI database and legal framework governing it does not address:

"(a) **Limited Disclosures:** The CTRI database does not contain three crucial pieces of information. The first piece of missing information is the **minutes of the meeting of the institutional Ethics Committee** where the clinical trial is to be carried out. These minutes are important because they will contain the details of the deliberations (including disclosure of conflict of interest) conducted by the Ethics Committee before allowing the institution to conduct the clinical trial. The second missing piece of information is **the application submitted to the DCGI for permission to conduct the clinical trial.** The application will presumably contain a host of pre-clinical data (study protocols, toxicology and pharmacology data, and other technical studies). This data needs to be made available to the public health community in order to ensure that the DCGI makes responsible decisions while granting permissions to conduct clinical trials in India. While the pharmaceutical industry would like to claim a proprietary interest in such data, it can be argued that the public interest in the disclosure of safety data outweigh any IP concerns. As per Section 8(1)(d) of the RTI Act, information can be disclosed if public interest outweighs IP concerns. The third critical piece of missing information is the reasoned **decision of the DCGI granting approval or rejecting an application for the conduct of clinical trials.** Without access to the DCGI's decision there is no way for the people to hold the DCGI accountable for its decision.

(b) **Disclosure of primary data:** The CTRI database only requires sponsors to indicate the status of the clinical trial. However, there is no legal obligation to disclose the primary datasets containing the results of the clinical trials. As a result, it has been alleged that pharmaceutical companies cherry pick the best data for publication in peer-reviewed journals while suppressing most of the damaging data. The reasons are self evident. Many in the pharmaceutical industry fear that publication of all clinical trial data may invite more public scrutiny of their claims and even adversely impact decisions by doctors to prescribe some of the riskier drugs. However, internationally, there has been a demand by the public health community for the release of all clinical trial data regardless of whether the trial succeeded or failed. Access to such health data will help both the regulatory community and the patient community in making more informed decisions regarding the true potential of a drug and the public interest in disclosure of this information outweighs the proprietary interests of the pharmaceutical companies. It maybe pertinent to mention that 'The Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subject' (2013) adopted by the World Medical Association (WMA) states "[r]esearchers have a duty to make publicly available the results of their research ... Negative and inconclusive as well as positive results must be published." ICMR also endorsed a global pledge to disclose results of trials in a timely manner. However, the disclosure is limited

to trials that are funded or supported by ICMR. The results of a vast majority of trials in India are unreported. Internationally, there has been a move in both the EU and the US to mandate the public disclosure of more clinical trial data.India should follow suit and make the disclosure of such clinical trial data a precondition to the approval of any new drug."

(A copy of the letter dated 20th September 2020 to the Hon'ble Health Minister, is annexed as **Annexure P11 (Page 113 to 125)**.

19. The petitioners submit that the disclosure of regulatory safety data under the RTI Act, have come before Central Information Commission. In Divya Raghunandan v. Dept. of Biotechnology(2007) and Kavita Kuruganti v. MoEF (2016)10 the CIC required the public disclosure of raw trial data (viz., biosafety, toxicity and allergencity data)pertaining to genetically modified brinjal studies because the public interest in making such data public, over-rode all other considerations such as commercial confidence, trade secrets or intellectual property. In the Kavita Kuruganti case,the CIC went as far as to require the publication of regulatory data even if the trials were a failure.

20. In Divya Raghunandan v. Dept. of Biotechnology (CIC/WB/A/2009/000668 (June 16, 2009), the CIC held:

""At the heart of the representation of Shri Deshpande of MAHYCO is the plea for exemption from disclosure u/s 8(1)(d) on the ground that "Information supplied in documents to the Department of Biotechnology (DBT) or other regulatory bodies contain undisclosed information (trade secrets) like protocols, confidential standard operating procedures, parental line information, event ID information, data generated from biosafety studies, methods, testing locations, etc, all of which may either be sensitive business information of the company, the unrestricted publication of which may adversely affect its business". Sec. 8(1)(d) reads as follows:

Sec. 8(1) (d) information including commercial confidence, trade secrets or intellectual property, the disclosure of which would harm the competitive position of a third party, unless the competent authority is satisfied that larger public interest warrants the disclosure of such information.

As has been quoted above, Shri Deshpande has dealt both on trade secrets and intellectual property being disclosed, thus harming their competitive position. However, both in this sub clause of Sec. 8(1) and in sub clause (2) of Sec. 8, access may be allowed to information "if public interest in disclosure outweighs the harm to the protected interests." The question here as per the orders of Dr. S. Natesh, a matter of recommending for large scale field trial the

products adjudicated upon by GEAC. In this case it is only toxicity and allergenicity data that Dr. Nitish has directed should be disclosed and that too after examination by GEAC There is therefore no question of "unrestricted publication", as emphasized by us in the plea of appellant Shri Deshpande It goes without saying that toxicity and allergenicity of any product to be put on large scale field trial is a matter of overriding public interest. The order of 18.5.06 of Dr. S. Natesh, Scientist H can indeed be faulted for not having clearly enunciated the requirement of public interest for disclosure. However, we would agree with learned Counsel for respondents Dr. Dubey that the exercise of processing by the GEAC is indeed an exercise in assessing public interest. The decision of Dr. S. Natesh is, therefore, upheld to this extent in the context of appeal CIC/WB/A/2009/000668. Issue No 3 is decided accordingly.

In light of our decision in File No. CIC/WB/A/2009/00668 upholding the orders of the Dep't. of 16.5.06, Public Information Officer Ms. Rajalaxmi M.V. Ramdharan Scientist D will now proceed to comply with our decision of 22.11.07 with regard to providing the existing data with regard to other agricultural products and obtain this data to be provided to the appellant, within ten working days of the receipt of this decision notice. However, this is with reference to "the existing data with regard to the other agricultural products" whether or not referred to GEAC. The

disclosure in this case will therefore adhere to exemption from disclosures provided u/s 8(1) (d), but keeping in mind our ruling above on disclosure before any massive farm trial. This disposes of Issue No 1."

21. In Kavita Kuruganti v. MoEF (CIC/SA/A/2015/901798 (April 01, 2016), the CIC held as follows:

The Commission had directed the public authority, Ministry of Environment, Forest and Climate Change to proactively publish information related to bio-safety data regarding transgenic mustard hybrid DMH -11 as well as agenda of meeting of Genetic Engineering Appraisal Committee and minutes of such meetings, which they are under statutory obligation to disclose.

The resolution of bio-safety with the crop developer has also been finalized; it should have been in public domain. Public authority is attempting to keep vital information out of public discussion. It amounts to prevention of Constitutionally guaranteed freedom of speech and expression of the appellant, who are interested in discussing the pros and cons of GMO related issues of GM Mustard, which if permitted would cause serious impact on the public health of consumers in large scale.

Justice Holmes (Abrams v US, 250 US 616 (1919)) characterized the discussion of public matters as essential to see that "the ultimate good desired is better reached by a free trade in ideas". One of the fathers of the American Constitution, James Madison, (1751--1836) said:

"Nothing could be more irrational than to give the people power, and to withhold from them information without which power is abused. A people who mean to be their own governors must arm themselves with power which knowledge gives. A popular government without popular information or the means of acquiring it is but a prologue to a farce or a tragedy, or perhaps both.

22. The petitioners submit that in the context of pharmaceutical safety data, the CIC in the past mandated the disclosure of clinical study reports of observational studies relating to HPV vaccines after redaction of the names of the patients and any information that may be considered the intellectual property of the pharmaceutical companies. (Deepa Venkatachalam v. Directorate General of Health Services). In a subsequent decision, Amresh Chandra Mathur v. Directorate General of Health Services, CIC/DTGHS/A/2018/609161-BJ+ (April 09, 2019), the CIC ordered the DCGI to suo motu disclose Regulatory Information redacting/obliterating the information exempted u/s 8 (1)/9 of the RTI Act, 2005 for the benefit of public at large. This order, however, has not been complied with by the DCGI. In, the CIC held:

"Keeping in view the facts of the case and the submissions made by both the parties, the Commission instructs the Respondent to suo motu disclose Regulatory Information redacting/ obliterating the information exempted u/s 8 (1)/9 of the RTI Act, 2005 for the benefit of public at large, within a period of 30 days from the date of receipt of this order, as agreed. No further intervention of the Commission is required in the matter. For redressal of his grievance, the Appellant/ Complainant is advised to approach an appropriate forum."

23. The petitioners therefore submit that the CDSCO has a legal obligation to disclose regulatory data especially primary datasets for all clinical trials authorized in India, after redacting private patient information. The information should be available in a searchable online database that can be freely accessed by citizens.

Removal of Clinical trial mode

24. Based on Bharat Biotech's own interim safety and efficacy data, which has also not been put out in the public domain for any oversight or independent scrutiny, the Subject Expert Committee on Vaccines (SEC) in its meeting dated 10.03.2021, recommended for omission of the condition of the use of the vaccine in "clinical trial mode". The petitioner submits that this has been done in haste to enable the vaccines acceptability and use despite non availability of any data on its phase 3 trial, which is still ongoing. They have thus removed the need to collect and report on adverse effects of the

vaccine. Given that Emergency Use Authorisation was granted before the completion of mandatory Phase 3 trials, such collection of data is crucial for ensuring safety of the product and thereby enhancing public confidence in the prophylactic measure. The arbitrary decision to take it off clinical trial mode is inimical to the public interest and dangerous.

(A copy of the recommendations of the SEC meeting to examine COVID-19 related proposal under accelerated approval process made in its 146th meeting held on 10.03.2021 at CDSCO, HQ New Delhi, is annexed as **Annexure P12 (Page 126 to -)**.

25. Furthermore, the petitioner submits, that despite the phase 3 trials of the Covaxin being underway, the removal of the "clinical trial mode" label attached to the emergency authorisation of the vaccine would mean that the vaccine would now be administered effectively in a phase 3 trials but without seeking informed consent of those to whom the vaccine is being administered. In clinical trial mode, informed consent is sought from participants in the trials and they are also compensated for any major adverse effects. The reason Covaxin had been given restricted emergency use authorisation "in clinical trial mode" in the first place was because Bharat Biotech had not completed recruitment of participants for phase 3 trials and thus not been able to submit information regarding the vaccines efficacy. No justification has been given for this, seemingly irrational, decision to administer the untested drug outside of clinical trial mode.

Lack of transparency in regulatory approvals, minutes and constitution of exert bodies

26. The minutes of the National Technical Advisory Group on Immunisations (NTAGI) do not specify which member raised an objection nor the evidence quoted by the member to support his contention. The NTAGI is the primary advisory committee advising the Ministry of Health and Family Welfare on all immunization-related issues. Whereas in countries like the US the public are admitted to the NTAGI equivalent (called ACIP in the USA) meetings, secrecy shrouds the deliberations of the NTGAI. The petitioner submits that this raises serious concerns regarding potential conflicts of interest and that cloak of secrecy cannot then be used to cloak conflicts of interests. Actions speak louder than words. A bland declaration of conflicts of interest by members cannot by itself reassure the public. The court must mandate that for the records there must be faithful recording of minutes specifying all the discussions and who participated. When the proceedings of parliament are broadcast nationwide the deliberation of a scientific committee does not need great secrecy.

27. As reported in the National Herald, the SEC meeting minutes do little to inspire confidence in the process. A perusal of the minutes of the Subject Expert Committee (SEC) meetings show that the SEC changed its mind about Bharat Biotech's Covaxin within a span of two days. The report states:

> "Minutes of the SEC's meetings show that on December 30, the members had asked Bharat Biotech to present the

immunogenicity, safety and efficacy data for consideration. On January 1, 2021, the committee noted that efficacy was yet to be demonstrated through the clinical trials and requested the company to expedite recruitment for Phase 3 trial. The committee members noted that the company could perform interim efficacy analysis, which could then be submitted for consideration of restricted use.

But on January 2, the firm presented 'updated data', though it was not specified what the 'updated data' was. The company only presented efficacy data from the non-human primate challenge study. At the meeting, Bharat Biotech provided justification for the data provided and additionally requested consideration of their proposal in the wake of incidence of new mutated corona virus infection.

Eventually, the SEC "recommended for grant of permission for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode, to have more options for vaccinations, especially in case of infection by mutant strains".

... "If you look at the minutes of the meeting from December 30 and Jan 1, 2, there is an intellectual leap. On the first two days, they are asking for data on immunogenicity and efficacy and then on Jan 2, they are saying they have considered Bharat Bio's request and will be giving them

'emergency approval'. There is no mention of data. The minutes do not reveal what made the SEC change its mind about the data submitted by Bharat Biotech over the course of two days," said Chinu Srinivasan of All India Drug Action Network (AIDAN).

Similarly, with respect to the SII vaccine, the report states: "...The Serum Institute of India (SII) on December 30 submitted safety immunogenicity and efficacy data of phase 2 and 3 clinical trials of AstraZeneca vaccine carried out in UK, Brazil and South Africa. Along with it, safety and immunogenicity data from the ongoing Phase 2/3 clinical trial of Covishield vaccine being manufactured by SII was also submitted. The SII informed the committee that AstraZeneca had received emergency use authorisation for the vaccine in UK subject to various conditions and restrictions.

Then on January 1, SEC observed that the safety and immunogenicity data presented by the firm from the Indian study is comparable with that of the overseas clinical trial data."

(A copy of the National Herald report dated 6th January 2021 is annexed as **Annexure 13 (Page 127 to 130).**

(A copy of the minutes of the SEC dated 30th December 2020, 1st January 2021 and 2nd January 2021 are annexed as **Annexure P14 (Page 131 to 135).**

28. Further, the petitioner states that the government does not disclose the names and institutional relationships of the experts present during each SEC meeting for COVID -19 vaccines. These subject expert committees review the proposals and send recommendations to the government's Central Drug Standard Control Organisation (CDSCO), which decided their approval. The opacity makes it impossible to evaluate potential conflicts of interest. If the committee of experts is representing the public, the people have the right to know who these experts are. The members present on each SEC must be disclosed in the minutes of each meeting. This is not done and it must be made mandatory.

29. Even the publicly funded Indian Council of Medical Research (ICMR) which is both supporting research and co-sponsoring some of the vaccine trials, has maintained opacity with regard to ICMRs terms of engagement, persons involved and quantum of public funds involved.

30. As reported in The Hindu, the ICMR is to get royalties from the sale of Covaxin and this should disqualify them from sitting on regulatory committees to license this product or similar competing products. Given all these pervasive conflicts of interest, only data transparency and its availability to independent scientists to reassess, can protect the public interest.

(A copy of The Hindu report dated 3rd May 2021 titled "ICMR to get royalty from Covaxin sale" is annexed as **Annexure P15 (Page 136 to 138)**

Parliamentary Standing Committee reports on need for transparency in drug regulation

31. The petitioners submit that in the specific context of drug regulation in India, the need for greater transparency has been noted by the Parliamentary Standing Committee on Health and Family Welfare, in its 59th Report (2012) and 66th Report (2013), which called for "increased transparency in decision-making" of the Central Drugs Standard Controls Organisation (CDSCO) and other regulatory authorities.

(A copy of the 59th Parliamentary Standing Committee Report is Annexed as **Annexure P16 (Page 139 to 190).**

32. The Central Information Commission (CIC) has repeatedly called upon the CDSCO and other regulatory bodies to take proactive steps to keep the public informed about various regulatory activities. Vide its order dated 26.05.2020, the CIC made the following observations in *Prashant Reddy T. v. Central Public Information Officer, Drug Controller General of India & Ministry of Health*, involving files that went missing from the Office of the Drug Controller General of India (DCGI)

"The Commission however expressed its serious concern over the record keeping methodology in the office of DCGI / CDSCO due to the fact that an important report relating to the review of procedures and practices followed by CDSCO for granting approval and clinical trials on certain drugs went missing from their office that had to be procured from the author after receipt of notice of hearing from the Commission. This is despite the fact that the Parliamentary Standing Committee had also taken cognizance of the lapses by the Public Authority. The intent and the conduct of the Public Authority should always be above board in matters relating to grant of approvals through a transparent and objective mechanism. The Commission advises Secretary, M/o Health and Family Welfare, Govt. of India to examine this matter appropriately for further necessary action at its end."

(A copy of the CIC order dated 26th May 2020 is annexed as **Annexure P17 (Page 191 to 201)** Prashant Reddy T. v. Central Public Information Officer, Drug Controller General of India & Ministry of Health)

33. The Parliamentary Standing Committee Report discussed the lapses and omission of the current Drug Approval System and their maintenance of public records. Some of the important findings of the report are quoted below. The lapses pointed out in the report make it even more urgent for data with regard to mass vaccination to be

disclosed considering that the manner in which drug approvals are being given by the CDSCO.

(i) The lack of clinical trials for new drugs

In para 7.14 of the PSC Report, the Committee observed the following:

"In the case of 11 drugs (28%) Phase III clinical trials mandated by Rules were not conducted. These drugs are i, Everolimus (Novartis), ii. Colistimethate (Cipla), iii. Exemestane (Pharmacia), iv. Buclizine (UCB), v. Pemetrexid (Eli Lilly), vi. Aliskiren (Novartis), vii. Pentosan (West Coast), viii. Ambrisentan (GlaxoSmithKline), ix. Ademetionine (Akums), x. Pirfenidone (Cipla), and xi. FDC of Pregabalin, Methylcobolamine, Alpha Lipoic Acid, Pyridoxine & Folic Acid (Theon); In the case of 2 drugs (Dronedarone of Sanofi and Aliskiran of Novartis), clinical trials were conducted on just 21 and 46 patients respectively as against the statutory requirement of at least 100 patients; In one case (Irsogladine of Macleods), trials were conducted at just two hospitals as against legal requirement of 3-4 sites; In the case of 4 drugs (10%) (Everolimus of Novartis; Buclizine of UCB; Pemetexid of Eli Lilly and FDC of Pregabalin with other agents**), not only mandatory Phase III clinical trials were not conducted but even the opinion of experts was not sought. The decision to approve these drugs**

was taken solely by the non-medical staff of CDSCO on their own;

(ii) Files that have gone "missing" from the CDSCO regarding certain controversial drugs.

In para 7.12 of the PSC Report, the following was observed:

"All these drugs had been approved on different dates and different years creating doubt if disappearance was accidental. Strangely, all these cases also happened to be controversial drugs; one was never marketed in US, Canada, Britain, Australia and other countries with well-developed regulatory systems while the other two were discontinued later on. In India, all the three drugs are currently being sold."

(iii) The dubious process of clearing certain drugs, based on suspicious expert medical opinions.

The relevant excerpt from para 7.31 of the PSC Report is reproduced as followed:

"A review of the opinions submitted by the experts on various drugs shows that an overwhelming majority are recommendations based on personal perception without giving any hard scientific evidence or data. Such opinions are

of extremely limited value and merely a formality. Still worse, there is adequate documentary evidence to come to the conclusion that many opinions were actually written by the invisible hands of drug manufacturers and experts merely obliged by putting their signatures"

(iv) The PSC also included certain letters supposedly written by medical experts, addressed to a drug manufacturer "Themis Medicare Ltd.", approving their drugs. Themis Medicare Ltd. sought the approval of Drotaverine (80 mg) plus Aceclofenac(100 mg) tablets as a fixed dose Combination. The PSC observed that the Fixed Dose Combination of Aceclofenac with Drotaverine was not permitted in any developed country including in North America, Europe or Australia. Upon closer examination, the PSC realised that these letters supposedly written by medical experts to the drug manufacturer, were in fact, drafted by the manufacturers themselves to gain approval of their drugs in an unscrupulous and illegal manner. The PSC recommended that the DCGI should conduct an enquiry and take action against such malpractices, in para 7.33 of the report. The relevant extract is reproduced hereunder:

"7.32 If the above cases are not enough to prove the apparent nexus that exists between drug manufacturers and many experts whose opinion matters so much in the decision making process at the CDSCO, nothing can be more

outrageous than clinical trial approval given to the Fixed Dose Combination of Aceclofenac with Drotaverine

which is not permitted in any developed country of North America, Europe or Australia. In this case, vide his letter number 12-298/06- DC dated 12-2-2007, an official of CDSCO advised the manufacturer, Themis Medicare Ltd. not only to select experts but get their opinions and deliver them to the office of DCGI. No wonder that many experts gave letters of recommendation in identical language apparently drafted by the interested drug manufacturer."

"7.33 In the above case, the Ministry should direct DCGI to conduct an enquiry and take appropriate action against the official(s) who gave authority to the interested party to select and obtain expert opinion and finally approved the drug".

Change in how the vaccine adverse effects are being evaluated in India

34. The petitioner submits that Adverse Event following Immunisation (AEFI) happen in people who may have an allergy or genetic predisposition to react to a vaccine. This is often rare and may happen only one in a few 1000 vaccinated. Phase three trials involve small controlled trials of a limited number of persons and may not find a significant increase in adverse events but when it is given to

the masses after licensure, rare reactions show up. That is why the law requires mandatory Phase 4 post marketing trials.

35. However, under the changed rules for investigating AEFI, all reactions that are not "known reactions" to the vaccine are not considered AEFI. By this rule now, all the reactions picked up in Phase 4 post marketing trials are now simply considered "Not an AEFI".

36. In a paper published by the petitioner, he describes how the WHO has recently revised how AEFI are classified. Only reactions that have previously been acknowledged in epidemiological studies to be caused by the vaccine are classified as a vaccine product related reaction. Deaths observed during post-marketing surveliance are not considered as 'consistent with casual association with vaccine', if there was no statistically significant increase in deaths recorded during the small Phase 3 trials that preceded it.

> "After licensure, deaths and all new serious adverse reactions are labeled as 'coincidental deaths/events' or 'unclassifiable', and the association with vaccine is not acknowledged. The resulting paradox is evident...
>
> The definition of causal association has also been changed. It is now used only if there is 'no other factor intervening in the processes'. Therefore, if a child with an underlying congenital heart disease (other factor), develops fever and cardiac decompensation after vaccination, the cardiac failure would not be considered causally related to the vaccine."

(A copy of the paper titled, "Revised World Health Organisation assessment of adverse events following immunization – a critique" dated 17th May 2019 is annexed as **Annexure P18 (Page 202 to 225).**

37. Till date there have been many adverse impacts and severe side effects including deaths post vaccination both in India and abroad. As reported in The Hindu a group of experts in public health, ethics, medicine, law and journalism have written to the Health Minister and the Drug Controller General of India, appealing for a time bound and transparent investigation following deaths and serious adverse effects after Covid-19 vaccination. The reports quotes from the letter and states as follows:

> "We understand that at least 65 deaths have occurred following vaccination for COVID-19 since the vaccination campaign started on January 16. However, the National AEFI (adverse event following immunisation) Committee's investigation findings of only two of these deaths have been made public. We believe that due to the possible linkages of vaccination and blood clotting, all these deaths and adverse events should be reviewed together for a possible causal relationship with the vaccine," reads the letter.
>
> The experts underline that even as the Indian health administration continues to be indifferent to the adverse

effects of vaccination, several countries across the world such as Denmark, Iceland, Norway, Italy, France, Bulgaria, Germany, Luxembourg, Estonia, Lithuania, Latvia and Ireland have paused immunisation with Astra Zeneca vaccine pending investigation of a small number of post-vaccination deaths from intravascular clotting/ thromboembolic events. Austria has even suspended the use of certain batches...
They have demanded a transparent investigation into each of the adverse incidents and sought details of all serious AEFIs till date, status of their investigation, findings of AEFI probe including cause of death by clinical diagnosis, autopsy findings, causality assessment and the process undertaken by AEFI committees to arrive at their conclusions.

"The vaccine programme should provide people complete information on the vaccines, a vaccination protocol that minimises the risk of harm, and an assurance of thorough and transparent investigation of injuries and death following immunisation. They are also owed medical care, and compensation for harm suffered post vaccination. The government has not met these obligations."

(A copy of The Hindu report dated 17th March 2021 titled, "Probe sought into death and adverse effects after Covid-19 vaccinations" is annexed as **Annexure P19 (Page 226 to 227).**

38. In a letter dated 27th April by the President of the Tamil Nadu Practitioners Association, Dr. CMK Reddy flags his concern about the reported deaths after taking Covid vaccine. The letter states:

> "Though the Adverse Effects Following Immunisation (AEFI) Committee comforts public and profession by saying they're unrelated to the vaccine, we have to take it with a grain of salt...
> If they are due to reasons other than vaccination, they should be evenly distributed during every week following vaccination, but 75% deaths occurred and 90% were hospitalised during the first 3 days. Hence let us not take it for granted and find out if we can prevent the complications."

(A copy of the letter dated 27.04.2021 is Annexed as **Annexure P20 (Page 228 to ___).**

39. According to a presentation made to the National AEFI Committee during a meeting held on March 31, there have been 617 severe and serious (including deaths) adverse events following immunisation. As on March 29, a total of 180 deaths (29.2%) have been reported following vaccination across the country. Complete documentation is available only for 236 (38.3%) cases. In all, 492 severe and serious AEFI have been classified by the AEFI Secretariat of the Immunisation Technical Support Unit (ITSU) at the Health Ministry. Classification has been completed for 124 deaths, 305 serious events that required hospitalisation, and 63 severe events that did not require hospitalisation.

(A copy of The Hindu report dated 09April 2021 "180 deaths following vaccination reported in India" is annexed as **Annexure P21 (Page 229 to 232).**

40. Since the ongoing vaccination is like gigantic vaccine trial, in order to assess the efficacy of the vaccine, especially with respect to the variants which are supposed to be significantly responsible for the current second wave of Covid in India, it was essential for the government to closely monitor Covid infections (variant wise) among vaccinees as also the vaccinees who get sick enough to be hospitalised and more importantly who die due to Covid. Only such data would reveal the true efficacy of these vaccines on getting infected with Covid. However even this data has not been made available.

41. Data released today by the Centers for Disease Control and Prevention (CDC) on the number of injuries and deaths reported to the Vaccine Adverse Event Reporting System (VAERS) following COVID vaccines revealed reports of blood clots and other related blood disorders associated with all three vaccines approved for Emergency Use Authorization in the U.S. — Pfizer, Moderna and Johnson & Johnson (J&J). So far, only the J&J vaccine has been paused because of blood clot concerns. Every Friday, VAERS makes public all vaccine injury reports received through a specified date, usually about a week prior to the release date. Today's data show that between Dec. 14, 2020 and April 30, a total of 157,277 total adverse events were reported to VAERS,

including 3837 deaths, including 21623 requiring urgent care, 1132 heart attacks, 213 miscarriages, 7463 severe allergic reactions.

(A copy of the screen shot of the openvaers.com/covid data database of the US as accessed on the 10th of May 2021 is annexed at **Annexure P22 (Page 233 to -)**.

42. In the UK, all spontaneous reports received post Covid-19 vaccination are available in the public domain. A March 16, 2021, report of Covid-19 vaccine Astra Zeneca analysis reported a total of 2,28,337 reactions from the drug, with 289 fatal outcomes from January 4, 2021 to March 7, 2021. Similar reporting in the UK is available even for the Pfizer vaccine analysis.

The reactions for Pfizer Vaccine as on 12th April 2021 are as follows:

Blood Disorders 4210, Cardiac Disorders 1675, Congenital Disorders 12, Ear Disorders: 1374, Endocrine Disorders: 28, Eye disorders 2034, Gastrointestinal disorders 14140, General Disorders 38,968, Immune System disorders 723, Infections: 3070, injuries 847". Detailed reports of the adverse events for Astra Zenca and Pfizer are submitted.

43. In another report of the The Daily Expose on 4th April 2021, Dr Polyakova, who is the Medical Director of a hospital in Kent has said that "the levels of sickness after vaccination is unprecedented"

among NHS staff, confirming that some are even suffering neurological symptoms which is having a "huge impact on the health service functioning". The doctor, who progressed into medical management of the hospital over the past three years says that she is struggling with the "failure to report" adverse reactions to the Covid vaccines among NHS staff, and clarified that the young and healthy are missing from work for weeks after receiving a dose of either the Pfizer or AstraZeneca experimental vaccine"

(A copy of the report in The Daily Expose dated 4th April 2021 is annexed as **Annexure P23 (Page 234 to 236).**

44. While these are only some of the adverse impacts with respect to the current vaccines, we do not know yet how these vaccines and their ingredients will affect the vaccinated population in the long term.

Vaccines not tested against a placebo

45. In order to test efficacy of a vaccine, every vaccine candidate in all trials must be tested against a saline placebo. However as indicated below, the trials were not conducted using a placebo in various phase of the trials. Using inert placebos are important, as only then would we be able to notice any statistically significant difference in deaths and adverse events between both groups. If other vaccines or adjuvants are used in the controls, then it is likely that both groups will experience side effects, and hence no difference will be

seen, hence the vaccine will be touted as being safe when it actually isn't.

46. In Phase 1 trials for Covaxin by Bharat Biotech participants were randomly assigned to receive either one of three vaccine formulations (3 µg with Algel-IMDG, 6 µg with Algel-IMDG, or 6 µg with Algel) or an Algel only control vaccine group. Among the enrolled participants, 100 each were randomly assigned to the three vaccine groups, and 75 were randomly assigned to the control group (Algel only).

(A copy of the paper published in The Lancet titled "Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomized, phase 1 trial" published on 21st January 2021 is annexed as **Annexure P24 (Page 237 to 246).**

47. In the Bharat Biotech Covaxin Phase 2 trial no placebo group was used at all, instead a comparison done between different vaccine doses. A total of 380 healthy children and adults were randomised to receive two vaccine formulations (n=190 each) with 3 µg with Algel-IMDG and 6 µg with Algel-IMDG. The primary outcome was seroconversion (≥4-fold above baseline) based on wild-type virus neutralisation (PRNT50). Secondary outcomes were reactogenicity and safety.

A copy of the report "Safety and immunogenicity clinical trial of an inactivated SARS-CoV-2 vaccine (BBV152 a phase 2, double blind,

randomized control trial) and persistence of immune responses fom a phase 1 follow up report" is Annexed as **Annexure P25 (Page** 247 **to** 280 **).**

48. Bharat Biotech Phase 3 trail data is not published yet while interim efficacy results have been reported in the media. Details of which placebo was used can be found on this clinical trials website https://clinicaltrials.gov/ct2/show/NCT04641481. A total of 25,800 subjects will be enrolled and randomized in a 1:1 ratio to receive the BBV152 vaccine and control.

Arm	**Intervention/treatment**
Experimental: Study vaccine BBV152B (6µg-Algel-IMDG)	Biological: BBV152 BBV152 (6µg-Algel - Imidazoquinoline)
Placebo Comparator: Placebo Phosphate buffered saline with Alum (without antigen)	Biological: Placebo Placebo (PBS+Alum, without antigen)

(A copy of the Phase 3 study description titled "An Efficacy and Safety Clinical Trial of an Investigational COVID-19 Vaccine (BBV152) in Adult Volunteers" as available on the clinical trials registry is Annexed as **Annexure P26 (Page** 281 **to** 289 **).**

49. For the Astra Zeneca vaccine, as published in The Lancet, a phase 1/2 single-blind, randomised controlled trial of ChAdOx1 nCoV-19 compared with a licensed meningococcal group A, C, W-135, and Y conjugate vaccine (MenACWY; Nimenrix, Pfizer, UK), as control vaccine, in healthy adults in the UK. For the phase 2/3 participants were recruited to a low-dose cohort, and within each age group, participants were randomly assigned to receive either intramuscular ChAdOx1 nCoV-19 ($2{\cdot}2 \times 10^{10}$ virus particles) or a control vaccine, MenACWY. An interim analysis was published in The Lancet in January 2021, for the safety and efficacy of the vaccine from an analysis of four randomized controlled trials in Brazil, South Africa and the UK. In this group, saline was used, but in the analysis, results of saline group & meningococcal group were pooled together, making it impossible to say which adverse events came from the saline group vs meningococcal vaccine group. Participants aged 18 years and older were randomly assigned (1:1) to ChAdOx1 nCoV-19 vaccine or control (meningococcal group A, C, W, and Y conjugate vaccine or saline).

Indemnity for Vaccine Manufacturers

50. The petitioners submit that coupled with the above changed policy for assessing vaccine side effects, earlier, vaccine manufacturers had sought indemnity from the Central Government in case of an adverse event during the vaccination drive. However, the government is yet to decide on the matter. If the companies are indemnified, they would be absolved from legal consequences arising out of adverse

clinical events in the vaccination drive and will embolden them to be more reckless on vaccine safety issues.

Mandating the use of the vaccines in the absence of informed consent is unconstitutional and violative of the principle of informed self determination which flows from Article 21

51. That some disturbing orders have been issued which directly or indirectly coerce citizens to get vaccinated. It appears to be a part of the public policy of the Union and State Governments to maximize the number of people receiving Covid 19 vaccines in as short a duration as is possible even without putting all 'information' in the public domain, enabling a citizen to make an 'informed' choice. It is submitted that coercing citizens directly or indirectly to get vaccinated is unconstitutional and violates the Right to Life of citizens on the grounds below mentioned. While the government has clearly stated in numerous RTIs that Covid vaccines are voluntary, there are many instances from across the country where now various authorities are mandating the vaccines.

52. In a reply dated 9th March 2021 to the RTI application filed by Anurag Sinha of Jharkhand, the Central Ministry of Health and Family Welfare has stated very clearly that "taking the Covid Vaccines was entirely voluntary and there is no relation whatsoever to provision of government facilities, citizenship, job etc to the vaccine".

(A translated copy of the original RTI reply (in Hindi) dated 9th March is annexed as **Annexure P27 (Page 290 to 291).**

53. In another RTI application to the Ministry of Health and Family welfare dated 21.04.2021, applicant Rakesh Singh requested for the following information;

"1. Is corona vaccine (Covid-19 vaccine compulsory?

2. Can private company force its employees to take Covid 19 vaccine?

3. Will I be debarred from public services like Metro rail, Indian railway, bus services, hospital, electricity, internet, food and inter and intra-city movement, if I don't take covid-19 vaccine?

4. what can I do it my senior officer forces me to take Covid-19 vaccine?

...

7. Can a government Health worker be suspended for not taking Covid 19 vaccine?

8. Does government or its any associate body have any reliable data of Covid 19 vaccine research so that citizens can trust the efficacy of vaccines?

Vide reply dated 2nd May 2021, from the Ministry of Health and Family Welfare stated:

"1. Vaccination for Covid-19 is voluntary.

However it is advisable to receive the complete schedule of Covid-19 vaccine for protecting oneself against this disease and also to limit the spread of this disease to the close contacts including family members, friends, relatives and co-workers.

2-8 – in view of the reply as SI. No. 1, these questions have no relevance."

(Copy of the RTI reply dated 2.05.2021 is annexed as **Annexure P28 (Page 292 to 293).**

54. An order dated 16.01.2021 was issued by Civil Surgeon (equivalent to CMO/CMHO) in Koderma, Jharkand, mandating local government health workers to take Covid-19 Vaccine or otherwise their salary will be withheld. The order was subsequently withdrawn.

(A copy of the order is annexed as **Annexure P29 (Pages 294 to _____).**

55. The Government of Maharashtra Department of Revenue and Forest Disaster Management, Relief and Rehabilitation, has issued a governmental order No: *DMU/ 2020 / CR. 92 / Dis M-1,* on the 13th of March 2021. In that Order under Section 3 (b) it was ordered that:

> "Essential shops owners and person working at all shops to get vaccinated at the earliest, as per criteria of GOI"

(A copy of the Order dated 13th March 2021 issued by the Department of Revenue and Forest, Government of Maharasthra is annexed as **Annexure P30 (Page 295 to 311).**

56. In a news item in the Lokmat Times, dated 18th April 2021, states:

"The Maharasthra government has imposed strict restrictions until May 1 to break the coronavirus chain. After that, the Aurangabad Municipal Corporation (AMC) will not allow unvaccinated traders and general people, aged 45 and above, to step out of home. So citizens eligible for vaccination should get vaccinated as soon as possible," said AMC administrator Astik Kumar Pandy."

(A copy of Lokmat Times report dated 18th April 2021, "Only vaccinated citizens can step out of home after May 1", is annexed as **Annexure P31 (Page 312 to -)**.

57. In the state of Gujarat, on 11th February 2021 The Indian Express reported that,

"The Circular from Garudeshwar taluka, falling in the tribal Narmada district, cites a video-conference held by the district primary education officer (DPEO) on February 8, and was issued to two nodal officers in the taluka on February 9. It said, "Teachers of the government primary schools, who have to interact with students and work among the students, have to mandatorily take the Covid-19 vaccine, which must be ensured. If any teacher refuses to take the vaccine or remains absent during the vaccination drive, and if any student thereafter contracts Covid-19 from the teacher, the entire responsibility of the same will be on the teachers."

Teachers who refuse to take the vaccine shot will have to submit a certificate in writing, citing reasons for the same the circular added".

While the district administration later called it a "draft copy" that was issued "by mistake", officers in charge of the nodal supervision of the vaccination drive for teachers said the decision to make teachers "accountable" was taken because many had refused to take the shot.

The same news report, mentions another circular: "the circular issued by the Ahmedabad Municipal Corporation School Board made it compulsory for its teachers and other staffers to get themselves vaccinated. Municipal school teachers told the The Indian Express on conditions of anonymity, they were asked to not sign the muster roll if they did not take the vaccine."

(A copy of The Indian Express report dated 11th February "Gujarat: Row over two circulars making Covid shot mandatory for school teachers" is annexed **as Annexure P32 (Page 313 to 318).**

58. In the letter number: G-1/2021/36650 dated 23-04-2021, issued by the Office of the District Education Officer, Tarn, Tarn, it is stated,

"This has reference to the meeting held by the Deputy Commissioner on 22-04-2021, regarding COVID Vaccination and the instructions were issued and received by this office on the mandatory COVID Vaccination of all the

officers/employees. It is clearly stated that if any officer/employee is unwilling or refuses to be vaccinated, the concerned DEOs shall not draw the salary of such officers/employees."

(A copy of the order dated 23rd April 2021 is annexed as **Annexure P33 (Page 319 to -)**.

59. On April 29 2021, the Administration of Whistling woods International, Goregaon East, Mumbai, sent an office Memo to All, by email titled, "Vaccination against Covid". In that mail it was stated, "We would like everyone who plans to come to campus post lockdown to be vaccinated, this will help us build a safer work place. Please ensure that you have your doses of vaccines before end of July 2021 so we can start our operations full force as soon as the restrictions are over. After getting vaccinated, kindly send your vaccination certificate."

(A copy of the email is annexed as **Annexure P34 (Page 320 to 321)**.

60. In the state of Punjab, the Governmental Order No: 7/56/2020/ 2H4/2142 dated 30th April 2021, addressed to all officers of the Police department including Divisional Commissioners, Zonal IGPs, Commissioners of Police, DIGs and SSPs, the Department of Home Affairs and Justice, stated in section 1(xv),

"In Government offices – Health / frontline workers and employees over 45 years who have not got at least one vaccine dose in last 15 days or more, should be encouraged to take leave and stay home until then Employees under 45 years to be allowed only on basis of negative RT-PCR not more than 5 days old or else should take leave and stay home".

(A copy of the order dated 30th April 2021 is annexed as **Annexure P35 (Page 322 to 324).**

61. In its order No: 7/56/2020/2H4/2143 dated 2nd May 2021, the Department of Home Affairs and Justice, Government of Punjab stated in section 2(ii),

"Nobody to enter the State whether by air, rail or road without either:

a- Negative Covid report not more than 72 hours old, or

b- Vaccination certificate (at least one dose) over 2 weeks old."

(A copy of the order of Government of Punjab dated 2nd May 2021 is annexed as **Annexure P36 (Page 326 to 328).**

62. In a circular issued on 22.04.2021 the Gujarat Technological University, Govt of Gujarat issued a circular regarding Covid-19 Vaccination before Winter -2021 Exam form filling. An excerpt from the circular is below:

"All students who have attained age of 18 years as on 1/05/2021 are hereby informed that it is mandatory to get Covid-19 vaccination before filling Winter 2021 exam forms. Along with the prevailing GTU norms, institutes will have to allow only the students who have taken Covid 19 vaccination to fill their Winter – 2021 exam forms"

A copy of the circular dated 22.04.2021 of the Gujarat Technological University, Govt of Gujarat is annexed as **Annexure P37 (Page 329 to –)**.

63. In the state of Telangana, on instruction from the District Collector of Bhadradri Kotthagudem district the Mandal Development Officer, MRO, Medical Officer and the Sub Inspector of Police of Sujathanagar Tehsil have been forcing the beneficiaries of the MNREGA that they can come to work only if they take the vaccines.

64. In the case of WP(C) 36065 of 2017 between the Parents Teachers Association, Government Higher Secondary School, Kokkur, Kerala and the State of Kerala **(2017 SCC Online Kerala 36408)**, the Hon'ble High Court of Kerala had passed order:

"If at all any parent has an objection, it has to be necessarily brought before the authorities, and there need not be any vaccination administered to such children whose parents object to the Vaccination. The learned government pleader also submits that no forceeful vaccination is attempted".

(A copy of the order of the Kerala High Court dated 10th November 2017, is annexed as **Annexure P38 (Page 330 to 331).**

65. Also, in the case of W.P.(C) 343/2019 & CM Nos.1604-1605/2019 between Master Haridaan Kumar (Minor through Petitioners Anubhav Kumar and Mr. Abhinav Mukherji) Versus Union of India, &W.P.(C) 350/2019 & CM Nos.1642-1644/2019 between Baby Veda Kalaan& Others Versus Director of Education & Others

the Hon'ble High Court of Delhi had observed that:

"13. Undisputedly, there is an urgent need to disseminate information regarding the MR campaign and the assumption that children could be vaccinated forcibly or without consent is unsustainable. This Court is of the view that all efforts are required to be made to obtain the decision of the parents before proceeding with the MR campaign. In this regard, it would be apposite to ensure that the consent forms/slips are sent to each and every student. Since the time period for implementing the campaign is short, the response period should be reduced and parents / guardians of students must be requested to respond immediately and, in any case, in not more than three working days. ***If the consent forms/slips are not returned by the concerned parent, the class teacher must ensure that the said parents are contacted telephonically and the decision of such parent is taken on phone.*** The concerned teacher ought to keep full records of such decisions received telephonically. In respect of those parents/guardians that

neither return the consent slips nor are available telephonically despite efforts by the concerned teacher, their consent can be presumed provided respondent nos. 1 and 2 ensure that full information regarding the commission is provided to all parents."

"14. ***The contention that indication of the side effects and contraindications in the advertisement would discourage parents or guardians from consenting to the MR campaign and, therefore, the same should be avoided, is unmerited.*** The entire object of issuing advertisements is to ensure that necessary information is available to all parents/guardians in order that they can take an informed decision. The respondents are not only required to indicate the benefits of the MR vaccine but also indicate the side effects or contraindications so that the parents/guardians can take an informed decision whether the vaccine is to be administered to their wards/children."

The Hon'ble High Court of Delhi thus passed the following orders:

"15.4 ***MR vaccines will not be administered to those students whose parents/guardians have declined to give their consent.*** The said vaccination will be administered only to those students whose parents have given their consent either by returning the consent forms or by conforming the same directly to the class teacher/nodal teacher and also to students whose

parents/guardians cannot be contacted despite best efforts by the class teacher/nodal teacher and who have otherwise not indicated to the contrary".

Further on the issue of informed consent, the The Hon'ble High Court of Delhi directed that:

"15.1Directorate of Family Welfare shall issue quarter page advisements in various newspapers as indicated by the respondents...The advertisements shall also indicate that the vaccination shall be administered with Auto Disable Syringes to the eligible children by Auxiliary Nurse Midwifery. ***The advertisement shall also clearly indicate the side effects and contraindications*** as may be finalised by the Department of Preventive Medicine, All India Institute of Medical Sciences"

(A copy of the Order of the Hon'ble Delhi High Court dated 22nd January 2019 is annexed as **Annexure P39 (Page 332 to 340)**

66. Covid Vaccines are experimental treatments. Those agreeing to receive them are agreeing to be participants in an ongoing medical experiment with several unknowns. There is no certainty about issues like long term safety. Coercing citizens to get the vaccines directly or directly violates the Nuremberg Code. The Nuremberg Trials Codes established, in the wake of horrific scientific abuse by

the German government during World War II, that coercion is *Verboten* and informed consent essential for participants of medical experiments. The ten point Nuremberg code given in the section of the Judges' verdict in the case of USA v Brandt entitled "Permissible Medical Experiments" states that: "The voluntary consent of the human subject is absolutely essential."

67. That the petitioner has not filed any other petition, suit or application in any manner regarding the matter is disputing in this Hon'ble court, or any High Court or any other court throughout the territory of India. The petitioner has no other better remedy available.

GROUNDS

A. BECAUSE the respondents have maintained opacity with respect to clinical trial data of the two vaccines being administered through emergency authorisation in India. Non disclosure of this important data violates the basic ethics of clinical research that requires results of clinical research studies to be published and brought to the knowledge of the medical community, participants to the research and the general population. The lack of transparency in the clinical trials data raises various concerns regarding the efficacy and safety of these vaccines.

B. Because the non publication of trial data violation the Declaration of Helsinki, an international document providing ethical guidance on research and adopted by the ICMR in India, which states that

"Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject." And that "Researchers have a duty to make publicly available the results of their research...Negative and inconclusive as well as positive results must be published or otherwise made publicly available"

C. BECAUSE the World Health Organisation (WHO) released a strong statement advocating for public disclosure of all clinical trial results. According to the statement, when data is not released it means that doctors, patients and medical regulators cannot make informed decisions about which treatments are best.

D. BECAUSE Transparency in publishing clinical trials data by the Central Drugs Standard Controls Organisation (CDSCO) that grants final approval for the vaccines by various manufactures to enter the immunization chain, flows from Section 4 of the Right to Information Act, 2005, which requires the government to make proactive disclosures of its records through the internet and other means of communications to the general public.

E. BECAUSE in Reserve Bank of India Versus Jayantilal N. Mistry Transferred Case (Civil) No. 91 Of 2015, a 2 judge bench of the Supreme Court while upholding peoples' right to access information, made the following observations regarding the Right to Information:

"Because an informed citizen has the capacity to reasoned action and also to evaluate the actions of the legislature and executives, which is very important in a participative democracy and this will serve the nation's interest better which as stated above also includes its economic interests. Recognizing the significance of this tool it has not only been made one of the fundamental rights Under Article 19 of the Constitution but also a Central Act has been brought into effect on 12th October 2005 as the Right to Information Act, 2005."..."The ideal of 'Government by the people' makes it necessary that people have access to information on matters of public concern. The free flow of information about affairs of Government paves way for debate in public policy and fosters accountability in Government. It creates a condition for 'open governance' which is a foundation of democracy."

F. BECAUSE despite the phase 3 trials of the Covaxin being underway, the removal of the "clinical trial mode" label attached to the emergency authorisation of the vaccine would mean that the vaccine would now be administered effectively in a phase 3 trials but without seeking informed consent of those to whom the vaccine is being administered. In clinical trial mode, informed consent is sought from participants in the trials and they are also compensated for any major adverse effects. Further under clinical trial mode there was the need to solicit from vaccine recipients any adverse events after 7 days as per the trial protocol. This is essential so that all early adverse events are recorded. The reason

Covaxin had been given restricted emergency use authorisation "in clinical trial mode" in the first place was because Bharat Biotech had not completed recruitment of participants for phase 3 trials and thus not been able to submit information regarding the vaccines efficacy.

G. BECAUSE disclosure of trial data has been held by this Hon'ble Court and by the CIC to be mandatory. In Aruna Rodrigues & Ors v UOI & Ors (WP C no. 260/2005) this Hon'ble Court vide order dated 8.04.2008, had considered the applications for data regarding toxicity and allergenicity to be placed in public domain by those conducting trials, in regard to nine crops to be field tested. It was submitted that unless the toxicity and allergenicity data are made known to the public the applicants and concerned scientists in the country would not be in a position to make effective representations to the concerned authorities and therefore the government was directed to make the disclosure. Further vide order dated 12.08.2008, the Court had directed the government to provide copy of guidelines for granting approval as well as to file satisfactory proof regarding compliance with its order regarding providing the data on the crops which were being field tested.

In Divya Raghunandan v. Dept. of Biotechnology(2007) and Kavita Kuruganti v. MoEF (2016)10 the CIC required the public disclosure of raw trial data (viz., biosafety, toxicity and allergencity data)pertaining to genetically modified brinjal studies because the public interest in making such data public, over-rode all other

considerations such as commercial confidence, trade secrets or intellectual property. In the Kavita Kuruganti case, the CIC went as far as to require the publication of regulatory data even if the trials were a failure.

H. BECAUSE, the Delhi High Court has held that mandates for vaccines without informed consent violate Article 21 rights. By order dated 22.01.2019 in W.P. (C) No. 343/2019, the Hon'ble Delhi High Court has struck down a notification by the State Government purportdedly in the public interest mandating all children to get the Measles Ruebella Vaccine without their parents explicit consent. The High Court directed that consent must be 'explicit' and 'implicit' consent or 'opt out' consent was not good enough. It was further directed that so as to allow parents to make an 'informed choice' the State was duty bound to disseminate widely the ill effects of the vaccine as well as under:

> *2. The petitioners are, essentially,* ***aggrieved by the decision of the respondents to forcibly administer MR vaccination without the consent of the parents/guardians*** *or family members of the beneficiaries (children aged between nine months to fifteen years). The petitioners in W.P.(C) 350/2019 pray that the impugned notification be set aside and further directions be issued that no vaccination be administered in cases where there is parental objection to such vaccination. The petitioners in W.P.(C) 343/2019, interalia, pray that an order be issued to the respondents restraining them from forcibly administering*

vaccinations to children without the consent of their parents/guardians.

5. Plainly, in order for any parent or guardian to give his/her consent (whether expressly or by inference), it would be necessary for such parent or guardian to have complete information with regard to the proposed vaccination campaign. Clearly, ***for any parent or guardian to take an informed decision, it would be necessary for such parent to be aware of (a) the vaccine proposed to be administered; (b) contraindications or side effects of such vaccine; (c) the date on which such vaccine administered to the ward/children; and (d) the personnel who would administer the same.***

7. In view of the above, ***impugned notification, to the extent it provides that no consent is required for the beneficiaries and/or their parents, is quashed.***

9. In view of the above, the ***controversy between the parties was narrowed down, essentially, on two issues, (a) whether an express consent of the parents/guardians was necessary or whether the same could be inferred by silence on the part of the concerned parents/guardians; and (b) whether the respondents were required to indicate the contraindications and the side effects of the vaccines in the newspaper advertisements as well as in other literature to be provided to parents/guardians of the beneficiaries.***

13. Undisputedly, ***there is an urgent need to disseminate information regarding the MR campaign and the assumption that children could be vaccinated forcibly or without consent is unsustainable.*** *This Court is of the view that all* ***efforts are required to be made to obtain the decision of the parents before proceeding with the MR campaign.*** *In this regard, it would be apposite to ensure that the consent forms/slips are sent to each and every student. Since the time period for implementing the campaign is short, the response period should be reduced and parents / guardians of students must be requested to respond immediately and, in any case, in not more than three working days. If the consent forms/slips are not returned by the concerned parent, the class teacher must ensure that the said parents are contacted telephonically and the decision of such parent is taken on phone. The concerned teacher ought to keep full records of such decisions received telephonically. In respect of those parents/guardians that neither return the consent slips nor are available telephonically despite efforts by the concerned teacher, their consent can be presumed provided respondent nos. 1 and 2 ensure that full information regarding the commission is provided to all parents.*

14. The contention that indication of the side effects and contraindications in the advertisement would discourage parents or guardians from consenting to the MR campaign and, therefore, the same should be

avoided, is unmerited. The entire object of issuing advertisements is to ensure that necessary information is available to all parents/guardians in order that they can take an informed decision. The respondents are not only required to indicate the benefits of the MR vaccine but also indicate the side effects or contraindications so that the parents/guardians can take an informed decision whether the vaccine is to be administered to their wards/children.

15. In view of the above, it is directed as under:

- ***(4) MR vaccines will not be administered to those students whose parents/guardians have declined to give their consent. The said vaccination will be administered only to those students whose parents have given their consent either by returning the consent forms or by conforming the same directly to the class teacher/nodal teacher and also to students whose parents/guardians cannot be contacted despite best efforts by the class teacher/nodal teacher and who have otherwise not indicated to the contrary.***

I. BECAUSE, this Hon'ble Court has held that no individual's bodily integrity can be violated without her explicit informed consent. A citizen has many available courses of treatment for any particular

medical concern and the State cannot mandate a particular course of treatment to her. This Hon'ble Court has affirmed the 'Principle of Self Determination' to the higher extent that a citizen even has the 'Right to Refuse Medical Treatment' as part of her right to live with dignity and make an informed choice. **In *Aruna Ramachandra Shanbaug v. Union of India*, (2011) 4 SCC 454 : (2011) 2 SCC (Cri) 294 : (2011) 2 SCC (Civ) 280** it was held;

At Page 482

Two of the cardinal principles of medical ethics are patient autonomy and beneficence:

1. ***Autonomy means the right to self-determination, where the informed patient has a right to choose the manner of his treatment. To be autonomous, the patient should be competent to make decisions and choices.*** *In the event that he is incompetent to make choices, his wishes expressed in advance in the form of a living will, or the wishes of surrogates acting on his behalf (substituted judgment) are to be respected.*

2. Omitted

at page 497

67. .... In India, if a person consciously and voluntarily refuses to take life-saving medical treatment it is not a crime.....

at page 500

> ***78.*** *.....First,* ***it is established that the principle of self-determination requires that respect must be given to the wishes of the patient, so that if an adult patient of sound mind refuses, however unreasonably, to consent to treatment or care by which his life would or might be prolonged, the doctors responsible for his care must give effect to his wishes, even though they do not consider it to be in his best interests to do so*** *[see Schloendorff v. Society of New York Hospital [211 NY 125 : 105 NE 92 (1914)] , NE at p. 93, per Cardozo, J.; S. v. McC. (Orse S.) and M (D.S. Intervener) [1972 AC 24 (HL)] , W v. W; AC at p. 43, per Lord Reid; and Sidaway v. Board of Governors of the Bethlem Royal Hospital [1985 AC 871 : (1985) 2 WLR 480 : (1985) 1 All ER 643 (HL)] AC at p. 882, per Lord Scarman]. To this extent,* ***the principle of the sanctity of human life must yield to the principle of self-determination...***

J. BECAUSE, this Hon'ble Court has held that 'autonomy' of the individual which can interchangeably be said to be her right to 'self determine' when it comes to her health flows from Article 21 and is a facet of her Right to Privacy. As much has been observed in Puttaswamy (Right to Privacy case) which was relied upon in ***Common Cause v. Union of India*****, (2018) 5 SCC 1,** wherein a Constitutional Bench [5 Judges] of this Hon'ble Court further affirmed Right of Self Determination as under:

at page 170 (JUSTICE SIKRI):

300. *In* ***K.S. Puttaswamy [K.S. Puttaswamy v. Union of India, (2017) 10 SCC 1] , the Constitution Bench*** *has recognised the dignity of existence. Liberty and autonomy are regarded as the essential attributes of a life with dignity. In this manner, sanctity of life also stands acknowledged, as part of Article 21 of the Constitution. That apart, while holding the right of privacy as an intrinsic part of right to life and liberty in Article 21, various facets thereof are discussed by the learned Judges in their separate opinions. A common theme which flows in all these opinions is that that privacy* ***recognises the autonomy of the individual; every person has right to make essential choices which affect the course of life; he has to be given full liberty and freedom in order to achieve his desired goals of life; and the concept of privacy is contained not merely in personal liberty, but also in the dignity of the individual.*** *Chelameswar, J. in K.S. Puttaswamy [K.S. Puttaswamy v. Union of India, (2017) 10 SCC 1] , made certain specific comments which are reflective of euthanasia, though this term is not specifically used. He observed: (SCC p. 530, para 373)*

> ***"373. ... Forced feeding of certain persons by the State raises concerns of privacy. An individual's right to refuse life prolonging medical treatment***

or terminate his life is another freedom which falls within the zone of privacy."

at page 177 (JUSTICE ASHOK BHUSHAN:)

316. *Dignity implies, apart from a right to life enjoyment of right to be free of physical interference.* ***At common law, any physical interference with a person is, prima facie, tortious.*** *If it interferes with freedom of movement, it may constitute a false imprisonment. If it involves physical touching, it may constitute a battery. If it puts a person in fear of violence, it may amount to an assault. For any of these wrongs, the victim may be able to obtain damages.*

317. When it comes to medical treatment, even there the general common law principle is that any medical treatment constitutes a trespass to the person which must be justified, by reference either to the patient's consent or to the necessity of saving life in circumstances where the patient is unable to decide whether or not to consent.

318. *Rights with regard to medical treatment fall essentially into two categories: first,* ***rights to receive or be free of treatment as needed or desired,*** *and not to be subjected involuntarily to experimentation which,* ***irrespective of any benefit which the subjects may derive, are intended to advance scientific knowledge and benefit people other than the subject in the long term;*** *secondly, rights connected incidentally with the*

provision of medical services, such as ***rights to be told the truth by one's doctor.***

PRAYER

In view of the abovementioned facts and in the interest of public safety, it is respectfully submitted that this Hon'ble Court may be pleased to

a) Direct the respondents to release the entire segregated trial data for each of the phases of trials that have been undertaken with respect to the vaccines being administered in India; and

b) Direct the respondent no 2 to disclose the detailed minutes of the meetings of the Subject Expert Committee and the NTGAI with regard to the vaccines as directed by the 59th Parliamentary Standing Committee Report and the members who constituted the committee for the purpose of each approval meeting; and

c) Direct the respondent no 2 to disclose the reasoned decision of the DCGI granting approval or rejecting an application for emergency use authorization of vaccines and the documents and reports submitted to the DCGI in support of such application; and

d) Direct the respondents to disclose the post vaccination data regarding adverse events, vacinees who got infected with Covid, those who needed hospitalization and those who died after such infection post vaccination and direct the respondents to widely publicize the data collection of such adverse event through the

advertisement of toll free telephone numbers where such complaints can be registered; and

e) Declare that vaccine mandates, in any manner whatsoever, even by way of making it a precondition for accessing any benefits or services, is a violation of rights of citizens and unconstitutional; and

f) Pass any other orders as this Hon'ble Court deems fit.

PETITIONER

THROUGH:

Prashant Bhushan

(PRASHANT BHUSHAN)
COUNSEL FOR THE PETITIONER

DRAWN BY: CHERYL D'SOUZA, ADVOCATE
DRAWN ON: 10TH MAY 2021

FILED ON: 12.05.2021
NEW DELHI

IN THE SUPREME COURT OF INDIA

(CIVIL ORIGINAL JURISDICTION)

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Writ Petition (Civil) No. ..... of 2021

IN THE MATTER OF:

Dr. JACOB PULIYEL

....PETITIONER

VERSUS

UNION OF INDIA & Ors ....RESPONDENTS

AFFIDAVIT

I, Dr. Jacob Puliyel, S/o Late Mr. P M Mammen, r/o 6A, 7 Raj Narayan Marg, Delhi – 110054, do hereby solemnly affirm and state on oath as under:

1. That I am the Petitioner in the aforementioned writ petition and being familiar with the facts and circumstances of the case, I am competent and authorized to swear this Affidavit.

2. That I have read and understood the contents of the Synopsis and List of Dates (Page B to 2), Writ Petition (Page 1 to 31), and all accompanying Miscellaneous Applications. I state that the facts therein are true to the best of my knowledge, belief and nothing material has been concealed therefrom.

3. The annexures are true copies of their respective originals.

4. The source of the information is media reports, parliamentary standing committee reports, government orders and Supreme Court and High court judgments and other information which is available in the public domain.

5. That this petition is only motivated by public interest. I affirm that I have no personal interest in this matter.

6. That I have done whatsoever enquiry that was possible and I state that no relevant facts in my knowledge have been withheld.

DEPONENT

Identify the Deponent who has Signed/Put ... Presence.

VERIFICATION:

I, the above named Deponent, do hereby verify that the contents of the above Affidavit are true and correct to my knowledge; that no part of it is false and that nothing material has been concealed therefrom.

Verified at New Delhi on 11th day of May 2021.

11 MAY 2021

ATTESTED

NOTARY PUBLIC

11 MAY 2021

DEPONENT

NOTARY DALEEP SINGH (ADVOCATE) Regn No. 19[illegible] Exp. May 2021 Saket Court Delhi GOVT OF INDIA

ANNEXURE- P1

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Ministry of Health and Family Welfare

Press Statement by the Drugs Controller General of India (DCGI) on Restricted Emergency approval of COVID-19 virus vaccine

Posted On: 03 JAN 2021 11:23AM by PIB Delhi

The Subject Expert Committee of Central Drugs Standard Control Organisation (CDSCO) met on 1st and 2nd January, 2021 and made recommendations in respect of proposal for Restricted Emergency Approval of COVID-19 virus vaccine of M/s Serum Institute of India and M/s Bharat Biotech as well as Phase III clinical trial of M/s Cadila Healthcare Ltd.

The Subject Expert Committee consists of domain knowledge experts from the fields of pulmonology, immunology, microbiology, pharmacology, paediatrics, internal medicine, etc.

M/s Serum Institute of India, Pune has presented a Recombinant Chimpanzee Adenovirus vector vaccine (Covishield) encoding the SARS-CoV-2 Spike (S) glycoprotein with technology transfer from AstraZeneca/Oxford University. The firm submitted safety, immunogenicity and efficacy data generated on 23,745 participants aged ≥ 18 years or older from overseas clinical studies. The overall vaccine efficacy was found to be 70.42%. Further, M/s Serum was granted permission to conduct Phase-II/III clinical trial on 1600 participants within the country. The firm also submitted the interim safety and immunogenicity data generated from this trial and the data was found comparable with the data from the overseas clinical studies. After detailed deliberations Subject Expert Committee has recommended for the grant of permission for restricted use in emergency situation subject to certain regulatory conditions. The clinical trial ongoing within the country by the firm will continue.

M/s Bharat Biotech has developed a Whole Virion Inactivated Corona Virus Vaccine (Covaxin) in collaboration with ICMR and NIV (Pune), from where they received the virus seed strains. This vaccine is developed on Vero cell platform, which has well established track record of safety and efficacy in the country & globally.

The firm has generated safety and immunogenicity data in various animal species such as mice, rats, rabbits, Syrian hamster, and also conducted challenge studies on non-human primates (Rhesus macaques) and hamsters. All these data has been shared by the firm with CDSCO. Phase I and Phase II clinical trials were conducted in approx.800 subjects and the results have demonstrated that the vaccine is safe and provides a robust immune response. The Phase III efficacy trial was initiated in India in 25,800 volunteers and till date, ~22,500 participants have been vaccinated across the

country and the vaccine has been found to be safe as per the data available till date.

The Subject Expert Committee (SEC) has reviewed the data on safety and immunogenicity of the vaccine and recommended for grant of permission for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode, to have more options for vaccinations, especially in case of infection by mutant strains. The clinical trial ongoing within the country by the firm will continue.

M/s Cadila Healthcare Ltd., has developed a Novel Corona Virus-2019-nCov-Vaccine using DNA platform technology. The firm initiated Phase-I/II clinical trial in India in more than 1000 participants which is ongoing. The interim data suggests that the vaccine is safe and immunogenic with three doses when administered intradermally. Accordingly, firm has sought permission to conduct Phase-III clinical trial in 26000 Indian participants, which has been recommended by the Subject Expert Committee.

M/s Serum and M/s Bharat Biotech vaccines have to be administered in two doses. All the three vaccines have to be stored at 2-8° C.

After adequate examination, CDSCO has decided to accept the recommendations of the Expert Committee and accordingly, vaccines of M/s Serum and M/s Bharat Biotech are being approved for restricted use in emergency situation and permission is being granted to M/s Cadila Healthcare for conduct of the Phase III clinical trial.

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MV/SJ
HFW/DCGI Media statement on COVID Vaccine/3rd January2021/2

Prashant Bhushan
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ANNEXURE- P2

Time of India

Covid-19 vaccines 110% safe, impotency rumours complete nonsense: DCGI
ANI | Updated: Jan 3, 2021, 14:48 IST

NEW DELHI: As India gears up for the world's largest vaccination programme, the Drugs Controller General of India (DCGI) on Sunday quelled rumours surrounding the Covid-19 vaccines regarding impotency, rubbishing such speculations as "complete nonsense".
"We will never approve anything if there is even the slightest safety concern. Vaccines are 110 percent safe. Some side effects like mild fever, pain and allergy are common for every vaccine. It (rumours of impotency) is complete nonsense," VG Somani, Drug Controller General of India said. When asked if people would face side effects after taking the vaccine, the DCGI said, "Yes, minor side effects will be there, including a little like pain in the shoulders, a slight fever, little allergies. This occurs in every vaccine but of-course, the vaccine is 110 per cent safe."
Meanwhile, he said, 'It (the vaccines) are very safe don't worry' in his interaction.

Earlier on Saturday, Samajwadi Party chief and former Chief Minister of Uttar Pradesh Akhilesh Yadav had said, "Covid-19 vaccine might contain something, which can cause harm. Tomorrow, people will say the vaccine was given to kill or decrease the population. You can even become impotent, anything can happen."
Earlier today, Covid-19 vaccines of Serum Institute of India and Bharat Biotech have been granted permission for restricted use in an emergency situation, said Drugs Controller General of India (DCGI).

"After adequate examination, CDSCO has decided to accept the recommendations of the Expert Committee and accordingly, vaccines of M/s Serum and M/s Bharat Biotech are being approved for restricted use in emergency situation and permission is being granted to M/s Cadila Healthcare for conduct of the Phase III clinical trial," said VG Somani, DCGI, during a media briefing today.

On December 31, Prime Minister Narendra Modi had urged people to be careful regarding rumours about vaccines and as responsible citizens refrain from forwarding messages on social media without checking.

"The number of new cases of Covid-19 is decreasing in the country now. We are preparing to run the world's largest vaccination programme in the next year. In our country, rumours spread quickly. Different people for their personal gains or due to irresponsible behaviour spread various rumours. Maybe rumours will be spread when vaccination begins, some have already begun," Prime Minister Modi had said.

Link: https://m.timesofindia.com/india/covid-19-vaccines-110-safe-impotency-rumours-complete-nonsense-dcgi/amp_articleshow/80082000.cms

Prashant Bhushan
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ANNEXURE: P3

Deccan Herald

Covaxin phase-3 trials to end today, average efficacy 60-70%

Recipients to be monitored for 1 year for reactions

Akhil Kadidal, DHNS, JAN 05 2021, 11:30 IST UPDATED: JAN 05 2021, 11:30 IST

Bharat Biotech's Covaxin is set to end its phase-3 trials on Tuesday, a research firm involved in monitoring the trials in Karnataka confirmed.

Dr Rajesh Naidu, managing director of Clintrac International Private Limited, a research company monitoring the clinical trials, told DH that the trials had so far seen 23,000 volunteers across India getting vaccinated.

This number is about 3,000 people short of the target number of volunteers set by the Indian Council of Medical Research (ICMR) with sources pointing to a consistent shortage in attracting volunteers to join the trials.

In Bengaluru, out of 800 registered participants, just 540 individuals had been included in the trials, half of which were the control group. "The results in Karnataka have been positive. The phase-3 trials showed that the vaccine has an average efficacy of 60% to 70%. In a few subjects, the efficacy is as high as 85 to 90%. No side-effects were seen," Dr Naidu said. An informed second source said the recipients would be monitored for up to one year for adverse reactions to the vaccine.

When asked how this would be done if the vaccine was potentially deployed in a backup capacity as had been stated by ICMR, the source said: "this post-vaccine monitoring was routine across the industry and the Pfizer vaccine required a post-observation period of up to three years. By that measure, we are relatively better."

The emergency-use approval for the vaccine has triggered furore over a lack of transparency of its proposed deployment even before its phase-3 clinical data has been made public. Dr Srinivas S, spokesperson for the Karnataka chapter of the Indian Medical Association (IMA), suggested that the backup status of the vaccine means that it will likely not be deployed on a large scale until it is formally approved as a registered vaccine.

"From the information we have, the vaccine will only be administered within government circles. It will not be supplied to the private sector and it will not be sold to consumers until it is fully approved," Srinivas said.

He said if Covaxin secured full approval, IMA would follow the Centre's lead on deployment and administration. Dr Chirag Trivedi, president, Indian Society for Clinical Research (ISCR), suggested that the DCGI's approval had likely been made using trial data which has not yet been made public.

https://www.deccanherald.com/national/covaxin-phase-3-trials-to-end-today-average-efficacy-60-70-935362.html

Prashant Bhushan
(TRUE COPY)

FULL DETAILS (Read-only)

CTRI Number	**CTRI/2020/11/028976** [Registered on: 09/11/2020] **Trial Registered Prospectively**
Last Modified On:	17/03/2021
Post Graduate Thesis	No
Type of Trial	Interventional
Type of Study	Vaccine
Study Design	Other
Public Title of Study Modification(s)	A Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity,and Lot-to-Lot consistency of BBV152, a Whole virion Inactivated Vaccine in Adults greater than or equal to 18 Years of Age.
Scientific Title of Study Modification(s)	An Event-Driven,Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity,and Lot-to-Lot consistency of BBV152, a Whole virion Inactivated SARS-CoV-2 Vaccine in Adults greater than or equal to 18 Years of Age.
Secondary IDs if Any	Secondary ID: BBIL/BBV152-C/2020 Version No: 3.0; Date: 20-10-2020 — Registry: Protocol Number
Details of Principal Investigator or overall Trial Coordinator (multi-center study)	**Name:** Dr Krishna Mohan **Address:** Medical Affairs Department, Bharat Biotech International Ltd, Genome valley, Shameerpet Medchal TELANGANA 500078 India **Phone:** 914023480567 **Fax:** 914023480560 **Email:** kmohan@bharatbiotech.com
Details Contact Person Scientific Query	Name: Dr Krishna Mohan **Address:** Medical Affairs Department, Bharat Biotech International Ltd, Genome valley, Shameerpet Medchal TELANGANA 500078 India **Phone:** 914023480567 **Fax:** 914023480560 **Email:** kmohan@bharatbiotech.com
Details Contact Person Public Query	**Name:** Dr Shashikanth Muni **Address:** Medical Affairs Department, Bharat Biotech International Ltd, Genome valley, Shameerpet Medchal TELANGANA 500078 India **Phone:** 914023480567 **Fax:** 914023480560 **Email:** shashikanth4257@bharatbiotech.com
Source of	Indian Council of Medical Research (ICMR), New Delhi

Monetary or Material Support	

Primary Sponsor	**Name**	Bharat Biotech International Ltd
	Address	Bharat Biotech International Ltd Genome Valley Shameerpet Hyderabad – 500 078 Telagana INDIA
	Type of Sponsor	Pharmaceutical industry-Indian

Details of Secondary Sponsor	**Name**	**Address**
	The Indian Council of Medical Research ICMR New Delhi	Indian Council of Medical Research V. Ramalingaswami Bhawan, P.O. Box No. 4911 Ansari Nagar, New Delhi - 110029, India

Countries of Recruitment	India

Sites of Study Modification(s)

No of Sites = **26**

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Details of Ethics Committee Modification(s)

No of Ethics Committees= 26

Name of Committee	Approval Status
Ethics Committee of the Prakhar Hospital	Approved
Ethics Committee Sir Ganga Ram Hospital	Approved
Institutional Ethics Committe Aligarh Muslim University UP	Approved
Institutional Ethics Committe, Jeevan Rekha Hospital, belgaum	Approved
Institutional Ethics Committe, Maharaja Agrasen Superspecilaity Hospital, Jaipur	Approved
Institutional Ethics Committee SRM College Hospital and Research Centre Tamil Nadu	Approved
Institutional Ethics Committee All India Institute of Medical Sciences Bihar	Approved
Institutional Ethics Committee All India Institute of Medical Sciences New Delhi	Approved
Institutional ethics committee DIRECTORATE OF PUBLIC HEALTH AND PREVENTIVE MEDICINE,Chennai	Approved
Institutional ethics committee Gmers Ahmedabad	Approved
Institutional Ethics Committee Grant Government Medical College and Sir J.J. Group of Hospitals Maharashtra	Approved
Institutional ethics committee ICMR-National Institute of Cholera and Enteric Diseases Kolkatta,West Bengal	Approved
Institutional Ethics Committee King George Hospital Visakhapatnam	Approved
Institutional Ethics Committee Lokmanya Tilak Municipal Medical College & General Hospital	Approved
Institutional Ethics Committee Mahatma Gandhi Medical College& Research Institute, Pondicherry	Approved

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	Institutional Ethics Committee Peoples university Bhopal, Madhya Pradesh	Approved
	Institutional Ethics Committee Pt BD Sharma,PGIMS/UHS.Rohtak, Harvana	Approved
	Institutional Ethics Committee Rahate Surgical Hospital & ICU Nagpur	Approved
	Institutional Ethics Committee Redkar Hospital and Research Centre Oshalbag Village Dhargal, Tai- Pernem. Goa	Approved
	Institutional Ethics Committee Vydehi Institute of Medical Sciences and Research Centre Bengaluru, Karnataka	Approved
	Institutional Ethics Committee, Guntur Medical College, Government Fever Hospital, Government General Hospital, Gorantla, Guntur	Approved
	Institutional Ethics Committee, IMS & SUM Hospital	Approved
	NIMS Institutional Ethics Committee, Nizams institute of Medical Sciences, Punjagutta,	Approved
	Prakash Medical college Institutional Ethics Committee	Approved
	RCSMGMCIEC	Approved
	Translational Health Science and Technology Institute(THSTI), ESIC Medical College and Hospital Faridabad	Approved

Regulatory Clearance Status from DCGI

Status
Approved/Obtained

Health Condition / Problems Studied

Health Type	Condition
Healthy Human Volunteers	Active immunization for the prevention of SARS-CoV-2 infection

Intervention / Comparator Agent

Type	Name	Details
Intervention	BBV152B: 6 µg antigen with Algel-IMDG	Whole-Virion Inactivated SARS-CoV-2 vaccine (BBV152) will be administered as a two dose intramuscular injection 28 days apart.
Comparator Agent	Placebo (Phosphate buffered saline with Algel)	Phosphate buffered saline with Alum (without antigen) will be used as the control.will be administered as a two dose intramuscular injection 28 days apart.

Inclusion Criteria

Age From	18.00 Year(s)
Age To	99.00 Year(s)
Gender	Both
Details	1. Ability to provide written informed consent and availability to fulfill the study requirements. 2. Participants of either gender of aged 18 years and above. 3. Participants with good general health as determined by the discretion of the investigator, or participants with stable medical conditions. A stable medical condition is defined as a disease not requiring significant change in therapy or hospitalization or worsening disease during the 3 months before enrolment. 4. For a female participant of child-bearing potential, planning to avoid becoming pregnant (use of an effective method of contraception or abstinence) from the time of study enrolment until at least eight weeks after the last vaccination. 5. Male subjects of reproductive potential: Use of condoms to ensure effective contraception with the female partner and to refrain from sperm donation from first vaccination until at least 3 months after the last vaccination. 6. Agrees not to participate in another clinical trial at any time during the study period. 7. Agrees not to take any COVID-19 licensed vaccination for the entire duration of the study. 8. Agrees to remain in the study area for the entire duration of the study. 9. Willing to allow storage and future use of biological samples for future research.

ExclusionCriteria

Details	1. History of any other COVID-19 investigational or licensed vaccination. 2. Known history of SARS-CoV-2 infection, as declared by the subject. 3. For women, positive urine pregnancy test before the first dose of vaccination, or any time during the study period. 4. Temperature >38.0°C (100.4°F) or symptoms of an acute self-limited illness such as an upper respiratory infection or gastroenteritis within three days prior to each dose of vaccine. 5. Resident of COVID-19 infection in same household.

	6. Known case of HIV, hepatitis B, or hepatitis C infection. 7. Receipt of any licensed/experimental vaccine within four weeks before enrolment in this study. 8. Receipt of immunoglobulin or other blood products within the three months before vaccination in this study. 9. Immunosuppression as a result of an underlying illness or treatment with immunosuppressive or cytotoxic drugs, or use of anticancer chemotherapy or radiation therapy within the preceding 36 months. 10. Immunoglobulins, anti-cytokine antibodies and blood products within 6 months prior to study vaccination, during and 21 days following last dose of vaccination. 11. Pregnancy, lactation, or willingness/intention to become pregnant during the first 6 months after enrolment. 12. Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder,, and neurological illness (mild/moderate well-controlled comorbidities are allowed) Re-Vaccination Exclusion Criteria 13. Pregnancy. 14. History of virologically (RT-PCR) confirmed SARS-CoV-2 infection 15. Anaphylactic reaction following administration of the investigational vaccine.
Method of Generating Random Sequence	Computer generated randomization
Method of Concealment	Centralized
Blinding/Masking	Participant, Investigator and Outcome Assessor Blinded

Primary Outcome

Outcome	TimePoints
To evaluate the efficacy of BBV152B to prevent symptomatic COVID-19(Virologically confirmed-(RT-PCR positive) which include any participant who meets the Case Definitions for Symptomatic Endpoint and Severe Symptomatic COVID-19	Day 42 to Month 12

Secondary Outcome

Outcome	TimePoints
EFFICACY:To evaluate the efficacy of BBV152B to prevent- 1. COVID-19 based on the case definition for the secondary efficacy symptomatic endpoint. 2.COVID-19-Virologically confirmed (RT-PCR positive) severe cases of COVID19. 3.Any severity of COVID-19 by age. 4.Asymptomatic COVID-19. 5.COVID-19 regardless of symptomatology or severity 6.COVID-19 related deaths 7.Symptomatic COVID-19, regardless of the previous infection	1.Day 42 to Month 12 2.Day 42 to Month 12. 3.Day 42 to Month 12 4.Month 2 to Month 12 5.Day 42 to Month 12 6.Day 42 to Month 12 7.Day 42 to Month 12
IMMUNOGENECITY To evaluate the immunogenicity of BBV152B 1.Geometric Mean Titer (GMT) of SARS-CoV-2 Specific Neutralizing Antibody (nAb) 2.Geometric Mean Fold Rise (GMFR) of SARS-CoV-2 Neutralizing Antibody (nAb). 3.Geometric Mean Titer (GMT) of SARS-CoV-2 S1 protein-specific Binding Antibody (bAb). 4.Lot-to-Lot consistency will be assessed based on the neutralizing titer of the three consistent lots used in the trial	1.Month 0 to Month 12 2.Month 0 to Month 12 3.Month 0 to Month 12 4.Month 0 to Month 2
SAFETY To assess the safety of BBV152B 1.Serious Adverse Events occurring at any time 2.Solicited local and systemic adverse events (AEs). 3.Unsolicited AEs occurring between the vaccination and 28 days after the final vaccination. 4.Immediate AEs with 30 minutes of vaccination 5. Medically attended adverse events (MAAEs) or AEs leading to withdrawal 6.The occurrence of enhanced respiratory disease episodes reported by participant/documented in hospital records 7.AE of Special interest	1.Throughout the study period 2.Within 7 days post each vaccination 3.Till 28 days post second dose vaccination 4. Within 30 minutes post each vaccination 5.Throughout the study period 6.Throughout the study period 7.Throughout the study period

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Target Sample Size	**Total Sample Size=**"25800" **Sample Size from India=**"25800"
Phase of Trial	Phase 3
Date of First Enrollment (India) Modification(s)	11/11/2020
Date of First Enrollment (Global)	No Date Specified
Estimated Duration of Trial	**Years=**"1" **Months=**"0" **Days=**"0"
Recruitment Status of Trial (Global) Modification(s)	Not Applicable
Recruitment Status of Trial (India)	Closed to Recruitment of Participants
Publication Details	NIL
Brief Summary	This is a phase 3 Event Driven, randomized, double-blind, placebo controlled ,multicentre study to evaluate the Efficacy, Safety, and Immunogenicity of BBV152B, a Whole-Virion Inactivated SARS-CoV-2 Vaccine in Volunteers aged 18 years and above. Protocol Version 1.0 to Version 2.0 · BBV-152B formulation is chosen based on the Phase 1 interim report which shows that the immunogenicity of BBV-152B is higher compared to BBV-152A although the difference was not statistically different. · The primary efficacy endpoint is modified to include the participants who meet the case definition for Severe symptomatic COVID-19 . · A safety endpoint to include the Adverse Events of Special Interest (AESIs) such as anaphylaxis, generalized convulsion, and vaccine associated enhanced respiratory disease (VAERD) is included. Protocol Version 2.0 to version 3.0 · The case definition of symptomatic COVID-19 Endpoint is modified based on the SEC recommendation. · Risks from study participation (Category 1 and Category 2 &3) is Updated for easy understanding for the participant A total of 25,800 subjects will be enrolled and randomized in a 1:1 ratio to receive BBV152B vaccine and control. All participants will be assessed for efficacy and safety endpoints and provide a NP swab and blood sample before the first dose of IP. The NP swab and blood collected will be subject to RT-PCR and Anti-SARS-CoV-2 IgG antibodies. The results of this will not affect enrollment of the participant. Participants who are found to be positive for either RT-PCR Or Anti-SARS-CoV-2 IgG antibodies will be excluded from the primary efficacy analysis. Safety follow up will be done for all. In addition, sites will be segregated based on the study objectives: **Category 1 (Symptomatic):** In addition to administering the IP, a series of post-dose telephonic follow-up visits will be scheduled to detect suspect symptomatic COVID-19 infections. If a suspect is identified, a nasopharyngeal sample will be collected from the participant for detecting the presence of COVID-19 infection. Telephonic follow-up will occur at 15 Day intervals. **Category 2 (Symptomatic/Asymptomatic):** In addition to administering the IP, a series of post-dose Nasopharyngeal samples for detecting incidence of asymptomatic COVID-19 infection at 1-Month intervals will be collected **Category 3 (Symptomatic/Asymptomatic+Immunogenicity):** In addition to administering the IP and collecting NP samples, a series of blood samples will be collected for analyzing serum for immunological assessments. The purpose of this Phase 3 study is to evaluate the protective efficacy, safety, and immunogenicity of the whole-virion inactivated SARS-CoV-2 vaccine, BBV152B. The Phase 3 study will follow randomized study participants for efficacy until virologically confirmed (RT-PCR positive) symptomatic COVID-19 participants will be eligible for the primary efficacy analysis. After reaching the target number (n=130) of symptomatic COVID-19 cases, the study will continue to assess safety until the completion of the study duration.It is planned to continue the Phase 3 trial until 130 study participants in the per-protocol population develop PCR-confirmed symptomatic COVID-19 disease during follow-up beginning 14 days after the second dose of vaccine or placebo. We estimate that approximately 25,800 participants should be randomized to accrue these 130 events. The Lot-to-Lot consistency (Immunogenicity) study will be nested within the Phase 3 (Efficacy) study (in three selected sites). The Immunogenicity study will assess the immune response of a 2-dose regimen of BBV152B vaccine through geometric mean titers (GMTs) by neutralizing antibody, S-protein, and RBD specific anti-IgG binding titer in a subset of 600 (450 vaccine: 150 control) participants, across three consecutive manufacturing Lots. Data generated through Day 56 (Month 2) will be unblinded only to the biostatistician for evaluation of immune responses in the Immunogenicity subset. A Formal interim analyses are planned when approximately 1/3 and 2/3 of the target number of participants with confirmed symptomatic COVID-19 have been accrued, to determine whether the sample size and/or length of follow-up should be increased .This interim report containing safety and immunogenicity data will be submitted to CDSCO.

Prashant Bhushan

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ANNEXURE-P5

The Hindu

Coronavirus | Covaxin for those who got placebo

R. Prasad
CHENNAI: April 01, 2021 05:06 PM IST

Subject Expert Committee allows Bharat Biotech to unblind trial participants aged above 45.

On March 24, the Subject Expert Committee (SEC) permitted Bharat Biotech to unblind all "participants of age group of more than 45 years and offer to administer the vaccine free of cost as and when they become eligible for the vaccine in the national programme". The Committee recommended that the company unblind the participants as "vaccines [including Covaxin] are [already] available under the immunisation programme, and therefore all the eligible age groups under the immunisation programme should be permitted for unblinding for vaccination".

Apparently, Bharat Biotech intends to carry out a phase 3 trial in a cohort in Brazil. The company is now required to submit the "detailed revised clinical trial protocol for inclusion of a cohort from Brazil along with the revised statistical calculation for assessing the efficacy of the vaccine".

On March 3, based on 43 cases — 36 cases in the placebo group and seven cases in the vaccine arm — Bharat Biotech announced the first interim vaccine efficacy of 80.6% for Covaxin. The second the final time points for further analyses were 87 cases and 130 cases, respectively.

But with the Committee now allowing everyone above 45 years age to be unblinded, the trial can continue only in those below that age bar. "A significant number of participants will no longer be available to study the vaccine efficacy once unblinding of participants above 45 years is carried out," says

Dr. Anant Bhan, global health and bioethics researcher based in Bhopal. "With the current surge in cases, more younger people are getting infected." In all likelihood, the phase 3 trial may achieve its final endpoint of 130 cases but the trial will not include the most vulnerable population of participants above 45 years.

"More cases might have been recorded in March. Reliability would increase if further analysis too showed efficacy of over 80%. It is not the ideal, but what else is the alternative now?" says Dr. Jacob John, formerly with CMC Vellore.

Editorial | Efficacious too: On Covaxin

Could the SEC have asked the company to request participants above 45 years to continue in the study for the successful completion of the trial and unblind only those who want to withdraw from the trial? According to Dr. Bhan, this could have been done as long as participants are provided adequate information about eligibility to get the vaccine and are allowed to exercise an informed choice. "We are not aware on what basis the decision was taken. More context would have been useful," he says. "But the decision to unblind those above 45 years will affect the study."

However, virologist Dr. Shahid Jameel, Director of the Trivedi School of Biosciences at Ashoka University, says the Indian regulator has taken the right decision by allowing Bharat Biotech to unblind everyone above 45 years. "It's the correct and ethical thing to do," he says.

"We have some efficacy data of the vaccine. Whether it increases or not when further analyses are done will not make any difference on the ground. It's only of academic interest," Dr. Jameel says. "There is so much focus on the efficacy of vaccines. What is ignored is that every COVID-19 vaccine approved for emergency use has 100% efficacy against severe disease and death. And that's the only efficacy that matters."

In the U.S., even when three highly efficacious vaccines are available, the AstraZeneca phase 3 trial is continuing without unblinding even after the first interim analysis showed 76% efficacy based on 190 cases. "Every regulator looks at it differently," says Dr. Jameel.

Dr. Jameel goes further to say that India should not insist on bridging studies especially in the case of Johnson and Johnson, Novavax, and Sputnik V vaccines, where there is an Indian company manufacturing the vaccines. "Restricted use authorisation was granted to Covishield even before the bridging studies were completed. Today, there is a surge in cases across many States. More groups will be eligible for a vaccine if vaccine supply is not limited. Israel has demonstrated how large scale vaccination can control the pandemic. We must rethink our policies," says Dr. Jameel.

LINK:Coronavirus | Covaxin for those who got placebo: https://thg.page.link/i4sXbJqsUwGnrLqH8

Prashant Bhushan

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ANNEXURE: P6

THE ATLANTIC

HEALTH

The False Dilemma of Post-Vaccination Risk
We'll never know for sure how contagious people are after they're vaccinated, but we do know how they should act

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JAMES HAMBLIN
FEBRUARY 27, 2021

A nurse administers a dose of the Moderna Covid-19 vaccine at a vaccination site at Dignity Health Sports Park on February 16, 2021 in Carson, California.PATRICK T. FALLON / AFP / GETTY

Every day, more than 1 million American deltoids are being loaded with a vaccine. The ensuing immune response has proved to be extremely effective—essentially perfect—at preventing severe cases of COVID-19. And now, with yet another highly effective vaccine on the verge of approval, that pace should further accelerate in the weeks to come.

This is creating a legion of people who no longer need to fear getting sick, and are desperate to return to "normal" life. Yet the messaging on whether they might still carry and spread the disease—and thus whether it's really safe for them to resume their unmasked, un-distanced lives—has been oblique. Anthony Fauci said last week on CNN that "it is conceivable, maybe likely," that vaccinated people can get infected with the coronavirus and then spread it to someone else, and that more will be known about this likelihood "in some time, as we do some follow-up studies." CDC Director Rochelle Walensky had been no more definitive on *Meet the Press* a few days before, where she told the host, "We don't have a lot of data yet to inform exactly the question that you're asking."

At this point in the pandemic, with deliverance in sight for so many people, the vagueness can justifiably be maddening. For a year now, the public-health message has been to *wait*. First we waited until it was safe to go outside. Then we waited for vaccines to be developed, tested, and approved. Now people are being asked to wait their turn to get vaccinated; then to wait a few more weeks until they've received their second dose; and then two weeks more to make sure that their immune responses have fully kicked in. And finally, when all that waiting is done, we're supposed to wait for "some time" more?

The experts urging patience are, of course, correct. There are myriad details of physiology and molecular immunology that remain to be understood, and we do not know how quickly transmission rates will drop as large numbers of people get vaccinated. At an individual level, though, the proper advice on what constitutes safe behavior does not depend on any scientific study whose results are pending. It depends on what's happening in the world around us.

As you've heard ad nauseam by now, the SARS-CoV-2 vaccines were developed at record speed. They were created in the heat of an emergency, while thousands of people were dying every day, as a way to stop the carnage. They are proving remarkably effective at this.

The vaccines were never expected to block infection by the virus altogether, explains Stephen Thomas, the chief of the infectious-disease division at SUNY Upstate and the coordinating principal investigator for the Phase 3 Pfizer-BioNTech vaccine clinical trial. "I don't really think that's feasible or plausible," he told me. Most vaccines work by training the body to prevent a virus from replicating to such a degree that a person gets sick. They don't typically prevent a person from getting infected; they simply make that infection less consequential, and enable the body to clear it more quickly.

If a vaccine could reliably prevent future infections from ever taking hold, it would provide what's known as "sterilizing immunity," Syra Madad, an epidemiologist at NYC Health + Hospitals, told me. This is an uncommon occurrence. The measles vaccine is often cited as an exception, but she says that there is no reason to expect the COVID-19 vaccines to fall into this rare category.

Indeed, there is no obvious mechanism by which they could. "To generate sterilizing immunity in a mucosal space using a vaccine that's injected into your muscle is extremely difficult," Angela Rasmussen, a virologist at Georgetown University, told me. She said that early evidence in rhesus macaques has suggested that the AstraZeneca vaccine could provide sterilizing protection, but only when administered as a nasal spray. Other researchers have begun to work on nasally delivered vaccines that could theoretically serve to coat our mucous membranes with antiviral armor, though there is no certainty that this approach would be effective at preventing severe disease.

So it's safe to assume that the current batch of COVID-19 vaccines won't stop viral transmission outright. But it's also safe to assume that they will reduce that transmission to some extent, because they impede viral replication. "It is highly plausible that a vaccine that prevents disease by lowering the amount of virus in a person could also lower that person's ability to infect others

through the same mechanism," Thomas said. The tricky part is determining the degree to which this happens.

"No definitive clinical trial can give you this evidence," Rasmussen said. The trials were really designed for speed and safety, so the researchers were most concerned with looking for symptomatic COVID-19 or adverse reactions, not asymptomatic infections. To know how often vaccinated people were asymptomatically carrying the virus, researchers would have had to test each of the tens of thousands of people in their clinical trials as frequently as possible.

Some ongoing trials have taken to swabbing the noses of vaccinated people occasionally, and this could add insight into how common it is for people to carry the virus after vaccination. Early evidence from Johnson & Johnson's clinical trial, for example, suggests a significant reduction in transmission after vaccination, though this remains to be verified. Still, occasional testing is bound to miss cases of infection, and finding some virus in some noses doesn't tell us how infectious the owners of those noses might be—or whether they're infectious at all.

The only way to answer this question for certain would be to run a "challenge" trial in which vaccinated and unvaccinated people were deliberately exposed to the virus under similar conditions, and then tested to see what percentage of them got infected. That's just step one. Then the vaccinated-but-infected people would need to hang out with a bunch of unvaccinated people to see if *they* got infected, and at what rate. This is not going to happen. Challenge trials are ethical minefields in normal times; at this point, any study that involves withholding a vaccine from a control group would be difficult to justify.

More trial data are expected over the next few months, and these may help narrow our uncertainty. It would certainly be useful to get a better sense of whether the risk of catching COVID-19 from your grandmother, for example, drops by something like 90 percent once she's vaccinated, or whether it's closer to 10 percent—but that number isn't going to be exact, and it won't be static, either. Even if we could somehow run the sort of challenge trial described above, whatever value it produced could change as new variants of the virus take hold, and it might well vary across regions with different patterns of prior infection, behavioral norms, local weather, and other variables we don't even know to look for.

All of this is academic. Whatever trial data might arrive in the coming months won't change the practical advice: As long as a lot of virus is still circulating in a community and many people remain unvaccinated, the mere fact that some have protection will not mean that it's responsible for them to forgo precautions and do whatever they like.

A different kind of data, though, will offer that reassurance and certainty. This is what we're really waiting on. "We will absolutely get to a point when we can say that vaccinated people don't need to wear masks," Madad said, but that will be driven largely by changes in the number of cases, and in the vaccination rate. The sooner we can drive the former down and the latter up, the sooner normalcy returns. As populations draw closer to herd immunity, the chance of a vaccinated person both carrying the virus and coming into close contact with a nonimmune person will become so low that the guidelines will change. But as long as the virus remains omnipresent, the risk of getting infected (and transmitting) the virus after being vaccinated remains too high to countenance.

This message need not be seen as pessimistic or ambiguous. It tells us very clearly that our social lives can resume, but only when the whole community is ready. The turning point does not arrive for individuals, one by one, as soon as they've been vaccinated; it comes for all of us at once, when a population becomes immune. How quickly this occurs depends on how reliably those vaccines reduce transmission. But it will primarily be a function of how quickly people get access to vaccines, how much immunity already exists in a population, and how much attention is given to basic preventive measures that should never go away, such as well-ventilated workspaces and responsible sick-leave policies. Much of this is in our hands now. We are not waiting on a clinical study; we are waiting on one another.

https://www.theatlantic.com/health/archive/2021/02/post-vaccination-risk-is-a-false-dilemma/618149/

Prashant Bhushan

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WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the

researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Prashant Bhushan

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ANNEXURE: P8

World Health Organization

WHO Statement on public disclosure of clinical trial results

9 April 2015 | Departmental news | Reading time: 3 min (892 words)

Background

Following a ministerial summit on Health Research in 2004, a World Health Assembly Resolution passed in 2005 called for unambiguous identification of all interventional clinical trials. This led to the establishment of the WHO International Clinical Trials Registry Platform, which collates information on trials that have been notified in a network of clinical trial registries (who.int/ictrp/network). WHO's existing position on registration is available at who.int/ictrp: "The registration of all interventional trials is a scientific, ethical and moral responsibility". Deposition of information on trials in such registries, prior to their initiation, is a condition for publishing the results of trials in many leading medical journals. However, concerns have been raised that there may be selective publication of trials dependent on their results, with particular concern that trial results which may be viewed as "negative", are less likely to be submitted, or accepted, for publication in the scientific literature or made public in other ways. Notification of trials to clinical trial registries has become more widespread, and it is possible to evaluate what proportions of recorded trials have not reported results at different times after the planned end dates of the trials. Multiple analyses have confirmed that a substantial number of clinical trials remain unreported several years after study completion, even in the case of large randomized clinical trials.

In the latest version of the Declaration of Helsinki it is stated that "Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject." and that "Researchers have a duty to make publicly available the results of their research

.... Negative and inconclusive as well as positive results must be published or otherwise made publicly available". There is an ethical imperative to report the results of all clinical trials, including those of unreported trials conducted in the past. Furthermore poor allocation of resources for product development and financing of available interventions, and suboptimal regulatory and public health recommendations may occur where decisions are based on only a subset of all completed clinical trials.

Reiteration of WHO position on clinical trial registry sites

Before any clinical trial is initiated (at any Phase) its details are to be registered in a publicly available, free to access, searchable clinical trial registry complying with WHO's international agreed standards. The clinical trial registry entry should be made before the first subject receives the first medical intervention in the trial.

Updating clinical trial registry entries

All clinical trial registry sites are to be updated as necessary to include final enrolment numbers achieved, and the date of actual study completion (defined as the last data collection timepoint for the last subject for the primary outcome measure). If clinical trials are terminated, their status is to be updated to note the termination, and to report the numbers enrolled up to the point of termination.

Reporting timeframes for clinical trials

Clinical trial results are to be reported according to the timeframes outlined below. Reporting is to occur in BOTH of the following two modalities.

1. The main findings of clinical trials are to be submitted for publication in a peer reviewed journal within 12 months of study completion and are to be published through an open access mechanism unless there is a specific reason why open access cannot be used, or otherwise made available publicly at most within 24 months of study completion.
2. In addition, the key outcomes are to be made publicly available within 12 months of study completion by posting to the results section of the primary clinical trial registry. Where a registry is used without a results database available, the results should be posted on a free-to-access, publicly available, searchable institutional website of the Regulatory Sponsor, Funder or Principal Investigator.

It is noted that several journals allow open access publication of clinical trial findings. Some journals have an explicit policy of supporting publication of negative trials. These 12 month and 24 month timeframes represent the longest possible acceptable timeframe for reporting and shorter timeframes are strongly encouraged. It should be possible in most instances for reporting to occur in shorter timeframes.

Reporting of past clinical trials results

Unreported clinical trials conducted in the past are to be disclosed in a publicly available, free to access, searchable clinical trial registry. In addition it is desirable that unreported clinical trials are published in a peer reviewed journal.

Inclusion of Trial ID in clinical trial publication

The Trial ID or registry identifier code/number is always to be included in all publications of clinical trials, and should be provided as part of the abstract to PubMed and other bibliographic search databases for easy linking of trial reports with clinical trial registry site records. Bibliographic search databases such as PubMed are encouraged to make Trial IDs easily available by inclusion in the abstract of each clinical trial record.

Note on Data Sharing Initiatives

The benefit of sharing research data and the facilitation of research through greater access to primary datasets is a principle which WHO sees as important. This statement is not directed towards sharing of primary data. However WHO is actively engaged with multiple initiatives related to data sharing, and supports sharing of health research datasets whenever appropriate. WHO will continue to engage with partners in support of an enabling environment to allow data sharing to maximise the value of health research data.

Prashant Bhushan
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ANNEXURE: P9

Green Med Indo

Anti-Vaccination; Pro-Science; Pro-Health; Anti-Industry

Saturday, April 13th 2019 at 1:15 pm
Written By:
Jagannath Chatterjee

There are unanswered questions about vaccine safety. We need studies on vaccinated populations based on various schedules and doses as well as individual patient susceptibilities that we are continuing to learn about. No one should be threatened by the pursuit of this knowledge. Vaccine policy should be the subject of frank and open debate, with no tolerance for bullying. There are no sides – only people concerned about the well being of our children."

Dr Bernadine Healy, MD, Former Director, National Institute of Health (NIH)

On 17th January 2019 the WHO while unveiling its new 5 year strategic plan, The 13th Global Programme of Work, declared vaccine hesitancy among global public health threats alongside Ebola.[1] On 21st March 2019 in a meeting at Geneva to decide the post 2020 vaccine strategy, it talked of deep and broad engagement of stakeholders to take forward the vaccination agenda globally and Kate Gilmore, UN Dy High Commissioner Human Rights, stated, "There is no such thing as the right to refuse vaccines."[2]

The intent is to neutralize a growing movement that has been raising critical questions regarding vaccines since the 18th century spurred by a broad range of issues like vaccination scandals, ill advised mandates and breach of civil liberties, refusal to acknowledge adverse effects, lack of oversight and unresolved issues on matters of vaccine safety and efficacy, conflict of interest, and collusion between the industry and regulating agencies.

Vaccination has a controversial history. Prior to vaccination there were three practices; olfaction, inoculation and variolation. These failed because they led to serious adverse effects, increased the death rate and helped the disease to spread among populations where they were practiced.[3]

Jenner's small pox vaccination was accepted upon a single case of James Phipps who after operation in May 1796 survived a disease challenge, deemed unethical by many[4], and it was assumed the immunity was for life. However the incidence

rapidly increased and the promised period of immunity reduced progressively from a lifetime to six months. Repeated revaccination was suggested which suited those implementing the practice for a handsome fee.[5]

Opposition to the vaccine grew as people witnessed deaths and very serious adverse effects from "the most dangerous vaccine" that Dr Paul Offit acknowledges "has an adverse effect profile we would not accept as a vaccine today".[6] An article in the JAMA attributes the deaths to serious adverse effects and specifies not only those vaccinated but the contacts too were coming down with the disease.[7] Parents preferred to pay fines and even accept jail terms rather than having their wards vaccinated, particularly as they had previous children who had succumbed.

As adverse effects were ignored people organized to form anti-vaccination groups. France banned vaccination after unrest in 1763.[8] Growing rejection of the vaccine and protests against it led to mandates in 1853 in Leicester, England and protests led to the launch of the Anti-Vaccination League in 1870. The Anti-vaccination Society of America came up in 1879. Two other leagues, the New England Anti Compulsory Vaccination League (1882) and the Anti-vaccination League of New York City (1885) followed.[9] In India Mahatma Gandhi opposed the small pox vaccine, advocated measures adopted by Leicester and declared himself anti-vaccine.[10] In 1955 the Governor General C Rajagopalachari published a booklet titled, "BCG - Why I oppose it" leading to ICMR's Chingleput Trial that proved the vaccine to "offer no overall protection".[11] The well organized and documented Indian opposition to vaccination considered it to be a fallacy, sacrilege, betrayal and conspiracy.[12]

The members of the anti-vaccination groups were stalwarts from all sections of society and received inputs from the medical profession and public health officials who engaged in documenting vaccination harm, designed pamphlets warning the public, analysed statistics, and submitted detailed petitions to governments against mandates.[13] Public meetings were held where political leaders pointed out mandates went against the right to liberty and bodily integrity; a point relevant to this day.[14]

Protests led to results. The Royal Commission gathered evidence for seven years and repealed England's compulsory vaccination law in 1907. Statistical analysis showed the epidemics increased dramatically after 1854 - the year the compulsory vaccination law was imposed. In England and Wales, 44,840 people died of smallpox when official estimates showed 97 percent of the population were vaccinated.[15] By 1919, England and Wales had become one of the least vaccinated countries and had only 28 deaths from smallpox out of a population of 37.8 million people.[16]

In 1941 Dr. C. Killick Millard, Medical Officer of Health (Leicester, England) published The Vaccination Question and admitted that the city of Leicester, with a population of around 300,000 at the time, had for 30 years abandoned infantile

vaccination and yet miraculously experienced an enormous decline in smallpox mortality.[17]

The National Anti-Vaccination League of Britain exposed statistical manipulation, "The Ministry of Health has admitted that the vaccinal condition is a guiding factor in diagnosis." If a person who is vaccinated comes down with the disease he was protected against, the disease was recorded under another name. Chickenpox, measles, rash and eczema were diagnostic options. This increased the efficacy of the vaccine.[18]

The same phenomenon was observed in Philippines as recorded by Ian Sinclair, "In the Philippines, prior to U.S. takeover in 1905, case mortality [death rate] from smallpox was about 10%. In 1918-1919, with over 95% of the population vaccinated, the worst epidemic in the Philippines' history occurred resulting in a case mortality of 65%.The 1920 Report of the Philippines Health Service stated 'hundreds of thousands of people were yearly vaccinated with the most unfortunate result that the 1918 epidemic looks prima facie as a flagrant failure of the classic immunization toward future epidemics."[19]

Many regions including Leicester rejected the vaccine and adopted sanitation, hygiene, isolation and nutrition and the disease rate declined remarkably.[20] Ironically small pox when it disappeared all over the world disappeared also in regions where people shunned the vaccine and adopted them. It is known the WHO too was forced to adopt isolation, sanitation and hygiene alongside. Incidentally what virus was present in the vaccine still remains a mystery leaving the space wide open for debate.[21]

The anti-vaccination movement, its accusations and alternative solutions were vindicated.

The wave of a future movement was sown in 1943 when Dr Leo Kanner, a psychiatrist, made a case study of children who suffered from a novel disorder he termed Autism. Documenting details of these thoroughly unresponsive children he mentioned they were vaccinated for small pox and DPT.[22]

However it was an epidemic of encephalopathy observed in children leading to deaths and a lifetime of disability that spurred parents in the USA to question vaccines again. Their anger was not unfounded. As early as 1933 the DPT vaccine was linked by Dr Madsen to deaths in children. In 1947 Dr Brody linked it to brain damage. A 1948 study by Dr Byers et al linked it to deaths, blindness, deafness, spasticity, convulsions, and other severe neurological disorders. [23] There was open admission of guilt by eminent immunologists in a US TV show DPT: Vaccine Roulette by investigative reporter Lea Thompson broadcast in 1982 where children who had turned into vegetables after receiving the shots were also featured.[24] The

US vaccine industry faced bankruptcy paying compensation to parents who went to the Court against them. The manufacturers shifted to the acellular pertussis vaccine, the DTaP as it was found the pertussis component was guilty.[25]

The anti-vaccine crowd was proven right again.

This second wave was dealt with in the most brazen manner possible. The industry approached the US government and pleaded they needed protection or they would go out of business. The government of Ronald Reagan provided limited liability to vaccine manufacturers in October 1986 and set up a federal compensation programme[26] to be funded by an excise duty on each vaccine component that would ironically be borne by the purchaser. [27] As on February 2019 this programme has paid out $ 4.06 billion to 4,172 cases decided by a Vaccine Court.[28]

The New York Times of 15th November 1986 reported, "The increase in the cost of liability insurance and the unpredictable nature of such liability has forced some manufacturers to consider abandoning production of vaccines." Also, "Mr. Reagan's action came after heavy lobbying in favour of the bill by a broad-based coalition including drug companies, physicians."[29]

There still remained a possibility that parents could opt out of the system to sue manufacturers. This loophole was blocked when the US Supreme Court supported the US Congress view in the Bruesewitz v. Wyeth case of 2011. The Court judgement noted, "No vaccine manufacturer shall be liable in a civil action for damages arising from a vaccine-related injury or death associated with the administration of a vaccine after October 1,1988, if the injury or death resulted from side effects that were unavoidable even though the vaccine was properly prepared and was accompanied by proper directions and warnings."[30] In short it agreed that vaccines were "unavoidably unsafe" and therefore awarded absolute immunity to vaccine manufacturers.

The pro-vaccination group won and left the industry with no incentive or intention to produce safe and effective vaccines. The US Department of Health and Human Services (HHS) was consequently instructed to submit safety reports to the government every two years acceding to public concerns. "The Informed Consent Action Network (ICAN) and Robert F. Kennedy Jr. sued the US government in an attempt to reveal the safety reports that received the response, "The Departments search for records did not locate any records responsive to your request".[31] According to a legal document entitled, "Mandate for Safer Childhood Vaccines," Health and Human Services (HHS) openly admitted to not having filed any vaccine safety reports in over 30 years!"[32]

Thus vaccine safety depends upon clinical trials of the manufacturers. How capable are they for revealing adverse effects? "According to the "2013 WHO Expert Consultation on the Use of Placebos in Vaccine Trials", the following replacements

are used in lieu of a true saline placebo: "In place of a placebo, a vaccine against a disease that is not the focus of the trial is given to participants who do not receive the trial vaccine." or, an "add-on" vaccine can be used: "In this design, the trial vaccine or placebo product is mixed with an existing vaccine not studied in the trial, and the subjects are given either (a) the trial vaccine mixed with the existing unrelated vaccine or (b) the combination of a placebo and the existing unrelated vaccine." Thus the trials can never provide a genuine risk assessment.[33]

The WHO admits: "A methodological disadvantage, however, is that trials using these types of placebos provide a less perfect control. It may be difficult or impossible to assess fully the safety and reactogenicity of the trial vaccine." The reasons offered are vaccines are classified as biological – therefore they do not require stringent safety tests, and it would be unethical to deny the control group the use of a vaccine.[34]

This is the same WHO which considers those questioning vaccines to be the greatest public health threat, which has decided to launch a vigorous grassroots campaign to promote vaccines involving all its stakeholders and feels there should be no right to refuse.

Clinical trials are also known to obfuscate troublesome data. In September 2017, a report titled "Infanrix hexa and sudden death: a review of the periodic safety update reports submitted to the European Medicines Agency" published in the Indian Journal of Medical Ethics[35] alleged that GlaxoSmithKline (GSK) apparently excluded certain cases of infant deaths in their official report to the European Medicines Agency. GSK stated that the deaths reported after the vaccine is "coincident" and not related to the vaccine. However analysis by Puliyel and Sathyamala, authors, showed that 83% of the reported deaths occurred within 10 days of vaccination and another 17% occurred in the following ten days. "Glossing over of the deaths after vaccination has potential to result in more, unnecessary deaths which are difficult to justify ethically," they observed in a Press Release.

The same vaccine and an MMR vaccine have also been embroiled in serious contamination scandals[36] and the list[37] grows by the day. In yet another shocking incident the Government of India preferred not to release clinical data of an indigenous Rotavirus vaccine that showed a very high incidence of a potentially lethal intestinal obstruction in vaccinated children[38] under the plea that revealing the data would "alarm the public".[39]

The third wave of the anti-vaccination movement was focussed on autism discovered in 1943. It appeared in children all over the globe and became unmanageable by the 1990's. The severity is reflected by the fact that in California the prevalence increased 600% in the period 1990 – 2002.[40] It was the parents who raised their voice only to be ridiculed and demonized. They were asked to deny their own eyes

as they watched and even video recorded their children regress after taking vaccines.

A lot happened during this period. In 3rd April 2000, a study titled "Autism, a novel form of mercury poisoning" by Sallie Bernard et al found 200 symptoms of autism to exactly match mercury poisoning and ascribed it to the use of the mercury containing compound Thiomersal in vaccines. Published in Medical Hypotheses in April 2001 after a thorough review, it created quite a stir and was vehemently criticized.[41]

The din refused to fade and became shriller still when a freedom of information act petition by Congressman David Weldon exposed the minutes of a high profile meeting of 51 officials belonging to the CDC, vaccine manufacturers, and highly placed government officials who had met in Simpsonwood, Northcross Georgia, USA on 7th – 8th June 2000 to discuss two CDC studies that found undeniable association between mercury containing vaccines and autism. The relative risk found in both the studies was 7.62[42]; any figure above 1 being a sure indication.[43]

CDC correspondence between the author Thomas Verstraeten and top notch scientists revealed he had manipulated the data at his level from a RR of 11.35 and unable to do so any further sent an SOS for help, "The association will not go away." Consequently the meeting was held where the guests decided to bury the association even as a member conceded his grandchild would not receive vaccines, another expressed concerns over targets to be met, while a third highlighted a similar role of the vaccine adjuvant aluminium which he felt had equally disastrous consequences. All of them agreed that these results should not reach the public.[44]

Verstraeten left the CDC to join the vaccine giant Glaxosmithkline, and one study published in the November 2003 issue of the journal Pediatrics concluded, "No consistent significant associations were found between TCVs (thiomersal containing vaccines) and neurodevelopmental outcomes. Conflicting results were found at different HMOs for certain outcomes"; in short, nothing to worry.[45] Researchers examined this and 15 other studies purporting to show Thiomersal is safe and uncovered malfeasance and cover ups.[46] The other Verstraeten study showing the same 7.62 association remains with the CDC and is available in its archives.

Faced with opposition the US Government decided in 1998 to remove mercury in drugs and pharmaceutical products[47] but old stock was allowed to be administered up to 2006. Mercury was allowed to remain as "trace amount" and vaccines like the Hep B and the annual Flu vaccines continued to have 25mcg of mercury in them.[48]

Researcher Neil Z Miller pointed out that yet another neurotoxin aluminium replaced mercury, "Prior to the mercury phase-out (pre-2000), babies received 3,925 micrograms (mcg) of aluminum in their first year-and-a-half of life. After pneumococcal and hepatitis A vaccines were added to the immunization schedule,

babies began receiving 4,925 mcg of aluminum during the same age period—a 25% increase. In 2011, CDC recommended that pregnant women receive a pertussis vaccine (Tdap), which also contains aluminum. Studies show that aluminum crosses the placenta and accumulates in fetal tissue. Thus, millions of babies in utero, infants, and young children were injected with, and continue to receive, unnaturally high doses of neurotoxic substances—mercury and aluminum—long after unsuspecting parents were led to believe that vaccines were purified and made safe." In developing nations the mercury compound continues to be present in all non live virus vaccines on the plea removing mercury would make vaccines costlier.[49]

CDC provided a grant to Dr Poul Thorsen of Denmark to conduct the famous Danish studies. They found that Thiomersal in vaccines and the MMR vaccine were not associated with autism. The studies came under a cloud when a CDC insider squealed that Dr Thorsen had misappropriated the grant. The case was investigated and Thorsen was found guilty of 22 counts of money laundering and wire fraud in April 2011. [50]

US Attorney Quillian Yates remarked, "This defendant is alleged to have orchestrated a scheme to steal over $1 million in CDC grant money earmarked for autism research. We will now seek the defendants extradition."[51] Thorsen remains on the "Most Wanted" list of the Office of Inspector General, US DHHS, and awaits extradition as Denmark does not have an extradition treaty with the US.[52] The CDC feels his financial misdemeanour has not affected his scientific integrity and defends the studies.

Another investigation was conducted on September 18, 2017. "The new evidence, uncovered by Children's Health Defense, showed that Thorsen and his collaborators did not obtain permission from an Institutional Review Board (IRB) to conduct their research, which was published in the New England Journal of Medicine in 2002 and Pediatrics in 2003. In 2009, when CDC discovered that Thorsen never applied for the IRB approvals, staff did not report the errors and retract the studies. Rather, FOIA documents show that CDC supervisors ignored the missteps and covered up the illegal activity."[53]

The next CDC study to run into a controversy was when Dr William Thompson, CDC Immunization Safety Researcher, turned whistleblower and handed over 10,000 documents he was asked to destroy to the US Congress that revealed gross incongruities in the CDC DeStefano study published in 2002 that investigated the role of MMR vaccines in autism in a bid to refute the 1998 investigation by Dr Andrew Wakefield. After Dr. Brian Hooker's requests through the Freedom of Information Act for original MMR study documentation Dr. Thompson, the co-author, buckled under the pressure of his conscience to hand over documents he was asked to destroy that demonstrated a 3.4 fold increase in the incidence of autism in African American boys, expunged from the final study results in an act of scientific

fraud.[54] Dr Brian Hooker accessed the raw data to confirm the allegations. The matter is currently under Congress investigation.[55]

The studies that strongly deny the vaccine autism connection are thus weak in their foundations. It must also trouble us that of the cases of vaccine injury compensated under NVICP, there exist 85 cases of autism awarded for encephalopathy.[56] The association is denied under the plea that they only resemble symptoms of autism. But autism is a symptomatic diagnosis.

In 13th January 2019 The Hill reported, "Pediatric neurologist Dr. Andrew Zimmerman who originally served as the expert medical witness for the government, which defends vaccines in federal vaccine court signed a sworn affidavit. During a group of 5,000 vaccine-autism cases being heard in court on June 15, 2007, he took aside the Department of Justice (DOJ) lawyers he worked for defending vaccines and told them he'd discovered "exceptions in which vaccinations could cause autism. "I explained that in a subset of children, vaccine-induced fever and immune stimulation did cause regressive brain disease with features of autism spectrum disorder." His opinion was based on scientific advances and his own experience with patients." However his confession was disregarded and the cases dismissed.[57]

The anti-vaccine movement spread worldwide when the HPV vaccine against cervical cancer introduced in 2007 became associated with clinical trial fraud, and numerous cases of deaths and serious disabilities. These cases received huge media publicity in Japan, Sweden, UK, Ireland and the USA. The vaccine adverse effect reporting system (VAERS) of the USA accessed by Sanevax reveals up to 14th March 2019, 61,552 adverse events that include 480 deaths and 9070 cases classified as serious.[58] It is estimated that VAERS records 1 to 10% of actual. [59]

Activists in India filed a case which was admitted in the Supreme Court in January 2013 when it emerged that PATH and the ICMR had conducted an illegal clinical trial in the year 2009 that killed seven tribal girls and sickened almost every girl that it was administered to defying informed consent norms and local laws.[60]

Afrikaners were jolted in November 2014 when the Catholic Doctors Association found evidence from reports of nine accredited laboratories that beta hcg, a birth control hormone, was present in tetanus vaccines being used by WHO and Unicef in Kenya targeting 14 to 49 year old women. "In February 2018 the Kenyan president Raila Odinga made a public televised statement acknowledging a tetanus vaccine given in 2014 – 2015 to approximately 500,000 women was confirmed to contain a sterilization hormone. The licence of the manufacturer was cancelled."[61]

In 2017 Philippines erupted in anger when it was revealed that the Dengue vaccine manufactured by Sanofi approved in the country and administered to 800,000 children had ignored a warning it could increase the cases of severe dengue in

persons previously exposed to the disease. The official death toll is 154 as on Sept 26, 2018.[62] Severe internal haemorrhage has been found in many cases. "Legal authorities have revealed there is a clear case against six Sanofi officials, mostly country representatives of the firm, and 14 current and former Philippine health officials including former Health Minister Janette Garin for 10 confirmed deaths."[63] Meanwhile the parents of the 800,000 children and 100,000 more in Brazil dread the day their wards would come down with dengue.

What is the strategy being used to push vaccines into an increasingly unwilling population? It starts with naming vaccines to be "immunization" whereas 100% of the suffering population can turn out to be "fully immunized"[64] and the discovery of cell mediated immunity by Merrill Chase in 1942 has all but negated this claim.[65] Portraying vaccines to be about "public health" and "preventive medicine" when vaccines have been linked so far to 248 diseases and disabilities including death by scientific published studies[66], and research proves most infectious diseases have therapeutic benefits. [67] The concept of "herd immunity" used to jack up vaccination rates has been argued to be a "dishonest marketing gimmick".[68]

The study of the human microbiome points to the fact that vaccines and antibiotics can lead to a whole host of illnesses. Prof Ruth Ley remarks on the BBC, "Where work on the microbiome comes in is seeing how changes in the microbiome, that happened as a result of the success we've had fighting pathogens(with antibiotics and vaccines), have now contributed to a whole new set of diseases that we have to deal with."[69] A study in April 2018 found that environmental genetic changes termed epigenetic changes can travel 14 generations.[70] Is it a wonder that people turn against vaccinations?

What should be done to stem the crisis? Dr Pushpa Mittra Bhargava, founder director of The Institute of Cellular and Molecular Biology, had suggested some steps to the author to ensure safe vaccination programmes when he was interviewed in the year 2009 at Secunderabad.

There is a system for introducing vaccines into India. Many factors have to be considered. What is the incidence of the disease in the country; are there some regions where it is concentrated? Does the incidence justify a vaccine?

"What is the mortality rate from the disease? Is it high enough to justify a vaccine? What is the safety profile of the vaccine? Has it been tested on Indian populations and found safe? What safety issues are being ignored? What are the alternatives to the vaccine? Can other safer public health measures control the disease better than the vaccine? Is the disease easily treatable at a lesser cost? Vaccines are a costly measure as they also involve logistics and staff to administer. Is there a cost benefit in using the vaccine or by avoiding it?

"Who are the children who should receive the vaccine and who should not? What are the contraindications of the vaccine? Must the vaccine be given to all or can it be restricted to regions of high incidence? Is there a mechanism in place to monitor the above process that consists of capable members free from conflict of interest? Is there a system of monitoring adverse effects and addressing them in a transparent manner and which too is free from conflict of interest? Is there pressure from international agencies to introduce the vaccine and influence the process?

"All these are important non negotiable issues whenever a vaccine is introduced into the country. I protested the oral polio vaccine because it is a hasty decision considering that the vaccine has a history of causing paralysis. We also do not know how it will affect the gut microbes. Are the cases of encephalitis we are witnessing in regions where intensive drives are on because of the vaccine?

"I am not opposed to vaccines but systems and procedures must be in place if we are to behave responsibly. Vaccines cannot be included in any schedule simply because someone somewhere is manufacturing them."[71]

These sage words must reverberate in all members of the scientific community who are interested in vaccine safety. We are aware of vaccination warnings being ignored in India. Dr Vipin Vashishtha, senior executive committee member of the IAP voiced his concern about 15 additional vaccines being given by IAP members and that "pharma money is corrupting paediatrics academy".[72] He alleged that the amount of Rs. 25,000 to 30,000 per child that led to annual revenue of Rs. 8100 crores was driving the urge to vaccinate. [73] Dr Vashistha was physically assaulted at an IAP function[74] and expelled from the IAP for raising his voice.[75]

Doctors in India have expressed concerns about the Pentavalent vaccine in the Indian Journal of Medical Ethics, and suggested it could be behind around 8100 deaths annually in Indian children. The WHO responded to the global reports of deaths by revising the reporting system such that the deaths could not be ascribed to the vaccine making Dr Jacob Puliyel lament, "Even deaths are no longer a contraindication to vaccination."[76]

An RTI query in 2018 made the Indian government concede 10,612 deaths after vaccinations provided under the universal immunization programme from 2008 to 2018.[77] It also revealed upwards of 600,000 adverse effects are reported every year. Government officials hint at coincidence. The OPV vaccine being given with religious fervour in India has been attributed to 491,704 cases of paralysis in Indian children from 2000 to 2017 and the criticism against the study methodology has been countered effectively.[78] Such figures do not inspire confidence, nor does the response. The private sector in India that vaccinates 2.7 million children or more annually has no monitoring system.

Parents in India have approached two High Courts; at Kerala, and New Delhi after children started dying and were hospitalized in hordes after being vaccinated with the measles rubella vaccine in a school based campaign. Deciding on the petitions the clear judgement in both cases has been, the parents can object to vaccination[79] and that the risks have to be revealed and informed written consent taken.[80] Preparations are on to challenge the decisions. It has been acknowledged by government sources that vaccination campaigns cannot succeed unless the parents are kept ignorant and the vaccines forced on the children.[81]

Our children are today in a deplorable state. According to a report, 54% of children today suffer from chronic disorders.[82] 1 in 10 children have asthma. 1 in 13 suffers from food allergies. 1 in 6 children suffer from developmental disorders. 1 in 8 suffers severe neurological disorders. The CDC's latest report released in April 2019 reveals 1 in 59 children suffer autism.[83] In the past 8 to 10 years: juvenile diabetes increased by 23%, cancer increased by 29%, ADHD increased by 43%, food allergies increased by 50%, asthma rates rose by almost 50%, Autism increased 150%.[84] Where is the healthy childhood that vaccines promised? All independent studies that have compared the health of vaccinated and non-vaccinated so far have found the non-vaccinated groups to be healthier on all counts studied.[85]

The collusion between the WHO, big philanthropies, the vaccination industry and the media cannot be denied.[86] A FDA medical advisor has stated, "The (US) Congress is owned by Pharma".[87] Can the vaccine industry that has paid billions of dollars in fines and is involved in felonies be trusted? Can the CDC that holds 50 vaccine patents and has a for profit wing be an impartial body free from conflict of interest when it recommends vaccines?[88] The industry on record donates to political parties to lobby for vaccine mandates.[89]

Must a campaign that raises crucial issues, seeks scientific interventions, and expects the medical profession to ensure health be attacked just for being anti-industry?

We can no longer ignore the elephant in the room. Vaccination mandates being imposed in the USA in response to anti-vaccination sentiments and the censoring of social media is not the solution. The scientific society must proceed on observation, evidence and facts and not be swayed by the manipulations of the vaccine industry and its lobbyists. History will judge the custodians of children according to what their response will be at the present moment. Let that decision be sane and scientific. We need courage and determination to face the bullies. Our children are precious, not the profits of an industry that stands exposed.

https://www.greenmedinfo.com/blog/anti-vaccination-pro-science-pro-health-anti-industry#_ftn18

Prashant Bhushan

(TRUE COPY)

ANNEXURE: P10

III

Online RTI Request Form Details

RTI Request Details :-

RTI Request Registration number	INCMR/R/E/20/00337
Public Authority	Indian Council of Medical Research

Personal Details of RTI Applicant:-

Name	JAGDISH CHANDA
Gender	Male
Address	21 M G SARANI THANA ROAD , SANTIPUR , NADIA
Pincode	741404
Country	India
State	West Bengal
Status	Urban
Educational Status	Literate
Phone Number	Details not provided
Mobile Number	+91-9564160480
Email-ID	jagdishchanda[at]yahoo[dot]com

Request Details :-

Citizenship	Indian
Is the Requester Below Poverty Line ?	No

(Description of Information sought (upto 500 characters)

Description of Information Sought
1. Please provide us with the detailed list of ingredients being present in the proposed COVAXIN to be produced with the partnershi Industries Ltd and the harmful side effects of those ingredients to human body. 2.Please provide us the methodology and techniques used in manufacturing the the COVAXIN by Bharat Biotech. 3. Please provide us the research papers published detailing the reports of pre clinical trial of the COVAXIN manufactured by Bharat Bi 4. Please provide us the detailed agreement happened between ICMR and Bharat Biotech and National Institute of Virology,Pur manufacture and launch of the said vaccine

Concerned CPIO	Nodal Officer
Supporting document ***(only pdf upto 1 MB)***	Supporting document not provided

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Select Language: English

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RTI

An Initiative of Department of Personnel & Tra

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Online RTI Status Form

Note:Fields marked with * are Mandatory.

Enter Registration Number	INCMR/R/E/20/00337
Name	JAGDISH CHANDA
Date of filing	06/07/2020
Public Authority	Indian Council of Medical Research
Status	RTI REQUEST APPLICATION RETURNED TO APPLIC
Date of action	05/08/2020
Reply / Remarks :-Since it is the third party information sought, which is under an agreement between the same can not be shared under PPP ethical code	
Nodal Officer Details :-	
Telephone Number	011-26588980
Email Id	devishanti[at]icmr[dot]gov[dot]in

Print RTI Application Print Status Go Back

Prashant Bhushan

(TRUE COPY)

ANNEXURE: P11

September 5, 2020

To,

Dr. Harsh Vardhan
Minister for Health & Family Welfare,
Government of India,
348-A, Nirman Bhawan,
Maulana Azad Road,
New Delhi – 110 011.

Sir,

Petition seeking greater transparency regarding drug regulation under the Drugs and Cosmetics Act, 1940

1. We are a group of citizens, concerned about the lack of transparency with which the pharmaceutical industry is regulated in India. For far too long, we have known about the corruption in drug approval process; the unholy nexus between drug manufacturers and medical experts; and the inaction against manufacturers of substandard and ineffective medicines. This troubling state of affairs, we believe, is a direct fallout of systemic opacity prevalent within the institutions responsible for regulating the pharmaceutical industry. This is an issue that you had expressed concern about several years ago, in an interview to the *Indian Express* wherein you had stated the following:

> "There is corruption in the approval of drugs. The Central Drugs Standard Controls Organisation, which is supposed to oversee clinical trials, is another snake pit of vested interests.....The corruption that goes behind approving drug approvals was exposed through Wikileaks and later confirmed by the Standing Committee of the Health Ministry in 2012."[1]

2. We could not agree more with your assessment of the situation back in 2014. We believe that the best way to reform drug regulation is by making the entire regulatory apparatus under the Drugs and Cosmetics Act, 1940 (D&C Act) more transparent. Our demand for greater transparency flows from Section 4 of the Right to Information Act, 2005 (RTI Act) which requires the government to make *proactive* disclosures of its records through the internet and other means of communications to the general public. This provision must be taken seriously by the government because the 'Right to Information' is a fundamental right of citizens flowing from the right to free speech and expression under Article 19(1)(a) of the Constitution.[2] The underlying rationale of reading the right to information into the right to free speech is the fact that citizens cannot

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[1] Pritha Chatterjee, *MCI corrupt, clinical trials body a snake pit: Harsh Vardhan, Indian Express* (July 18, 2014), available at: indianexpress.com/article/india/politics/mci-corrupt-clinical-trials-body-a-snake-pit-harsh-vardhan/ (last accessed on July 10, 2020).

[2] *See* S.P. Gupta v. Union of India, (1981) Supp SCC 87; State of Uttar Pradesh v. Raj Narain, (1975) 4 SCC 428; Dinesh Trivedi v. Union of India, (1997) 4 SCC 306; People's Union for Civil Liberties v. Union of India, (2004) 2 SCC 476.

effectively assert their fundamental right to free speech against the state without access to information about the internal workings of the state. By making available more information to the public regarding the workings of the Indian drug regulatory system, the government will make it possible for important stakeholders like doctors, pharmacists, journalists and patients to hold both the regulators and the pharmaceutical industry accountable for their actions. The availability of such information will also provide doctors with the information required to make better medical decisions with regard to treatment of patients.

3. In the specific context of drug regulation in India, the need for greater transparency has been stressed on by the Parliamentary Standing Committee on Health & Family Welfare, in its 59th Report (2012) and 66th Report (2013), which called for "increased transparency in decision-making" of the Central Drugs Standard Controls Organization (CDSCO) and other regulatory authorities. Even the Central Information Commission (CIC) has repeatedly called upon the CDSCO and other regulatory bodies to take *proactive* steps to keep the public informed about various regulatory activities. And more recently, the CIC made the following scathing observations in a case involving files that went missing from the Office of the Drug Controller General of India (DCGI):[3]

> "The Commission however expressed its serious concern over the record keeping methodology in the office of DCGI / CDSCO due to the fact that an important report relating to the review of procedures and practices followed by CDSCO for granting approval and clinical trials on certain drugs went missing from their office that had to be procured from the author after receipt of notice of hearing from the Commission. This is despite the fact that the Parliamentary Standing Committee had also taken cognizance of the lapses by the Public Authority. The intent and the conduct of the Public Authority should always be above board in matters relating to grant of approvals through a transparent and objective mechanism. The Commission advises Secretary, M/o Health and Family Welfare, Govt. of India to examine this matter appropriately for further necessary action at its end."

4. In this petition, we identify specific aspects of drug regulation that are required to be made far more transparent than is the case currently and we explain how exactly such transparency may be achieved in this regard:

   (i) Clinical trial data, along with final outcomes, must be disclosed through Clinical Trial Registry of India or such other database regardless of the success or failure of the trial;

   (ii) Decisions and file notings relating to applications for approval of new drugs decided by DCGI, including the ones that are rejected or withdrawn, must be made public;

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[3] Prashant Reddy T. v. Central Public Information Officer, Drug Controller General of India & Ministry of Health, CIC/MH&FW/A/2018/159460-BJ (May 26, 2020), available at: indiankanoon.org/doc/115080764/ (last accessed on July 10, 2020).

(iii) Applications for state manufacturing licenses and accompanying safety data for generic drugs must be made public;

(iv) Inspection reports by Drug Inspectors and lab test results by the Government Analysts, at Central and State levels must be available in the public domain;

(v) Enforcement actions under the D&C Act, such as criminal complaints initiated against drug manufacturers and judgments must be made available to the public; and

(vi) The latest and previous editions of Indian Pharmacopeia should be made available to the public at free of cost.

A. Ensuring greater transparency of Clinical Trials by mandating disclosure of both positive and negative results

5. The regulation of clinical trials in India has for long been a controversial issue. After much litigation before the Supreme Court, the Ministry of Health began the process of increasing transparency around clinical trials in India by creating the Clinical Trials Registry of India (CTRI), as an online database administered by the Indian Council of Medical Research (ICMR). As per the New Drugs and Clinical Trials Rules, 2019, it is mandatory for all sponsors to register clinical trials in the CTRI database before enrolling the first subject for the trial.[4]

6. Launched in 2007, the CTRI database is valuable for doctors and researchers to learn from developments in medical research. Furthermore, the CTRI database allows citizens to monitor the recruiting practices employed by pharma companies during trials conducted in India. With nearly 30 data fields, the CTRI database captures various aspects of clinical study; viz., title, subject matter, nature and stage of trial, locations, details of ethics committee review, outcomes, and concludes with a 'brief summary.'[5]

7. Be that as it may, the CTRI database and the legal framework governing it does not address two critical issues related to transparency. These issues are discussed in greater detail below:

(a) **Limited Disclosures**: The CTRI database does not contain three crucial pieces of information. The *first* piece of missing information is the minutes of the meeting of the institutional Ethics Committee where the clinical trial is to be carried out. These minutes are important because they will contain the details of the deliberations (including disclosure of conflict of interest) conducted by the Ethics Committee before allowing

[4] *See* Rules 25(v), 35(vi) & 49.

[5] NATIONAL INSTITUTE OF MEDICAL STATISTICS, 'CTRI Dataset and Description', ctri.nic.in/Clinicaltrials/CTRI_Dataset_and_Description.pdf (last accessed on June 27, 2020).

the institution to conduct the clinical trial. The *second* missing piece of information is the application submitted to the DCGI for permission to conduct the clinical trial. The application will presumably contain a host of pre-clinical data (study protocols, toxicology and pharmacology data, and other technical studies). This data needs to be made available to the public health community in order to ensure that the DCGI makes responsible decisions while granting permissions to conduct clinical trials in India. While the pharmaceutical industry would like to claim a proprietary interest in such data, it can be argued that the public interest in the disclosure of safety data can outweigh any IP concerns. As per Section 8(1)(d) of the RTI Act, information can be disclosed if public interest outweighs IP concerns. The *third* critical piece of missing information is the reasoned decision of the DCGI granting approval or rejecting an application for the conduct of clinical trials. Without access to the DCGI's decision there is no way for the people to hold the DCGI accountable for its decision.

(b) **Disclosure of primary data**: The CTRI database only requires sponsors to indicate the status of the clinical trial. However, there is no legal obligation to disclose the primary datasets containing the results of the clinical trials. As a result, it has been alleged that pharmaceutical companies cherry pick the best data for publication in peer-reviewed journals while suppressing the most damaging data. The reasons are self-evident. Many in the pharmaceutical industry fear that publication of all clinical trial data may invite more public scrutiny of their claims and even adversely impact decisions by doctors to prescribe some of the riskier drugs. However, internationally, there has been a demand by the public health community for the release of all clinical trial data regardless of whether the trial succeeded or failed. Access to such health data will help both the regulatory community and the patient community in making more informed decisions regarding the true potential of a drug and the public interest in disclosure of this information outweighs the proprietary interests of the pharmaceutical companies. It maybe pertinent to mention that 'The Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subject' (2013) adopted by the World Medical Association (WMA) states "[r]esearchers have a duty to make publicly available the results of their research ... Negative and inconclusive as well as positive results must be published."[6] ICMR also endorsed a global

[6] WORLD MEDICAL ASSOCIATION, *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, 310 (20) JOURNAL OF MEDICAL ASSOCIATION 2191 (2013), available at: wma.net/wp-content/uploads/2016/11/DoH-Oct2013-JAMA.pdf (last accessed on June 27, 2020).

pledge to disclose results of trials in a timely manner.[7] However, the disclosure is limited to trials that are funded or supported by ICMR. The results of a vast majority of trials in India are unreported. Internationally, there has been a move in both the EU and the US to mandate the public disclosure of more clinical trial data.[8] India should follow suit and make the disclosure of such clinical trial data a precondition to the approval of any new drug.

8. Similar issues, regarding the disclosure of regulatory safety data under the RTI Act, have come before CIC. In *Divya Raghunandan v. Dept. of Biotechnology* (2007)[9] and *Kavita Kuruganti v. MoEF* (2016)[10] the CIC required the public disclosure of raw trial data (viz., biosafety, toxicity and allergencity data) pertaining to genetically modified brinjal studies because the public interest in making such data public, over-rode all other considerations such as commercial confidence, trade secrets or intellectual property. In the *Kavita Kuruganti* case, the CIC went as far as to require the publication of regulatory data even if the trials were a failure. Further in context of pharmaceutical safety data, the CIC in the past mandated the disclosure of clinical study reports of observational studies relating to HPV vaccines after redaction of the names of the patients and any information that may be considered the intellectual property of the pharmaceutical companies.[11] In a subsequent decision, the CIC ordered the DCGI to "suo motu disclose Regulatory Information redacting/obliterating the information exempted u/s 8 (1)/9 of the RTI Act, 2005 for the benefit of public at large."[12] This order, however, has not been complied with by the DCGI.

9. **Therefore, we submit that the CDSCO has a legal obligation to disclose regulatory data especially primary datasets for all clinical trials authorized in India, after redacting private patient information. The information should be available in a searchable online database that can be freely accessed by any citizen.**

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[7] 'Joint statement on public disclosure of results from clinical trials' (May 18, 2017), available at: who.int/ictrp/results/ICTRP_JointStatement_2017.pdf?ua=1 (last accessed on June 27, 2020).

[8] Sergio Bonini et. al., *Transparency and the European Medicines Agency – Sharing of Clinical Trial Data*, 371 (26) NEW ENGLAND JOURNAL OF MEDICINE 2452, available at:nejm.org/doi/pdf/10.1056/NEJMp1409464?articleTools=true (last accessed on July 10, 2020); Lev Facher, *Federal judge rules clinical trial sponsors must publish a decade's worth of clinical data Stat News* (February 25, 2020), available at: statnews.com/2020/02/25/clinical-trial-sponsors-publish-missing-data/ (last accessed on July 20, 2020).

[9] CIC/WB/A/2009/000668 (June 16, 2009), available at: indiankanoon.org/doc/103342038/ (last accessed on July 20, 2020).

[10] CIC/SA/A/2015/901798 (April 01, 2016), available at: indiankanoon.org/doc/145596348/ (last accessed on July 20, 2020).

[11] Deepa Venkatachalam v. Directorate General of Health Services, CIC/AD/A/2011/000115 (March 24, 2011), available at: ciconline.nic.in/cic_decisions/CIC_AD_A_2011_000116_M_54028.pdf (last accessed on June 27, 2020).

[12] Amresh Chandra Mathur v. Directorate General of Health Services, CIC/DTGHS/A/2018/609161-BJ+ (April 09, 2019), available at: indiankanoon.org/doc/4580255/ (last accessed on July 20, 2020).

II. Make public all records pertaining to new drug approvals

10. As per the New Drugs and Clinical Trial Rules, 2019 the DCGI is the designated licensing authority responsible for granting approvals to import or market 'new drugs' in India. This approval is distinct from the manufacturing license which is granted by the State Licensing Authorities for individual manufacturing plants. Over the last decade the DCGI has been heavily criticized for the manner in which it has given approval to dubious new drugs. The 59th report of the Parliamentary Standing Committee on Health & Family Welfare harshly criticized the DCGI for approving drugs that have not been approved in other countries. The fact that the Ministry of Health had to ban several hundred irrational Fixed Dose Combinations (FDCs) from the Indian market also pointed to the fact that unapproved drugs were being sold in India without permission from the DCGI. Since that report of the Parliamentary Standing Committee, the drug approval process was revamped by creating Subject Expert Committees (SEC) consisting of external experts with expertise in different areas. These SECs make a recommendation to the DCGI on approval of drugs and the DCGI is the final authority who can make a decision on whether a new drug can be sold in India.

11. As of today, the DCGI publishes very little information, compared to foreign regulators, regarding the approval of new drugs. The only information of some worth that is published, are the recommendations of the SECs but even this information is inadequate because these recommendations are very brief and do not contain the reasoning of the SEC or the deliberations of the Committee prior to making recommendations.[13] Usually the recommendations do not even contain the names of the experts who attended the meeting, whether they have any potential conflict of interests and whether they agreed or dissented with the recommendations of their peers. On the other hand, foreign drug regulators in the Western world release extensive information about the review process conducted by their regulators prior to approving or rejecting and application for a new drug. For example, the United States Food and Drugs Administration (USFDA) publishes at least 6 reviews of an application for a new drug, on different aspects of the new drug.[14] This includes a medical review, chemistry review, pharmacology review, statistical review, microbiology review and a clinical pharmacology biopharmaceutics review. Similarly, the European Medicines Agency (EMA) publishes a detailed EPAR (European Public

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[13] The Minutes of the different SEC meetings can be accessed here: cdsco.gov.in/opencms/opencms/en/Committees/SEC/ (last accessed on July 20, 2020)

[14] For example, see the following approval granted by the USFDA: www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022257_021304s007_valcyte_valganciclovir%20hydrochloride_toc.cfm (last accessed on July 20, 2020).

Assessment Report) for all its decision (including rejections) that outlines the scientific justification for granting approvals.[15]

12. The following is a list of information that we think should be made public with regard to new drugs approvals in order to fulfill the requirements of Section 4 of the RTI Act:

    a. The entire application dossier submitted by pharmaceutical companies for approval of a new drug, inclusive of data pertaining to efficacy, toxicity and other clinical data must be proactively published by the DCGI on its website and the Gazette of India at least 90 days prior to any final approval so as to enable public comment.

    b. As mentioned earlier, it is not enough to make available the recommendation of the SEC. It is also necessary to make available the deliberations of the SEC along with any internal memos or file notings of the DCGI regarding the decision to grant approval. Unless such information is made publicly available, there is no scope for citizens to verify whether the DCGI is discharging its duty as per the law. Most other countries provide detailed information about the review process followed for each application requesting approval of a new drug.

    c. Along with publishing the above details regarding approved drugs, the CDSCO must also publish the details of applicants and drugs that fail to receive final approval. Other regulators like the EMA and Australia's TGA publishes 'negative opinions' in respect of applications that fail to meet approval standards. Such assessment reports are intended to benefit the scientific community in future endeavors.[16]

13. **To conclude, we believe that the DCGI must be directed to disclose details of the entire lifecycle of a drug's approval process so that the public health community can be informed of the basis of decisions taken by the DCGI. Additionally, disclosure of such information will provide both doctors and patients with more information about the efficacy and toxicity of new drugs. The information should be available in a searchable online database that can be freely accessed by any citizen.**

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[15] For more information on the European approval process please see the following: ema.europa.eu/en/medicines/what-we-publish-when/european-public-assessment-reports-background-context (last accessed on July 20, 2020).

[16] Tafuri G, Trotta F, Leufkens HG, Pani L., 'Disclosure of grounds of European withdrawn and refused applications: a step forward on regulatory transparency' Br J Clin Pharmacol. 2013;75(4):1149-1151. doi:10.1111/j.1365-2125.2012.04424.x

III. Disclosure of applications for state manufacturing licenses and accompanying regulatory data

14. While the marketing approval for new drugs is granted by the DCGI, the manufacturing licenses for all drugs are granted by individual State Drug Controllers, also referred to as State Licensing Authorities (SLA). An individual manufacturing licence is given for each individual drug manufactured by a pharmaceutical company. If the same drug is being manufactured at more than one plant of the same company, separate licenses will have to be issued for each plant.

15. As per the mandate under Rule 79 of the D & C Rules, 1945 each manufacturing plant is required to be physically inspected by a Drug Inspector at the time of granting or renewing a license. The inspection is to cover the premises, plant, appliances and the process of manufacture and testing of drugs. After the inspection, an 'inspection report' as per Rule 80 of the D & C Rules, 1945 containing descriptive findings as well as recommendations is required to be sent by the Drug Inspector to the licensing authorities.

16. Apart from the inspection of the premises, the approval process for generic drugs (i.e. not 'new drugs') also requires an assessment of bioequivalence and stability data for each drug, in order to assess the capacity of the manufacturer to synthesis the drug in a manner that ensures its therapeutic efficacy over a long duration of time. The bioequivalence data is a measure of the ability of the drug to become bioavailable within a patient's body. If a drug is not properly synthesized it will not dissolve in the blood in a proper manner and that will affect its bioavailability and therapeutic efficacy.[17] Stability data measures whether the drug can withstand different atmospheric conditions such as temperature and humidity, that it is expected to encounter through the supply chain, without breaking down. This data is required to be recorded through the lifecycle of a drug by testing retained samples from each manufactured batch. From the many exposes by the USFDA, it is very clear that many pharmaceutical companies in India regularly fabricate both bioequivalence and stability data for drugs that were intended for foreign markets.[18]

17. From a public health point of view, it is important for each and every central and state licensing authority under the D&C Act to disclose all of the above mentioned information so that citizens can better inform themselves about the workings of the state regulators. A centralized and open database of

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[17] *See generally* Jerome P. Skelly, "Bioavailability and Bioequivalence", 16(10) THE JOURNAL OF CLINICAL PHARMACOLOGY 539-545 (1976) available at: accp1.onlinelibrary.wiley.com/doi/10.1177/009127007601601013 (last accessed on July 20, 2020).

[18] *See* Katherine Eban, "Bottle of Lies: The Inside Story of the Generic Drug Boom", Harper Collins, (2019).

manufacturing licences along with the accompanying inspections reports, licensing decisions, bioequivalence and stability data will go a long way in providing the healthcare industry with better information about every manufacturer and drug being sold within the country. Such transparency of information will also help procurement officers at hospitals, pharmacies and individual patients to make better procurement decisions while purchasing drugs.

18. **Therefore we submit that the Ministry of Health must take steps to create a publically accessible searchable national online database that contains all necessary information manufacturing/loan licences (including decisions regarding approval or rejections), all inspections reports and all bioequivalence and stability data.**

IV. Disclosure of test reports prepared by Government Analysts of drugs drawn from the market

19. Under the D&C Act, the Drug Inspectors appointed at the central and state levels collect hundreds of samples every month for quality testing. These samples are then tested by Government Analysts working at the Central Drug Laboratories (CDL) and State Drug Laboratories (SDLs) as per the requirements mentioned in the Indian Pharmacopeia. The findings of the Government Analyst guide the decision of the Drug Inspectors on whether the manufacturer is required to be prosecuted under the law for violation of quality requirements.

20. Given the importance of the test reports prepared by the Government Analyst, it is crucial that all these reports be made publicly available. In an excellent move towards transparency, the Central Government and 14 states have come together to deploy a platform called 'XLN – Xtended Licensing, Laboratory & Legal Node' that operates as a consolidated database of all the drugs/manufacturers that failed quality testing.[19] When originally created, the XLN database used to provide an option to download the test report prepared by Government Analysts after testing in government laboratories. For reasons not clear, the test reports prepared by Government Analysts are no longer being made available on the website, instead only some of the results of the report are provided in an inconvenient hover-over mode. However, as per the RTI Act even the primary documents i.e. test reports are required to be made publicly available.

21. The more significant problem is the fact that not all government laboratories are contributing their test reports to the XLN database. As of now only 14 states are

[19] The database can be accessed over here: https://xlnindia.gov.in/GP_FailedSample.aspx

contributing their test reports to the XLN database. It is not clear as to why the remaining states are not participating in this noteworthy exercise to boost administrative transparency. If required, the Central Government must consider a statutory mandate for all states to participate in the XLN database.

22. **Therefore, we submit that the test reports conducted by CDL and SDLs must be published *suo motu* in a searchable national database. By creating a consolidated, searchable, digital database that is open to the public, the government will make it considerably easier for citizens to be informed about the quality of drugs available in the market. This same information will allow procurement officers of public and private hospitals to make a determination about the track record of pharmaceutical companies before purchasing drugs from any of them.**

V. Enforcement actions against the pharmaceutical industry must be disclosed in public domain

23. If a drug sample fails a quality test conducted by a Governmental Analyst, it is standard procedure for the Drug Inspector to conduct a root-cause investigation. Such investigation is summarized usually in the form of an inspection report of the manufacturing facility where the drug was manufactured. This report is sent to the State Drug Controller who may or may not grant sanction to prosecute the pharmaceutical company for violations of the D&C Act. If permission for criminal prosecution is granted, the Drug Inspector files a criminal complaint before a criminal court to initiate a prosecution. None of these documents are proactively published by any of the State Governments or the Central Government. As a result it is impossible for citizens to inform themselves of the state of enforcement of drug regulatory laws.

24. It should be noted at this stage that the 59th Report of the Parliamentary Standing Committee on Health & Family Welfare recommended to the Ministry that it maintain a centralized database of prosecutions launched all over the country.[20] The 66th Report recorded the Ministry's acceptance and commitment to create such an infrastructure on a 'priority basis.'[21] Despite the passage of over 7 years, the CDSCO has failed to create such a database.

25. Transparency over enforcement actions is vital for the following reasons. *First,* secrecy over inspections creates a doubt about the impartiality and independence of drugs inspectors. *Second,* secrecy allows unscrupulous pharmaceutical companies to escape accountability and encourage further violations without adequate notice to the public.

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[20] See Para 4.8.
[21] See Para 3.19 & 3.21.

26. **Therefore, we submit that the CDSCO must create a digital database to disseminate all enforcement actions (civil or criminal) at all levels of drugs regulation. In particular we request that the following documents be made proactively available online in a publically accessible searchable database in order to ensure that citizens are well informed of the working of the enforcement mechanism under the D & C Act:**

(a) Inspection Reports by Drug Inspectors
(b) Decisions on whether or not to grant sanction for prosecutions by the State Drug Controllers;
(c) The criminal complaints filed by Drug Inspectors before criminal courts;
(d) The judgments delivered by criminal courts in such cases.

VI. Enable Free and Open Access to the Indian Pharmacopoeia (IP)

27. One of the critical regulatory functions under the D&C Act is the setting of standards of drug quality which are required to be followed by all pharmaceutical manufacturers in India. Section 16 of the D&C Act read along with the Second Schedule to the legislation entrust this standard setting function to primarily the Indian Pharmacopeia Commission (IPC) (an autonomous body under the Ministry of Health) which publishes the Indian Pharmacopeia (IP). The IP contains monographs prescribing testing mechanisms for almost all drugs being sold in the Indian market. A drug manufacturer who fails to comply with standards of "identity, purity and strength" of the drug specified in IP, is criminally liable for manufacturing "not of standard quality" drugs and can be sentenced to prison.[22] In other words, the IP assures patients that the drugs sold in the market are safe and meet the requisite quality parameters. Thus, for all practical purposes the IP is "law" within India.

28. Despite the IP being law in the country, it is not freely available to the members of the public. The latest edition (8th) of IP standards, for instance, costs a whopping Rs. 52,500.[23] The IPC which publishes the IP has so far refused to make the IPC freely available and has instead been treating it as a cash-cow which is to be milked for profits despite the fact that the IPC receives significant subsidies from the Central Government to support its functioning. Simply put, the IPC is charging citizens to access the law.

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[22] See Section 27.
[23] Product listing on the website of the IPC:
http://www.ipc.gov.in/shop/index.php?route=product/category&path=59

29. The Supreme Court has made it clear that while 'ignorance of the law' is no defense, the state is required to ensure that the law must be accessible to all citizens.[24] More recently, the CIC has reiterated that the government has a duty to make available the law to people.[25] In pertinent part, the CIC stated the following:

> "6. Needless to say that a duty upon the state to inform citizens about the Law as and when it was made and the citizens also have right to know of the Law. It is impossible for any Government to expect obedience to their Law without informing the people in legible form. It is more difficult especially when the text of Law is not available in easy accessible format. It will result in two major problems, (1) People will be kept in dark about their Laws, (2) Private Publishers will exploit this in-access to Law to make money by publishing updating Acts as their copyrighted work. It is surprising that the Ministry has not used the Information technology to provide access to text of law.
>
> 7. The law and enactments are in public domain and none can claim copyright in the law. Apart from this general right to know, RTI Act has offered a specific and enforceable right to information. Section 4 mandates the Ministry of Law to place the texts of enactments. It is the duty of Legislative Department to provide information about access of every updated enactment. It is not just an recommended obligation under Section 4(1)(a) of RTI Act, but a constitutional mandate, a legal necessity, and an essential requirement for peace. It is not possible to imagine 'enactment' becoming secret because of this ambiguity and non-legibility."

30. When this decision was appealed to the Delhi High Court, not only did the court uphold the ruling of the CIC but it also oversaw the entire process wherein the Law Ministry entirely refurbished the website (https://www.indiacode.nic.in/) to ensure the availability of the latest version of the law for free to all citizens. In the course of its ruling, the Delhi High Court held the following:[26]

> "The directions given by the CIC in the impugned order are not only fair and reasonable but also promote the concept of rule of law. It is unfortunate that the petitioner did not take the initiative on its own to upload the latest amended bare Acts.
>
> 5. Public can be expected to follow the law only if law is easily accessible 'at the click of a button'. In fact, as rightly pointed out by the CIC, the RTI Act itself mandates the Government to place the texts of enactments in public domain."

31. **We submit that since the IP is for all practical purposes the law of the land, it is incumbent on the IPC to make it publicly available on its website without charge because of the manner in which Section 4 of the RTI Act has been interpreted by the CIC and the Delhi High Court. The IPC must not forget that it was setup to improve public health and it receives funding**

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[24] Harla v. State of Rajasthan, [1952] SCR 110.
[25] Vansh Sharad Gupta v. PIO, Legislative Department, CIC/SS/C/2013/900008SA, Central Information Commission decided on November 4, 2015.
[26] W.P.(C) No. 4761/2016 (May 24, 2016), available at: indiankanoon.org/doc/123116384/(last accessed on July 20, 2020).

from Parliament to perform its function. It cannot be allowed to profiteer from the sale of the IP.

32. Please do let us know if you have any queries or doubts regarding the contents of this petition and we would be glad to clarify the same. We can be contacted at dinesh.thakur@gmail.com.

Best Regards,

Dinesh Thakur

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Prashant Bhushan

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Recommendations of the SEC meeting to examine COVID-19 related proposal under accelerated approval process made in its 146th meeting held on 10.03.2021 at CDSCO, HQ New Delhi:

Agenda No	File Name & Drug Name, Strength	Firm Name	Recommendation
Biological Division			
1.	BIO/MA/20/000103 Whole Virion, Inactivated Corona Virus Vaccine (BBV152) (Phase III interim report)	M/s Bharat Biotech, International Limited, Hyderabad	In continuation to the SEC meeting dated 08.03.2021, firm presented updated interim safety and efficacy data of its phase III clinical trial of Whole Virion, Inactivated Corona Virus Vaccine (BBV152) in the country. The committee noted that the firm has carried out interim analysis after 43 cases of symptomatic RT-PCR positive COVID-19 have been reported out of which 36 were in the placebo arm and 7 in the vaccine arm. After detailed deliberation, the committee recommended for omission of the condition of the use of the vaccine in clinical trial mode. However, the vaccine should be continued to be used under restricted use in emergency situation condition. Further, the ongoing phase III clinical trial should be continued as per the approved protocol. The firm should update the prescribing information and factsheet accordingly (under restricted use in emergency situation condition). All other conditions of the marketing authorisation shall continue to remain effective.

Prashant Bhushan

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ANNEXURE: P 13

National Herald

INDIA

COVID-19 vaccine approval: Expert committee meeting minutes do little to inspire confidence in process The minutes do not reveal what made the committee change its mind about the data submitted by Bharat Biotech for its Covaxin vaccine over the course of just two days and grant approval to it

Representative Image (Photo Courtesy: IANS)

Ashlin Mathew
Published: 06 Jan 2021, 8:22 AM
Engagement:436

It has come to light from a perusal of the minutes of the Subject Expert Committee (SEC) meetings, which were released by the Central Drugs Standard Control Organisation (CDSCO) on Tuesday, that the SEC changed its mind about Bharat Biotech's Covaxin within a span of two days.

Further, the approval for Serum Institute of India's vaccine candidate Covishield has been given on the condition that the firm would submit safety, efficacy and immunogenicity data from the ongoing national clinical trials. Covishield is the Indian version of the vaccine developed by the University of Oxford and pharma company AstraZeneca.

India's drug regulator approved the two COVID-19 vaccines on January 3 and the Drugs Controller General of India VG Somani said that though Covaxin was still recruiting participants, it was needed to control the spread of the new variant of SARS COV2, which was first found in the United Kingdom.

Minutes of the SEC's meetings show that on December 30, the members had asked Bharat Biotech to present the immunogenicity, safety and efficacy data for consideration. On January 1, 2021, the committee noted that efficacy was yet to be demonstrated through the clinical trials and requested the company to expedite recruitment for Phase 3 trial. The committee members noted that the company could perform interim

efficacy analysis, which could then be submitted for consideration of restricted use.

But on January 2, the firm presented 'updated data', though it was not specified what the 'updated data' was. The company only presented efficacy data from the non-human primate challenge study. At the meeting, Bharat Biotech provided justification for the data provided and additionally requested consideration of their proposal in the wake of incidence of new mutated corona virus infection.

Eventually, the SEC "recommended for grant of permission for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode, to have more options for vaccinations, especially in case of infection by mutant strains".

It is not known if there was political pressure to approve the locally developed vaccine during these three days. There were several tweets and posts questioning the approval for the so-called 'English vaccine' and not the Indian vaccine.

"If you look at the minutes of the meeting from December 30 and Jan 1, 2, there is an intellectual leap. On the first two days, they are asking for data on immunogenicity and efficacy and then on Jan 2, they are saying they have considered Bharat Bio's request and will be giving them 'emergency approval'. There is no mention of data. The minutes do not reveal what made the SEC change its mind about the data submitted by Bharat Biotech over the course of two days," said Chinu Srinivasan of All India Drug Action Network (AIDAN).

Public health expert Dr Anant Phadke agreed. " On December 30, the committee members had one view and two days later, they had another view when in reality the material reality has not changed. These are experts, so why did they not realise the same thing on December 30 itself," asked Phadke. He added that this significant shift of stand and the CDSCO's decision hardly inspires confidence.

He said that the minutes still did not clarify what 'in clinical trial mode' meant. "Does it mean the vaccine-recipients will get compensation if there is a vaccine injury? In a clinical trial, all participants are eligible to get compensation in case of adverse events. There is silence on this. This has to be clarified," pointed out Phadke..

In America, Pfizer was given emergency-use approval only after the efficacy data was submitted. "Why didn't they wait for the interim efficacy data before the permission was given?" questioned Srinivasan.

The Serum Institute of India (SII) on December 30 submitted safety immunogenicity and efficacy data of phase 2 and 3 clinical trials of AstraZeneca vaccine carried out in UK, Brazil and South Africa. Along with it, safety and immunogenicity data from the ongoing Phase 2/3 clinical trial of Covishield vaccine being manufactured by SII was also submitted. The SII informed the committee that AstraZeneca had received emergency use authorisation for the vaccine in UK subject to various conditions and restrictions.

Then on January 1, SEC observed that the safety and immunogenicity data presented by the firm from the Indian study is comparable with that of the overseas clinical trial data.

Here too, the committee decided to consider the serious nature of the COVID-19 pandemic to grant of permission for restricted emergency use of the vaccine subject to certain conditions. SEC noted that it could only be administered to those above 18 years of age and SII must submit safety, efficacy and immunogenicity data from the ongoing clinical trials nationally and internationally for review. The company has also been asked to submit the India specific risk management plan.

"We heard from the reliable sources that SII only submitted data for 100 persons and not that of all the 1,600 participants. The government should clarify this and release the data they relied on. Did they consider only UK's Medicines and Healthcare Products Regulatory Agency (MHRA) data? It is not clear as to why SII has not submitted independent efficacy studies comparing efficacy of the SII produced vaccine and the Oxford-produced vaccine," said Srinivasan.

Dr Phadke asked whether the situation in India is desparate like in UK? On the contrary, Covid-19 cases are on a downward trend. He contended that when such quick approvals are given there is always some compromise.

"The new virus is only faster, not deadlier. At the most, what will happen is that the spread will be faster. The possibility of a faster spread has been exhausted in Indian cities. All of this does not inspire confidence in the decision-making process," underscored Phadke.

Earlier, AIDAN had said that CDSCO guidelines state that SII is required to carry out a bridging study to prove that its vaccine Covishield can elicit an immune response comparable with the original AstraZeneca vaccine amongst Indians.

Dr Gagandeep Kang, microbiologist at the Christian Medical College in Vellore and a board member of the Coalition for Epidemic Preparedness Innovations, had underscored, in a news report, that vaccine makers must show a minimum efficacy of 50% in phase 3 trials for their vaccines to be approved. "CDSCO has gone against its own guidelines," pointed out Dr Kang.

https://www.nationalheraldindia.com/india/covid-19-vaccine-approval-expert-committee-meeting-minutes-do-little-to-inspire-confidence-in-process

Prashant Bhushan

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ANNEXURE-P14

Recommendations of the SEC meeting to examine COVID-19 related proposal under accelerated approval process made in its 133rd meeting held on 30.12.2020 at CDSCO, HQ New Delhi:

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Agenda No	File Name & Drug Name, Strength	Firm Name	Recommendations
Vaccine Division			
1.	BIO/MA/20/000102 ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) (EUA)	M/s Serum Institute of India Pvt. Ltd. (SIIPL), Pune	In light of the earlier recommendations the firm presented safety immunogenicity & efficacy data of phase II/III clinical trials of AstraZeneca vaccine carried out in UK & Brazil & South Africa along with the safety & immunogenicity data from the ongoing Phase II/III clinical trial of COVISHIELD vaccine manufactured by SIIPL in the country. The firm also presented the draft factsheet & prescribing information of the vaccine. The firm also mentioned that AstraZeneca had received Emergency Use Authorization for the vaccine in UK subject to various conditions & restrictions. The committee discussed the safety, efficacy & immunogenicity data, draft factsheet & prescribing information as provided by the firm & decided that clarification/justification on various aspects are still needed. After detailed deliberation, the committee recommended that the firm should submit complete details of the conditions & restrictions under which AstraZeneca was granted Emergency Use Authorization in UK and also present the revised factsheet & prescribing information in Indian context as required by the committee for further consideration. Also the firm was informed during the meeting regarding other requirements including clarification/justification on factsheet & prescribing information.
2.	BIO/MA/20/000103 Whole Virion, Inactivated Corona Virus Vaccine (BBV152) (EUA)	M/s Bharat Biotech International limited, Hyderabad	In light of the earlier recommendations of the committee, the firm presented updated recruitment status & safety data including SAE data of the ongoing Phase III clinical trial in the country. After detailed deliberation, the committee recommended that firm should update & present Immunogenicity, Safety & Efficacy data for further consideration.
3.	BIO/IMP/20/000110 COVID-19 mRNA Vaccine BNT162b2	M/s Pfizer Ltd., Mumbai	The firm did not turn up for the presentation

Recommendations of the SEC meeting to examine COVID-19 related proposals under accelerated approval process made in its 134th meeting held on 01.01.2021 CDSCO, HQ New Delhi:

Agenda No	File Name & Drug Name, Strength	Firm Name	Recommendations
Biological Division			
1.	BIO/MA/20/000102 ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) (COVISHIELD)	M/s Serum Institute of India Pvt Ltd.	In light of the recommendations of the committee in its earlier meeting dated 30.12.2020, the firm presented the details of the conditions & restrictions under which AstraZeneca was granted Emergency Use Authorization in UK and the revised factsheet & prescribing information in Indian context as required by the committee for further consideration. Further, the firm also presented the proposed Summary of Product Characteristics (SmPC) and risk management plan including Pharmacovigilance plan. The committee deliberated on various critical areas for consideration including safety, immunogenicity, efficacy data, indication, age group, dosing schedule, precautions, storage, warnings, adverse effects of special interest, risk benefit evaluation, proposed factsheet, PI, SmPC, Risk management plan etc. The committee reviewed the proposal of restricted emergency use along with above details in its meetings dated 09.12.2020, 30.12.2020 and 01.01.2021 as well as reviewed continuously the data as and when received. The MHRA approval dated 30.12.2020 along with its conditions/restrictions was also reviewed by the committee. The committee noted that the safety & immunogenicity data presented by the firm from the Indian study is comparable with that of the overseas clinical trial data. Considering the serious nature of the COVID-19 pandemic, emergency situation, there is an urgent need of vaccine in the country. After detailed deliberation, the committee recommended for grant of permission for restricted emergency use of the vaccine subject to various regulatory provisions including following: **1.** The vaccine is indicated for active immunization to prevent COVID-19 disease in individuals of $\geq$ 18 years of age. **2.** The vaccine should be administered intramuscularly in two doses of 0.5 ml each (containing $5x10^{10}$ vp per dose) with interval of 4 to 6 weeks. **3.** The vaccine should be supplied along with factsheet & separate leaflet for the guidance of the healthcare provider. **4.** The firm should submit the updated PI,

Agenda No	File Name & Drug Name, Strength	Firm Name	Recommendations
			SmPC & factsheet incorporating the changes as discussed during the meeting. 5. The firm should ensure that factsheet for the vaccine recipient/his attendant is provided prior to administration of the vaccine. 6. The firm should disseminate the instructions & educational material including factsheet, PI, SmPC, storage instructions etc. in their website. 7. The firm should submit safety, efficacy & immunogenicity data from the ongoing clinical trials nationally and internationally for review at the earliest. 8. The firm should submit safety data including the data on AEFI and AESI with due analysis every 15 days for the first two months & monthly thereafter till the completion of the ongoing clinical trial in the country. Thereafter, the firm should submit the safety data as per the provisions and standard procedures. 9. The firm should submit India specific Risk management plan. Dr. Sushant H Meshram didn't participate in this deliberation.
2.	BIO/MA/20/000103 Whole Virion, Inactivated Corona Virus Vaccine (BBV152) (EUA)	M/s Bharat Biotech International limited, Hyderabad	In light of the earlier recommendations of the committee dated 30.12.2020, the firm presented safety & immunogenicity data, GMT, GMFR including SAE data from the Phase I & Phase II clinical trial along with the data from the ongoing Phase III clinical trial in the country. The committee noted that this vaccine is Inactivated Whole Virion, Corona Virus Vaccine having potential to target mutated corona virus strains. The data generated so far demonstrates a strong immune response (both antibody as well as T cell) and in-vitro viral neutralization. The ongoing clinical trial is a large trial on 25800 Indian subjects in which already 22000 subjects have been enrolled including subjects with comorbid conditions as well which has demonstrated safety till date. However, efficacy is yet to be demonstrated. After detailed deliberation, the committee recommended that the firm should try to expedite the recruitment and may perform interim efficacy analysis for further consideration of restricted emergency use approval.
3.	BIO/IMP/20/000110 COVID-19 mRNA	M/s Pfizer Ltd., Mumbai	The firm did not turn up for the deliberation.

Agenda No	File Name & Drug Name, Strength	Firm Name	Recommendations
	Vaccine BNT162b2		

Recommendations of the SEC meeting to examine COVID-19 related proposals under accelerated approval process made in its 135th meeting held on 02.01.2021 CDSCO, HQ New Delhi:

Agenda No	File Name & Drug Name, Strength	Firm Name	Recommendations
Biological Division			
1.	BIO/CT/20/000194 Novel Corona Virus 2019-nCoV vaccine	M/s Cadila Healthcare Limited, Ahmedabad	The firm presented interim safety and immunogenicity data of ongoing Phase I/II clinical trial of Novel Corona Virus 2019-nCoV vaccine along with proposed phase III clinical trial protocol before the committee. After detailed deliberation, the committee recommended for grant of permission for conduct of proposed phase III clinical trial protocol subject to the condition that the vaccine efficacy should be assessed on the data generated after day 84 from the first dose.
2.	BIO/MA/20/000103 Whole Virion, Inactivated Corona Virus Vaccine (BBV152) (EUA)	M/s Bharat Biotech International limited, Hyderabad	In light of the recommendations of the committee dated 01.01.2021, the firm further presented the updated data, justification and requested for consideration of their proposal in the wake of incidence of new mutated corona virus infection. As already noted by the committee, this vaccine is Inactivated Whole Virion, Corona Virus Vaccine having potential to target mutated corona virus strains. The data generated so far demonstrates a strong immune response (both antibody as well as T cell) and in-vitro viral neutralization. The ongoing clinical trial is a large trial on 25800 Indian subjects in which already 22500 subjects have been enrolled including subjects with comorbid conditions as well which has demonstrated safety till date. Moreover, firm has presented the safety and efficacy data from Non-human primate challenge study where the vaccine has been found to be safe and effective. In view of above, after detailed deliberation, the committee recommended for grant of permission for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode, to have more options for vaccinations, especially in case of infection by mutant strains. Further, the firm shall continue the on-going Phase III clinical trial and submit data emerging from the trial as and when available.

Prashant Bhushan
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ANNEXURE: P15

The Hindu

ICMR to get Royalty from Covaxin Sale
Jacob Koshy
NEW DELHI: May 3, 2021 10:41 PM IST

Intellectual property governing use of vaccine jointly developed by Bharat Biotech and ICMR is 'shared'

The intellectual property governing the use of Covaxin, jointly developed by Bharat Biotech and the Indian Council of Medical Research, was "shared" and the ICMR would receive royalty payments, the organisation confirmed to The Hindu.

"The Public-Private Partnership was executed under a formal Memorandum of Understanding (MoU) between the ICMR and the BBIL which includes a royalty clause for the ICMR on net sales and other clauses like prioritisation of in-country supplies. The product IP is shared. It is also agreed that the name of ICMR-National Institute of Virology (NIV) will be printed on the vaccine boxes. The same is being done now," ICMR Director-General Balram Bhargava said in an email.

However he didn't say how much money was spent.

12 activities
The partnership between the two organisations involves 12 activities that include clinical and preclinical studies. Five of these were funded entirely by Bharat Biotech: Candidate vaccine development, preclinical safety and toxicity studies in small animals (rats, mice and rabbits), phase-1 clinical trials including funding of sites, hiring Clinical Research Organisation (CRO) for trial monitoring, insurance,

laboratory testing; phase 2 clinical trials including funding of sites, hiring CRO for trial monitoring, insurance, laboratory testing and all other logistics and hiring a CRO for phase-3 trial monitoring, insurance and laboratory testing.

The activities funded by the ICMR were: Isolating the SARS-CoV-2 virus from a "huge number" of clinical samples, passage testing and confirmation; BSL-3 facility validation of BBIL for Covaxin production; vaccine strain characterisation by ELISA tests, electron microscopy, next generation sequencing; testing serum samples from preclinical studies in small animals; preclinical safety and efficacy in golden Syrian hamsters and preclinical safety and efficacy studies in rhesus macaques (monkeys); testing sera of Covaxin vaccinated individuals for U.K. strain, Brazil strain, South African strain and double mutant strain of SARS-CoV-2; U.K. variant virus isolation and characterisation, titration, sequencing from clinical specimens and funding the site for the phase 3 clinical trial.

Covishield constitutes over 90% of the country's vaccine supply so far and has been developed as a partnership between the Oxford University and AstraZeneca. Serum Institute of India is one among the many manufacturers in the world with a production licence and has to pay royalty to a foreign company. Covaxin on the other hand is almost entirely indigenous and yet is priced higher than Covishield. Both are so far being bought by the Central government for □150 a dose. However, Covishield was first offered to States at □400 a dose and □600 to private hospitals and Covaxin was offered at □600 for State governments and at □1,200 for private hospitals.

Later Covishield's price was reduced to □300 a dose for States and Covaxin reduced theirs to □400.

So far however, the Centre had procured 40 million doses of Covaxin till March. An order for 20 million doses, presumably for April, had been half fulfilled (8.8 million doses) and orders for 50 million were placed for supply in May, June and July.

In the case of Covishield, the Centre had ordered 260 million doses. About 150 million had already been supplied and 110 million was in the process. Another 110 million was being supplied to States and private hospitals.

Link: https://www.thehindu.com/news/national/icmr-to-get-royalty-from-covaxin-sale/article34474504.ece

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ANNEXURE: P16

सत्यमेव जयते

PARLIAMENT OF INDIA
RAJYA SABHA

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DEPARTMENT-RELATED PARLIAMENTARY STANDING COMMITTEE ON HEALTH AND FAMILY WELFARE

FIFTY-NINTH REPORT

ON

THE FUNCTIONING OF THE CENTRAL DRUGS STANDARD CONTROL ORGANISATION (CDSCO)

(PRESENTED TO THE RAJYA SABHA ON 8TH MAY, 2012)
(LAID ON THE TABLE OF THE LOK SABHA ON 8TH MAY, 2012)

RAJYA SABHA SECRETARIAT
NEW DELHI
MAY, 2012/VAISHAKHA, 1934 (SAKA)

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PARLIAMENT OF INDIA
RAJYA SABHA

DEPARTMENT-RELATED PARLIAMENTARY STANDING COMMITTEE ON HEALTH AND FAMILY WELFARE

FIFTY-NINTH REPORT

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RAJYA SABHA SECRETARIAT
NEW DELHI

APRIL, 2012/VAISHAKHA, 1934 (SAKA)

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COMPOSITION OF THE COMMITTEE
(MAIN COMMITTEE)

RAJYA SABHA

1. Shri Brajesh Pathak — *Chairman*
#2. Shri Janardhan Dwivedi
*3. Shrimati Viplove Thakur
4. Dr. Vijaylaxmi Sadho
5. Shri Balbir Punj
6. Dr. Prabhakar Kore
7. Shrimati Vasanthi Stanley
@8. Shri Rasheed Masood
9. Shrimati B. Jayashree
10. Shri Derek O'Brien

LOK SABHA

11. Shri Ashok Argal
12. Shrimati Harsimrat Kaur Badal
13. Shri Vijay Bahuguna
14. Shrimati Raj Kumari Chauhan
15. Shrimati Bhavana Gawali
16. Dr. Sucharu Ranjan Haldar
17. Dr. Monazir Hassan
18. Dr. Sanjay Jaiswal
19. Shri S. R. Jeyadurai
20. Shri P. Lingam
21. Shri Datta Meghe
22. Dr. Jyoti Mirdha
23. Dr. Chinta Mohan
24. Shri Sidhant Mohapatra
25. Shrimati Jayshreeben Kanubhai Patel
26. Shri M. K. Raghavan
27. Shri J. M. Aaron Rashid
28. Dr. Arvind Kumar Sharma
29. Shri Radhe Mohan Singh
30. Shri Ratan Singh
31. Dr. Kirit Premjibhai Solanki

SECRETARIAT

Shri P.P.K. Ramacharyulu, *Joint Secretary*
Shri R.B. Gupta, *Director*
Shrimati Arpana Mendiratta, *Joint Director*
Shri Dinesh Singh, *Deputy Director*

Ceased to be a Member *w.e.f.* 27th January, 2012 and re-nominated to the Committee on 2nd February, 2012.
* Ceased to be a Member *w.e.f.* 2nd April, 2012.
@ Ceased to be a Member *w.e.f.* 9th March, 2012.

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SUB-COMMITTEE III ON DRAFT REPORTS –

1. Dr. Jyoti Mirdha — *Convenor*

RAJYA SABHA

2. Shri Balbir Punj

LOK SABHA

3. Dr. Sanjay Jaiswal

SECRETARIAT

Shri P.P.K. Ramacharyulu, *Joint Secretary*
Shri R.B. Gupta, *Director*
Shrimati Arpana Mendiratta, *Joint Director*
Shri Dinesh Singh, *Deputy Director*

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PREFACE

I, the Chairman of the Department-related Parliamentary Standing Committee on Health and Family Welfare, having been authorized by the Committee hereby present this Fifty-Ninth Report of the Committee on the functioning of the Central Drugs Standard Control Organisation.

2. During the course of examination of the subject mentioned above, the Committee heard the views of Secretary, Department of Health and Family Welfare along with the representatives of the Central Drugs Standard Control Organisation (CDSCO) on the 5th January, 12th October, 2011 and 04th May, 2012.

3. During the course of the finalization of its Report, the Committee relied upon the following documents/papers received from the Department of Health and Family Welfare:–

(i) Status Note;

(ii) Questionnaire Part I and II on the functioning of CDSCO; and

(iii) Questionnaire Set I and II on the functioning of CDSCO.

4. Study Note on the visit of the Committee to Tamil Nadu and Karnataka from 1st to 5th November, 2011 on functioning of CDSCO is also attached with Report of the Committee.

5. The Committee at its meeting held on 4th May, 2012, considered and adopted the Draft Report.

6. The Sub-Committee-III on Draft Reports considered and adopted the Report at its meeting held on 11th April, 2012.

7. For facility of reference and convenience, observations and recommendations of the Committee have been printed in bold letters in the body of the Report.

BRAJESH PATHAK
Chairman,
Department-related Parliamentary
Standing Committee on Health and Family Welfare.

NEW DELHI;
4rd May, 2012
Vaishakha 14, 1934 *(Saka)*

REPORT

INTRODUCTION

1. Drug Regulation

1.1 Drugs are an integral and inseparable part of medical care. As per the directory of pharmaceutical manufacturing units in India brought out by the National Pharmaceutical Pricing Authority in 2007, more than 10,500 drug manufacturers are operating in the country with estimated turnover of just over Rs. 50,000 crore for domestic sale alone.

1.2 Medicines apart from their critical role in alleviating human suffering and saving lives have very sensitive and typical dimensions for a variety of reasons. They are the only commodity for which the consumers have neither a role to play nor are they able to make any informed chokes except to buy and consume whatever is prescribed or dispensed to them because of the following reasons:

- Drug regulators decide which medicines can be marketed;
- Pharmaceutical companies either produce or import drugs that they can profitably sell;
- Doctors decide which drugs and brands to prescribe;
- Consumers are totally dependent on and at the mercy of external entities to protect their interests.

1.3 It is because of these typical dimensions that the state's responsibility to regulate the import, manufacture and sale of medicines so as to ensure that they are both safe, effective and of standard quality acquire almost sacrosanct dimensions. Under the circumstances, effective, transparent drug regulation free from commercial influences is essential to ensure the safety, efficacy and quality of drugs with just one objective, *i.e.,* welfare of patients.

1.4 Taking into account the immense importance and impact of drug regulation on humanity, the Committee examined the functioning of The Central Drugs Standards Control Organisation (CDSCO), the agency mandated with the task of drug regulation in India to determine if rules and laws were being implemented efficiently and honestly in the interest of patients. It did not go into the scientific Issues such as merits of medicines being sold in the country. As the successive narrative would unravel, the drug regulatory system in the counhy suffers from several deficiencies and shortcomings, some systemic and severa] manmade.

15. Drug regulation covers many functions, namely:

- Marketing approval of new medicines based on safety and efficacy studies,
- Licensing and monitoring of manufacturing facilities and distribution channels,
- Post-marketing adverse drug reaction (ADR) monitoring,
- Quality control (QC),
- Periodic review and re-evaluation of approved drugs,
- Conhol of drug promotion
- Regulation of drug trials.

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1.6 While most functions pertaining to drug regulation come under the jurisdiction of Central Government and are carried out by the Central Drug Standards Conhol Organization (CDSCO), others *viz.* licensing and monitoring of manufacturing units and distribution channels; quality control etc. are carried on by state level drugs authorities under the administrative control of State Governments.

17. Drugs and Cosmetics Act, 1940 and Rules 1945, Drugs & Magic Remedies (Objectionable Advertisements) Act, 1954 as amended from time to time are the principal legislations that govern the functioning of CDSCO and state drug authorities.

1.8 Drugs belonging to various systems of medicine (Allopathy, Homoeopathy, Ayurveda, Siddha and Unani) as well as cosmetics are regulated by CDSCO. However the present Report is confined to the aspect of regulation by the CDSCO and related agencies of drugs used in modem medicine only.

2. Mandate and Structure of CDSCO

2.1 In its Status Report on CDSCO, the Ministry of Health and Family Welfare stated that the mission of CDSCO was to "meet the aspirations.... demands and requirements of the pharmaceutical industry." As against this, the stated missions of Drug Regulatory Authorities of developed countries are as follows:

> **United States:** The Food and Drugs Administration (USFDA) mission is, "protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs."
>
> **United Kingdom:** The Medicine and Healthcare Regulatory Authority's (MHRA) mission is "to enhance and safeguard the health of the public by ensuring that medicines and medical devices work, and are acceptably safe."
>
> **Australia:** The mission statement of Therapeutic Coods Administration (TGA) states: "Safeguarding public health & safety in Australia by regulating medicines...."

2.2 **The Committee is of the firm opinion that most of the ills besetting the system of drugs regulation in India are mainly due to the skewed priorities and perceptions of CDSCO. For decades together it has been according primacy to the propagation and facilitation of the drugs industry, due to which, unfortunately, the interest of the biggest stakeholder *i.e.* the consumer has never been ensured. Taking strong exception to this continued neglect of the poor and hapless patient, the Committee recommends that the Mission Statement of CDSCO be formulated forthwith to convey in very unambiguous terms that the organization is solely meant for public health.**

2.3 The Ministry, in the status note, has stated that CDSCO, headed by the Drugs Controller General (India) [DCGI] in the Directorate General of Health Services under the Ministry of Health and Family Welfare is responsible for performing regulatory functions under the Drugs and Cosmetics Act, 1940 and Rules.

2.4 The Committee has noted that the CDSCO with its Headquarters at New Delhi has six zonal offices situated at Mumbai, Chennai, Kolkata, Ghaziabad, Hyderabad, Ahmedabad and three sub-zonal offices at Bangalore, Jammu and Chandigarh for performing certain activities in coordination with the State Drug Authorities. It has offices at 11 seaports/airports at Mumbai (sea and airport), Nhava Sheva (sea port), Kolkata (sea and airport), Chennai (sea and airport), Hyderabad (Airport), Delhi (Airport), Kochi (seaport) and Ahmedabad (airport), to regulate the import and export of drugs and cosmetics. It has six drug-testing laboratories situated at Kolkata, Mumbai, Chennai, Guwahab, Chandigarh and Hyderabad.

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2.5 The Ministry has further informed the Committee that CDSCO performs the following functions at its Headquarters:

(i) Grant of approval to manufacture and/or import of new drugs including vaccines and bio-therapeutic products after examining their safety and efficacy.

(ii) Grant of permission to conduct clinical trials.

(iii) Approval of the licenses to manufacture certain categories of drugs as Central License Approving Authority (CLAA), *i.e.*, blood banks, large volume parenterals, vaccines/sera, r-DNA derived products, in-vitro diagnostic kits for detection of HIVI & 2, HCV & HBsAg and notified medical devices.

(iv) Registration of foreign manufacturers whose products are to be imported into the country, in respect of drug formulations/Bulk drugs, Medical Devices, Blood products.

(v) Grant of licenses to import drugs in the country.

(vi) Grant of Test Licenses for import of drugs for the purpose of examination, test and analysis.

(vii) Grant of licenses to import drugs by Government hospitals or Medical Institutes for the use of their patients.

(viii) Grant of permissions for manufacture of drugs for the purpose of exports which are otherwise not permitted to be manufactured in the country.

(ix) Convening the meetings of Drugs Technical Advisory Board (DTAB) to discuss matters arising out of the administration of the D&C Act and the Rules and recommend amendments, if required.

(x) Convening the meetings of the Drugs Consultative Committee (DCC) to secure uniformity throughout India in the administration of this Act and Rules.

(xi) Coordinating the activities of the State Drug Authorities and advising them on matters relating to uniform administration of the Act and Rules in the country.

(xii) Monitoring of adverse drug reactions as a part of Pharmaco-vigilance programme.

(xiii) Recommend banning of drugs considered harmful or sub-therapeutic under Section 26A of the Drugs and Cosmetics Act.

(xiv) Clinical trial site inspections.

(xv) Conducting workshops and training programs in respect of various issues related to quality control of drugs.

2.6 The Committee noted from the background note that the zonal/sub-zonal offices perform the following functions:

- Inspection of manufacturing premises jointly with State Drug Authorities for drugs covered under the CLAA Scheme, *i.e.*, IV Fluids, large volume parenterals, vaccine & sera, blood & blood products, r-DNA products (biotech products), etc., for the purpose of grant/renewal of licenses.
- Inspection of private testing laboratories in coordination with the State Drug Inspectors for approval of these laboratories for carrying out tests on drugs/ cosmetics on behalf of the licensees.

- Inspection of manufacturing facilities of the firms for grant of WHO GMP Certification Scheme.
- Inspection of firms for capacity assessment and other provisions at the request of the Central Government.
- Inspections to investigate complaints received from various forums.
- Coordination with the State Drug Authorities to sort out problems involved in the investigations of drugs manufactured in one State and declared "Not of Standard Quality" in another State and other such matters.
- Launching of prosecutions in cases detected by the zonal offices of CDSCO.

2.7 According to the Ministry, the Airport and Seaport Offices monitor and regulate import and export of drugs and cosmetics and also draw samples for verifying the quality.

2.8 The Central Drug Testing Laboratories perform the following functions:

(i) To undertake the testing/analysis of drugs and cosmetics;

(ii) Act as an Appellate Authority for the class of drugs notified under the Act; and

(iii) Central Drug Laboratory, Kolkata maintains reference standards as per Indian Pharmacopoeia for testing of drugs.

2.9 The Ministry also stated that the activities of zonal/sub-zonal and port offices have been harmonized in a manner so as to strengthen CDSCO during the last two years. Comprehensive guidelines for harmonization of activities of zonal/sub zonal/port offices of CDSCO have been prepared and came into effect on 1.6.2011. These are available on CDSCO website.

2.10 The Committee was also informed that the following functions have been delegated to the zonal offices of CDSCO *w.e.f.* 1.6.2011.

(i) Grant of NOC for obtaining licence from State Drug Authority to manufacture drugs for examination, test and analysis purpose.

(ii) Grant of NOC for manufacture of unapproved/ approved new drugs and banned drugs for the purpose of exports.

(iii) To grant permission for import of small quantities of drugs for personal use as per Drugs and Cosmetics Rules.

(iv) NOC for import of dual use items not for medicinal use.

2.11 On a query as to how far CDSCO has been successful in carrying out its wide-ranging regulatory functions, the Ministry stated that CDSCO with limited manpower and infrastructure is carrying out functions assigned to it to the best of its capabilities. The Ministry, however, felt that to meet the aspirations of industry and other stakeholders and bringing it at the lever of developed countries, a strong, well-equipped, independent and professionally managed CDSCO is the need of the day. The pharmaceutical industry is growing at the rate of approximately 10% per year. The Ministry stated that the workload of CDSCO is increasing at the rate of approximately 20% per year while there is no corresponding rise in the manpower and infrastructure to meet the demand of the industry and discharge mandatory functions.

2.12 The Ministry, explaining about the initiatives taken to strengthen the CDSCO stated that it is being expanded to meet the requirements of the pharmaceutical industry. Two sub-zonal offices at Hyderabad and Ahmedabad have been converted into zonal offices. Three new sub-zonal offices

at Bangalore, Jammu and Chandigarh have been set up to cater to the need of the pharmaceutical industry.

2.13 It was also stated that in order to maintain quality of drugs stored at the Air Ports for import or export, pharmaceutical zones at Delhi, Hyderabad and Mumbai Air Ports are being set up for proper storage of drugs.

2.14 On being asked to comment as to whether CDSCO (Hqrs) has the requisite infrastructure, the Committee was informed that there were four Deputy Drugs Controllers and five Assistant Drugs Controllers in Headquaters. These nine officers have to handle each year the work load of approximately 20,000 applications, over 200 meetings, attending to 11,000 public/industry representatives, responding to 700 parliament questions, around 150 court cases etc. Further, these nine officers also attend the meetings of DTAB and its sub-committees, Drugs Consultative Committee, National List of Essential Medicines (NELM), prepare the guidance documents on various subjects, provide inputs for amendments of Drugs and Cosmetics Act and Rules, build up pharmacovigilance programme, train the newly recruited staff and attend any other tasks assigned by Director-General of Health Services or Ministry of Health and Family Welfare, from time to time. Each officer, thus, handles multiple responsibilities and is in charge of various sections of different technical requirements leading to their being overburdened and overstretched.

2.15 The Ministry is of the opinion that there is very poor infrastructure to handle matters like budget, recruitment, administration, and procurement. On a question as to whether there exists any effective mechanism by which the CDSCO Headquarters is in a position to co-ordinate and monitor the functioning of its zonal offices, sub-zonal offices, sea ports & airports offices and drug testing laboratories, the Ministry stated that CDSCO, at present, does not have a separate division for coordinating activities of all these offices. It is, however, proposed to have a separate division to coordinate such activities as and when the manpower is available. It was also brought to the notice of the Committee that there is a need for computer management system and video conferencing facilities for quick availability of information, creation of database and better co-ordination between the offices by linking through the networking managed by a professional agency.

2.16 Explaining about the steps taken to strengthen the manpower at CDSCO, the status of various posts sanctioned/ created/proposed has been given as under:

No. of permanent posts as on 2008	No. of new posts created in 2008 and 2009	No. of additional proposed posts
111	216	1045

2.17 The Committee noted that the permanent staff, in position, as on October, 2011 is 124 out of 327 sanctioned posts. Besides, 140 contractual staff are working at the Headquarters of the CDSCO. It was also stated that filling up of 203 vacant posts in CDSCO through UPSC, in consultation with the Ministry, was bein8 done and filling up of following posts was in process including:

- 2 posts of Joint Drugs Controller (India) *UDC(I)]* being filled up by deputation through UPSc.
- 5 posts of Deputy Drugs Controller (India) [DDC(I)] being filled up by direct recruitment through UPSc.
- 16 posts of Assistant Drugs Controller (India) [ADC(I)] being filled up by deputation through UPSc.
- 100 posts of Drug Inspectors being filed up by direct recruitment through UPSc.

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- 31 posts of Assistant Drugs Inspectors being filled up by direct recruitment through Staff Selection Commission.

2.18 In regard to appointment of medical doctors in CDSCO, the Health Secretary informed the Committee that the doctors do not wish to join CDSCO. It was further stated that though recruitment rules provide for appointing people with MBBS Degree or/with pharmacology, microbiology, but usually, there was no response from the persons from these fields.

2.19 The Committee notes with serious concern that CDSCO is substantially under-staffed. Of the 327 sanctioned posts, only 124 are occupied. At this rate, what would be the fate of 1,045 additional posts that have been proposed is a moot point. If the manpower requirement of the CDSCO does not correspond with their volume of work, naturally, such shortage of staff strains the ability of the CDSCO to discharge its assigned functions efficiently. This shortcoming needs to be addressed quickly. Consideration can also be given to employ medically qualified persons as Consultants/Advisers (on the pattern of Planning Commission) at suitable rank.

2.20 The Committee also gathers that the average time taken for the completion of recruitment process is approximately 12 to 15 months. The Committee, therefore, recommends that to overcome the staff shortage, the Ministry should engage professionally qualified persons on short-term contract or on deputation basis until the vacancies are filled up. Due to the very sensitive nature of regulatory work, great care will need to be taken to ensure that persons employed for short periods did not and will not have Conflict of Interest for a specified period.

2.21 At the same time, the optimal utilization of the current staff in the best interest of public is the responsibility of those who run the CDSCO. In a resource-constrained country like India, it is extremely difficult to meet the demands, however, genuine, of all the State entities in full. Hence, prioritization is the key. For example, work relating to an application for Marketing Approval of a New Drug that will be used by millions and thus have an impact on the well being of public at large in India for years to come, is far more important and urgent than giving permission to a foreign company to conduct clinical trials on an untested new patented, monopoly drug.

2.22 The Committee also observes that the strengthening of drugs regulatory mechanisms cannot be achieved by manpower augmentation alone. A host of issues involving capacity-building of CDSCO like upgradation of existing offices, setting up of new offices, creation of new central drugs testing laboratories and equipping them with the state-of-the-art technology to enable them to carry out sophisticated analysis of drugs, upgradation of the existing 6 Central Drugs Testing Laboratories, skill development of the regulatory officials, implementation of an effective result-oriented pharmacovigilance programme drawing on global experience, increased transparency in decision-making of CDSCO etc. will have to be addressed before the desired objectives are realized.

2.23 In the absence of any reasons for unwillingness on the part of medically qualified persons to join CDSCO, the Committee is of the opinion that emoluments and perquisites may not be the main or only reason. It is noticed that minimum prescribed academic qualifications for the post of DCGI is barely B.Pharm. On the other hand for Deputy Drugs Controller (DDC), the prescribed minimum qualification is post-graduation for medically qualified persons. The stumbling block is the requirement that DCGI should have experience in the "manufacture or testing of drugs or enforcement of the provisions of the Drugs and Cosmetic Act for a minimum period of five years." This requirement virtually excludes even highly qualified medical doctors from occupying the post of DCGI. Moreover

the rule stipulates that doctors with post-graduation should be either in pharmacology or microbiology only, thus excluding post-graduates, even doctorates (like DM) in a clinical subject. Besides, highly qualified medical doctors may be reluctant to work under and report to a higher officer with lesser qualifications in a technology driven regulatory authority set-up. Unless these concerns are addressed, it would be difficult to get the desperately required medically qualified professionals on the rolls of CDSCO.

3. Qualification and Powers of DCGI

3.1 The drug sector has two distinct manifestations nowadays. On one hand, drugs development and manufacturing is a very capital intensive and long term affair, on the other, the end product is to be made available to a multitude of very differently placed people so as to ensure their health and well being. In such a peculiar situation, the role of the drugs regulator has undoubtedly assumed critical significance. S/he has to be an outstanding professional of proven merit and standing who ensures that the massive investment compulsions of the drugs industry never outweigh the public health interests. With this aim in mind, the Committee went into details of qualifications and experience of Heads of National Drugs Regulatory Authorities of United States and United Kingdom.

3.2 The Commissioner of United States Food and Drugs Administration (USFDA) is an experienced medical doctor, scientist, and public health specialist. After doing medical course at Harvard Medical School, she conducted research on neuroscience at Rockefeller University, studied neuron pharmacology at the National Institute of Mental Health, and later focused on AIDS research as an Assistant Director of the National Institute of Allergy and Infectious Diseases. In 1994, she became one of the youngest persons ever elected to the Institute of Medicine. In 1997, at the request of the then President of USA, she accepted the position of Assistant Secretary for Policy and Evaluation in the U.S. Department of Health and Human Services (HHS) before taking over as chief of USFDA.

3.3 The Committee also noted that the current Chief Executive of the British Medicine and Healthcare Regulatory Authority (MHRA) is a professor qualified in medicine from Cambridge, followed by post-graduation and epidemiological training at Harvard School of Public Health in the United States. He then taught as Senior Lecturer in Clinical Pharmacology at Leicester University. His clinical and research interests have been in coronary heart disease. He was the Regional Director of Research and Development, National Health Service Executive, Trent. Before taking up the current position in MHRA, he was the Director, NHS Health Technology Assessment Program.

3.4 Compared to the above, the academic qualifications of the Licensing Authority (*i.e.* Drugs Controller General, India) are specified in Rule 49A and 50A of the Drugs and Cosmetic Rules. As per these Rules, the Licensing Authority (DCGI) should be (a) a graduate in pharmacy or pharmaceutical chemistry (B.Pharm) or (b) a graduate in medicine with specialization (post-graduation) in clinical pharmacology or microbiology (MD) with five years' experience.

3.5 The Ministry informed the Committee that the Mashelkar Committee, 2003, had recommended for providing financial power to the DCGI at par with heads of CSIR and ICMR. The specific observation of the Mashelkar Committee is that the functions of CDSCO involve considerable sourcing of expertise from external experts and institutions. It is necessary that such consultations are managed speedily, since drug regulatory activities are very time-sensitive. This would require provision of sufficient funds at the disposal of DCGI to mitke payments of honorarium and travel expenses without delay, as per the systems available with CSIR and ICMR

3.6 **The Committee fails to understand as to how a graduate in pharmacy or pharmaceutical chemistry (B.Pharm) is being equated with a medical graduate with MD in**

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Pharmacology or Microbiology. Apart from the obvious anomaly, with rapid progress in pharmaceutical and biopharmaceutical fields, there is urgent need to revise the qualifications and experience as minimum eligibility criteria for appointment as DCGI. The Committee is of the view that it is not very rational to give powers to a graduate in pharmacy, who does not have any clinical or research experience to decide the kinds of drugs that can be prescribed by super specialists in clinical medicine such as those holding DM and PhD qualifications and vast experience in the practice of medicine and even research.

3.7 **On a larger plane, the Committee is disillusioned with the qualifications provided in the age old Rules for the head of a crucial authority like CDSCO. The extant Indian system is nowhere in so far as sheer competence and professional qualifications are concerned when compared with countries like USA and UK. There is, therefore, an urgent need to review the qualifications, procedure of selection and appointment, tenure, emoluments, allowances and powers, both administrative and financial of the DCGI. While doing so, the Government may not only rely on the Mashelkar Committee Report which recommended augmented financial powers to DCGI but also take cue from similar mechanisms functioning in some of the developed countries like USA, UK, Canada, etc. in order to ensure that only the best professional occupies this onerous responsibility. The Committee should be kept informed of the steps taken to address this issue.**

3.8 **In the considered opinion of the Committee, there can never be a more opportune time than now, to usher in these changes recommended by it. The post of DCGI is vacant as of now, with an official holding temporary charge. They, therefore, desire that the Government should take immediate measures in terms of their instant recommendations to ensure that CDSCO is headed by an eminent and professionally qualified person.**

4. Role of the State Drug Regulatory Authorities

4.1 In reply to a query, the Ministry has informed the Committee that the condition of state drugs regulatory systems is a matter of serious concern. The Committee was informed that in order to make the State Governments appreciate their responsibilities and obligations and for strengthening their licensing and enforcement apparatus, the issue was discussed in the 39th meeting of the Drugs Consultative Committee held on 10 December, 2008 and in the Conference of the State Health Ministers and Health Secretaries held at Hyderabad from 11 to 13 January, 2011. One of the key resolutions adopted in the aforesaid Conference was that the Centre and State Governments should draw up a time-bound action plan for creation of new posts and filling up of vacant posts mainly of Drugs Inspectors and upgradation of Drugs Testing Laboratories.

4.2 The Ministry also informed the Committee that the Mashelkar Committee in 2003 had recommended one drugs inspector per 50 manufacturing units and one drugs inspector per 200 sales/distribution outlets for effective implementation of functions assigned to them. It was also informed that there were approximately 600,000 retail sales outlets and around 10,500 manufacturing units in the country, which, require just over 3,200 Drugs Inspectors. However, in reality, there were only 846 Drugs Inspectors in place against 1,349 sanctioned posts in States. Hence, the main problem faced by the States Drug Authorities was inadequate infrastructure, shortage of drugs inspectors, non-existence of data bank and accurate information, non-uniformity of enforcement among the states and lack of pro-active interaction between the States particularly, in connection with investigations relating to drugs found 'Not of Standard Quality'.

4.3 The Committee, during the visit to Bangalore, had interaction with the representatives of the State Drugs Control Department. The Committee was informed that the Department had three wings, *viz.*, Enforcement Wing, Drugs Testing Laboratory and Education in Pharmacy. At present,

the sanctioned strength of the Department was 702 out of which 408 posts were filled. The Committee was apprised of the various challenges facing it, *viz.,* inadequate staff for enforcement as well as for the laboratories.

4.4 The Committee was informed that a request had been made to Karnataka Public Service Commission for recruitment of 10 Drugs Inspectors and proposal had been submitted to the Government for creation of 430 posts, which included posts of Drugs Inspectors. Besides, there was need for adequate funds for construction of infrastructure and for procurement of necessary equipment/books.

4.5 **From an analysis of the above facts, the Committee concludes that shortcomings witnessed in respect of coordination with and between the States as also in implementation of applicable legislations in the States are primarily an offshoot of inadequacies in manpower and infrastructure in the States. Strengthening the regulatory mechanism in the States will remain a far cry unless these infirmities are taken care of.**

4.6 **Given the lack of adequate resources in the States it would be unrealistic to expect them to improve the infrastructure and increase manpower without Central Assistance for strengthening drug control system. The Committee, therefore, recommends that the Ministry of Health and Family Welfare should work out a fully centrally sponsored scheme for the purpose so that the State Drug Regulatory Authorities do not continue to suffer from lack of infrastructure and manpower anymore. The Committee desires to be kept apprised of the initiatives taken by the Ministry in this regard.**

4.7 **It is a matter of grave concern that there are serious shortcomings in Centre- State coordination in the implementation of Drugs & Cosmetics Act and Rules. This, the Committee notes, is despite the Ministry's own admission that Section 33P of the Drugs and Cosmetics Act contains a provision that enables the Central Government to give such directions to any State Government as may appear to it to be necessary for implementation of any of the provisions of the Drugs and Cosmetics Act and Rules made thereunder. The Committee understands that these provisions are meant to be used sparingly. However, there have been several situations which warrant intervention through Rule 33 P. Therefore the Committee hopes that in future the Ministry would not be found wanting in considering the option of using Section 33P to ensure that provisions of central drug acts are implemented uniformly in all States.**

4.8 **As regards lack of databank and accurate information, the Committee would like to observe that given the information technology resources currently available, developing an effective system of coordination amongst State Drug Authorities for providing quality and accurate data could have been accomplished long back had the Ministry taken any initiative towards encouraging the States to establish a system of harmonized and inter-connected databanks. Evidently, no serious efforts seem to have been made in this regard. The Committee, however, expects that the Ministry would, at least now, play a more pro-active role in encouraging the States to employ modern information technology in the implementation of tasks assigned to them. At the same time a centralized databank (*e.g.* licenses issued, cancelled, list of sub-standard drugs, prosecutions etc.) may be created to which all the State Drug Authorities should be linked.**

5. **Capacity-building of Central and State Drug Testing Laboratories**

5.1 The Committee was informed that the Central Drug Testing Laboratory, Hyderabad was yet to be equipped and the other five Central Drug Testing Laboratories at Kolkata, Mumbai, Chennai, Guwahati, and Chandigarh were reasonably equipped but not fully equipped and required

upgradation with the state-of-the-art facilities for testing/analyzing complex formulations and detect spurious, misbranded, sub-standard and adulterated drugs. The Ministry has indicated that up-gradation of the Central Drug Testing Laboratories would require 442 additional posts and augmentation of their infrastructure on a large scale. The present drug testing capacity of the six laboratories is 8,000 samples per annum, which is targeted to be increased to 24,000 samples per annum.

5.2 As per information furnished, there are 160 Drugs Testing Laboratories in the approved private and Government sectors in various States. The State Drugs Testing Laboratories test statutory samples from the Drugs Inspectors of the respective State Drugs Control Departments.

5.3 The Ministry informed the Committee that the private Drug Testing Laboratories test the samples on behalf of manufacturers who do not have their own testing and analysis facilities as the manufacturers are required to test the final product before releasing it into the market either at their own laboratory or private approved testing laboratory. These Drug Testing Laboratories are approved and monitored/ inspected by the State Drug Authorities.

5.4 The State Governments or State Drug Authorities are expected to undertake the assessment of State Drugs Testing Laboratories with respect to the compliance of Good Laboratory Practices (GLP).

5.5 It has been admitted by the Ministry that the State Drugs Testing Laboratories are not fully equipped with adequate manpower and infrastructure.

5.6 The Committee, during the visit to Chennai undertook a visit to Central Drug Testing Laboratory and State Drug Testing Laboratory. The Central Laboratory has a total sanctioned staff of 33, out of which 29 were filled up and 4 vacancies were in the process of being filled up. The Committee was informed that this Laboratory needs a 5 storeyed building with 10,000 sq.ft., in each floor.

5.7 The Committee was informed that the Tamil Nadu Drugs Control Administration had a sanctioned strength of 337, out of which 203 were in position and 134 were vacant. The State testing laboratory was having only two HPLC systems bought more than a decade ago that had become obsolete. Hence there was a need for enhancement of facilities to keep up with the increased number of tests.

5.8 The Committee, during its visit to Chennai, also held discussions with the representatives of pharmaceutical industry. The representatives felt that there was need to provide more funds for upgradation of drug testing laboratories and more training for staff of Government Laboratory for proper analysis of samples. Other measures suggested by them included opening of 5 additional laboratories, need for more Appellant Laboratories in all zones in addition to the one located at Kolkata.

5.9 The representatives of the Ministry informed the Committee that the Government was planning upgradation of all Government Laboratories in the country and had proposed a massive investment in the Twelfth Plan proposals sent to the Planning Commission. As regards the issue of more appellate laboratories, the Ministry was examining the matter.

5.10 The Committee, during its visit to Bangalore, undertook a visit to Biocon Ltd., a pharmaceutical manufacturer. This in-house Testing Laboratory is approved by the Drug Authorities and tests samples from various plants belonging to the Biocon Group of Companies and also undertakes testing of samples upon customer request.

5.11 **The Committee agrees that the capacity-building of the Central Drugs Testing Laboratories is the need of the hour. In this era of newer innovations coming up at rapid**

pace, equipping the Drug Testing Laboratories with the high-end sophisticated equipments is very essential. However, the Committee is aware that monitoring the quality of drugs is primarily the responsibility of the State Drugs Authorities, supplemented by CDSCO, which play a major role in collection of samples and testing them. Without manpower augmentation and upgradation of State Drugs Testing Laboratories, the objective of ensuring availability of quality drugs to the public cannot be realized. The Committee, therefore, recommends strengthening of both Central and State Drug Testing Laboratories.

6. Provision of requisite infrastructure at Airport and Seaport Offices

6.1 The CDSCO has eleven airport and seaport offices. During its visit to Chennai-Bangalore-Coonoor from 1 to 5 November, 2011, the Committee interacted with the authorities at Air Cargo Complex, Chennai to understand the systems and procedures followed by Assistant Drugs Controller's Office to facilitate processing of pharmaceutical imports and exports. Subsequently, Airports Authority of India, in a written submission, informed that the freight forwarders/shippers were required to bring the cargo requiring cold storage facility through refrigerated trucks only at Air Cargo complex to avoid spoilage of the contents of such cargo. The custodians at air cargo complexes were required to provide necessary infrastructure for the temperature sensitive cargo, at all stages, and ensure timely and proper handling of such cargo whilst in their custody. It was further stated that the role of the airlines was of paramount importance when the cargo stands released from the custodian and is to be uploaded to the connected flight. It was pointed out that the grey area was on the apron of the Airport where the incoming/outgoing cargo was often under the scorching sun for few hours by the airlines before loading of the same on their planes. It was suggested that the cooled dollies and thermal blankets could be pressed into service on the apron side by the airlines to provide requisite care to pharmaceutical products, thereby avoiding the deterioration/decay of the inside contents or potency of the vaccines/drugs/medicines etc.

6.2 **The Committee agrees with the above suggestion and recommends that the Ministry of Health and Family Welfare should take initiative towards addressing the shortcomings forthwith in coordination with the Ministry of Civil Aviation at all seaports/airports handling import and exports of pharmaceutical products. The Committee will like to be informed of steps taken to address this problem.**

7. New Drugs Approval

7.1 One of the most sensitive responsibilities of the CDSCO is to approve new drugs for marketing (both manufacture and import) in the country as empowered by and in compliance with Rule 122 and Schedule Y of the Drugs and Cosmetics Rules 1945.

7.2 The Committee was informed that currently the work involved in approval of New Drugs, including biologicals was being handled by 25 regular staff assisted by 25 contractual technical staff.

7.3 It was also stated that for smooth functioning of New Drugs Division, minimum additional staff required was three Deputy Drugs Controllers (I), 11 Assistant Drugs Controllers (I) and 31 Drugs Inspectors. One each of Biostatistician, Clinical Pharmacologist, Biochemist was also required, on a regular basis, for assisting in scrutiny of New Drugs applications. It was further stated that New Drugs Division was further required to be assisted by 12 Experts Committees to advise on various scientific issues of new drugs. For examination of applications of medical devices, at least, six Expert Committees were required. Apart from this, the New Drugs Division also required a state-of-the-art file storage system as it had voluminous technical data, a proper archival and retrieval system and creation of database in electronic format.

7.4 When asked as to the number of applications for import and manufacture of new drugs received by the New Drugs Division every year, and the time schedule prescribed for disposal of applications, it was stated that on an average (year 2005-2009), approximately, 1,600 applications of various categories of new drugs, including biologicals are received in a year.

7.5 These applications include New Drugs to be introduced for the first time in the country, subsequent applications of new drugs already approved by CDSCO, modified or new claims of approved drugs, namely, indications, dosage forms, etc., and new Fixed-Dose Combinations (FDCs) of two or more drugs.

7.6 It was stated that there are no statutory time lines prescribed for processing of new drug applications under Drugs and Cosmetics Act and Rules. The Committee was informed that the CDSCO had set 45 days as the deadline for the first response. No time schedule for final disposal is prescribed as it may vary from drug to drug (consultation with experts, if required, review of clinical trials etc.) and adequacy of the data furnished by the applicant.

7.7 The Committee was informed that there was no permanent panel of medical experts attached with the CDSCO. However, two Expert Committees, namely, Investigational New Drug (IND) Committee and Cellular Biology-based Therapeutic Drug Evaluation Committee had been set up by the Ministry of Health and Family Welfare for advice to DCG (I). Apart from this, experts from subject specialties are identified from time to time amongst the medical specialists from institutes like PGI, Chandigarh; AIIMS; ICMR; KEM Hospital, Mumbai; CMC, Veil ore, etc., as well as individual practicing clinicians for their expert opinion.

7.8 Explaining about the different stages of approval of new drugs, the Ministry stated that applications of new drugs are examined as per provisions of Schedule Y of Drugs and Cosmetics Rules. The different stages of approval of new drugs, including vaccines, are as under:

- Examination of the application in respect of the following documents:
  - Application in Form 44, *i.e.* Fee and Chemistry-Manufacturing-Control (CMC) data;
  - Data submitted in respect of chemical, toxicological, pharmacological, clinical and other documents.
- In case of incomplete application, the applicant is asked to provide requisite data;
- Examination of the complete data as submitted by the firm;
- Consultation of the expert, wherever considered necessary;
- Testing of sample of new drugs (bulk/imported formulation) at Central Drugs Laboratories;
- Review of the essentiality of clinical trial in the country;
- In case clinical trial is considered necessary, the applicant is requested to furnish clinical trial protocol. However, for drugs indicated in life threatening/serious disease, or diseases of special relevance to the Indian health scenario, the toxicological and clinical data requirement may be abbreviated, deferred or omitted;
- If protocols of clinical trial are found in order, permission for clinical trial is granted;
- Clinical trial reports submitted by the firm after completion of the trial are examined and, if required, opinion of the experts is solicited;
- The applicant may then be asked for technical presentation on the drugs;

- If the application is complete in all respects, permission/approval is granted;
- In case of Investigational New Drug, the proposal, starting from the clinical trial application stage, is referred to IND Committee and decision to approve or otherwise is taken as per recommendation of the Committee.

7.9 The Ministry further stated that in order to ensure the adherence to the guidelines and regulatory requirements, the new drugs applications are examined/reviewed, through a channel of submissions as follows:

Technical Data Associates/Technical Officer/Drugs Inspectors/Asstt. Drugs Controller (I)/Dy. Drugs Controller (I)/DCGI.

7.10 Briefly the statutory rules require that apart from submitting specified documentation (pharmacology, toxicology, animal studies, overseas clinical trials etc.), the applicant for New Drugs discovered outside India should conduct Phase-III trials on not less than 100 patients at 3-4 different hospitals in India to test the efficacy and safety of new drugs for proposed indication(s). The basic purpose of Phase III trials is to determine if there are any ethnic differences that can alter the metabolism, efficacy and safety of the drug when administered to patients of different ethnicities living in India (such as Indo-Aryans, Dravidians, Mongoloids, Tribals etc.). There is evidence that the effect of some drugs can vary among various ethnic groups. For example, the blood levels reached after intake of lipid lowering agent rosuvastatin are far higher in Asians, compared to Europeans and North American Caucasians, Hispanics and Blacks needing lowering of dosage. Failure to lower dose in Indians can result in severe toxicity, including life-threatening muscle injury leading to fatalities. Hence, testing drugs in the Indian ethnic groups is of paramount importance before approving any drug of foreign origin.

7.11 In order to scrutinize new drug approvals, the Committee sought details [sponsors; pre-approval Phase III clinical trials; overseas regulatory status in US, Canada, Britain, Australia and European Union; indications; names of experts if consulted and Post-Marketing Safety Update Reports (PSURs)] in respect of randomly selected 42 medicines from the list of new drugs uploaded by CDSCO on its website. Of these, 38 drugs were approved in the years 2004 to August 31, 2010; one drug had been approved earlier in 2001. Three drugs had been approved earlier in mid 90s. In all DCGI had approved 2,167 drugs in the period January 2001 to 30-11-2010. Thus the sample size for random scrutiny was less than 2 percent.

7.12 Out of 42 drugs picked up randomly for scrutiny, the Ministry could not provide any documents on three drugs (pefloxacin, lomefloxacin and sparfloxacin) on the grounds that files were non-traceable. All these drugs had been approved on different dates and different years creating doubt if disappearance was accidental. Strangely, all these cases also happened to be controversial drugs; one was never marketed in US, Canada, Britain, Australia and other countries with well developed regulatory systems while the other two were discontinued later on. In India, all the three drugs are currently being sold. It is not possible to monitor if manufacturers are abiding by the conditions of approval *viz.* indications, dosage, contra-indications, precautions etc. Updation of product monographs and safety information in the light of recent developments is also not possible putting patients at risk. Before being withdrawn, major changes in safety profile, includirlg Black Box Warnings (meant to draw attention to serious side effects), were incorporated to the prescribing guidelines of the two drugs sold in the United States but later withdrawn from the market.

7.13 **The Committee is of the view that due to untraceable files on three drugs, it is not possible to determine if all conditions of approval (indications, dosage, safety precautions) are being followed or not. Moreover the product monographs cannot be updated in the light of recent developments and regulatory changes overseas. Therefore all the missing files should be re-constructed, reviewed and monographs updated at the earliest.**

7.14 On scrutiny of 39 drugs on which information was available, the Committee found the following shortcomings:

- In the case of 11 drugs (28%) Phase III clinical trials mandated by Rules were not conducted. These drugs are (i) Everolimus (Novartis), (ii) Colistimethate (Cipla), (iii) Exemestane (Pharmacia), (iv) Buclizine (UCB), (v) Pemetrexid (Eli Lilly), (vi) Aliskiren (Novartis), vii. Pentosan (West Coast), (viii) Ambrisentan (GlaxoSmithKline), (ix) Ademetionine (Akums), (x) Pirfenidone (Cipla), and (xi) FDC of Pregabalin, Methylcobolamine, Alpha Lipoic Acid, Pyridoxine & Folic Acid (Theon);
- In the case of 2 drugs (Dronedarone of Sanofi and Aliskiran of Novartis), clinical trials were conducted on just 21 and 46 patients respectively as against the statutory requirement of at least 100 patients;
- In one case (Irsogladine of Macleods), trials were conducted at just two hospitals as against legal requirement of 3-4 sites;
- In the case of 4 drugs (10%) (Everolimus of Novartis; Buclizine of UCB; Pemetexid of Eli Lilly and FDC of Pregabalin with other agents), not only mandatory Phase III clinical trials were not conducted but even the opinion of experts was not sought. The decision to approve these drugs was taken solely by the non-medical staff of CDSCO on their own.
- Of the cases scrutinized, there were 13 drugs (33%) which did not have permission for sale in any of the major developed countries (United States, Canada, Britain, European Union nations and Australia). None of these drugs have any special or specific relevance to the medical needs of India. These drugs are: (i) Buclizine for appetite stimulation (UCB); ii. Nimesulide injection (Panacea); (iii) Doxofylline (Mars) (iv) FDC of Nimesulide with Levocetirizine (Panacea); (v) FDC of Pregabalin with other agents (Theon); (vi) FDC of Tolperisone with Paracetamol (Themis); (vii) FDC of Etodolac with Paracetamol (FDC); (viii) FDC of Aceclofenac with Thiocolchicoside (Ravenbhel); (ix) FDC of Ofloxacin with Ornidazole (Venus), (x) FDC of Aceclofenac with Drotaverine (Themis); (xi) FDC of Clucosamine with Ibuprofen (Centaur); (xii) FDC of Diclofenac with Serratiopeptidase (Emcure) and (xiii) FDC of Gemifloxacin with Ambroxol (Hetero).
- In the case of 25 drugs (64%), opinion of medically qualified experts was not obtained before approval.
- In those cases (14 out of 39 drugs), where expert opinion was sought, the number of experts consulted was generally 3 to 4, though in isolated cases the number was more. In a country where some 700,000 doctors of modern medicine are in practice such a miniscule number of opinions are hardly adequate to get diverse views and come to a well considered rational decision apart from the possibility of manipulation by interested parties. As against this, to review just the dose of popular pain-killer paracetamol, the United States Food and Drug Administration (USFDA) constituted a panel of 37 experts drawn from all over the country. After extensive debate 20 members sought ban on the combination of paracetamol with narcotics (17 opposed), 24 members sought reduction of dose from 500mg to 325mg (13 opposed) and 26 members advised to make high dose (1000mg) formulation a prescription only medicine (11 opposed). The voting pattern shows independent application of mind by each member. The opinions and decisions are in public domain (website of USFDA) so that anyone is free to scrutinize, offer comments and give suggestions. In India, every discussion and document is confidential away from public scrutiny. **This**

matter needs to be reviewed to ensure safety of patients, fair play, transparency and accountability.

7.15 **Unless there is some legal hitch, the Committee is of the view that there is no justification in withholding opinions of experts on matters that affect the safety of patients from public. Consideration should be given to upload all opinions on CDSCO website.**

7.16 **According to information provided by the Ministry, a total of 31 new drugs were approved in the period January, 2008 to October, 2010 without conducting clinical trials on Indian patients. The figure is understated because two drugs (ademetionine and FDC of pregabalin with other ingredients) were somehow not included in the list. Thus there is no scientific evidence to show that these 33 drugs are really effective and safe in Indian patients.**

7.17 The Ministry explained that under the rules, DCGI has the power to approve drugs without clinical trials in "Public Interest." No explanation is available as to what constitutes Public Interest. How can approvals given to foreign drugs without testing on Indians be in Public Interest? Some of the reasons given for irregular approvals are: "Serious disease" (all the more reason to conduct clinical trials to ensure that patients in India really benefit from such imported, exorbitantly expensive drugs), "Rare disease status according to United States Food and Drugs Administration" (How can USFDA decide which is rare disease in India?), "Orphan drug status in Europe and USA" (There is no provision in Indian laws to give special treatment to such foreign drugs).

7.18 When asked about the reasons for approving New Drugs without clinical trials, the Health Secretary, during the course of oral evidence, stated that approval of new drugs without Phase-III clinical trials in "public interest" was being done with the support of technical advice. Explaining about the basis for deciding to waive off the condition of local clinical trials for manufacture/ import of new drugs, the Ministry stated that the Drugs and Cosmetics Rules do not prescribe specific situation under which clinical trial exemption can be granted due to "public interest". However, the DCGI can abbreviate, defer or omit the toxicological and clinical data requirements for drugs meant for life-threatening/serious diseases and diseases of special relevance to Indian health scenario. It was further claimed that in such cases status of regulatory approval of the said drug in other countries and opinion from the medical specialists of the relevant field is obtained for taking decision. Further, the marketing approval is conditional to applicants submitting post-marketing surveillance data.

7.19 In cases where foreign drugs were approved without clinical trials in the country, the Ministry offered the following explanation: *"Most of the drugs are approved in other countries based on multinational clinical trials.... on various ethnic/racial populations"* implying that Indians would be included and hence conducting trials in India was not necessary. However, this presumptive remark is not accompanied by any evidence. The interest is in those ethnicities that live in India, not Slavs, Caucasians, Hispanics and Negroes. The information in the Status Note on the very first drug of a total of 31 in the list of new drugs permitted in "public interest" without clinical trials, daptomycin, shows that pre-approval studies conducted by the American innovator recruited just 558 patients in United States, South Africa, Europe, Australia and Israel. There is absolutely no evidence of major ethnic groups of India being enrolled in these small trials.

7.20 It would appear that the intention of those who framed the Act and Rules was to leave a small door ajar for entry of new drugs without undergoing trials in serious emergency situations such as epidemic of a new hitherto unknown disease (*e.g.* SAARS, Bird Flu or Swine flu) where there may not be time enough to test new drugs and there is no alternative but to take calculated risk. None of the 33 drugs fall in this category of emergency treatments. Besides many drugs were launched in overseas markets years ago with ample time to conduct trials in India. The following are some examples:

- Daptomycin (Cubicin) of Novartis was launched overseas on 13-9-2003 and approved in India on 28-1-2008 after a gap of over four years. There was no tearing hurry to approve the drug without trials.
- Pemetrexed (Alimta) of Eli Lilly was approved on 5-2-2004 in the United States. After a gap of more than two years, it was approved by DCGI on 28-6-2006 without trials. There was more than adequate time to conduct Phase III trials in India and yet undue favour was shown to the manufacturer.
- Raltegravir (Isentress) of Merk Sharp and Dhome was launched abroad on 12-10-2007 and approved in India on 27-01-2010 without conducting clinical trials even though there was adequate time to conduct mandatory clinical trials.

7.21 Such irregular approvals spare drug producers the cost and efforts but put Indian patients at risk. On an average DCGI is approving one drug every month without trials. This cannot be in public interest by any stretch of imagination. Moreover it was stated that in such cases (i) expert opinion is sought and (ii) Post-Marketing Surveillance Data is mandatory.

- However a look at the information on approvals given by DCGI shows that expert opinion was sought in only 5 of 33 such out-of-the-way approvals.
- With regard to Post-Marketing Surveillance data, the Ministry failed to provide even one out of randomly selected 4 drugs approved without trials.

7.22 As stated earlier, the very purpose of Phase III trials is to determine any ethnic/racial differences in the safety, efficacy and metabolism of drugs. Henee to serve any useful purpose, patients of different ethnicities living in India should be enrolled. For example, the results of a trial conducted only on Indo-Aryans may not be applicable to Mongoloids or Dravidians due to genetic differences.

7.23 In response to a question as to how various ethnic groups are being enrolled in Phase III clinical trials, the Committee was informed that *"most trials were taking place in cosmopolitan towns. It* is *understood that cosmopolitan cities have a heterogeneous population comprising various ethnic groups. Otherwise there* is *no proactive, specific procedure to test new drugs on different ethnic groups."*

7.24 However, a scrutiny of randomly selected trial sites shows that the Ministry's submission is incorrect and the basic purpose of Phase III trials, even when conducted, is not being served. The following are some illustrative examples:

- A trial (rifaximin) took place at Kota, Jaipur and Mumbai. Kota and Jaipur can hardly be classified cosmopolitan in demography.
- Another trial (doxofylline) took place just in Hyderabad and Aurangabad. Aurangabad certainly is not a cosmopolitan city.
- Sites of another trial (ramosetran) were limited to Betul, Indore and Bhopal (all in Madhya Pradesh) and Vadodara (Gujarat). None of them is a cosmopolitan town.
- Trial on FDC of etodolac with paracetamol was conducted just in Maharashtra (Nagpur, Pune and Mumbai).
- Trials on another FDC of aceclofenac with drotaverine were conducted only in Maharashtra (Aurangabad, Pune and Mumbai).
- In the case of FDC of diclofenac with serratiopeptidase (India being the sole country in the world to have approved such a combination), though trials were held at 8 sites

but 6 of them were in Pune alone and 2 in Mumbai; all of them by private practitioners.

7.25 Even if a handful of individuals of different ethnic origins were residing in the towns/cities listed above, the chances of their being patients and then recruitment into clinical trials were remote.

7.26 On the other hand an analysis of 164 randomly selected sites of pre-approval drug trials shows that only one site was located in Guwahati, where one can find adequate number of patients of Mongoloid origin since many of them also come from other North East states for treatment.

7.27 **It is obvious that DCGI clears sites of pre-approval trials without application of mind to ensure that major ethnic groups are enrolled in trials to have any meaningful data. Thus such trials do not produce any useful data and merely serve to complete the formality of documentation.**

7.28 **The Committee recommends that while approving Phase III clinical trials, the DCGI should ensure that subject to availability of facilities, such trials are spread across the country so as to cover patients from major ethnic backgrounds and ensure a truly representative sample. Besides, trials should be conducted in well equipped medical colleges and large hospitals with round the clock emergency services to handle unexpected serious side effects and with expertise in research and not in private clinics given the presence of well equipped medical colleges and hospitals in most parts of the country in present times.**

7.29 **The Committee is of the view that taking into account the size of our population and the enormous diversity of ethnic groups there is an urgent need to increase the minimum number of subjects that ought to be included in Phase III pre-approval clinical trials to determine safety and efficacy of New Drugs before marketing permission is granted. In most western countries the required numbers run into thousands. However since the major objective in India is to determine the applicability or otherwise of the data generated overseas to Indian population, the requirement should be re-assessed and revised as per principles of medical statistics so that major ethnic groups are covered. A corresponding increase in the number of sites so as to ensure a truly representative sample spread should also be laid down in black and white. Furthermore, it should be ensured that sites selected for clinical trials are able to enroll diverse ethnic groups. For domestically discovered drugs, the number of subjects should be revised as well. This can be easily achieved by changes in the Good Clinical Practice (GCP) guidelines.**

7.30 The Committee was informed that while taking decision on new drugs opinion of independent experts is obtained whenever considered necessary by CDSCO. The Committee scrutinized some random cases to assess the credibility and utility of such opinions.

7.31 **A review of the opinions submitted by the experts on various drugs shows that an overwhelming majority are recommendations based on personal perception without giving any hard scientific evidence or data. Such opinions are of extremely limited value and merely a formality. Still worse, there is adequate documentary evidence to come to the conclusion that many opinions were actually written by the invisible hands of drug manufacturers and experts merely obliged by putting their signatures.** The Committee observed the following facts on scrutiny of opinions:

- In the case of clevudine (of Phamasset Inc.), three experts (a Professor of Medicine of All India Institute of Medical Sciences, New Delhi; a Professor of Medicine of K. B. N. Medical College, Gulbarga; a Professor of Medicine of R. G. Kar Medical College, Kolkata) located at different places thousands of miles apart from each other

sent word to word identical letters of recommendation. In addition all of them went out of the way and gave unsolicited advice, in identical language, to the DCGI to give permission to the company to market the drug without conducting mandatory clinical trials in India **(Annexure 1).**

- In case of sertindole (Serdolect of Lundbeck), an anti-psychotic drug, three experts located at three different places (a Professor and Head of the Department of Psychiatry of Stanley Medical College, Chennai; Professor of SKP Psychiatric Nursing Home, Ahmedabad and a Professor and Head of the Department of Psychiatry of LTM Medical College, Mumbai) wrote letters of recommendation in nearly word-to-word, identical language and not surprisingly all of them used the incorrect full form of DCGI in the address! Is such a coincidence possible unless the person behind the scene who actually drafted the letters is one and the same person? **(Annexure 2).**

- In the case of doxofylline, an anti-asthmatic, two opinions (from Professor of Medicine of M. G. M. Medical College, Indore and Consultant, Indraprastha Apollo Hospital, New Delhi) are exactly, word-to-word identical. **(Annexure 3).**

- The three opinions (from Professor of Orthopaedics, All India Institute of Medical Sciences, New Delhi; Consultant at Dayanand Medical College, Ludhiana and Professor of Orthopaedics, St. Johns Medical College, Bangalore) on rivaroxaban (Bayer) a drug for prevention of clotting are merely ditto copies of each other. **(Annexure 4).**

- In case of ademetionine, all four letters of recommendation (from Professor of the Department of Gastroenterology, Lokmanya Tilak Medical College, Mumbai and Professor of Gastroenterology, Medical College, Thiruvananthapuram; Professor and Head of the Digestive and Liver Diseases, IPGMER, Kolkata; Chairman and Chief of Hepatology Services, Sir Ganga Ram Hospital, New Delhi) made similar comments; three out of four letters are undated (is it merely a coincidence?) while one is dated 11-8-2010. The letter from Asst. Drugs Controller (India) seeking expert opinion is dated 9-8-2010. It is amazing that letter dated 9th August, 2010 from New Delhi not only reached Mumbai on 11th August, 2010 but was replied the very same day, that too, after reviewing 131 of pages of scientific papers. All the four letters are addressed incorrectly though identically to "Directorate General of Health Services" without any address and without even a PIN code. None of the letters were diarized by the office of the Drugs Controller General (India) when received. The drug was approved on 1-9-2010 without Phase III clinical trials. **(Annexure 5).**

- Letters of opinion recommending approval for pirfenidone of Cipla from Professor of Pulmonary Medicine, AIIMS, New Delhi dated 19th June, 2010, Consultant Chest Physician, Lilavati Hospital Mumbai dated May 25, 2010; Additional Professor of Pulmonary Medicine, PGI Chandigarh dated 14th June, 2010; Pulmonologist of Yashoda Hospitat Secunderabad dated 12th June 2010 were all received exactly on the same day 2-7-2010 and diarized by DCGI office under consecutive references 4877, 4878, 4879 and 4880. **Is the Committee mistaken in coming to the conclusion that all these letters were collected by interested party from New Delhi, Mumbai, Chandigarh and Secunderabad and handed over to office of the DCGI on the same day? If so, it is obvious that the interested party was in the loop in the entire process of consultation with experts. (Annexure 6).**

- Letters of opinion recommending approval of dapoxetine from Professor and Head, Department of Urology, T. N. Medical College, Mumbai dated 25-3-2010; Professor

and Head, Department of Psychiatry, L. T. M. Medical College, Mumbai dated 19-3-2010; Professor and Head, Department of Urology, Calcutta National Medical College, Kolkata dated 24-2-2010 all reached the office of DCGI exactly on the same date 6th April, 2010 and were diarized under consecutive references 3667, 3668 and 3669. It is surprising that letter dated 24-2-2010 from Kolkata took more than six weeks to reach Delhi. Is it unreasonable on the part of the Committee to come to the conclusion that all these letters were conected by interested party from New Delhi, Mumbai and Kolkata and delivered to the office of DCGI on the same day? **(Annexure 7).**

- Letters of opinion recommending approval of nimesulide injection from Professor and Head, Department of Medicine, Government Medical College, Aurangabad dated 17-8-2005 and Sr. Consultant Orthopaedic Surgeon, Indraprastha Apollo Hospital, New Delhi dated 17-6-2005 reached exactly on the same day *i.e.* 23-8-2005 and were diarized under consecutive reference 3537 and 3538. **It is inconceivable that a letter dated 17-6-2005 from New Delhi will be delivered to the office of DCGI also in New Delhi after more than two months. The conclusion, as in aforementioned cases, is obvious. (Annexure 8).**

7.32 **If the above cases are not enough to prove the apparent nexus that exists between drug manufacturers and many experts whose opinion matters so much in the decision making process at the CDSCO, nothing can be more outrageous than clinical trial approval given to the Fixed Dose Combination of aceclofenac with drotaverine which is not permitted in any developed country of North America, Europe or Australia. In this case, *vide* his letter number 12-298/06-DC dated 12-2-2007, an official of CDSCO advised the manufacturer, Themis Medicare Ltd. not only to select experts but get their opinions and deliver them to the office of DCGI. No wonder that many experts gave letters of recommendation in identical language apparently drafted by the interested drug manufacturer.** These experts include:

(i) Professor and Head, Department of Pharmacology, PGI, Chandigarh.

(ii) Professor and Head, Department of Pharmacology and Clinical Pharmacology, Christian Medical College, Vellore.

(iii) Professor of Surgery, L. T. M. Medical College, Mumbai.

(iv) Professor of Medicine, Gandhi Medical College, Sccunderabad.

(v) Professor and Head of Postgraduate Department of Surgery, S. C. B. Medical College, Cuttack.

(vi) Professor of Medicine and Civil Surgeon, Gandhi Medical College, Secunderabad. **(Annexure 9).**

7.33 **In the above case, the Ministry should direct DCGI to conduct an enquiry and take appropriate action against the official(s) who gave authority to the interested party to select and obtain expert opinion and finally approved the drug.**

7.34 **Such expert opinions in identical language and/or submitted on the same day raise one question: Are the experts really selected by the staff of CDSCO as mentioned in written submission by the Ministry? If so how can they, situated thousands of miles away from each other, draft identically worded letters of recommendation? Is it not reasonable to conclude the names of experts to be consulted are actually suggested by the relevant drug manufacturers? It has been admitted that CDSCO does not have a data bank on**

experts, that there are no guidelines on how experts should be identified and approached for opinion.

7.35 **The Committee is of the view that many actions by experts listed above are clearly unethical and may be in violation of the Code of Ethics of the Medical Council of India applicable to doctors. Hence the matter should be referred to MCI for necessary follow up and action. In addition, in the case of Government-employed doctors, the matter must also be taken up with medical colleges/hospital authorities for suitable action.**

7.36 **There is sufficient evidence on record to conclude that there is collusive nexus between drug manufacturers, some functionaries of CDSCO and some medical experts.**

7.37 **On a more fundamental issue the Committee has come to the conclusion that when it comes to approving new drugs, too much is left to the absolute discretion of the CDSCO officials. There are no well laid down guidelines for determining whether consultation with experts is required. Thus the decision to seek or not to seek expert opinion on new drugs lies exclusively with the non-medical functionaries of CDSCO leaving the doors wide open to the risk of irrational and incorrect decisions with potential to harm public health apart from the possibility of abuse of arbitrary discretionary powers.**

7.38 **The Committee, therefore, strongly recommends that there should be non-discretionary, well laid down, written guidelines on the selection process of outside experts with emphasis on expertise including published research, in the specific therapeutic area or drug or class of drugs. Currently, the experts are arbitrarily chosen mainly based on their hierarchical position which does not necessarily correspond to the area or level of expertise. All experts must be made to file the Conflict of Interest declaration outlining all past and present pecuniary relationships with entities that may benefit from the recommendations given by such experts. The consulted experts should be requested to give hard evidence in support of their recommendations.**

7.39 There has been extensive adverse media coverage with allegations that many drugs have been approved unlawfully. The Committee sought comments from the Ministry on some selected cases and based on the information received and other documented sources has come to the following conclusion:

Buclizine (applicant: UCB, Belgium) was approved on 28-6-2006 for appetite stimulation without clinical trials and without consulting experts for use in children. Under the law of the land if an old drug approved for a disorder (such as allergy) is to be used for another indication (such as appetite stimulation), then it is deemed to be a New Drug and must undergo the entire procedure apphcable to New Drugs and meet all regulatory requirements. In response to the questionnaire from the Committee, the Ministry gave incorrect and misleading information. When asked whether the drug is approved in the US, Canada, Britain, European Union and Australia, instead of saying "Yes" or "No" answer to each of the specified countries, the Ministry went out of the way to volunteer incorrect information that it was approved in "Belgium, Brazil, Luxemburg, Bolivia, South Korea, Venezuela, Malaysia and others." Firstly, regulatory status in developing countries such as Bolivia, Venezuela, Malaysia is not of much help in determining the safety and efficacy of a drug [according to a survey done by the World Health Organization (WHO), only about half of 192 member states have drug controllersl Secondly, the Company's own Core Data Sheet (detailed product information document) issued from its headquarters in Belgium says: *"Because of lack of approoed clinical studies and scientific data, the benefit/risk is negative for the indication of buclizine for appetite stimulation."* Thus, buclizine is not currently approved in Belgium, the innovator country, for appetite stimulation. The correct status in other countries, even for use in allergy, is as follows:

- Brazil (discontinued for all indications),
- Bolivia (authorization not renewed in December, 2003 for all indications),
- Luxemburg (not permitted to be used as appetite stimulant),
- Malaysia (discontinued for all indications),
- South Korea (banned).

7.40 The Core Data Sheet is on record in the CDSCO files. Buclizine is just one of the many drugs that have been approved in violation of the Indian laws.

7.41 **The Committee is of the view that responsibility needs to be fixed for unlawfully approving Buclizine, a drug of hardly any consequence to public health in India, more so since it is being administered to babies/children. At the same time the approval granted should be reviewed in the light of latest scientific evidence, regulatory status in developed countries, particularly in Belgium, the country of its origin.**

7.42 Letrozole discovered by Novartis, is an anti-cancer drug for use only in post- menopausal women and is contraindicated (not permitted) to be used in women of reproductive age. If it is to be used for any other indication except breast cancer, then the drug is categorized as a New Drug under Indian laws. On 10-04-2007, DCGI approved the use of letrozole for improving female fertility. The Drugs and Cosmetic Rules require that while approving a drug for use in females of reproductive age, animal studies are to be done in this specific group. No such studies were done in India. The innovator also did not conduct such studies abroad because there was no plan to use letrozole in women of reproductive age. Under Indian rules, Phase II studies should have been conducted before Phase III since such studies were not conducted anywhere. Permission to conduct Phase III studies was given without prior Phase II studies. Phase III clinical trial was conducted on just 55 women by three doctors in private practice while the minimum requirement as per mandatory Good Clinical Practice (GCP) rules is at least 100. *After* approval, the sponsor, Sun Pharmaceuticals did not submit periodic PSURs due every six months as required by law. No action was taken against the Company in such a sensitive case since India is the only country where the drug is permitted to be used for female infertility. Post-marketing data is crucial and critical in detecting adverse effects both in women and babies born to them if they use letrozole before the onset of pregnancy. Clearly there was a serious lapse on the part of CDSCO. In the wake of media outcry, in a diversionary move, the DCGI instead of investigating the allegations of regulatory lapse and taking corrective measures referred the matter to clinical experts, DTAB etc. on the restricted issue of safety and efficacy. **DCGI is expected to take action against those CDSCO functionaries who colluded with private interests and got the drug approved in violation of laws. The drug has since been banned by the Ministry for use in female infertility.**

7.43 **The Committee takes special note of this case of gross violation of the laws of the land by the CDSCO. First, in approving the drug for use in case of female infertility and thereafter, in exhibiting overt resistance in taking timely corrective steps despite very strong reasons favouring immediate suspension of use of letrozole for the said indication. Belatedly, the drug has been banned for use in female infertility.**

7.44 **FDC of flupenthixol and melitracen (Deanxit):** Except for giving file number (12-62.95-DC) and the date of approval (28-10-1998), the Ministry failed to provide any documents and information on the regulatory process that led to its approval (such as import permission, mandatory clinical trials etc.). The combination contains two drugs, flupenthixol and melitracen. Melitracen has never been approved and used in India. Therefore under Schedule Y, Appendix VI (a), the combination is a "New Drug" for two reasons (i) because one of the two ingredients has

not been approved in the past and (ii) because all combinations (FDCs) are classified as New Drugs. CDSCO violated the rules by approving the drug on following counts;

- Drugs and Cosmetic Rule 30-B bans the import and marketing of any drug the use of which is prohibited in the country of origin. Deanxit was and continues to be prohibited for sale and use in Denmark, its country of origin. Therefore permission to import and market was given unlawfully.
- Since Melitracen was not individually approved earlier, the Combination had to undergo all phases of development (Phase I, II and III). Permission to conduct the last phase III, if given was in violation of rules.
- Before approving the indications of a New Drug, it is mandatory to conduct clinical trials individually for all the different indications. A perusal of the Marketing Approval dated 28th October, 1998 shows that the approved indications were: (i) Psychogenic depression, (ii) Depressive neuroses, (iii) Masked depression and (iv) Psychosomatic affections accompanied by anxiety and apathy. In its submission the Ministry failed to give details of trials at 3-4 sites with at least 100 patients for each indication as required by law. As per the package insert on Deanxit, the brand is being indicated and promoted for two unapproved indications *i.e.* "Menopausal depression", Dysphoria and depression in alcoholics and drug addicts." (Annexure 10). The approval letter issued to the sponsor clearly states at serial number 7: *"No claims except those mentioned above shall be made for this drug without the prior approval of this Directorate (DCGI).*

7.45 **The Committee is of the opinion that there must be some very good reasons for Danish Medicine Agency (Denmark) not to approve a domestically developed drug where an anti-depressant drug would perhaps be in greater demand as compared to India. Curiously, Deanxit is allowed to be produced and exported but not allowed to be used in Denmark.**

7.46 **The Committee feels that the DCGI should have gone into the reasons for not marketing the drug in major developed countries such as United States, Britain, Ireland, Canada, Japan, Australia just to mention a few. United States alone accounts for half of the global drug market. It is strange that the manufacturer is concentrating on tiny markets in unregulated or poorly regulated developing countries like Aruba, Bangladesh, Cyprus, Jordan, Kenya, Myanmar, Pakistan, and Trinidad instead of countries with far more patients and profits. Many of these developing countries are handicapped due to lack of competent drug regulatory authorities. Instead of examining and reversing regulatory lapses, DCGI has referred the matter to an Expert Committee to look at the isolated and restricted issue of "safety and efficacy" instead of unlawful approval in the first place.**

7.47 **The approval of this drug is in clear violation of the Drugs and Cosmetics Rules. As per Rules,** a New Drug is deemed t9 be a New Drug for four years. After four years, the State Drug Authorities have the powers to issue manufacturing licenses without reference to DCGI. Therefore, if initial approval is given unlawfully by the DCGI, the doors open for other manufacturers to market the drug after four years. This is exactly the situation with FDC of flupenthixole and melitracen. **The Committee recommends that in view of the unlawful approval granted to Deanxit, the matter should be re-visited and re-examined keeping in mind the regulatory status in well developed countries like Denmark, the country of origin; the United States, Britain, Canada, European Union and Japan etc. It is important to keep in mind that in Europe, there are two types of marketing approvals: Community-wide (cleared by European Medicine Agency) and individual regulators of member nations. EMEA is known to clear drugs after great deal of scrutiny while the competence and expertise of**

drug regulatory authorities of individual nations is not uniform and varies greatly from country to country.

7.48 **Placenta Extract:** As per Drugs and Cosmetics Rules, whenever there is either an additional formulation (such as tablets, solutions, suspensions, injections, controlled release, gels etc.) or proposal to use in additional indications, the drug is deemed to be a 'New Drug'. In violation of this clear rule, *vide* its letter number 4-97/89-DC dated 11th February, 2000, an official of the office of the Drugs Controller General (India) wrote a letter to the manufacturer that Placenta Extract was *"not a New Drug'* and gave permission to promote placenta extract *gel* [a new formulation and hence classified as a New Drug as per Rule 122E(b)] in additional indications (Burns and Wounds, Non-Healing Indolent Ulcers, Bed Sores, Mucositis etc.). By including the term *"etc."* (An unknown and unheard of terminology in the history of drug approval), loopholes were left wide open to add other indications. Thus CDSCO went out of the way to unlawfully and wrongly certify, in black and white, that the drug was *"not* a New Drug" thus helping the manufacturer to market an additional formulation for additional indications.

The manufacturer's letter dated 7th February, 2000 from Kolkata reached CDSCO in Delhi and was processed with super speed in a record time of just 4 days (inclusive of postal transit) and permission granted on 11th February, 2000 **(Annexure 11).** Since then the Delhi High Court has reduced the approved indications to just two disorders: Wound Healing (for topical gel) and Pelvic Inflammatory Disorder (for injection).

7.49 **The Committee recommends an enquiry into the said letter. The responsibility should be fixed and appropriate action taken against the guilty. The Committee should be kept informed on this case.**

7.50 **Nimesulide for use in children:** The drug was approved in 1996 for use in children of all age groups (from Day 0 to 12 years) without conducting any clinical trials in India. Following some deaths due to liver injury in Europe, the drug was banned all over the world for use in children nearly 7 years ago. There was extensive media coverage in India. Instead of addressing the concern on regulatory lapse the matter was referred to an Experts Committee of DTAB to examine the "efficacy and safety issues." Since the drug has been banned on 10.2.2011 for use in children, the matter is being mentioned in this report as a matter of record.

7.51 **The Committee takes special notice of this case of persistent insolence on the part of CDSCO and hopes that never again shall the DCGI approve drugs in violation of laws, that too for use in neonates and young children.**

7.52 **The Committee expresses its deep concern, extreme displeasure and disappointment at the state of affairs as outlined above. The Ministry should ensure that the staff at CDSCO does not indulge in irregularities in approval process of new drugs that can potentially have adverse effect on the lives of people. It is difficult to believe that these irregularities on the part of CDSCO were merely due to oversight or unintentional. Hence all the cases listed above and cases similar to these should be investigated and responsibility fixed and action taken against erring officials whether currently in service or retired.**

8. **Drugs withdrawn/discarded/banned abroad**

8.1 There has been lot of public concern on the continued availability of potentially harmful drugs in India years after such products were banned and/or withdrawn abroad, more particularly in highly developed countries like United States, Canada, Britain, European Union, Australia etc. For example anti-diabetic agent phenformin due to unacceptable side effects and introduction of safer medicines was banned abroad in 70s but continued to be sold in India till 2003 *i.e.* for over 30 years, that too when Delhi High Court raised the issue.

8.2 The Committee had initially decided to examine all the controversial drugs. However in the recent past, though belatedly, the Central Government has banned five of them. Therefore, only few drugs are being taken up for consideration as illustrations.

Analgin remained in the market worldwide until the 1970s, when it was found that the drug carried risk of causing severe fall of white cells (agranulocytosis) - a potentially fatal condition. The global status of ban orders, based on information from WHO is as follows: (Countries where analgin was never approved are not listed.)

United States: banned with effect from June 27, 1977. Analgin was also banned for use in animals in 1995 in the United States.

Sweden: banned in 1997 due to reports of agranulocytosis in Sweden.

France 2006: Analgin withdrawn due to negative benefit/risk evaluation.

Armenia: banned in February, 2000 by the Drug and Medical Technology Agency.

Morocco banned in May, 2000 on the recommendation of the National Advisory Commission for Pharmacovigilance following an official survey which showed severe adverse reactions associated with this product.

Syria: The Suprim Technical Committee and the Ministry of Health banned the manufacture of analgin in 1996.

Yemen: In 1998, the Supreme Board of Drugs and Medical Appliances banned analgin because of its potential to cause anaphylactic shock and agranulocytosis.

Zimbabwe: In 1998, the Medicines Control Authority cancelled the registration of analgin due to the potential risks.

Lithuania: In September, 2000, the marketing authorization for tablets was not renewed for safety reasons.

Democratic Republic of Timor-Leste 2005: Analgin to be removed due to reports of agranulocytosis.

Nigeria 2005: In view of recorded cases of adverse reactions the National Agency for Food and Drug Administration and Control (NAFDAC) ordered that with effect from 1st January, 2006, the sale and use of analgin drugs are banned.

Serbia May, 2005: Prohibited the use of analgin in children and adolescents under the age of 18 years.

Philippines June, 2009: Analgin banned.

The drug is also banned in **Nepal, Vietnam, Canada, Australia, New Zealand, Japan** and **Iran.**

8.3 There are some specific problems in India with regard to rampant use of pain-killers without medical advice. Analgin is an NSAID but virtually sold as Over the Counter (OTC) without prescription. Hence there is misuse and overuse. Since 1920 when the drug was discovered, much safer alternatives have been launched. Analgin does not appear in the National List of Essential Medicines (NLEM). The approved indication of drug in India is *"severe pain or pain due to tumour and also for bringing down the temperature in refractory cases when other anti-pyretics fail to do so."* However the product insert of Baralgan-M and Novalgin, the two top selling brands of analgin recommend its use in *"severe or resistant pain and fever"* and the words *"when other anti-pyretics fail to do so"* have been omitted thus leading to over promotion in violation of rules **(Annexure 12).**

Analgin crosses the placenta and should not be used during pregnancy. Similarly women who are breast feeding must not use the drug. How many people know this? As per documents submitted by the Ministry, the issue of withdrawing analgin has not been seriously considered.

8.4 **The Committee has noted that there are a very large number of alternative analgesics, antipyretics in the Indian market. With so many countries banning Analgin, not to mention unlawful over-promotion by manufacturers, the CDSCO should be directed to re-examine the rationality of continued marketing of Analgin.**

8.5 **It is to be kept in mind that a drug becomes a candidate for withdrawal not only due to serious side effects but also when safer, more efficacious drugs are launched. Unfortunately, no attention is being paid to this issue. This principle should apply to all cases and all drugs need to be evaluated periodically.**

8.6 In some cases, such as nimesulide, CDSCO officials have argued that *"no adverse reports have been received from India; hence there* is *no reason to ban."* Unfortunately the infrastructure and system required to pick up adverse effects in India is lacking. CDSCO has acknowledged that under a World Bank funded programme (23.11.2004 to 30.6.2008) to detect side effects, not a single new adverse drug reaction was reported from anywhere in the country.

8.7 **The documents submitted by the Ministry show that even in large developed countries with well developed drug regulation such as US the adverse reactions are not detected by spontaneous reports from doctors in practice. All major side effects were detected in large scale controlled, focused Post-Marketing Phase IV trials involving thousands of patients such as SCOUT on anti-obesity drug sibutramine (now banned) and the RECORD trial on rosiglitazone (now banned). Therefore to expect that any spontaneous reports from medical profession, either in private practice or even institutions (medical colleges, large hospitals) will pick up hitherto unknown side effects in India is not realistic. There is hardly any alternative but to take immediate cognizance of serious adverse drug reactions reported from countries with well developed and efficient regulatory systems. The health and lives of patients in India cannot be put to risk in the hope of detecting ADRs within the country.**

8.8 **The Committee feels that since the chances of picking up unknown serious adverse effects of drugs being marketed in the country are remote, therefore CDSCO should keep a close watch on regulatory developments that take place in countries with well developed regulatory systems in the West and take appropriate action in the best interest of the patients.**

8.9 On this issue, the responses from the Ministry are vague, not convincing and not to the point. The reply merely states that such dubious drugs are examined in *"consultations with the experts/DTAB."* The response raises many questions:

- Firstly, at the time of approval of drugs, the matter is not referred to DTAB, then why should DTAB be involved when drugs are to be banned? Secondly, many drugs have been approved by DCGI without consultations with experts; why involve them when banning? There is no answer to these specific questions. It must be made clear that the Committee is not suggesting that DTAB should not be consulted. On the contrary, extensive consultations should take place not only while banning but also approving the drugs. There should be no double standards.
- There is no standard, uniform, transparent system of referral for expert opinion before a drug is banned. In some cases the opinion of DTAB is obtained such as rimonabant, sibutramine and rosiglitazone; in others it is not obtained but is referred

to an Expert Committee appointed by CDSCO such as levonorgesterol, letrozole, nimesulide. In yet other cases such as rofecoxib and valdecoxib, the matter was neither referred to DTAB nor to CDSCO-appointed expert committee.

8.10 **In most cases, most of these experts whether appointed by CDSCO or DTAB are from Delhi. The following facts reveal this pattern:**

- **Rimonabant was referred to a committee of six experts, all from Delhi.**
- **Levonorgestrel: Four out of five from Delhi.**
- **Letrozole: Four out of five from Delhi.**
- **Sibutramine: All five from Delhi.**
- **Rosiglitazone: All five from Delhi.**

A review of membership shows that one expert sat on 5 of the 6 committees. One wonders whether expertise on drugs is confined to Delhi.

8.11 **The Committee strongly recommends that with some 330 teaching medical colleges in the country, there are adequate number of knowledgeable medical experts with experience who can be requested to give their opinion on the safety and efficacy of drugs. The need is to make such consultations very broad based so as to get diverse opinion. The opinions, once received, can be put in public domain inviting comments. Once the experts know that their opinions will be scrutinized by others, including peers, they would be extra cautious and give credible evidence in support of their recommendation.**

9. Fixed Dose Combinations (FDCs)

9.1 When two or more drugs, already approved individually, are combined for the first time in an FDC, then under the law the product is deemed to be a New Drug. Such FDCs have to undergo the procedure applicable to New Drugs such as clinical trials etc. to determine safety and efficacy. Once such FDCs receive approval from CDSCO, manufacturers can approach State Drugs Authorities to obtain Manufacturing Licenses.

9.2 **Unfortunately some State Drug Authorities have issued manufacturing licenses for a very large number of FDCs without prior clearance from CDSCO. This is in violation of rules though till May 2002, there was some ambiguity on powers of the State Drug Authorities in this respect. However the end result is that many FDCs in the market have not been tested for efficacy and safety. This can put patients at risk.**

9.3 **To remove such unauthorized FDCs from the market, the Central Government can either issue directions under Section 33P to states to withdraw the licences of FDCs granted without prior DCGI approval or the Central Government can itself ban such FDCs under Section 26A.**

9.4 **The Committee was informed that DCGI has been requesting State Drug Authorities not to issue manufacturing licences to new FDCs and suspend licences of unauthorized FDCs issued in the past. However in exercise of powers under Section 33P specific directions have not been issued. The Ministry failed to provide any coherent reason for lack of action under this Rule. The Ministry informed the Committee that even if Section 33P was invoked, there was no provision to take action against States if directions were not carried out. If considered necessary, the Ministry may examine the possibility of amending the law to ensure that directions under Section 33P are implemented.**

9.5 **It is also possible to ban FDCs, not authorized by CDSCO by invoking Section 26A which empowers the Central Government to ban any drug to protect public health. The Committee was informed that the Government has not evoked Section 26A either so far. No explanation was offered for not using powers under Section 26A.**

9.6 **The Committee was informed that the issue regarding grant of Manufacturing Licenses for unapproved FDCs by some State Drug Authorities were first deliberated in 49th DTAB meeting held on 17 February, 2000 *i.e.* 11 years ago. It is a matter of great concern that even after a lapse of a decade, no serious action has been taken.**

9.7 **The Committee is of the view that those unauthorized FDCs that pose risk to patients and communities such as a combination of two antibacterials need to be withdrawn immediately due to danger of developing resistance that affects the entire population.**

9.8 **The Committee is of the view that Section 26A is adequate to deal with the problem of irrational and/or FDCs not cleared by CDSCO. There is a need to make the process of approving and banning FDCs more transparent and fair. In general, if an FDC is not approved anywhere in the world, it may not be cleared for use in India unless there is a specific disease or disorder prevalent in India, or a very specific reason backed by scientific evidence and irrefutable data applicable specifically to India that justifies the approval of a particular FDC. The Committee strongly recommends that a clear, transparent policy may be framed for approving FDCs based on scientific principles.**

10. Drugs Advisory Committees

10.1 The Health Secretary stated that twelve new Drugs Advisory Committees are in the process of being constituted to provide technical inputs and assist CDSCO in examining applications for new drugs to be introduced in the country, These Drugs Advisory Committees would basically be specific subject-oriented and each will have ten experts. These are being constituted so as to further strengthen the reviewing process and they would be permanent in nature. Normally, the Ministry tries to see that eminent people from the institutions such as All India Institute of Medical Sciences or Maulana Azad Medical College are a part of these Committees.

10.2 **The Committee feels that though the Ministry is forming DACs, which are given very important powers, there is no transparent procedure for the selection of experts of such Committees. The Committee also recommends that institutions from which experts are chosen should be from different parts of the country.**

11. Similar Brand Names

11.1 New drugs are approved by CDSCO under their generic (chemical/salt) names. The brand names are decided by the manufacturers and intimated to State Drug Authorities. Due to lack of coordination between various State Drug Authorities, many identical brands are being used for different medicines by various manufacturers located in different States. For example, Lona is being used for low sodium salt as well as for clonazepam (anti-epilepsy drug); AZ brand is being used for azithromycin (antibiotic), albendazole (for worms) and alprazolam (for anxiety). Needless to say this is a highly dangerous situation where wrong medicine can be sold and consumed leading to serious injury. CDSCO has expressed its inability to resolve the issue due to lack of rules and powers.

11.2 **The Committee strongly recommends that all such cases should be thoroughly reviewed in close coordination with State Drug Authorities. Specific procedures may be framed for approval of brand names. The procedure adopted by the Registrar of Newspapers**

to avoid duplication may be worth emulating. As a beginning, a data bank of all branded pharmaceutical products along with their ingredients should be uploaded on the CDSCO website and regularly updated.

12. Post-marketing Surveillance

12.1 Once New Drugs are approved, rules require that manufacturers submit post-marketing Periodic Safety Update Reports (PSURs) listing side effects, fatalities, injuries etc. in Indian patients once every six months in the first two years and then annually in the following two years.

12.2 **In order to scrutinize the compliance of this rule, the Ministry was asked to furnish PSURs in respect of 42 randomly selected new drugs. Since files in respect of three drugs were reportedly missing, PSURs should have been supplied for the balance 39 drugs. The Committee is, however, constrained to note that PSURs in respect of only 8 drugs were submitted by the Ministry. The Committee was informed that 14 drugs though approved were not being marketed or were launched lately and hence PSURs would be expected later. There was no explanation for not submitting PSURs in respect of rest of 17 drugs.**

12.3 **Out of 14 drugs that were reported to be either not yet launched or lately launched, the Committee discovered that, at least, two products (FDC of glucosamine with ibuprofen; and moxonidine) were indeed in the market for some time and concerned manufacturers should have submitted PSURs. But the Committee has not been given any explanation for non-submission of PSURs for these two drugs.**

12.4 **The Committee observed that even, in those cases where the PSURs were submitted, the frequency and/or format was not as per rules. In the case of two drugs of MNCs (dronedarone of Sanofi Aventis and pemetrexid of Eli Lilly), the PSURs were neither India specific nor in the approved format as required by law. Some companies submitted PSURs for the products being marketed in the country but very few PSURs were India-specific.**

12.5 **The Committee is of the firm view that there is a poor follow-up of side effects in Indian patients both by doctors and manufacturers. The objective of PSURs is to collect information about adverse effects on patients in India which would help to determine ethnic differences, if any and result in dosage adjustment, revision of precautions and warnings, if necessary. The Committee takes strong exception to such rampant violation of the mandatory requirements.**

12.6 **The Committee strongly recommends that the Ministry should direct CDSCO to send a stern warning to all manufacturers of new drugs to comply with mandatory rules on PSURs or face suspension of Marketing Approval. PSURs should be submitted in CDSCO-approved format which would help track adverse effects discovered in Indian ethnic groups.**

13. Pharmacovigilance

13.1 The Committee was informed that the Ministry has recently launched 'Pharmacovigilance Scheme' that will enable CDSCO to collect adverse drugs reactions data in a systematic manner. This data will be used while taking decisions on banning/placing of restrictions on drugs along with data from abroad. The Health Secretary further clarified that medical colleges are enrolled in pharmacovigilance in phases as monitoring centres. Forty-three colleges were already enrolled and they hope to go up to 75 by adding more. But, ultimately, the aim was to include all the medical colleges in the country under this programme so that the spread of pharmacovigilance programme is across the country.

13.2 Determination of side effects of marketed medicines is an extremely complicated exercise that requires infrastructure, appropriate result-oriented methodology and expertise. CDSCO has admitted that in the past in the World Bank funded project, not even one additional hitherto unknown serious side effect was identified worth reporting to the global WHO monitoring centre in Sweden. In the period 2006 to 2010, other Drugs Regulatory Authorities discovered the following number of serious ADRs:

USFDA (United States)	223
Health Canada	123
MHRA (Britain)	85
Medsafe (New Zealand)	62
EMEA (European Community)	59
TGA (Australia)	45

13.3 **The Committee feels that the conventional system of locating side effects through spontaneous reporting by doctors to either drug companies or drug regulators has been found to be unsatisfactory. The most effective system is by controlled post-marketing Phase IV studies on a very large number of patients. In the past decade, all the major adverse effects that led to banning of drugs were identified in large scale Phase IV trials. The Ministry may wish to consider the possibility of using this format in the country.**

14. Updation of Information on Marketed Drugs

14.1 Based on inputs from drug regulatory authorities in different countries rapid changes are taking place in the dosage, safety, efficacy and precautions of currently approved drugs leading to alterations in authorized monographs (prescribing information and safety guidelines). For example it was not earlier known that the drug modafinil can cause serious skin reactions, that concurrent use of two anti-hypertensive agents, telmisartan with ramipril, is risky etc. To protect patients, it is vital that approved prescribing information is updated and amended as soon as new information is received. Accordingly, the Committee asked the Ministry to give details of changes in the prescribing information on drugs sold in India in the year 2009 and 2010. In response the Ministry submitted a list of just 14 products, that too only from MNCs. During the same period WHO in its publicly available Bulletin gave information on changes in 274 medicines while USFDA and British MHRA ordered changes in over 500 drugs.

14.2 One of the conditions while approving drugs is obligation on the part of manufacturers to intimate all changes in efficacy, safety, dosage, side effects etc. that may take place globally. Apparently manufacturers are not su bmitting such vital information to the CDSCO in violation of rules and continue to use outdated information in their promotion, label, package insert etc. Naturally patients are suffering. CDSCO also failed in its statutory duty of enforcing laws and penalizing those who did not comply with rules on updation of information.

14.3 **The Committee feels that unless information on marketed drugs is continuously updated, there is risk of irrational or inappropriate use of medicines putting patients at risk. The Committee, therefore, recommends that immediate steps need to be taken to address this issue. The CDSCO should be directed to continuously update monographs based on information from regulatory authorities the world over.**

15. Spurious/Sub-standard Drugs

15.1 The Committee was apprised that the propaganda on alleged availability of spurious drugs

is motivated and manipulated by foreign drug manufacturers with a view to damage the reputation of Indian domestic manufacturers, who have successfully competed with MNCs in both domestic sales and export at much lower prices. The MNCs are deliberately confusing the issue by clubbing and interchanging 'spurious' with 'counterfeit drugs. The Indian definition of counterfeit refers to the unauthorized use of a registered brand name, even when the product is of acceptable quality. The Western definition is far wider and includes the so-called 'generic' medicines manufactured by anyone other than patent holders without innovators permission, even when there is no valid patent in India. If the medicines are of high quality and legally produced in India, they are still dubbed as 'counterfeits' by innovators in the West. According to a study by the CDSCO, the prevalence of spurious drugs in India is less than 0.5 per cent as against the allegations by MNCs of 25-30 per cent.

15.2 Taking advantage of the confusion created by MNCs over fake and counterfeits, the so-called anti-counterfeit solution providers that sell barcode and other technologies are propagating and lobbying for the use of such expensive, impractical methods by making them legally compulsory. Use of barcodes will increase the cost of drugs without any benefit to consumers.

15.3 The Committee observed that unfortunately, the problem with sub-standard, classified as 'Not of Standard Quality' drugs is more serious. An analysis of the data generated by State and Central drug testing laboratories shows the prevalence to be in the region of 7-8 per cent over the past decade.

15.4 **A drug can be categorized 'Not of Standard Quality' for a variety of both major and minor technical reasons such as not stating the name of the pharmacopoeia correctly, problem with quality of bonding agent, colouring agent, dissolution time, etc. However, there are other more serious cases, where the active ingredient is significantly less in quantity that can harm patients. Therefore, this problem needs to be addressed with all the seriousness that it deserves both by more rigorous checks in procuring bulk drugs (particularly from developing countries with not so stringent quality checks and export controls) and by in-house quality control by manufacturers or solving the problem in transportation and/or storage at distribution/retail levels.**

15.5 **By the time a sample is tested, a large number of packs get sold out with undeterminable injury to patients. There is no effective method of recalling unsold stocks lying in the distribution network. This cannot be allowed to go on.**

15.6 **The Committee feels that there should be severe punishment for manufacturing and for allowing sub-standard drugs to enter the distribution chain. Products with severe deficiencies should be penalized the same way as producers of spurious drugs by amending rules. There is also a case to incorporate penal provisions for manufacturing misbranded and adulterated drugs.**

15.7 **It is known that retail chemists also stock and sell items other than drugs including chocolates, cold drinks etc. During summer these items are stored in the refrigerator while due to paucity of space temperature-sensitive medicines may be lying outside. When samples are picked up, tested and found to be sub-standard, the State Drug Authorities blame and prosecute manufacturers. Therefore the Committee recommends that specifically in the case of temperature sensitive products such as insulins, due consideration should be given to the reference samples of the same batch preserved by the manufacturers.**

15.8 A large number of finished ready-to-use drugs, in excess of 1,000 have been approved by CDSCO to be imported not only by pharmaceutical companies but traders as well. Most traders import and sell the drugs directly to patients on receiving tips from prescribers. The Ministry informed the Committee that random samples of such finished formulations are collected at the port

of entry and tested by approved laboratories. However there is no mechanism in place to test such formulations once they leave the port of entry because they are not sold at retail chemists. Drugs inspectors collect samples from either the premises of manufacturers or more commonly from retailers. Most of such imported drugs are highly temperature-sensitive and may loose their potency if not stored properly. There is no procedure to test drugs being sold outside the retail chain. Besides being exorbitantly expensive, there is always the possibility of spurious/duplicates entering the supply chain. For example just one ampoule of anti-cancer drug, Herceptin, is priced at over Rs.1.20 lacs.

15.9 **The Committee is extremely anxious on both counts: such hugely costly imported drugs losing their potency before use and the possibility of fakes entering the chain. It is strange that multinational drug companies that have well staffed marketing offices in India, instead of importing drugs from their overseas affiliates and selling them are using traders to handle this activity. Apart from risk to patients, there is leakage of revenue to income tax. While the promotional expenses on imported formulations are being paid by the Indian branch of MNCs thus reducing income tax liability, there is no corresponding income since traders are paying directly to overseas offices of MNCs. The Committee would like the Ministry to ensure that in cases where MNCs have offices in India, traders are not permitted to import formulations of such companies. The Committee would like to be kept informed of the steps taken on this issue.**

15.10 The Ministry has recently approved a programme for CDSCO for conducting inspections of drug manufacturing sites located abroad to ensure that only quality drugs, including bulk drugs registered and compliant with the regulatory norms in the countries of origin are imported into our country.

15.11 **The Committee recommends that once a batch of a drug is found to be sub-standard and reported to CDSCO, it should issue a press release forthwith and even insert paid advertisements in the newspapers apart from uploading the information on the CDSCO website. Retail chemists should be advised to stop selling unsold stocks and return the same to local Drugs Inspectors as per rules. The Committee understands that at least two State Drug Authorities, that of Maharashtra and Kerala, have taken the initiative to upload information on spurious and sub-standard drugs on their websites on a monthly basis. These are welcome measures worth emulating by other States and the Centre.**

16. Advertising of Prescription Drugs in the Lay Media

16.1 It has come to the notice of the Committee that some manufacturers advertise prescription drugs (Schedule H) in the lay press. Based on incomplete information, patients tend to self-medicate more so because such medicines are generally available without prescription. Such practices can adversely impact not only the health of individuals but even communities and countries. For example misuse of antibiotics can lead to bacterial resistance with serious consequences for public health. Recent cases of lay press advertisements are those of:

- Anti-depressant Deanxit (Lundbeck) **(Annexure 13)**
- Anti-epileptic agents Desval ER (Ranbaxy), Lametec DT (Cipla), C-Tsoin (USV)
- Cholesterol lowering Coltro (USV).

16.2 **The Committee would like the Ministry to take appropriate action against the companies that have advertised the above Schedule H drugs in the lay press. The provisions in the Drugs and Magic Remedies Act are not stringent enough with the result that manufacturers violate them at will. It also recommends that apart from giving sharper**

teeth to the Drugs and Magic Remedies Act, a provision should also be incorporated in the Drugs and Cosmetics Rules to ban such practices and penalize offenders. The Committee would like to be informed of the action taken to implement these recommendations.

17. Consumer Information

17.1 Explaining about labels and package inserts, the Committee was informed that although label was mandatory for manufacturers, to provide package inserts with each pack of drugs were not mandatory. It was also stated that labels are meant for consumers while package inserts are meant for doctors. Even when they are provided by manufacturers in the outer carton in insufficient numbers (for example just one insert in a box of 10 strips), they are in technical language and strangely state that they are "for use of medical practitioners", even though they are supplied to consumers.

17.2 The Committee was informed that there is no mandatory provision of providing information to the consumers of drugs in the form of Product Information Leaflet (mandatory in western countries) in simple language. The Committee feels that in our country, overworked doctors do not have the time to explain the use, side effects, drug interactions and other precautions to be taken while taking prescribed drugs to each and every patient. According to World Medicines Situation, 2011 of the WHO, doctors in developing countries spend less than 60 seconds in prescribing and explaining the therapy to patients. Thus, patients are at risk because of lack of information on proper use of drugs, expected side effects etc. The label on the product, mostly written in very small print, does not carry information useful to patients.

17.3 **The Committee is of the firm opinion that accurate information on drugs for patients is absolutely essential to prevent inappropriate use more particularly in children, elderly, during pregnancy and lactation. The Committee recommends that the matter may be looked into to ensure that consumers have the required information to use medicines safely. Given the widespread internet connectivity, it is advisable to devise a system where patients can get unbiased information on drugs at the click of the mouse in any language.**

18. Clinical Trials on New Drugs

18.1 A very larger number of clinical trials are being conducted in India after liberalization of relevant Rules (Schedule Y) in January, 2005. The Committee was informed that a total of 2,282 trials have been approved from the year 2005 up to September, 2010. The Committee also observed that there has been extensive media coverage, both in India and abroad such as BBC, US NBC, French TV, Al Jazeera etc. with serious, documented cases of poor, illiterate citizens including children of India being used as 'guinea pigs' by MNC drug manufacturers. As per the Ministy's status note, a total of 1,514 subjects have died in the years 2008 to August 2010 during clinical trials. In some isolated cases, in response to media reports, CDSCO investigated the trials and found irregularities.

18.2 **Due to the sensitive nature of clinical trials in which foreign companies are involved in a big way and a wide spectrum of ethical issues and legal angles, different aspects of Clinical trials need a thorough and in-depth review. This Committee has, accordingly, taken it up as a subject for detailed examination separately under the heading 'Clinical Trials of Drugs'.**

STUDY NOTE ON VISIT OF DEPARTMENT-RELATED PARLIAMENTARY STANDING COMMITTEE ON HEALTH AND FAMILY WELFARE TO TAMIL NADU AND KARNATAKA FROM 1ST TO 5TH NOVEMBER, 2011

CDSCO

The Committee visited the Airport Halt Office at Chennai on 1st November, 2011. The Committee was informed that the Airport Halt Office (APHO), Chennai is a subordinate office under the control of DGHS, Ministry of Health and Family Welfare and is responsible for discharge of functions as enjoined upon the Airport Health Office under the provision of Indian Air Craft (Public Health) Rules, 1954 framed under the Indian Aircraft Act, 1934. The Organisation is headed by Airport Health Officer (APHO). The APHO, Chennai has three working sections/units namely the administrative unit, medical inspection room and the quarantine centre. The major functions of APHO were health screening of international passengers and quarantine, disinfection, disinsection and derating of Air crafts, supervision of general sanitation, etc.

The Committee then undertook a visit to Central Drug Testing Laboratory and State Drug Testing Laboratory in Chennai on 2nd November, 2011. The Committee was informed that the Central Drug Testing Lab was started in 1965 was previously known as Biological Laboratory and Animal House which was a service Laboratory to Government Medical Stores Depots, Ministry of Health and family Welfare, Chennai. The said lab was taken over by CDSCO and rechristened as the Central Drugs Testing Laboratory in the year 1992. The total sanctioned strength of the staff was 33 out of which 29 were filled up and 4 vacancies were being in the process of being filled up. The Committee was informed that this Laboratory needs a 5 storied Building with 10000 sq. feet in each floor for testing Drugs and Cosmetics. The Committee was informed that the State Drug Testing Laboratory undertakes testing of samples drawn randomly by Drug Inspector (other than parenteral preparation) from various retail, whole sale units etc. and tests them. The parenteral Preparations are tested at the King Institute of Preventive Medicine and Research, Guindy, Chennai. The Committee was informed that the Drugs Control Administration had a sanctioned Strength of 337 out of which 203 were in position and 134 were vacant. The total number of prosecutions in 2011-12 (upto 30.9.11) was 139. More than 95% of the above cases were ended in conviction. The Committee was informed that at present the testing laboratory is having only two HPLC system which were also brought more then a decade ago and the present system is obsolete one and was not compatible with the present rating of analysis. Hence there was a need for enhancement of facilities to keep up with the increased number of tests.

The Committee then held discussions with the representatives of Pharmaceutical Industry Organisations, the representatives of CDSCO and Ministry officials. The representatives of the pharma Industry apprised the Committee of the recent trend of taking over of Indian Pharma Companies by multinational companies (MNCs) like the case of acquisition of Piramal by another MNC. They suggested that there was a need to stop this trend by bringing in regulations to stop MNCs from capturing Indian Markets. They also felt that there was need to provide more funds for upgradation of drug testing Laboratories and more training for Government Lab staff for proper analysis of samples. Other measures suggested by them included upgradation of existing labs, need for opening 5 additional Labs need for more appellant Labs in all zones in addition to the one at Kolkata; need to curb the monopoly of Chinese distributors; need for streamlined logistics management and expansion at Chennai port; need for decentralization for permission in respect of

manufacturing of new drugs; support to the Small Medium Enterprises sector; need to reduce the time taken for seeking license to undertake manufacture of new drugs which takes 3 months whereas in other countries it takes only 2 weeks. The representatives of the Ministry informed the Committee that the Government was planning upgradation of all Government Labs in the country and had proposed a massive investment in the 12th Plan proposals sent to the Planning Commission, and as regards the issue of appellate lab, the ministry was looking into it. The representative further informed the Committee that the Government was closely monitoring the impact of FDI in pharma sector and had recommended that all approvals in FDI in pharma sector must be routed through Foreign Investment Promotion Board. On the issue of the time taken for granting licences in 3 months, the representative informed that the Ministry was looking into it. Regarding the matter of Chinese monopoly in distributorship, the representative informed that it was a trade related matter and hence under the jurisdiction of the Department of Commerce.

The Committee then undertook a visit to Biocon Ltd, Bangalore on 5th November, 2011. Mr. Murali Krishnan, President, Finance informed the Committee that the said Lab *viz.* Biocon testing Laboratory was an integral part of Biocon Limited and was approved by the Drug Authorities in 1997 and analysed samples from various plants belonging to the Biocon Group of Companies and also testing of samples upon customer request. The academic knowledge of the Scientists working there helped in analysis of new molecules and contributed towards introduction of new monographs in pharmacopoeia. He then informed the Committee the need for deputing an officer of DCGI in Bangalore for collecting samples. Further there was a need to streamline the existing Licensing procedure in the field of Biotechnology which was very lengthy and cumbersome at present. The Committee then had interaction with the representatives of the State Government on the functioning of State Drugs Control Department, Bangalore. The Committee was informed that the Drugs Control Department, Karnataka was established in 1965 and had three wings *viz.* Enforcement Wing, Drugs Testing Laboratory and Education in Pharmacy. He informed that at present the sanctioned strength of the Department was 702 out of which 408 posts were filled and 294 were vacant across various posts in Group A, B, C and D. The Committee was then informed of the various activities carried out by the Department. The Committee was then apprised of the various challenges facing the Department namely inadequate field staff and Ministerial staff for enforcement as well as for the laboratories (at present only 60% of the sanctioned posts had been filled). The Committee was further apprised that as per recommendation of Dr. Mashelkar Committee constituted by the Govt. of India:–

(a) There was a need for one Inspector for every 200 sales establishments.

(b) There was a need for one Inspector for every 50 manufacturing units.

(c) The total number of inspectors required in Karnataka was 164, at present the sanctioned posts were 62.

The Committee was informed that the request had been made to KPSC for recruitment of 10 Drug Inspectors and proposal had been submitted to the Government for creation of 430 posts which included posts of Drug Inspectors. Besides, there is need for adequate transportation facilities and adequate budget sanction for completion of construction of infrastructure and for procurement of necessary equipment/books.

The Committee then had interaction with the representatives of Pharmaceutical industry organisations. The representatives of the Industry informed the Committee that there was a need to strengthen the existing Central Laws; need to revise the Capital Subsidy Scheme of the Department of Pharmaceuticals to make it friendly for entrepreneurs; repeal of the present DPCO (based on the cost of production) and to move forward to a monitoring system of control; need to reduce turnover clause for tender procedure of purchase of medicines by Government

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institutions so as to enable MSMEs to bid for tender and rate contract of govt. institutions and quasi govt. institutions as the present turnover clause is very high to the detriment of SSIs; decenttralizing new drug licensing approvals by giving powers to the 5 zonal offices in this regard; reduction of new drugs status cap from 4 years to 2 years to enable smaller companies to manufacture the small molecule/drug at much economical prices so as to create a healthy competition which would directly benefit the public; issue of Form 10 Licence for imports of registered products from zonal CDSCO offices; Establishment of more Appellate laboratories in India especially in the four different zones of India; upgradation of Testing Laboratories and need for adequate training to be given for the Government Analysts; need for uniform norms regarding printing, packing, superscription for Pharmaceutical companies on medicines being supplied to both Government and quasi governmental institutions will save the SSI companies a lot of money, which would increase their efficiency; timely intimation by the Central Government in any matter related to Pharmaceutical industry, so as to allow the industry get some time for implementation of the same; need to protect the domestic industry in face of competition from China; procurement of 20% of Drugs from SME sectors; protection to manufacturers to manufacture 74 drugs under DPCO; need for control on the large number of small medical shops which were mushrooming all over the country which could prevent spurious drugs being sold from such medical shops; need for expansion of API clusters needed. The Committee then concluded its visit at Bangalore and dispersed.

OBSERVATIONS/RECOMMENDATIONS — AT A GLANCE

2. MANDATE AND STRUCTURE OF CDSCO

The Committee is of the firm opinion that most of the ills besetting the system of drugs regulation in India are mainly due to the skewed priorities and perceptions of CDSCO. For decades together it has been according primacy to the propagation and facilitation of the drugs industry, due to which, unfortunately, the interest of the biggest stakeholder *i.e.* the consumer has never been ensured. Taking strong exception to this continued neglect of the poor and hapless patient, the Committee recommends that the Mission Statement of CDSCO be formulated forthwith to convey in very unambiguous terms that the organization is solely meant for public health. (Para 2.2)

The Committee notes with serious concern that CDSCO is substantially understaffed. Of the 327 sanctioned posts, only 124 are occupied. At this rate, what would be the fate of 1,045 additional posts that have been proposed is a moot point. If the manpower requirement of the CDSCO does not correspond with their volume of work, naturally, such shortage of staff strains the ability of the CDSCO to discharge its assigned functions efficiently. This shortcoming needs to be addressed quickly. Consideration can also be given to employ medically qualified persons as Consultants/Advisers (on the pattern of Planning Commission) at suitable rank. (Para 2.19)

The Committee also gathers that the average time taken for the completion of recruitment process is approximately 12 to 15 months. The Committee, therefore, recommends that to overcome the staff shortage, the Ministry should engage professionally qualified persons on short-term contract or on deputation basis until the vacancies are filled up. Due to the very sensitive nature of regulatory work, great care will need to be taken to ensure that persons employed for short periods did not and will not have Conflict of Interest for a specified period. (Para 2.20)

At the same time, the optimal utilization of the current staff in the best interest of public is the responsibility of those who run the CDSCO. In a resource- constrained country like India, it is extremely difficult to meet the demands, however, genuine, of all the State entities in full. Hence, prioritization is the key. For example, work relating to an application for Marketing Approval of a New Drug that will be used by millions and thus have an impact on the well being of public at large in India for years to come, is far more important and urgent than giving permission to a foreign company to conduct clinical trials on an untested new patented, monopoly drug. (Para 2.21)

The Committee also observes that the strengthening of drugs regulatory mechanisms cannot be achieved by manpower augmentation alone. A host of issues involving capacity-building of CDSCO like upgradation of existing offices, setting up of new offices, creation of new central drugs testing laboratories and equipping them with the state-of-the-art technology to enable them to carry out sophisticated analysis of drugs, upgradation of the existing 6 Central Drugs Testing Laboratories, skill development of the regulatory officials, implementation of an effective result-oriented pharmacovigilance programme drawing on global experience, increased transparency in decision-making of CDS CO etc. will have to be addressed before the desired objectives are realized. (Para 2.22)

In the absence of any reasons for unwillingness on the part of medically qualified persons to join CDSCO, the Committee is of the opinion that emoluments and perquisites may not be the main or only reason. It is noticed that minimum prescribed academic qualifications for the post of DCGI is barely B.Pharm. On the other hand for Deputy Drugs Controller (DDC), the prescribed minimum qualification is post-graduation for medically qualified persons. The stumbling block is the requirement that DCGI should have experience in the "manufacture or testing of drugs or enforcement of the provisions of the Drugs and Cosmetic Act for a minimum period of five years." This requirement virtually excludes even highly qualified medical doctors from occupying the post of DCGI. Moreover the rule stipulates that doctors with post-graduation should be either in pharmacology or microbiology only, thus excluding post-graduates, even doctorates (like DM) in a clinical subject. Besides, highly qualified medical doctors may be reluctant to work under and report to a higher officer with lesser qualifications in a technology driven regulatory authority set-up. Unless these concerns are addressed, it would be difficult to get the desperately required medically qualified professionals on the rolls of CDSCO. (Para 2.23)

3. QUALIFICATION AND POWERS of DCGI

The Committee fails to understand as to how a graduate in pharmacy or pharmaceutical chemistry (B.Pharm) is being equated with a medical graduate with MD in Pharmacology or Microbiology. Apart from the obvious anomaly, with rapid progress in pharmaceutical and biopharmaceutical fields, there is urgent need to revise the qualifications and experience as minimum eligibility criteria for appointment as DCGI. The Committee is of the view that it is not very rational to give powers to a graduate in pharmacy, who does not have any clinical or research experience to decide the kinds of drugs that can be prescribed by super specialists in clinical medicine such as those holding DM and PhD qualifications and vast experience in the practice of medicine and even research. (Para 3.6)

On a larger plane, the Committee is disillusioned with the qualifications provided in the age old Rules for the head of a crucial authority like CDSCO. The extant Indian system is nowhere in so far as sheer competence and professional qualifications are concerned when compared with countries like USA and UK. There is, therefore, an urgent need to review the qualifications, procedure of selection and appointment, tenure, emoluments, allowances and powers, both administrative and financial of the DCGI. While doing so, the Government may not only rely on the Mashelkar Committee Report which recommended augmented financial powers to DCGI but also take cue from similar mechanisms functioning in some of the developed countries like USA, UK, Canada, etc in order to ensure that only the best professional occupies this onerous responsibility. The Committee should be kept informed of the steps taken to address this issue. (Para 3.7)

In the considered opinion of the Committee, there can never be a more opportune time than now, to usher in these changes recommended by it. The post of DCGI is vacant as of now, with an official holding temporary charge. They, therefore, desire that the government should take immediate measures in terms of their instant recommendations to ensure that CDSCO is headed by an eminent and professionally qualified person. (Para 3.8)

4. ROLE OF THE STATE DRUG REGULATORY AUTHORITIES

From an analysis of the above facts, the Committee concludes that shortcomings witnessed in respect of coordination with and between the States as also in implementation

of applicable legislations in the States are primarily an offshoot of inadequacies in manpower and infrastructure in the States. Strengthening the regulatory mechanism in the States will remain a far cry unless these infirmities are taken care of. (Para 4.5)

Given the lack of adequate resources in the States it would be unrealistic to expect them to improve the infrastructure and increase manpower without Central Assistance for strengthening drug control system. The Committee, therefore, recommends that the Ministry of Health and Family Welfare should work out a fully centrally sponsored scheme for the purpose so that the State Drug Regulatory Authorities do not continue to suffer from lack of infrastructure and manpower anymore. The Committee desires to be kept apprised of the initiatives taken by the Ministry in this regard. (Para 4.6)

It is a matter of grave concern that there are serious shortcomings in Centre-State coordination in the implementation of Drugs & Cosmetics Act and Rules. This, the Committee notes, is despite the Ministry's own admission that Section 33P of the Drugs and Cosmetics Act contains a provision that enables the Central Government to give such directions to any State Government as may appear to it to be necessary for implementation of any of the provisions of the Drugs and Cosmetics Act and Rules made thereunder. The Committee understands that these provisions are meant to be used sparingly. However, there have been several situations which warrant intervention through Rule 33 P. Therefore the committee hopes that in future the Ministry would not be found wanting in considering the option of using Section 33P to ensure that provisions of central drug acts are implemented uniformly in all states. (Para 4.7)

As regards lack of databank and accurate information, the Committee would like to observe that given the information technology resources currently available, developing an effective system of coordination amongst State Drug Authorities for providing quality and accurate data could have been accomplished long back had the Ministry taken any initiative towards encouraging the States to establish a system of harmonized and inter-connected databanks. Evidently, no serious efforts seem to have been made in this regard. The Committee, however, expects that the Ministry would, at least now, playa more pro-active role in encouraging the States to employ modern information technology in the implementation of tasks assigned to them. At the same time a centralized databank (*e.g.* licenses issued, cancelled, list of sub-standard drugs, prosecutions etc.) may be created to which all the State Drug Authorities should be linked. (Para 4.8)

5. CAPACITY-BUILDING OF CENTRAL AND STATE DRUG TESTING LABORATORIES

The Committee agrees that the capacity-building of the Central Drugs Testing Laboratories is the need of the hour. In this era of newer innovations coming up at rapid pace, equipping the Drug Testing Laboratories with the high-end sophisticated equipments is very essential. However, the Committee is aware that monitoring the quality of drugs is primarily the responsibility of the State Drugs Authorities, supplemented by CDSCO, which play a major role in collection of samples and testing them. Without manpower augmentation and up gradation of State Drugs Testing Laboratories, the objective of ensuring availability of quality drugs to the public cannot be realized. The Committee, therefore, recommends strengthening of both Central and State Drug Testing Laboratories. (Para 5.11)

6. PROVISION OF REQUISITE INFRASTRUCTURE AT AIRPORT AND SEAPORT OFFICES

The Committee agrees with the above suggestion and recommends that the Ministry of Health and Family Welfare should take initiative towards addressing the shortcomings

forthwith in coordination with the Ministry of Civil Aviation at all seaports/airports handling import and exports of pharmaceutical products. The Committee will like to be informed of steps taken to address this problem. (Para 6.2)

7. NEW DRUGS APPROVAL

The Committee is of the view that due to untraceable files on three drugs, it is not possible to determine if all conditions of approval (indications, dosage, safety precautions) are being followed or not. Moreover the product monographs cannot be updated in the light of recent developments and regulatory changes overseas. Therefore all the missing files should be re-constructed, reviewed and monographs updated at the earliest. (Para 7.13)

.....This matter needs to be reviewed to ensure safety of patients, fair play, transparency and accountability. (Para 7.14)

Unless there is some legal hitch, the Committee is of the view that there is no justification in withholding opinions of experts on matters that affect the safety of patients from public. Consideration should be given to upload all opinions on CDSCO website. (Para 7.15)

According to information provided by the Ministry, a total of 31 new drugs were approved in the period January 2008 to October 2010 without conducting clinical trials on Indian patients. The figure is understated because two drugs (ademetionine and FDC of pregabalin with other ingredients) were somehow not included in the list. Thus there is no scientific evidence to show that these 33 drugs are really effective and safe in Indian patients. (Para 7.16)

It is obvious that DCGI clears sites of pre-approval trials without application of mind to ensure that major ethnic groups are enrolled in trials to have any meaningful data. Thus such trials do not produce any useful data and merely serve to complete the formality of documentation. (Para 7.27)

The Committee recommends that while approving Phase III clinical trials, the DCGI should ensure that subject to availability of facilities, such trials are spread across the country so as to cover patients from major ethnic backgrounds and ensure a truly representative sample. Besides, trials should be conducted in well equipped medical colleges and large hospitals with round the clock emergency services to handle unexpected serious side effects and with expertise in research and not in private clinics given the presence of well equipped medical colleges and hospitals in most parts of the country in present times. (Para 7.28)

The Committee is of the view that taking into account the size of our population and the enormous diversity of ethnic groups there is an urgent need to increase the minimum number of subjects that ought to be included in Phase III pre-approval clinical trials to determine safety and efficacy of New Drugs before marketing permission is granted. In most western countries the required numbers run into thousands. However since the major objective in India is to determine the applicability or otherwise of the data generated overseas to Indian population, the requirement should be re-assessed and revised as per principles of medical statistics so that major ethnic groups are covered. A corresponding increase in the number of sites so as to ensure a truly representative sample spread should also be laid down in black and white. Furthermore, it should be ensured that sites selected for clinical trials are able to enroll diverse ethnic groups. For domestically discovered drugs, the number of subjects should be revised as well. This can be easily achieved by changes in the Good Clinical Practice (GCP) guidelines. (Para 7.29)

A review of the opinions submitted by the experts on various drugs shows that an overwhelming majority are recommendations based on personal perception without giving any hard scientific evidence or data. Such opinions are of extremely limited value and merely a formality. Still worse, there is adequate documentary evidence to come to the conclusion that many opinions were actually written by the invisible hands of drug manufacturers and experts merely obliged by putting their signatures..... Is the Committee mistaken in coming to the conclusion that all these letters were collected by interested party from New Delhi, Mumbai, Chandigarh and Secunderabad and handed over to office of the DCGI on the same day? If so, it is obvious that the interested party was in the loop in the entire process of consultation with experts. (Annexure 6).....It is inconceivable that a letter dated 17-6-2005 from New Delhi will be delivered to the office of DCGI also in New Delhi after more than two months. The conclusion, as in aforementioned cases, is obvious. (Annexure 8) (Para 7.31)

If the above cases are not enough to prove the apparent nexus that exists between drug manufacturers and many experts whose opinion matters so much in the decision making process at the CDSCO, nothing can be more outrageous than clinical trial approval given to the Fixed Dose Combination of aceclofenac with drotaverine which is not permitted in any developed country of North America, Europe or Australasia. In this case, vide his letter number 12-298/06-DC dated 12- 2-2007, an official of CDSCO advised the manufacturer, Themis Medicare Ltd. not only to select experts but get their opinions and deliver them to the office of DCGI! No wonder that many experts gave letters of recommendation in identical language apparently drafted by the interested drug manufacturer. (Para 7.32)

In the above case, the Ministry should direct DCGI to conduct an enquiry and take appropriate action against the official(s) who gave authority to the interested party to select and obtain expert opinion and finally approved the drug. (Para 7.33)

Such expert opinions in identical language and/or submitted on the same day raise one question: Are the experts really selected by the staff of CDSCO as mentioned in written submission by the Ministry? If so how can they, situated thousands of miles away from each other, draft identically worded letters of recommendation? Is it not reasonable to conclude the names of experts to be consulted are actually suggested by the relevant drug manufacturers? It has been admitted that CDSCO does not have a data bank on experts, that there are no guidelines on how experts should be identified and approached for opinion. (Para 7.34)

The Committee is of the view that many actions by experts listed above are clearly unethical and may be in violation of the Code of Ethics of the Medical Council of India applicable to doctors. Hence the matter should be referred to MCI for necessary follow up and action. In addition, in the case of government-employed doctors, the matter must also be taken up with medical colleges/hospital authorities for suitable action. (Para 7.35)

There is sufficient evidence on record to conclude that there is collusive nexus between drug manufacturers, some functionaries of CDSCO and some medical experts. (Para 7.36)

On a more fundamental issue the Committee has come to the conclusion that when it comes to approving new drugs, too much is left to the absolute discretion of the CDSCO officials. There are no well laid down guidelines for determining whether consultation with experts is required. Thus the decision to seek or not to seek expert opinion on new drugs lies exclusively with the non- medical functionaries of CDSCO leaving the doors wide open to the risk of irrational and incorrect decisions with potential to harm public health apart from the possibility of abuse of arbitrary discretionary powers. (Para 7.37)

The Committee, therefore, strongly recommends that there should be non-discretionary, well laid down, written guidelines on the selection process of outside experts with emphasis on expertise including published research, in the specific therapeutic area or drug or class of drugs. Currently, the experts are arbitrarily chosen mainly based on their hierarchical position which does not necessarily correspond to the area or level of expertise. All experts must be made to file the Conflict of Interest declaration outlining all past and present pecuniary relationships with entities that may benefit from the recommendations given by such experts. The consulted experts should be requested to give hard evidence in support of their recommendations. (Para 7.38)

The Committee is of the view that responsibility needs to be fixed for unlawfully approving Buclizine, a drug of hardly any consequence to public health in India, more so since it is being administered to babies/children. At the same time the approval granted should be reviewed in the light of latest scientific evidence, regulatory status in developed countries, particularly in Belgium, the country of its origin. (Para 7.41)

.....DCGI is expected to take action against those CDSCO functionaries who colluded with private interests and got the drug approved in violation of laws. The drug has since been banned by the Ministry for use in female infertility. (Para 7.42)

The Committee takes special note of this case of gross violation of the laws of the land by the CDSCO. First, in approving the drug for use in case of female infertility and thereafter, in exhibiting overt resistance in taking timely corrective steps despite very strong reasons favouring immediate suspension of use of letrozole for the said indication. Belatedly, the drug has been banned for use in female infertility. (Para 7.43)

The Committee is of the opinion that there must be some very good reasons for Danish Medicine Agency (Denmark) not to approve a domestically developed drug where an anti-depressant drug would perhaps be in greater demand as compared to India. Curiously, Deanxit is allowed to be produced and exported but not allowed to be used in Denmark. (Para 7.45)

The Committee feels that the DCGI should have gone into the reasons for not marketing the drug in major developed countries such as United States, Britain, Ireland, Canada, Japan, Australia just to mention a few. United States alone accounts for half of the global drug market. It is strange that the manufacturer is concentrating on tiny markets in unregulated or poorly regulated developing countries like Aruba, Bangladesh, Cyprus, Jordan, Kenya, Myanmar, Pakistan, and Trinidad instead of countries with far more patients and profits. Many of these developing countries are handicapped due to lack of competent drug regulatory authorities. Instead of examining and reversing regulatory lapses, DCGI has referred the matter to an Expert Committee to look at the isolated and restricted issue of "safety and efficacy" instead of unlawful approval in the first place. (Para 7.46)

The Committee recommends that in view of the unlawful approval granted to Deanxit, the matter should be re-visited and re-examined keeping in mind the regulatory status in well developed countries like Denmark, the country of origin; the United States, Britain, Canada, European Union and Japan etc. It is important to keep in mind that in Europe, there are two types of marketing approvals: Community-wide (cleared by European Medicine Agency) and individual regulators of member nations. EMEA is known to clear drugs after great deal of scrutiny while the competence and expertise of drug regulatory authorities of individual nations is not uniform and varies greatly from country to country. (Para 7.47)

The Committee recommends an enquiry into the said letter. The responsibility should be fixed and appropriate action taken against the guilty. The Committee should be kept informed on this case. (Para 7.49)

The Committee takes special notice of this case of persistent insolence on the part of CDSCO and hopes that never again shall the DCGI approve drugs in violation of laws, that too for use in neonates and young children. (Para 7.51)

The Committee expresses its deep concern, extreme displeasure and disappointment at the state of affairs as outlined above. The Ministry should ensure that the staff at CDSCO does not indulge in irregularities in approval process of new drugs that can potentially have adverse effect on the lives of people. It is difficult to believe that these irregularities on the part of CDSCO were merely due to oversight or unintentional. Hence all the cases listed above and cases similar to these should be investigated and responsibility fixed and action taken against erring officials whether currently in service or retired. (Para 7.52)

8. DRUGS WITHDRAWN/DISCARDED/BANNED ABROAD

The Committee has noted that there are a very large number of alternative analgesics, antipyretics in the Indian market. With so many countries banning Analgin, not to mention unlawful over-promotion by manufacturers, the CDSCO should be directed to re-examine the rationality of continued marketing of Analgin. (Para 8.4)

It is to be kept in mind that a drug becomes a candidate for withdrawal not only due to serious side effects but also when safer, more efficacious drugs are launched. Unfortunately, no attention is being paid to this issue. This principle should apply to all cases and all drugs need to be evaluated periodically. (Para 8.5)

The documents submitted by the Ministry show that even in large developed countries with well developed drug regulation such as US the adverse reactions are not detected by spontaneous reports from doctors in practice. All major side effects were detected in large scale controlled, focused Post-Marketing Phase IV trials involving thousands of patients such as SCOUT on anti-obesity drug sibutramine (now banned) and the RECORD trial on rosiglitazone (now banned). Therefore to expect that any spontaneous reports from medical profession, either in private practice or even institutions (medical colleges, large hospitals) will pick up hitherto unknown side effects in India is not realistic. There is hardly any alternative but to take immediate cognizance of serious adverse drug reactions reported from countries with well developed and efficient regulatory systems. The health and lives of patients in India cannot be put to risk in the hope of detecting ADRs within the country. (Para 8.7)

The Committee feels that since the chances of picking up unknown serious adverse effects of drugs being marketed in the country are remote, therefore CDSCO should keep a close watch on regulatory developments that take place in countries with well developed regulatory systems in the West and take appropriate action in the best interest of the patients. (Para 8.8)

In most cases, most of these experts whether appointed by CDSCO or DTAB are from Delhi. The following facts reveal this pattern:

- **Rimonabant was referred to a committee of six experts, all from Delhi.**
- **Levonorgestrel: Four out of five from Delhi.**

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- **Letrozole: Four out of five from Delhi.**
- **Sibutramine: All five from Delhi.**
- **Rosiglitazone: All five from Delhi.**
- **A review of membership shows that one expert sat on 5 of the 6 committees. One wonders whether expertise on drugs is confined to Delhi.** (Para 8.10)

The Committee strongly recommends that with some 330 teaching medical colleges in the country, there are adequate number of knowledgeable medical experts with experience who can be requested to give their opinion on the safety and efficacy of drugs. The need is to make such consultations very broad based so as to get diverse opinion. The opinions, once received, can be put in public domain inviting comments. Once the experts know that their opinions will be scrutinized by others, including peers, they would be extra cautious and give credible evidence in support of their recommendation. (Para 8.11)

9. FIXED DOSE COMBINATIONS (FDCs)

Unfortunately some State Drug Authorities have issued manufacturing licenses for a very large number of FDCs without prior clearance from CDSCO. This is in violation of rules though till May 2002, there was some ambiguity on powers of the State Drug Authorities in this respect. However the end result is that many FDCs in the market have not been tested for efficacy and safety. This can put patients at risk. (Para 9.2)

To remove such unauthorized FDCs from the market, the Central Government can either issue directions under Section 33P to states to withdraw the licences of FDCs granted without prior DCGI approval or the Central Government can itself ban such FDCs under Section 26A. (Para 9.3)

The Committee was informed that DCGI has been requesting State Orug Authorities not to issue manufacturing licences to new FDCs and suspend licences of unauthorized FDCs issued in the past. However in exercise of powers under Section 33P specific directions have not been issued. The Ministry failed to provide any coherent reason for lack of action under this Rule. The Ministry informed the Committee that even if Section 33P was invoked, there was no provision to take action against States if directions were not carried out. If considered necessary, the Ministry may examine the possibility of amending the law to ensure that directions under Section 33P are implemented. (Para 9.4)

It is also possible to ban FDCs, not authorized by CDSCO by invoking Section 26A which empowers the Central Government to ban any drug to protect public health. The Committee was informed that the Government has not evoked Section 26A either so far. No explanation was offered for not using powers under Section 26A. (Para 9.5)

The Committee was informed that the issue regarding grant of Manufacturing Licenses for unapproved FDCs by some State Drug Authorities were first deliberated in 49th DTAB meeting held on 17 February, 2000 *i.e.* 11 years ago. It is a matter of great concern that even after a lapse of a decade, no serious action has been taken. (Para 9.6)

The Committee is of the view that those unauthorized FDCs that pose risk to patients and communities such as a combination of two antibacterials need to be withdrawn immediately due to danger of developing resistance that affects the entire population. (Para 9.7)

The Committee is of the view that Section 26A is adequate to deal with the problem of irrational and/or FDCs not cleared by CDSCO. There is a need to make the process of

approving and banning FDCs more transparent and fair. In general, if an FDC is not approved anywhere in the world, it may not be cleared for use in India unless there is a specific disease or disorder prevalent in India, or a very specific reason backed by scientific evidence and irrefutable data applicable specifically to India that justifies the approval of a particular FDC. The Committee strongly recommends that a clear, transparent policy may be framed for approving FDCs based on scientific principles. (Para 9.8)

10. DRUGS ADVISORY COMMITTEES

The Committee feels that though the Ministry is forming DACs, which are given very important powers, there is no transparent procedure for the selection of experts of such Committees. The Committee also recommends that institutions from which experts are chosen should be from different parts of the country. (Para 10.2)

11. SIMILAR BRAND NAMES

The Committee strongly recommends that all such cases should be thoroughly reviewed in close coordination with State Drug Authorities. Specific procedures may be framed for approval of brand names. The procedure adopted by the Registrar of Newspapers to avoid duplication may be worth emulating. As a beginning, a data bank of all branded pharmaceutical products along with their ingredients should be uploaded on the CDSCO website and regularly updated. (Para 11.2)

12. POST-MARKETING SURVEILLANCE

In order to scrutinize the compliance of this rule, the Ministry was asked to furnish PSURs in respect of 42 randomly selected new drugs. Since files in respect of three drugs were reportedly missing, PSURs should have been supplied for the balance 39 drugs. The Committee is, however, constrained to note that PSURs in respect of only 8 drugs were submitted by the Ministry. The Committee was informed that 14 drugs though approved were not being marketed or were launched lately and hence PSURs would be expected later. There was no explanation for not submitting PSURs in respect of rest of 17 drugs. (Para 12.2)

Out of 14 drugs that were reported to be either not yet launched or lately launched, the Committee discovered that, at least, two products (FDC of glucosamine with ibuprofen; and moxonidine) were indeed in the market for some time and concerned manufacturers should have submitted PSURs. But the Committee has not been given any explanation for non-submission of PSURs for these two drugs. (Para 12.3)

The Committee observed that even, in those cases where the PSURs were submitted, the frequency and/or format was not as per rules. In the case of two drugs of MNCs (dronedarone of Sanofi Aventis and pemetrexid of Eli Lilly), the PSURs were neither India specific nor in the approved format as required by law. Some companies submitted PSURs for the products being marketed in the country but very few PSURs were India-specific. (Para 12.4)

The Committee is of the firm view that there is a poor follow-up of side effects in Indian patients both by doctors and manufacturers. The objective of PSURs is to collect information about adverse effects on patients in India which would help to determine ethnic differences, if any and result in dosage adjustment, revision of precautions and warnings, if necessary. The Committee takes strong exception to such rampant violation of the mandatory requirements. (Para 12.5)

The Committee is extremely anxious on both counts: such hugely costly imported drugs losing their potency before use and the possibility of fakes entering the chain. It is strange that multinational drug companies that have well staffed marketing offices in India, instead of importing drugs from their overseas affiliates and selling them are using traders to handle this activity. Apart from risk to patients, there is leakage of revenue to income tax. While the promotional expenses on imported formulations are being paid by the Indian branch of MNCs thus reducing income tax liability, there is no corresponding income since traders are paying directly to overseas offices of MNCs. The Committee would like the Ministry to ensure that in cases where MNCs have offices in India, traders are not permitted to import formulations of such companies. The Committee would like to be kept informed of the steps taken on this issue. (Para 15.9)

The Committee recommends that once a batch of a drug is found to be sub-standard and reported to CDSCO, it should issue a press release forthwith and even insert paid advertisements in the newspapers apart from uploading the information on the CDSCO website. Retail chemists should be advised to stop selling unsold stocks and return the same to local Drugs Inspectors as per rules. The Committee understands that at least two State Drug Authorities, that of Maharashtra and Kerala, have taken the initiative to upload information on spurious and sub-standard drugs on their websites on a monthly basis. These are welcome measures worth emulating by other states and the Centre. (Para 15.11)

16. ADVERTISING OF PRESCRIPTION DRUGS IN THE LAY MEDIA

The Committee would like the Ministry to take appropriate action against the companies that have advertised the above Schedule H drugs in the lay press. The provisions in the Drugs and Magic Remedies Act are not stringent enough with the result that manufacturers violate them at will. It also recommends that apart from giving sharper teeth to the Drugs and Magic Remedies Act, a provision should also be incorporated in the Drugs and Cosmetics Rules to ban such practices and penalize offenders. The Committee would like to be informed of the action taken to implement these recommendations. (Para 16.2)

17. CONSUMER INFORMATION

The Committee is of the firm opinion that accurate information on drugs for patients is absolutely essential to prevent inappropriate use more particularly in children, elderly, during pregnancy and lactation. The Committee recommends that the matter may be looked into to ensure that consumers have the required information to use medicines safely. Given the widespread internet connectivity, it is advisable to devise a system where patients can get unbiased information on drugs at the click of the mouse in any language. (Para 17.3)

18. CLINICAL TRIALS ON NEW DRUGS

Due to the sensitive nature of clinical trials in which foreign companies are involved in a big way and a wide spectrum of ethical issues and legal angles, different aspects of Clinical trials need a thorough and in-depth review. This Committee has, accordingly, taken it up as a subject for detailed examination separately under the heading 'Clinical Trials of Drugs'. (Para 18.2)

Prashant Bhushan
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The Committee strongly recommends that the Ministry should direct CDSCO to send a stern warning to all manufacturers of new drugs to comply with mandatory rules on PSURs or face suspension of Marketing Approval. PSURs should be submitted in CDSCO-approved format which would help track adverse effects discovered in Indian ethnic groups. (Para 12.6)

13. PHARMACOVIGILANCE

The Committee feels that the conventional system of locating side effects through spontaneous reporting by doctors to either drug companies or drug regulators has been found to be unsatisfactory. The most effective system is by controlled post-marketing Phase IV studies on a very large number of patients. In the past decade, all the major adverse effects that led to banning of drugs were identified in large scale Phase IV trials. The Ministry may wish to consider the possibility of using this format in the country. (Para 13.3)

14. UPDATION OF INFORMATION ON MARKETED DRUGS

14.3 **The Committee feels that unless information on marketed drugs is continuously updated, there is risk of irrational or inappropriate use of medicines putting patients at risk. The Committee, therefore, recommends that immediate steps need to be taken to address this issue. The CDSCO should be directed to continuously update monographs based on information from regulatory authorities the world over.** (Para 14.3)

15. SPURIOUS/SUB-STANDARD DRUGS

A drug can be categorized 'Not of Standard Quality' for a variety of both major and minor technical reasons such as not stating the name of the pharmacopoeia correctly, problem with quality of bonding agent, colouring agent, dissolution time, etc. However, there are other more serious cases, where the active ingredient is significantly less in quantity that can harm patients. Therefore, this problem needs to be addressed with all the seriousness that it deserves both by more rigorous checks in procuring bulk drugs (particularly from developing countries with not so stringent quality checks and export controls) and by in-house quality control by manufacturers or solving the problem in transportation and/or storage at distribution/retail levels. (Para 15.4)

By the time a sample is tested, a large number of packs get sold out with undeterminable injury to patients. There is no effective method of recalling unsold stocks lying in the distribution network. This cannot be allowed to go on. (Para 15.5)

The Committee feels that there should be severe punishment for manufacturing and for allowing sub-standard drugs to enter the distribution chain. Products with severe deficiencies should be penalized the same way as producers of spurious drugs by amending rules. There is also a case to incorporate penal provisions for manufacturing misbranded and adulterated drugs. (Para 15.6)

It is known that retail chemists also stock and sell items other than drugs including chocolates, cold drinks etc. During summer these items are stored in the refrigerator while due to paucity of space temperature-sensitive medicines may be lying outside. When samples are picked up, tested and found to be sub-standard, the State Drug Authorities blame and prosecute manufacturers. Therefore the Committee recommends that specifically in the case of temperature sensitive products such as insulins, due consideration should be given to the reference samples of the same batch preserved by the manufacturers. (Para 15.7)

ANNEXURE: P17

केन्द्रीय सूचना आयोग
Central Information Commission
बाबा गंगनाथ मार्ग, मुनिरका
Baba Gangnath Marg, Munirka
नई दिल्ली, **New Delhi – 110067**

द्वितीय अपील संख्या / Second Appeal No.:- CIC/MH&FW/A/2018/159460-BJ

Mr. Prashant Reddy

....अपीलकर्ता/Appellant

VERSUS
बनाम

1. CPIO
Directorate General of Health Services
O/o the DCG (1) (RTI Cell)
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2. CPIO & Under Secretary
Drugs Regulation Section
Ministry of Health & Family Welfare
Nirman Bhawan, New Delhi - 110011

...प्रतिवादीगण /Respondent

Date of Hearing : 12.05.2020
Date of Decision : 26.05.2020

Date of RTI application	07.05.2018
CPIO's response	30.05.2018
Date of the First Appeal	05.06.2018
First Appellate Authority's response	04.07.2018
Date of diarised receipt of Appeal by the Commission	28.09.2018

ORDER

FACTS:

The Appellant vide his RTI application sought information regarding the copy of the reports and recommendations of the Office Order issued by the DCGI on 26 March 2013 and review processes adopted by CDSCO in granting approval for new drugs and clinical trials, in response to the comments made by the Parliamentary Standing Committee on Health and Family Welfare in its 59th Report headed by Dr. T. M. Mohapatra.

The CPIO, RTI Cell (O/o the DCG-I) vide its letter dated 30.05.2018 informed that Dr. T. M. Mohapatra Committee report was not readily available and therefore refused to provide information. The CPIO further transferred his application to the M/o H&FW u/s 6(3) of the RTI Act, 2005. Dissatisfied by the response of the CPIO, the Appellant approached the FAA. The

FAA, vide its order dated 04.07.2018 stated that as per the information obtained from the concerned division of CDSCO, report submitted by Prof. T. M. Mohapatra Committee was not available.

HEARING:

Facts emerging during the hearing:

The following were present:

Appellant: Mr. Prashant Reddy through WhatsApp / TC;

Respondent: Mr. R. G. Singh, CPIO through WhatsApp / TC; and Mr. Abhishek Chawardol, Drugs Inspector, Mr. Sushanta Sarkar, CPIO & ADC (I) (M: 8108523891), Mr. A. K. Pradhan, FAA & DDC (I) and Mr. R. K. Singh, Legal Consultant, CDSCO in person;

The Appellant reiterated the contents of the RTI application and stated that he had essentially sought the copy of the Mohapatra Committee Report which was malafidely denied by the Respondent claiming it was untraceable. However, subsequent to the issuance of the notice of instant hearing, the Respondent (DCG-I, RTI Cell) after waiting for 2 years, emailed a copy of the Mohapatra Committee on May 11, 2020 at 9:28 PM which was neither signed nor certified which indicated their malafide conduct. Elaborating his contention regarding the malafide conduct, the Appellant stated that the true reasons for the Respondent to suppress a copy of the report was due to the reason that the Mohapatra committee pointed out shocking lapses by the office of the DCGI in the approval of new drugs under the Drugs & Cosmetics Act. Many of these lapses border on criminal negligence. Similarly, Respondent (Drug Regulation Section, M/o Health and Family Welfare) also misled him. In its reply dated June 21, 2018 after Respondent No. 1 transferred the application to it, the CPIO stated it did not have a copy of the Mohapatra Committee Report. However as per the content of the report, Dr. Shailendra Kumar, Director, Ministry of Health was made a member of the committee. It follows that the Ministry of Health had to have a copy of the report. The Appellant further stated that there appeared to be a long running problem of missing files at the office of the DCGI. In its 59th report, the Parliamentary Standing Committee on Health and Family Welfare (Annexure E) made several observations regarding missing files at the office of the DCGI. In support of his contention, the Appellant referred to para 7.12 and 7.13 of the said report. Similarly, the Mohapatra Committee has also commented on the issue of poorly maintained records and missing files at the office of the DCGI. A reference was made to para 15 and 16 of the said report. It was also submitted that the Commission has pointed out in several previous cases that a missing file is an offence under the Public Records Act, 1993 and a legal inquiry must be conducted if a file goes missing. The Appellant requested to allow him the time to file a detailed written submission elaborating his contentions with supporting case laws.

In its reply, the Respondent (Drugs Regulation Section, M/o Health and Family Welfare) re-iterated the response of the CPIO/ FAA and stated that since the information sought was not available with them the application was forwarded to the M/o Health and Family Welfare u/s 6(3) of the RTI Act, 2005. It was further mentioned that the department on a number of occasions in its reply to the Parliament Questions had given a detailed action taken report on the recommendations made in the Report of Department Related Parliamentary/ Standing Committee with regard to the functioning of CDSCO. Thus while stating that an appropriate reply was given to the Appellant, the Respondent requested to furnish a detailed written submission through email by 15.05.2020 to elaborate the aforementioned submission.

In its reply, the Respondent (CDSCO, RTI Cell) stated that initially the documents sought by the Appellant were not held and available with them. However, subsequent to the receipt of the notice of hearing from the Commission, they had approached Prof T.M. Mohapatra personally who had provided

them a copy of the "Report of the Committee Constituted to review the Procedures and Practices followed by CDSCO for Granting Approval and Clinical Trials on Certain Drugs" which was forwarded to the Appellant in the form it was made available to them. During the hearing, the Respondent emphasized that the documents that were held and available with them were provided by them. It was also assured that a certified copy of the documents would be provided to the Appellant in accordance with the provisions of the RTI Act, 2005. On being queried by the Committee regarding the system of record keeping and the steps initiated by the Respondent to ensure to overall strengthen the drug Regulatory System, the Respondent requested to submit a detailed written submission through email by 15.05.2020 highlighting the various steps taken to strengthen the Drug Regulatory System and the Parliamentary Questions answered by the Government regarding the functioning of the CDSCO. The Respondent also submitted that since 2015, they had devised a mechanism for digitization and archiving their records. During the hearing, the Appellant provided his email id(preddy85@gmail.com) so that the Respondent could provide a copy of their written submissions to him and also requested for time till 16.05.2020, to submit his response.

The Commission was in receipt of a written submission from the Appellant dated 11.05.2020 wherein it was stated that he intended to raise the issue of missing files and that in the interest of transparency all the information related to drug approval should be placed in the public domain.

The Commission was also in receipt of a written submission from the Respondent M/o Health and Family Welfare, D/o Health and Family Welfare, Drugs Regulation Section dated 05.05.2020 wherein it was inter alia stated that the matter was examined and it was noted that the Appellant had sought the report submitted by the Committee headed by Dr T M Mohapatra to review processes adopted by CDSCO in granting approval of new drugs and clinical trials. The said committee had been constituted by CDSCO. As the report was stated to be not available with CDSCO thorough physical search of the Section was conducted for tracing a copy of the report. Electronic search was also conducted to trace the report. However, it was found that no such report was received in Drugs Regulation Section. Accordingly, a reply was sent to the Appellant on 21.06.2018. Furthermore, no first appeal was filed against the reply of the Ministry. The First Appeal filed with the CDSCO was disposed off on 04.07.2018.

The Commission was also in receipt of a written submission from the Respondent (CPIO, CDSCO, RTI Cell) dated 11.05.2020 wherein it was inter alia stated that with all possible efforts the relevant files were not available. However, the documents as received from the Expert Committee Chairman's record had been provided to the Appellant vide letter dated 11.05.2020. It was also stated that the CPIO always acted reasonably and diligently with bonafide intent and did not have any intention to hide the information as sought by the Appellant.

Subsequent to the hearing, the Commission was in receipt of a written submission from the Respondent (Drugs Regulation Section, M/o Health and family Welfare) dated 15.05.2020 wherein in addition to the submission dated 05.05.2020 it was stated that a reply on the 59th report of the Department Related Parliamentary Standing Committee of Rajya Sabha on functioning of the Central Drugs Standard Control Organization (CDSCO) was sent to the Rajya Sabha Secretariat by the Ministry which was laid on the table of the house on 26.04.2013. It was further mentioned that the department on a number of occasions in its reply to the Parliament Questions had given a detailed action taken on the recommendations made in the Report of Department Related Parliamentary/ Standing Committee with regard to functioning of CDSCO. A copy each of the replies to three questions (Rajya Sabha Unstarred Question No.304 dated 18.07.2017, Lok Sabha Starred Question No.361 dated 13.12.2019 and Lok Sabha Unstarred

Question No.2714 dated 06.03.2020) was attached with the written submission. It was stated that the Department had in its reply dated 18.07.2017 to Rajya Sabha Unstarred Question No.304, had given the details of the action taken on the issue of grant of manufacturing license by State Licensing Authorities for a number of Fixed Dose Combinations (FDC) without prior clearance from Central Drugs Standard Control Organization (CDSCO). Similarly, in its replies dated 13.12.2019/ (Lok Sabha Starred Question No.361) and 06.03.2020 (Lok Sabha Unstarred Question 2714), the Department had informed the Parliament about the measures taken, based on regular review of CDSCO and its functioning, to address the various issues highlighted in the 59th Report of the Department Related Parliamentary: Standing Committee.

The Commission was also in receipt of a written submission from the CPIO, DGHS (CDSCO, RTI Cell) dated 15.05.2020 wherein while referring to the 59th report to the Parliament submitted on 08.05.2012, it was stated that the M/o Health and Family Welfare submitted its final action taken replies on the aforementioned report on 28.12.2012. The Ministry submitted the details of various steps taken to strengthen the Drug Regulatory System including the measure taken to streamline the process of New Drug approval and the recommendations of Dr Katoch Committee of experts constituted by the Ministry to examine the validity of the scientific and statutory basis adopted for the approval of New Drug without Clinical Trial and pointed out in the 59th report, etc. Subsequently, the Parliamentary Standing Committee had considered the action taken replies and made various recommendations for the implementation in its 66th report. Since then the matter relating to drug regulatory structures were being made more efficient had been taken on the findings and recommendations of those committees. The recommendations made by Dr Katoch Committee were further gone into by Prof Ranjit Roy Chowdhury Committee and various recommendations implemented. While referring to the various measures taken to address the issues, the Respondent referred to two Parliament Questions on functioning of CDSCO (1) L.S. Starred Q No 361 for 13.12.2019 and (2) L.S. Unstarred Q No 2714 for 06.03.2020 wherein the MPs had asked among others whether the Government had reviewed the functioning of Central Drugs Standard Control Organization (CDSCO) and if so, the details and the outcome thereof. Moreover, between 2017 to 2020, the Appellant had filed about 30 RTIs on various matters relating to the approval of three drugs (Buclizine, Letrozole & Aceclofenac and Drotaverin) which were also covered under the review by the Prof T.M. Mohapatra Committee. Thus, the CPIO had always acted reasonably and diligently with bonafide intent and did not have any intention to hide any information as sought by him.

The Commission was also in receipt of a written submission from the Appellant dated 15.05.2020 wherein it was inter alia stated that he had requested for a copy of the Mohapatra Committee report since May 7th, 2018. The Mohapatra Committee was constituted by an order of the DCGI on March 26, 2013 after a Parliamentary Standing Committee pointed out glaring irregularities in the grant of drug approvals. In their responses to the RTI application, Respondents No. 1 and No. 2 denied having a copy of the Mohapatra Committee Report claiming that it was untraceable. After waiting for 2 years, Respondent No. 1 emailed a copy of the Mohapatra Committee on May 11, 2020 at 9:28 PM which was neither signed nor certified. The actions of Respondent No. 1 smack of a malafide intent. It was evident from reading the Mohapatra Committee report as to the true reasons for the Respondent No. 1 suppressing a copy of the report. In pertinent part, the Mohapatra committee pointed out shocking lapses by the office of the DCGI in the approval of new drugs under the Drugs & Cosmetics Act. Many of these lapses border on criminal negligence. Similarly, Respondent No. 2 also misled the RTI applicant. In its reply dated June 21, 2018 after Respondent No. 1 transferred the application to it, the CPIO stated it did not have a copy of the Mohapatra Committee Report. However as per the content of the report, Dr. Shailendra Kumar, Director, Ministry of Health was made a member of the committee. It follows that the

Ministry of Health had to have a copy of the report. The Appellant further stated that there appeared to be a long running problem of missing files at the office of the DCGI. In its 59th report, the Parliamentary Standing Committee on Health and Family Welfare (Annexure E) made several observations regarding missing files at the office of the DCGI. In support of his contention, the Appellant referred to para 7.12 and 7.13 of the said report. Similarly, the Mohapatra Committee has also commented on the issue of poorly maintained records and missing files at the office of the DCGI. A reference was made to para 15 and 16 of the said report. It was also submitted that the Commission has pointed out in several previous cases that a missing file is an offence under the Public Records Act, 1993 and a legal inquiry must be conducted if a file goes missing. In this context, a reference was made to the decisions of the Commission in Shri. Om Prakash v. Land & Building Dept., GNCTD (CIC/DS/A/2013/001788SA) dated Aug. 29, 2014; Balendra Kumar v. PIO, M/o Labour & Employment (CIC/BS/C/2016/000025) dated Apr. 03, 2017 and Shahzad Singh v Department of Posts (CIC/POSTS/A/2016/299355) dated July 31, 2017. Thus, it was prayed to (a) provide him with a certified and signed copy of the report, along with the missing annexures; (b) impose a penalty on both Respondent No. 1 and Respondent No. 2 for not providing a copy of the Mohapatra committee report for a period of 2 years; (c) invoke its power under Section 19(8)(iii) of the RTI Act to order Respondent No. 1 to publish all information regarding approvals of new drugs on its website; (d) invoke its power under Section 19(8)(iv) of the RTI Act to order Respondent No. 1 to conduct an audit of all files and present a report to the CIC regarding the plan of action for missing files; (e) Invoke its power under Section 19(8)(vi) of the RTI Act to order Respondent No. 1 to provide a report of its compliance with Section 4(1)(b) of the RTI Act; (f) To order the Respondent No. 1 to register a FIR under the Public Records Act, 1993 so that an investigation may be conducted into the missing files.

The Commission referred to the definition of information u/s 2(f) of the RTI Act, 2005 which is reproduced below:

> *"information" means any material in any form, including records, documents, memos, e-mails, opinions, advices, press releases, circulars, orders, logbooks, contracts, report, papers, samples, models, data material held in any electronic form and information relating to any private body which can be accessed by a public authority under any other law for the time being in force."*

Furthermore, a reference can also be made to the relevant extract of Section 2 (j) of the RTI Act, 2005 which reads as under:

> *"(j) right to information" means the right to information accessible under this Act which is held by or under the control of any public authority and includes ....."*

In this context a reference was made to the Hon'ble Supreme Court decision in 2011 (8) SCC 497 (CBSE and Anr. Vs. Aditya Bandopadhyay and Ors), wherein it was held as under:

> *35..... "It is also not required to provide 'advice' or 'opinion' to an applicant, nor required to obtain and furnish any 'opinion' or 'advice' to an applicant. The reference to 'opinion' or 'advice' in the definition of 'information' in section 2(f) of the Act, only refers to such material available in the records of the public authority. Many public authorities have, as a public relation exercise, provide advice, guidance and opinion to the citizens. But that is purely voluntary and should not be confused with any obligation under the RTI Act."*

Furthermore, the Hon'ble Supreme Court of India in Khanapuram Gandaiah Vs. Administrative Officer and Ors. Special Leave Petition (Civil) No.34868 OF 2009 (Decided on January 4, 2010) had held as under:

> *6. "....Under the RTI Act "information" is defined under Section 2(f) which provides:*
>
> *"information" means any material in any form, including records, documents, memos, e-mails, opinions, advices, press releases, circulars, orders, logbooks, contracts, report, papers, samples, models, data material held in any electronic form and information relating to any private body which can be accessed by a public authority under any other law for the time being in force."*
>
> *This definition shows that an applicant under Section 6 of the RTI Act can get any information which is already in existence and accessible to the public authority under law. Of course, under the RTI Act an applicant is entitled to get copy of the opinions, advices, circulars, orders, etc., but he cannot ask for any information as to why such opinions, advices, circulars, orders, etc. have been passed."*
>
> *7. "....the Public Information Officer is not supposed to have any material which is not before him; or any information he could have obtained under law. Under Section 6 of the RTI Act, an applicant is entitled to get only such information which can be accessed by the "public authority" under any other law for the time being in force. The answers sought by the petitioner in the application could not have been with the public authority nor could he have had access to this information and Respondent No. 4 was not obliged to give any reasons as to why he had taken such a decision in the matter which was before him."*

The Commission observed that subsequent to the issuance of notice of hearing, the Respondent CDSCO provided a copy of the Mohapatra Committee Report which was not certified as per the RTI Act, 2005. In this context, a reference can be made to OM issued by the DoP&T No. 10/1/2013-IR dated 06.10.2015 wherein it was mentioned as under:

> "2. In addition, wherever the applicant has requested for 'certified copies' of the documents or records, the CPIO should endorse on the document "True copy of the document/record supplied under RTI Act", sign the document with .date, above a seal containing name of the officer, CPIO and name of public authority."

Furthermore, the Hon'ble Kerala High Court in John *Numpeli v. The PIO* in W.P. (C) No. 31947 of 2012 (P) dated 31.01.2017 had held as under:

> *"I also find no merit or force in the contention of the respondents that grant of certified copies may give authenticity to the documents which may not be genuine or even fabricated. In the event of an applicant's request for information being granted all that the Public Information Officer would have to do is to certify that the copy is one issued under the Right to Information Act, 2005. He is not called upon to certify that it is a copy of a genuine document. I therefore, find no reason why the first relief prayed for by the petitioner cannot be granted.*
>
> *I accordingly allow the writ petition and direct the first respondent to issue a fresh set of documents sought for in Ext.P1 application other than the No Objection Certificate*

issued by the Fire and Rescue Services Department on the petitioner paying the requisite fees and to certify the copies as copies issued under the Right to Information Act, 2005. The needful in the matter shall be done and copies of documents issued within one month from the date of receipt of a copy of this judgment."

The Commission thus observed that as per the provisions of the RTI Act, 2005 and various judgements on the subject matter clearly establishes that it is the duty of the CPIO to provide clear, cogent and precise response to the information seekers. Section 7 (8) (i) of the RTI Act, 2005 also states that where a request for disclosure of information is rejected, the CPIO shall communicate the reasons for such rejection. The Commission also referred to the decision of the Hon'ble Delhi High Court in J P Aggarwal v. Union of India (WP (C) no. 7232/2009 wherein it was held that:

*" 7**"it is the PIO to whom the application is submitted and it is who is responsible for ensuring that the information as sought is provided to the applicant within the statutory requirements of the Act. Section 5(4) is simply to strengthen the authority of the PIO within the department; if the PIO finds a default by those from whom he has sought information. The PIO is expected to recommend a remedial action to be taken".** The RTI Act makes the PIO the pivot for enforcing the implementation of the Act."*

8.....The PIO is expected to apply his / her mind, duly analyse the material before him / her and then either disclose the information sought or give grounds for non-disclosure."

Furthermore, the Hon'ble High Court of Delhi in the matter of R.K. Jain vs Union of India, LPA No. 369/2018, dated 29.08.2018, held as under:

"9..... That apart, the CPIO being custodian of the information or the documents sought for, is primarily responsible under the scheme of the RTI Act to supply the information and in case of default or dereliction on his part, the penal action is to be invoked against him only."

The Commission also noted that it should be the endeavour of the CPIO to ensure that maximum assistance should be provided to the RTI applicants to ensure the flow of information. In this context, the Commission referred to the OM No.4/9/2008-IR dated 24.06.2008 issued by the DoP&T on the Subject "*Courteous behavior with the persons seeking information under the RTI Act, 2005*" wherein it was stated as under:

*"**The undersigned is directed to say that the responsibility of a public authority and its public information officers (PIO) is not confined to furnish information but also to provide necessary help to the information seeker, wherever necessary.**"*

The Commission thus felt that there was an urgent need to develop a robust system of record keeping in the Respondent Public Authority and to review its efficaciousness periodically. In this context, a reference was made to the decision of the Hon'ble High Court of Bombay in the matter of *Union of India v. Vishwas Bhamburkar*, W.P.(C) 3660/2012 dated 13.09.2013 wherein the Court had in a matter where inquiry was ordered by the Commission observed as under:

"6.....It is not uncommon in the government departments to evade disclosure of the information taking the standard plea that the information sought by the applicant is not available. Ordinarily, the information which at some point of time or the other was available in the records of the government, should continue to be available with the concerned department unless it has been destroyed in accordance with the rules framed by that department for destruction of old record. Therefore, whenever an information is sought and it is not readily available, a thorough attempt needs to be made to search and locate the information wherever it may be available. It is only in a case where despite a thorough search and inquiry made by the responsible officer, it is concluded that the information sought by the applicant cannot be traced or was never available with the government or has been destroyed in accordance with the rules of the concerned department that the CPIO/PIO would be justified in expressing his inability to provide the desired information. Even in the case where it is found that the desired information though available in the record of the government at some point of time, cannot be traced despite best efforts made in this regard, the department concerned must necessarily fix the responsibility for the loss of the record and take appropriate departmental action against the officers/officials responsible for loss of the record. Unless such a course of action is adopted, it would be possible for any department/office, to deny the information which otherwise is not exempted from disclosure, wherever the said department/office finds it inconvenient to bring such information into public domain, and that in turn, would necessarily defeat the very objective behind enactment of the Right to Information Act."

The Hon'ble High Court of Gujarat in the matter of Chandravadan Dhruv vs. State of Gujarat and Ors, Special Civil Application No. 2398 of 2013 dated 21.12.2013 held as under:

"24. Since the issue raised by the petitioner is of a vital public importance, we, on our own, made a little research on the subject and found that the Department of Personnel and Training of the Government of India has constituted a Task Force for the effective implementation of Section 4 of the RTI Act. As a part of this Task Force, IT for Change is facilitating a sub group on 'Guidelines for Digital Publication under RTI supporting Proactive Disclosure of Information'. As a part of the work of this sub-group a one day consultation was held on the said subject i.e. 'Formulating guidelines for digital publication under RTI supporting proactive disclosure of information' in Bengaluru.

25.3 How to ensure proper record keeping?

• The required level of proactive disclosure is not possible without appropriate record keeping, and this aspect needs focused attention. There are detailed rules for record keeping and they should be strictly followed and the scheme for it should be published. Record keeping practices may have to be reviewed from the point of view of comprehensive proactive disclosure requirements, especially through digital means.

• Section 4.1.a is very clear about the need for proper record keeping, inducing in digital and networked form. Funds should be earmarked for digitizing records. Complete details of all records that are maintained and available digitally, and about those which are not, with due justification thereof, should be published. Annual reports on compliance with section 4.1.a should be sought by the Information Commissions.

• *The costs involved in digitizing resources and maintaining networked computer based record-keeping and information systems is often cited as a major deterrent. It was felt that it is no longer a major issue. India is at par or better in terms of IT issues than many developed countries that maintain high standards of digital publishing of public information. The real cost is in terms human resources, including skills, and these are easily available at all levels in India today.*

• *An example was given about how a government office in Bangalore was able to scan all its documents at a very low cost. Another example that was discussed was of 'Bhoomi' project in Karnataka, whereby, it was contended that, if open public access to such complex spatial data as the land records of the entire state can be ensured, how can giving access to all textual documents of an office or department be any more difficult."*

The Commission observed that a voluntary disclosure of all information that ought to be displayed in the public domain should be the rule and members of public who *having to seek* information should be an exception. An open government, which is the cherished objective of the RTI Act, can be realised only if all public offices comply with proactive disclosure norms. Section 4(2) of the RTI Act mandates every public authority to provide as much information *suo-motu* to the public at regular intervals through various means of communications, including the Internet, so that the public need not resort to the use of RTI Act.

The Hon'ble Supreme Court of India in the matter of CBSE and Anr. Vs. Aditya Bandopadhyay and Ors 2011 (8) SCC 497 held as under:

"37. The right to information is a cherished right. Information and right to information are intended to be formidable tools in the hands of responsible citizens to fight corruption and to bring in transparency and accountability. The provisions of RTI Act should be enforced strictly and all efforts should be made to bring to light the necessary information under Clause (b) of Section 4(1) of the Act which relates to securing transparency and accountability in the working of public authorities and in discouraging corruption."

The Commission also observes the Hon'ble Delhi High Court ruling in WP (C) 12714/2009 Delhi Development Authority v. Central Information Commission and Another (delivered on: 21.05.2010), wherein it was held as under:

"16.It also provides that the information should be easily accessible and to the extent possible should be in electronic format with the Central Public Information Officer or the State Public Information Officer, as the case may be. The word disseminate has also been defined in the explanation to mean - making the information known or communicating the information to the public through notice boards, newspapers, public announcements, media broadcasts, the internet, etc. It is, therefore, clear from a plain reading of Section 4 of the RTI Act that the information, which a public authority is obliged to publish under the said section should be made available to the public and specifically through the internet. There is no denying that the petitioner is duty bound by virtue of the provisions of Section 4 of the RTI Act to publish the information indicated

in Section 4(1)(b) and 4(1)(c) on its website so that the public have minimum resort to the use of the RTI Act to obtain the information."

Furthermore, High Court of Delhi in the decision of General Manager Finance Air India Ltd & Anr v. Virender Singh, LPA No. 205/2012, Decided On: 16.07.2012 had held as under:

"8. The RTI Act, as per its preamble was enacted to enable the citizens to secure access to information under the control of public authorities, in order to promote transparency and accountability in the working of every public authority. An informed citizenry and transparency of information have been spelled out as vital to democracy and to contain corruption and to hold Governments and their instrumentalities accountable to the governed. The said legislation is undoubtedly one of the most significant enactments of independent India and a landmark in governance. The spirit of the legislation is further evident from various provisions thereof which require public authorities to:

A. Publish inter alia:

i) the procedure followed in the decision making process;

ii) the norms for the discharge of its functions;

iii) rules, regulations, instructions manuals and records used by its employees in discharging of its functions;

iv) the manner and execution of subsidy programmes including the amounts allocated and the details of beneficiaries of such programmes;

v) the particulars of recipients of concessions, permits or authorizations granted. [see Section 4(1) (b), (iii), (iv), (v); (xii) & (xiii)].

B. Suo moto provide to the public at regular intervals as much information as possible [see Section 4(2)]."

DECISION:

Keeping in view the facts of the case and the submissions made by both the parties, it was noted by the Commission that on its intervention, a reply was furnished to the Appellant. The Commission however expressed its serious concern over the record keeping methodology in the office of DCGI / CDSCO due to the fact that an important report relating to the review of procedures and practices followed by CDSCO for granting approval and clinical trials on certain drugs went missing from their office that had to be procured from the author after receipt of notice of hearing from the Commission. This is despite the fact that the Parliamentary Standing Committee had also taken cognizance of the lapses by the Public Authority. The intent and the conduct of the Public Authority should always be above board in matters relating to grant of approvals through a transparent and objective mechanism. The Commission advises Secretary, M/o Health and Family Welfare, Govt. of India to examine this matter appropriately for further necessary action at its end.

The Commission instructs the Respondent (CDSCO) to provide a certified copy of the information provided to the Appellant vide letter dated 11.05.2020 within a period of 30 days from the date of receipt of this order depending upon the condition for containment of the Corona Virus Pandemic in the Country or through email, as agreed. Moreover, taking into consideration the observations made in the preceding paragraphs, the Commission without commenting on the merits of the case, advises the Respondent to urgently initiate steps to streamline the process of digitization of records within the Public Authority so that the RTI applications/ First Appeals are dealt with in a time bound manner. The Commission also instructs the Public Authority officials to suo moto disclose its reports and other associated documents in the Public Domain for the benefit of public at large.

The Appeal stands disposed accordingly.

(The Order will be posted on the website of the Commission)

(Bimal Julka) (बिमल जुल्का)
(Chief Information Commissioner) (मुख्य सूचना आयुक्त(

Authenticated true copy
(अभिप्रमाणित सत्यापित प्रति)

(K.L. Das) (के.एल.दास)
(Dy. Registrar) (उप-पंजीयक)
011-26186535/ kl.das@nic.in
दिनांक / Date: 26.05.2020

Copy to:

1. The Secretary, Ministry of Health and Family Welfare, 'A' Wing, Nirman Bhawan, New Delhi-110011.

2. Drugs Controller General of India, Central Drugs Standard Control Organization Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India FDA Bhavan, ITO, Kotla Road, New Delhi -110002

Prashant Bhushan
(TRUE COPY)

OPINION ARTICLE

REVISED Revised World Health Organization (WHO)'s causality assessment of adverse events following immunization—a critique [version 2; peer review: 2 approved]

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Latest published: 29 May 2018, **7**:243 (https://doi.org/10.12688/f1000research.13694.2)

Abstract

The World Health Organisation (WHO) has recently revised how adverse events after immunization (AEFI) are classified. Only reactions that have previously been acknowledged in epidemiological studies to be caused by the vaccine are classified as a vaccine-product–related-reaction. Deaths observed during post-marketing surveillance are not considered as 'consistent with causal association with vaccine', if there was no statistically significant increase in deaths recorded during the small Phase 3 trials that preceded it. Of course, vaccines noted to have caused a significant increase in deaths in the control-trials stage would probably not be licensed. After licensure, deaths and all new serious adverse reactions are labelled as 'coincidental deaths/events' or 'unclassifiable', and the association with vaccine is not acknowledged. The resulting paradox is evident.

The definition of causal association has also been changed. It is now used only if there is 'no other factor intervening in the processes'. Therefore, if a child with an underlying congenital heart disease (other factor), develops fever and cardiac decompensation after vaccination, the cardiac failure would not be considered causally related to the vaccine. The Global Advisory Committee on Vaccine Safety has documented many deaths in children with pre-existing heart disease after they were administered the pentavalent vaccine. The WHO now advises precautions when vaccinating such children. This has reduced the risk of death. Using the new definition of causal association, this relationship would not be acknowledged and lives would be put at risk. In view of the above, it is necessary that the AEFI manual be revaluated and revised urgently. AEFI reporting is said to be for vaccine safety. Child safety (safety of children) rather than vaccine safety (safety for vaccines) needs to be the emphasis.

Keywords

Pentavalent vaccine; quinvaxim; pharmacovigilance; Hill criteria; macrophagicmyofasciitis; periodic safety update reports; Brighton classification; adverse drug reactions; sudden unexpected death; TOKEN study

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REVISED **Amendments from Version 1**

1. Corrections in language and for better readability.
2. Article divided into two sections with Section A covering AEFI assessment till Brighton and Section B dealing with the Revised AEFI categories after Brighton.
3. The Bradford Hill criteria introduced and Bradford Hill's biological gradient is discussed in the context of the harms of using multiple antigens all together.
4. Also the limitation of current knowledge (biological plausibility) delaying the acknowledgement of deaths in girls with high dose measles has been introduced.
5. Reference to death of children with congenital heart disease after pentavalent vaccine introduced in main body of article.
6. Box 5 It is clarified that with some rotavirus vaccines, *rotavirus diarrhea* is reduced but there no difference in the overall incidence of diarrhea (all-cause diarrhea).
7. The matter of the difference in death rates in boys and girls with high potency measles vaccine for which there is yet no scientifically plausible explanation has been added
8. A new paragraph on the mechanism of deaths after multiple vaccines related a cytokine storm (and deaths in susceptible babies) as held in a court ruling was added
9. A paragraph on the ruling that Italian army men must receive no more than 5 antigens simultaneously has been introduced.
10. The heading Conclusion was removed.
11. A new paragraph on "Where do we go from here" has been introduced.
12. Mention has been made of the efforts made to get the WHO to respond to the points made here.

See referee reports

Introduction

One of the earliest countries to introduce the pentavalent vaccine (combined diphtheria, tetanus, pertussis, Hib, and hepatitis B) was Sri Lanka[1]. A pentavalent vaccine Quinvaxem (Crucell) was introduced in Sri Lanka on January 1, 2008. On 29 April that year the vaccine was withdrawn by the government following five deaths. A World Health Organization (WHO) team of experts investigated the adverse events following immunization (AEFI) and reported the deaths were 'unlikely' to be related to vaccination. The full report was not widely available before it was presented to the High Court in Delhi, India[2]. From the full report it became clear that there was no alternate explanation for three deaths. Thus, they should have been classified as 'probable / likely' related to immunization, using the WHO Brighton criteria for classification of AEFI (see Box 1). The experts deleted the categories 'probable' and 'possible' from the AEFI Classification they used for assessment and then reported that the deaths were 'unlikely' related to vaccination. The way the Brighton Classification was altered to enable this misleading classification of the deaths in Sri Lanka was reported in the Indian Journal of Medical Research and the British Medical Journal[3,4].

On 4 May 2013 the Ministry of Health of Vietnam suspended the use of Quinvaxem (Crucell) after it had caused 12 deaths[5]. The WHO experts investigated the Vietnam deaths. This time they reported, 'Quinvaxem was pre-qualified by WHO..., no fatal adverse event following immunisation (AEFI) has ever been associated with this vaccine'[5]. This is the same brand of pentavalent vaccine that was used in Sri Lanka where WHO experts had previously documented AEFI deaths. It appears that after the Sri Lanka investigation and shortly preceding the Vietnam investigation, the methodology used for AEFI classification was revised. Using the revised AEFI causality assessment, AEFI reported from Sri Lanka could be classified as 'Not a case of [AEFI]'. Both Sri Lanka and Vietnam were persuaded to reintroduce the Pentavalent vaccine after the WHO report. The new mechanism that allows AEFI to be classified as 'Not a case of [AEFI]' will be discussed.

Section A

Historical background of causality assessment: from Hume up to Brighton

The evolution of the logic of causality assessment is fascinating. Eminent philosophers, scientists, legal luminaries, and statisticians have grappled with the issue and a great deal has been written about it. It will be impossible to distil all of that for this write-up, except at the risk of oversimplification. As we are concerned primarily with assigning causality to alleged drug reactions, only some aspects of the debate are germane to this discussion.

Defining cause and effect (X is the cause of Y) has not been easy. According to Hume[6], the major features of causation are temporal precedence (X must precede Y), contiguity and regularity of the association of causes and their effects. Confounding, however, is possible by a third factor.

It is known that the consumption of ice cream is higher when there is a spike in the incidence of sunburns. One can conclude wrongly that eating ice cream can cause sunburns. The third factor in this case is hot weather conditions. Both eating ice cream and getting sun burnt are associated with sunny days. Hume avoided the confounding problem by stipulating that X can be considered as cause of Y only if X is sufficient for Y. That is, however, fallacious. Striking a match can light a fire only if there is oxygen. In itself, striking the match is not sufficient. The alternate position could be that X is cause of Y if, and only if, X is necessary for Y[7]. John Mackie suggested that in nature there could be multiple reasons (causes) for the same outcome[8]. Thus X may not be necessary for Y but at the same time, X may be sufficient for Y. A building may be set on fire by a spark from a short circuit in the electrical wiring (X) or as the result of an act of arson (Z). Thus neither X) nor (Z) is necessary for Y, but both (X) and (Z) are sufficient causes for Y. The question then is whether Y would have occurred were it not for the factor X. This is known as the 'but for' test. In jurisprudence, it has been acknowledged that where there are multiple causes working simultaneously the 'but for test is unworkable and the question of causality is whether the putative cause materially contributed to the result[9]. This has been argued in the case of Graham Dickie V. Flexcon Glenrothes Limited [2009] ScotSC 143 (04 September 2009). Peter M. Willcock and James M. Lepp have discussed 'Causation in medical negligence cases' which elaborates on these issues.

Box 1. WHO adverse events following immunization (AEFI): Causality assessment Brighton criteria

Causality Term	Assessment Criteria
Very likely/Certain	A clinical event with a plausible time relationship to vaccine administration and which cannot be explained by concurrent disease or other drugs or chemicals
Probable	A clinical event with a reasonable time relationship to vaccine administration; is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Possible	A clinical event with a reasonable time relationship to vaccine administration, but which could also be explained by concurrent disease or other drugs or chemicals.
Unlikely	A clinical event whose time relationship to vaccine administration makes a causal connection improbable, but which could be plausibly explained by underlying disease or other drugs or chemicals
Unrelated	A clinical event with an incompatible time relationship and which could be explained by underlying disease or other drugs or chemicals
Unclassifiable	A clinical event with insufficient information to permit assessment and identification of the cause

Reference

http://www.rho.org/files/rb3/AEFI_Causality_Assessment_WHO_2005.pdf

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In biology, there is a further probabilistic element to causation. If men of the same height and women of the same height were to have children, their children will not all be of the same height. For the same set of observed causal factors, there is probability distribution of possible heights[7].

To evaluate causation Bradford Hill[10] described 9 guiding principles favouring a causative association: 1) Strength - effect size; 2) Consistency – reproducibility with similar observations at different places by different people;3) Specificity – absence of an alternate explanation; 4) Temporarily with cause always proceeding the effect; 5) Biological gradient demonstrating a dose response gradient; 6) Biological plausibility – although this may be limited by the state of current knowledge; 7) Coherence between epidemiology and laboratory findings; 8) Experimental evidence; and 9) Analogy - looking at the effect of similar factors. These considerations are applicable to alleged vaccine reactions also.

Adverse drug reactions

Adverse drug reactions (ADRs) can follow after the use of any drug. Careful evaluation is required to distinguish the events that are causally related to the drug from coincidental events. Causality assessment is crucial because the events could be iatrogenic and avoidable. Usually only a few react adversely to drugs on the market, whereas others are unharmed. The attribution of causality for such occasional happenings is particularly complex. Investigations of ADRs put causative association on a probability scale. The causality-assessment system developed by the World Health Organization Collaborating Centre for International Drug Monitoring is called the Uppsala WHO Centre (WHO-UMC) Scale. This is widely used as it offers a simple methodology (see Box 2). In consonance with Hume's postulates, the first step is to confirm temporal precedence and contiguity. The adverse event must appear after the suspected drug is administered and within a reasonable time-frame. Events where the time-to-drug-intake makes a relationship improbable are classified as 'unlikely' to be related. Events within a reasonable time and for which there is no alternate explanation (which cannot be attributed to disease or other drugs) are classified as 'probable / likely' related to the drug in question. Drug reaction is classified as 'possible' where there is a reasonable time relationship, but for which there are also alternate explanations. In terms of John Mackie's aphorism, the drug is considered sufficient but not necessary for the effect.

To be classified as 'very likely/certain' the reaction needs to be an objective and specific medical disorder or a recognized pharmacologic phenomenon, and there must be evidence of dose-related reaction or proof in terms of reappearance of symptoms on rechallenge. If death should occur as ADR, rechallenge is impossible. It is usually difficult to be certain about the causality of fatal ADR and the reaction is often classified as 'probable/likely' or 'possible'.

The difference between certain and probable/likely is simply the acceptable standard of proof. For "certainly," a high-standard irrefutable proof is called for (falsification of the theory by a single irregular outcome). A single well-documented spontaneous rechallenge is strong evidence of regularity (even though in just one patient). For 'very likely', the standard of proof is proof beyond reasonable doubt.

Box 2. WHO–UMC causality categories

Causality Term	Assessment Criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake, Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or Contradictory • Data cannot be supplemented or verified

Reference The Uppsala Monitoring Center. The use of the WHO-UMC system for standardised case causality assessment. Reproduced with permission of *Uppsala monitoring centre*. Available at https://www.who-umc.org/media/2768/standardised-case-causality-assessment.pdf

'Balance of probability' is the level of proof needed to classify as 'probable' or 'possible'and this is the standard of proof, which is relevant to medicine and for pharmacovigilance. With this level of proof (prima facie true), the 'Precautionary Principle' must be triggered. This is described later.

Adverse events following immunization

Vaccines are drugs used as a preventive measure, given to entire cohorts of healthy persons. As they are administered in the absence of any disease, there is very high expectation that they will produce few adverse effects. But there is low tolerance for serious adverse events and deaths. Adverse events following immunization (AEFI) must be monitored more carefully than other drugs. A credible immunization safety evaluation and monitoring system is essential for the success of immunization programmes. The WHO developed the 'Adverse Events Following Immunization (AEFI): Causality Assessment' otherwise known as the Brighton Classification. It is very similar to the WHO-UMC causality categories for ADR. Until recently, this was the touch-stone used by WHO experts when AEFI were reported (see Box 1).

One measure of the sensitivity and responsiveness of the WHO-UMC causality categories (which preceded the Brighton classification) is the alacrity with which the rotavirus vaccine RotaShield was withdrawn in 1999 after 12 cases of vaccine-induced intussusceptions were reported. About 1 in 2000 children younger than 2 months of age develops intussusception from other causes. Based on the results of the investigations, the Centre for Disease Control (CDC) estimated that one or two additional cases of intussusception would be caused among each 10,000 infants vaccinated with the RotaShield vaccine. After about 100,000 infants were immunized, the vaccine was withdrawn[11]. In 2013, the Brighton classification was abandoned and replaced by the revised AEFI classification. The reasoning that prompted the switch away from the Brighton classification has not been stated explicitly in the revised AEFI manual[12].

Section B

Brighton Abandoned: Revised Causality Assessment

The Council for International Organizations of Medical Sciences (CIOMS) / WHO: Report on vaccine pharmacovigilance. In October 2010, after a series of meetings, 40 experts (of whom 19 were industry representatives with possible conflicts of interest) helped rewrite the classification criteria for AEFIs. The document titled 'Definitions and Application of Terms for Vaccine Pharmacovigilance' is reported to 'provide tools for higher excellence of signal detection and investigation of adverse events following immunization'[13].

On page 170 of this 193-page document, under the heading Notes for Guidelines, it is stated in small print: 'If there is adequate evidence that an event does not meet a case definition, such an event should be rejected and should be reported as 'Not a case of

[AEFI]'. Such evidence is considered adequate, if an exclusion criteria is met, or an investigation reveals a negative finding of a necessary criterion (necessary condition) for diagnosis. Such an event should be rejected and classified as 'Not a case of [AEFI]".'[13]

The CIOMS/WHO 'tool for excellence in signal detection' works by turning a blind eye to AEFI—classifying AEFI as 'Not a case of [AEFI]'. Not only is the causative association of AEFI to immunization denied, but it is made to appear the AEFI never occurred. Signal detection is no longer possible once AEFIs are removed from the system after being designated as 'Not a case of [AEFI]'. The story in the *Introduction* above where the WHO asserted in May 2013 that no fatal AEFI has ever been associated with pentavalent vaccine[5], suggests the Sri Lanka AEFI deaths[2] are now reclassified as 'Not a case of [AEFI]' using the CIOMS/WHO tool.

Only reactions that meet case definitions of reactions associated with the vaccine previously are considered. According to the CIOMS / WHO report (page 11), a case definition can be adopted from the standard literature or by the reviewers themselves.

The case definition helps draw on previous epidemiological research and facilitates further research to confirm a causal link. However, excluding causality in relation to an individual event cannot be dependent on that event conforming to a pre-existing case definition. The pejorative use of the term 'rejected' (in the statement; 'Such an event should be rejected and classified as "Not a case of [AEFI]"'), suggests a defensive posture. It has been pointed out previously that reports of AEFIs should be assessed for causality and classified: they are not to be 'rejected'[14].

The WHO revised AEFI manual

In March 2013, the revised WHO 'User Manual for AEFI' was published with a new algorithm[12]. The manual acknowledges that it has adapted definitions and concepts from the CIOMS / WHO report. The new algorithm for AEFI is reproduced in Figure 1.

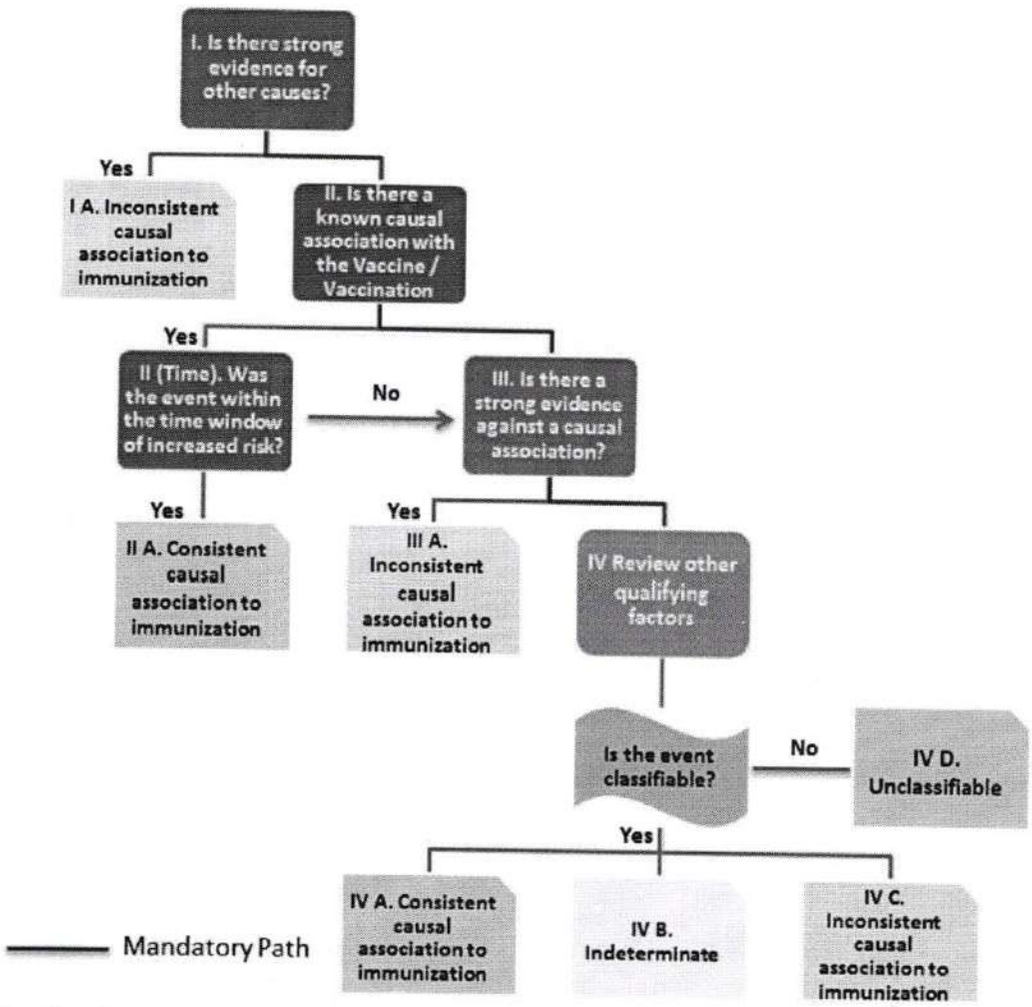

Figure 1. **Flow chart demonstrating the revised AEFI classification new algorithm.**

Revised AEFI classification: new categories of causality

Only events that occur after vaccine administration are eligible for AEFI causality assessment. This first step is reminiscent of Hume's dictum regarding precedence and contiguity. In the new scheme, causality is classified in four categories: 'Consistent causal association to immunization,' 'Indeterminate', 'inconsistent causal association to immunization', and 'Unclassifiable'.

Consistent causal association to immunization

This is the highest level of causal association in this new classification. It is less definitive than 'very likely / certain' in the old scheme. It does not call for irrefutable proof or even proof beyond reasonable doubt. Not even is the balance of probability assessed. In the new scheme, an adverse event can simultaneously be classified as 'Consistent causal association with immunization' and 'Inconsistent causal association with immunization'. On page 36 of the revised manual for AEFI[12] is the example of acute flaccid paralysis in a child after oral polio vaccine, who had had a fever 1 month prior to onset of paralysis. The stool culture showed vaccine strain polio virus. It was classified as 'Consistent causal association with immunization' as it is a known reaction after polio vaccination and the paralysis happened within time window of increased risk. It was also classified as 'Inconsistent causal association with immunization' because the fever, 1 month prior to paralysis had not been investigated completely. This ambiguity, which admits diametrically opposite conclusion simultaneously, is a hallmark of the new scheme.

It is suggested in the revised AEFI manual that before the question 'Did the vaccine given to a particular individual cause the particular event reported?' (the question of 'Did it?') is answered, one has to answer the question 'Can the given vaccine cause a particular adverse event?' (Can it?). The inference is that only if there is evidence at the population level that the vaccine can cause the adverse event, is the reaction classified as 'Consistent with causal association with immunization'.

This inference is flawed on two grounds. On the one hand, it denies all new associations seen in Phase 4 trials. On the other, if it is a known adverse reaction, causal association is accepted even where the events could have happened by coincidence. Just because intussusceptions are acknowledged as an adverse event following rotavirus vaccination, it does not follow that all intussusceptions in the critical window of increased susceptibility are necessarily caused by it. The residual uncertainty at this highest level of causal association robs it of value in addressing the problem of AEFI caused by vaccines.

Inconsistent causal association to immunization

At the bottom of the new causality classification hierarchy is 'Inconsistent causal association to immunization'. This group can include reactions for which there is no alternate explanation (and which would have been classified in the 'Probable' category previously). They would fall in the group 'Inconsistent causal association with vaccination' merely because causal association with immunization has not been documented in prior epidemiological studies. Into the same group are placed reactions that would have been considered 'Unlikely' to be associated, and those that would have been classified as 'Unrelated'. The use of the same category 'Inconsistent causal association to immunization' for such a wide variety of clinical situations merely obfuscates the issues. In the revised scheme, this term is used to suggest that there is no relation between the AEFI and immunization. No matter how frequently the reaction categorized as 'Inconsistent with causal association' occurs, it would not be investigated as a new signal of a causal association.

Indeterminate

Classification in the 'Indeterminate' group is reserved for reactions that could have been caused by immunization, but for which causal association has not been documented previously. It is projected that information on AEFI that are classified as indeterminate will be pooled and analysed in order to understand if the AEFI represents a new signal of an unrecognized event. The scheme is however loaded such that literally no AEFI are categorized into this group. How this is accomplished is discussed later on.

Unclassifiable

Clinical events with insufficient information to permit assessment and identification of cause are put in the 'Unclassifiable' group.

Revised AEFI classification: the new algorithm

Just as the final categories of causality association are vague, overlapping, and not clearly differentiated, the algorithm used to make a decision on causality[12] does not appear to be logical or well thought through.

The algorithm is shown in Figure 1.

Causality assessment algorithm

Four sets of questions need to be answered in sequence:

1. Is there strong evidence of other causes?
2. Is there known causal association with the vaccine or vaccination and if so, whether the event was within the time window of increased risk?
3. If there is no causal association known or if it is not within the time window of increased risk: Is there strong evidence against a causal association?
4. If there is no such strong evidence against causal association, the next step is to look at other qualifying factors for classification:
    a. Could it happen independently of vaccination (background rate)?
    b. Could the event be manifestation of another health condition?
    c. Did a comparable event occur after a previous dose of a similar vaccine?
    d. Was there exposure to a potential risk factor or toxin prior to the event?
    e. Was there acute illness prior to the event?
    f. Did the event occur in the past independently of vaccination?

g. Was the patient taking any medication prior to vaccination?

h. Is there biological plausibility?

Step 1

The first step in the revised algorithm is to look for strong evidence for other causes. If there is an alternate explanation, the AEFI is classified as 'Inconsistent with causal association to immunization'. John Mackie has noted that in nature there could be multiple reasons (causes) for the same outcome, and if two possible causes exist simultaneously either of them could be the causative factor[8]. It is to be noted that with the WHO-UMC classification of ADR and the old WHO/Brighton Classification of AEFI, even if an alternate explanation is available, a causative association with drug or vaccine is still considered 'Possible'. Moreover, the two causes could be working synergistically. An example of this is where genetic and other individual susceptibility factors make one susceptible to developing an AEFI[15,16]. In the new algorithm, if there is an alternate explanation for the AEFI, or another factor is involved, causative association with vaccine is rejected[12,14].

Step 2

The COIMS / WHO Report on pharmacovigilance is used at this level[13]. AEFI-specific case definitions for some reactions have been developed. In instances where specific case definitions and criteria are not available for a particular AEFI, it is permissible to improvise using case definitions adopted from 'standard medical literature, or national guidelines or they may be adopted locally by the reviewers' (page 11 CIOMS / WHO report). AEFI that meet case definitions and which occur within the time window of increased risk are classified as 'consistent causal association to immunization'.

The acceptable time window for each adverse event is different. The macrophagic myofasciitis affected patients usually are middle-aged adults presenting diffuse arthromyalgias, chronic fatigue, and marked cognitive deficits, fatigue, or depression due to long-term persistence of aluminium hydroxide within macrophages at the site of previous immunization[17]. However, AEFI surveillance seldom extents for so long.

Step 3

Theoretically, reactions that are not known to have a causal association or those that are not in the time window of increased risk can move to Step 3. At this stage, an enquiry is made whether there is strong evidence against causal association. Proving of a negative is notoriously difficult as it is impossible to affirm that in every circumstance, an irregular outcome is impossible. The example provided in the manual relates to MMR and autism.

It is reported that the Global Advisory Committee on Vaccine Safety (GACVS) and Council for International Organizations of Medical Sciences (IOM committee) have concluded that no evidence exists of a causal association between MMR vaccine and autistic disorders. Such AEFI must be classified as 'inconsistent with causal association to immunization' according to the new algorithm.

After publication of this AEFI user's manual, the conclusion about MMR and autism have become disputed again (see Box 3). This shifting evidence calls into question the usefulness of introducing this step in the algorithm of AEFI.

Step 4

Assuming that no such 'strong evidence against a causal association' exists, reactions that are not known to have a causal association with the vaccine, can go to Step 4. It is from here that reactions may be classified as indeterminate allowing it to be evaluated in future as a new signal.

The question at this point is whether it is 'classifiable — meaning whether all the tests needed have been performed to allow it to be classified under the CIOMS / WHO definitions. This is the second time these definitions are invoked during the AEFI evaluation.

Box 3. MMR and autism risk in African American children.

In 2004 the CDC published research demonstrating that there was no link between the vaccinated children's risk of a subsequent diagnosis of autism and the age at which the child is vaccinated with MMR[a]. It has now been revealed through the testimony of one of the authors Dr. W. W. Thompson who turned whistle blower, that the risk of autism among African American children vaccinated before the age of two years was 340% that of those vaccinated later. However this data was deliberately removed from the analysis to arrive at the CDC's proclaimed conclusion. CNN published the story of the CDC whistle-blower[b], and Thomson was granted whistleblower immunity by the Obama administration[c].

References:

a. DeStefano F, Bhasin TK, Thompson WW, Yeargin-Allsopp M, Boyle C. Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta. Pediatrics. 2004;113:259–66. doi: 10.1542/peds.113.2.259

b. Goldschmidt D. Journal questions validity of autism and vaccine study [Internet]. CNN.com. 2014 Aug 28 [cited 2014 Sep 29]. Available from: http://edition.cnn.com/2014/08/27/health/irpt-cdc-autism-vaccine-study

c. http://dailycaller.com/2015/02/03/obama-admin-grants-immunity-to-cdc-scientist-that-fudged-vaccine-rep4rt-whistleblower-plans-to-testify-before-congress

If some investigations are not done or not available, the AEFI is labelled as 'Unclassifiable' (or classified as 'Inconsistent with causal association to immunization' like how flaccid paralysis following OPV was classified, because investigations during an illness 1 month prior to paralysis were not available — see Appendix 3, page 36 of the AEFI manual[12] for this example).

If all the required investigations had been done and they met case definition criteria, they would have been classified as 'consistent causal association to immunization' at Step 2 and would not have come to Step 4.

The third possibility is that all the investigations had been done so it is classifiable but it did not meet case definitions. The CIOMS / WHO dictum is applied here: 'if there is adequate evidence that an event does not meet a case definition, such an event should be rejected and should be reported as "Not a case of [AEFI]". (See CIOMS / WHO Definitions and Application of Terms for Vaccine Pharmacovigilance, page 170[13]). It removes any chance that AEFI that has not been recognized as causatively associated with immunization in previous epidemiological studies will be included in the 'Indeterminate' group and evaluated as a new signal. Thus there seems to be only two options at step 4 : - either the reaction is classified as 'Unclassifiable' or it is categorized as 'Inconsistent causal association to immunization'. Categorization as 'Indeterminate' or 'Consistent causal association to immunization' are logically impossible given the riders mentioned above.

The exercise does not end there. Other qualifying factors are also enquired into at Step 4. It is recommended that alternate explanations in terms of background rate, other health conditions, exposure to a potential risk factor or toxin, acute illness, and other medication are again enquired into. Many of these 'other qualifying factors', like prior illness and concurrent drug use would presumably have been eliminated at Step 1 when looking for evidence for other causes. This enquiry is repeated again at Step 4 quite unnecessarily. Box 4 illustrates how, in spite of

Box 4. Sudden unexpected deaths (SUD) after pentavalent vaccine and the TOKEN Study.

With regard to AEFI a cluster of cases is defined as two or more cases of the same adverse event related in time or place or to the vaccine administered[a]. Pentavalent vaccine has caused numerous deaths in Asia but it is yet to be considered a new signal[b–e].

After the AEFI algorithm was revised, the deaths are now classified as 'Not a case of [AEFI]' on the grounds that deaths have not been reported as AEFIs in epidemiological studies involving the vaccine. However, the TOKEN Study contradicts this assertion[f].

The TOKEN Study was done specifically to assess a possible causal relationship between vaccination and unexplained sudden unexpected death (SUD) of children between their 2nd and 24th month of life. vonKries had previously found a statistically significantly increased standardized mortality ratio (SMR) within two days after vaccination with one (Hexavac®) of the two licensed hexavalent vaccines and the TOKEN study was done to confirm or refute the association[g]. The study was sponsored and supported by the Paul-Ehrlich-Institute (PEI) and the Federal Ministry of Health (Bundesministeriumfür Gesundheit).

A self-controlled case series (SCCS) was examined to look for a temporal association of vaccination to SUD. Parents were invited to participate in the study if their child had died of SUD. 37.6% of the eligible parents participated. The researchers found that parents were twice as likely to participate if their child had died within one week of vaccination. They used an inverse probability weighted analysis to compensate for this bias. The authors note that this was helpful to overcome the selection bias in infants under 9 months, but even so, the results are still likely to overestimate the risk of SUD in older children.

The weighted SCCS analysis, relative risk of SUD after pentavalent vaccination (first and second year of life) looking at risk period 0–3 days after vaccination versus control period 4–28/183 days showed RR of 8.11 (p= 0.006, 95% CI=1.81-36.24; Table 41 in the TOKEN Report). The weighted SCCS analysis, relative risk of SUD after hexa- or pentavalent vaccination (1st and 2nd year of life) looking at risk period 0–3 days versus control period 4–28/183 days was RR.2.19 (p= 0.031, 95% CI=1.08-4.45; Table 36 in the TOKEN Report)

It is clear from the above that there is reasonable evidence in epidemiological studies that SUDS can occur as AEFI following use of the pentavalent vaccine and the deaths following the use of this vaccine should not be a priori classified as 'Not a case of [AEFI]'.

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a. http://vaccine-safety-training.org/detection-and-reporting.html

b. Lone Z, Puliyel J. Introducing pentavalent vaccine in the EPI in India: A counsel for caution. Indian J Med Res 2010; 132,: pp 1-3

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there being epidemiological evidence (the TOKEN Study) that pentavalent vaccine can cause sudden unexpected death, the numerous deaths (as discussed in the introduction) are not acknowledged as caused by the vaccine, and the WHO expert report denies that deaths were ever reported as AEFI. The causality assessment of 132 serious AEFI cases uploaded on the website of the Ministry of Health and Family Welfare in India illustrates the consequence of deploying this new classification. 54 of these babies died, whereas 78 survived. The causality assessment found 50% of those who survived had reactions to vaccination but not even one death was classified as vaccine-related. Nearly all the deaths (96%) were simply classified as unclassifiable or coincidental, presumably because death has not previously been acknowledged as an adverse event caused by this vaccine[18]. Children admitted to hospital after vaccination with intractable convulsions, could be classified as having a vaccine-product related reaction, but if they died, the deaths would be classified as 'coincidental deaths'.

Other subtle changes in the definition of terms

'Causal association' redefined

The term causal association now means 'a cause-and-effect relationship between causative factor and a disease with no factor intervening in the processes'. This is a major step backward for patient safety. The old scheme recognized, for example, that an elderly person with chronic cardiac failure might develop symptoms of cardiac decompensation after influenza vaccination due to a vaccine-caused elevation in temperature or stress from a local reaction at the site of vaccination. The vaccine is therefore considered to have contributed to cardiac failure in this specific situation[19]. Under the new scheme, this outcome would not be considered as causally related to the vaccine. The question of whether the death would have occurred at that time, had it not been provoked by immunization, would not be acknowledged. Without this recognition, many elderly persons may be exposed to this risk of death unnecessarily when using this vaccine. If the vaccination of an infant was reported to have been followed by sudden death but the child was malnourished or otherwise unwell it does not mean that causality assessment should conclude no cause and effect relationship between the vaccine and the death. There is no scope in this definition to consider interacting causalities[14,15]. The Global Advisory Committee on Vaccine Safety has documented many deaths in children with pre-existing heart disease after they were administered the pentavalent vaccine. The WHO now advises precautions when vaccinating such children and this has reduced the risk of death[1]. Using the new definition of causal association, this relationship would not be acknowledged and lives would be put at risk.

According to Collet and colleagues, it is possible that some individuals experience greater immunogenic response to vaccines compared to the general population and therefore, understanding genetically determined predispositions to developing AEFIs is important[15]. However, these considerations will not be accounted for, in the new CIOMS /WHO causality assessment scheme. The contribution of vaccine in precipitating encephalopathy in patients who are susceptible on account of genetic factors will also not be considered[15]. Berkovic has used genetic analyses to identify *de novo* mutations in the sodium channel gene SCNIA in patients with alleged vaccine-induced encephalopathy[16]. Unwisely, in all these cases the contribution of the vaccine in precipitating the encephalopathy will be ignored.

It is a pity that after all these years, the authors should fall for the Hume fallacy that causality can be claimed only if X is sufficient in itself for Y. The fact that the immunization could have 'materially contributed' to the adverse events is ignored.

Biological plausibility

Biological plausibility is one of the Bradford Hill 'guiding principles' that favor causative association[16]. However, this is limited by the state of current knowledge and it should not be used in itself to deny causative association. For example it is now acknowledged that high-titer measles vaccine is associated with excess female mortality[20]. The recognition of this association was delayed because of the absence of a biologically plausible explanation. WHO experts now acknowledge that vaccines have non-specific effects which up-regulate or down-regulate both the innate and the adaptive immune system and this can influence child survival[21].

The association of intussusception with rotavirus vaccination was also accepted at a time when a biologically plausible explanation was not available[11] (See Box 5). Vaccine can therefore have both non-specific beneficial effects and also unexpected deleterious effects which should not be disregarded simply because a ready explanation for the same is not available at the time when it is first noticed.

Biological plausibility redefined

The meaning of the term biological plausibility has itself been redefined in the Revised AEFI manual. The manual specifies that biological plausibility can only be invoked when laboratory findings or symptom or sign are similar or consistent with natural history and pathophysiology of the infection or antigen. Other biologically plausible explanations (demonstrating there is a mechanism and capacity to lead from the cause to the effect)[7], do not qualify. The four approaches to ascertaining causality described by Brady include detection of neo-Humean regularity, examining the counterfactual, experimental manipulation and examining mechanisms and capacities[7]. The new AEFI recognizes only the experimental approach to the exclusion of other valid approaches and, as a result, can fail to detect causality in a number of cases resulting in harm.

Chronic fatigue syndrome and the HPV vaccine trial

The above discussion has assumed that adverse events that are reported in the original prelicensure randomised control trials, would be classified as adverse events known to be associated with the vaccine.

Slate investigated randomised trials of human papillomavirus (HPV) vaccines and found that potential side effects were collected for only two weeks in the year-long study. After 2 weeks, individual trial investigators decided, on personal judgment, whether to report medical problems as adverse events. Often they listed new problems as 'new medical history'. Myalgic encephalomyelitis, otherwise known as chronic fatigue syndrome

Box 5. Indian Rotavirus vaccine trials

The prequalification of Rotavac without safety data

RotaShield was withdrawn as it caused 1 excess case of intussusception per 10,000 children given the vaccine[1].

However, a new rotavirus vaccine Rotavac (Bharat Biotec) was licensed in India after a trial in 3 centres where the vaccine was administered to a total of 4500 children (a sample size too small to show up a rare event that occurs 1 in 10,000)[a,b]. In spite of this small sample it appears intussusceptions were so common with this vaccine[c] in one of the centres (Vellore), it was significantly higher than controls. The trial doctors refused to provide this segregated data in spite of repeated requests[d]. The government promised to monitor safety in a post marketing surveillance. However, the participants in this trial were not explained the risk seen in the RCT (as is mandatory for ethical clinical trials) and surveillance was for a limited window period of a few weeks after vaccination, whereas the adverse events noticed in the RCT were outside that window period. In remote parts of this country where the vaccine is deployed, in the absence of pediatric surgeons and radiologists, deaths from intussusception are likely to be misclassified as deaths from dysentery.

Even before the data of this post marketing surveillance is available, the WHO recently prequalified the vaccine to be used internationally[e].

Clinical trials of other rotavirus vaccines that reduce rotavirus diarrhoea but does not reduce overall incidence of diarrhoea[f] and another vaccine that increases the overall incidence of diarrhoea[g] instead of decreasing it, have been published.

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(CFS), is a condition characterized by long-term fatigue that limits a person's ability to carry out ordinary daily activities. Participants in the HPV trial reported to Slate that these debilitating symptoms of theirs were not even registered as adverse events.

Given that CFS was not recorded as an adverse event, it allowed the manufacturers to claim that CFS is not a 'known adverse event with the vaccine' and so to discount every case that was reported subsequently.

Rotavirus vaccine trials

Box 5 describes how adverse events, recorded in a randomized clinical trial (RCT) and sent to the regulatory authority for vaccine approval and license, are not made public. This goes against the European Court of Justice ruling that clinical study reports are made publically accessible.

Other problems with recording and reporting AEFI

Box 6 describes how the Periodic Safety Update Reports (PSUR) 15 and 16 of Infanrix Hexa and the findings from the reports was opened to public scrutiny by an Italian court. Box 7 describes how PSUR 19 was obtained under the Freedom of Information rules and shows how deaths reported in PSUR 16 were deleted from PSUR 19, when it was evident that the reported deaths exceeded the deaths expected by chance[22]. In 1986 President Ronald Reagan signed the National Childhood Vaccine Injury Act (NCVIA) (42 U.S.C. §§ 300aa-1 to 300aa-34) which created a no-fault system to compensate vaccine related injuries. This made it difficult to sue vaccine manufactures. It also set up Vaccine Adverse Event Reporting System (VAERS) mandating the reporting of adverse events. Box 8 describes the changes that prevent patients from holding manufacturers to account for adverse events caused by their products. Box 9 shows how AEFI data is no longer available easily. While on the one hand, the new classification discounts AEFI as 'Not a case of [AEFI]', safety data is being manipulated and made inaccessible.

Biological plausibility: reactions with multi-valent vaccines

Looking at the VAERS data of deaths after immunization, Goldman and colleagues found there was more mortality among babies who had received five to eight vaccines together, compared to those receiving fewer vaccines[23]. In the case of Boatman v. Secretary of Health and Human Services, 13-611 (Fed. Cl 2017) where the infant aged 4 months had received 7 vaccine antigens on one day, the court, after hearing expert opinion, held that vaccine-stimulated inflammatory-cytokines can act as neuro-modulators and cause depression of the serotonergic 5-hydroxytryptophan (5-HT) system in the infant medulla and blunt the normal chemo-sensitive

Box 6. Periodic safety update reports : unfit for public consumption?

Justice Nicola Di Leo in Italy made public the 'confidential' 15th and 16th Periodic Safety Update Report (PSUR) on Infanrix hexa (GlaxoSmithKline Biological) and this is now available on the Internet[a].

Pages 246-9 document an analysis of the number of 'sudden deaths' after receiving the vaccine to examine if it exceeds the number of deaths one could expect from the natural background incidence of sudden death. The background incidence was calculated as 0.454/1000 in the first year and 0.062/1000 live births in the second year. No allowance is made for the notoriously poor AEFI reporting rate. The number of sudden deaths expected to occur by chance between day 1 and 20, is tabulated in Table 36 on page 24. The denominator used to examine deaths following vaccination is the number of doses of the vaccine distributed not the number of children vaccinated. This denominator would dilute any potential signal because many more vaccine doses are distributed than are actually administered!

Further, the number of doses actually administered may be appropriate for milder reactions that can recur with each dose, but it is not appropriate for deaths which can happen only once. Appendix 5A shows that 13 fatal cases were reported. There were more deaths after the first dose than after the second and third doses and the deaths after the second was more than after the third dose. This pattern is commonly seen with AEFIs that are causatively related. The appropriate denominator in all these cases is the number of babies vaccinated.

There were 42 deaths in the first three days after vaccination where there were only 16 deaths in the next 3 days. The fact that the deaths were clustered soon after vaccination suggests that the deaths may be related to the vaccination event.

Patient safety data should not be considered as trade secrets by any stretch of imagination. The practice of keeping safety reports confidential permits such data manipulation in a cosy relationship with the regulators, away from public scrutiny. Such practice ought to be reformed.

Reference

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Box 7. EMA and Failure of Regulatory Oversight: absence of critical appraisal of PSUR

GlaxoSmithKline (GSK), 19th confidential periodic safety update reports[a] (PSUR 19 (deaths up to October 22, 2014)) on Infanrix hexa makes interesting reading. Infanrix hexa has all the components of the pentavalent vaccine except that it has replaced the whole cell pertussis with an acellular pertussis component and, in addition, it has injectable polio vaccine. The cumulative number of deaths after vaccination reported in the 19th report is less than that reported in the 16th PSUR. It can be seen that deaths in children older than 1 year was significantly higher than the deaths expected by coincidence, if the deaths deleted from the 16th PSUR were restored[b].

It appears that the EMA accepts PSUR reports filed by manufacturers without reviewing them critically. Regulatory authorities internationally rely on due diligence by the EMA in such circumstances. This may need to be reappraised.

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response to excess carbon dioxide and this can result in the death of vulnerable infants during sleep. Multiple vaccines provoke greater release of cytokines. Hill's criteria of a dose- response gradient (number of antigens in this case), may be satisfied here[10].

Multiple vaccines limited to 5 in the Italian Army

The harm from vaccine-stimulated cytokines is not limited to infancy. The Final Report of the Italian Parliamentary Committee (Doc. XXII-bis N.23) inquiry into cases of death and severe injury affecting Italian personnel assigned to military missions abroad, has recommended that no more than 5 monovalent single-dose vaccines may be given simultaneously to military personnel, in order to avoid adverse reactions. All this suggests the need for caution in using multiple vaccines simultaneously. Ironically, while it is proscribed for healthy adult army men, Hexavac (which combines 6 antigens) is still licensed for use in infants in Italy.

Revised AEFI classification and the precautionary principles

It is evident from the discussion earlier that the revised AEFI evaluation scheme produced by the CIOMS / WHO is designed to deny the possibility that any newly observed adverse event may be causally related to the immunization. The AEFI manual states 'Allegations that vaccines / vaccination cause adverse events must be dealt with rapidly and effectively. Failure to do so can undermine confidence in a vaccine and ultimately have dramatic consequences for immunization coverage…'[12]

Figure 2 shows how all cases AEFI except those that are known adverse effects of vaccine are classified as not causally related.

The AEFI-denialism is a clear violation of the 'precautionary principle' (European Union law), which mandates that 'when an activity raises threats of harm to the environment or human health,

Box 8. Product liability: Protecting patients not patents.

Hexavac - a hexavalent vaccine (DTaP-IPV-HepB/Hib) - was withdrawn by the manufacturers without giving reasons after 5 cases of SIDS were reported by Zinka within 48 hours of being administered the vaccine[a]. vonKries found that in the 2nd year of life, the standardized mortality rate (SMRs) for sudden unexplained deaths (SUD) within 1 day of vaccination was 31.3 (95% CI 3.8–113.1); and within 2 days after vaccination it was 23.5 (95% CI 4.8–68,6)[b].

Similarly RotaShield was voluntarily removed from the market after 12 cases of intussusceptions were reported. The background rate of intussusceptions at this age was 5 times the risk of intussusceptions from the vaccine. There was no biologically plausible explanation to link the intussusceptions to the immunization. Yet the vaccine was withdrawn[c].

The manufacturers withdrew the vaccines voluntarily without indicating the reasons. It is not clear whether the prospect of product liability suits influenced manufacturer caution.

Two significant changes have taken place after 1980. The threat of vaccine manufacturers being held responsible for marketing a defective product has diminished greatly as a consequence of these changes.

1. A no-fault compensatory mechanism has been put in many countries in the 1980s and 1990s[d] This means that vaccine injured children need not provide clear evidence of negligence as cause of the harm, before they qualify for compensation. However, it also means that manufacturers do not have to admit to faults. The risk of product liability has now greatly decreased with no fault compensation being provided by governments. As a result, manufacturers may be emboldened to be more reckless on vaccine safety issues.

2. The second significant change was in 2013, when the methodology for assessment of AEFI was completely overhauled. It is no longer sufficient to show temporal association of the AEFI happening repeatedly. The flow diagram below depicts all conditions that need to be satisfied before an AEFI is labelled 'Consistent causal association to immunization'. This too could embolden manufacturers to be more reckless with regard to adverse reactions.

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Box 9. Difficulties in accessing AEFI data

1. Polio and Acute Flaccid Paralysis in India

As awareness of adverse events is increasing among the public it is becoming more difficult to access data on these adverse events. The National Polio Surveillance provided monthly data on acute flaccid paralysis in India. An analysis of the data showed that in 2011, an additional 47,500 children were newly paralysed in the year, over and above the standard 2/100,000 non-polio AFP that is generally accepted as the norm. The non-polio AFP rate best correlated with the cumulative number of doses received in the previous three years[a].

The analysis was repeated after 2 years when the number of doses administered to children below 5 was reduced and it showed the AFP rate had begun to decline[b].

However, the data is no longer provided on the National Polio Surveillance Project/WHO website.

2. Data Analysis Prints on Vaccines

Medicines and Healthcare products Regulatory Agency (MHRA) of the government of UK provides easily accessible Drug Analysis Prints and Interactive Drug Analysis Profiles (iDAPs)[c] from 'Yellow Card' notifications of adverse events. But this is not provided for vaccines. One is required to request MHRA Pharmacovigilance for this.

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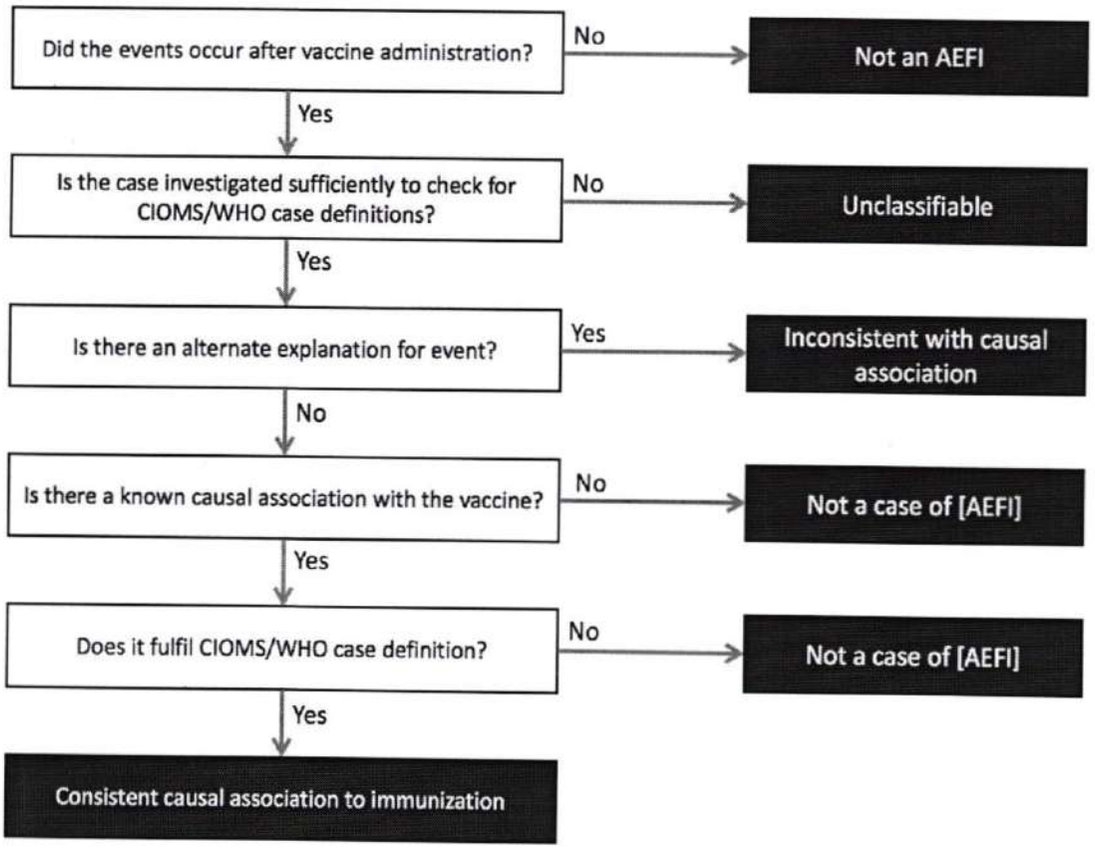

Figure 2. **Pathway to achieving 'consistent causal association to immunization' status.**

precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically. Society and Government is urged that until the full scientific evidence is available, where there is evidence of risk, it must take precautionary measures'. This new AEFI classification scheme that allows for an outright denial of any new causative association with vaccination could also fall foul of Article 2 European Convention on Human Rights (Art 2 ECHR), which mandates governments to establish a framework of laws, precautions, and means the enforcement of which will, to the greatest extent reasonably practicable, protect life.

Paradoxically, the AEFI algorithm is said to be for vaccine safety. Perhaps we need a scheme for public safety rather than vaccine safety.

The story of pentavalent vaccine was introduced at the beginning of this paper and is summarised in Box 10. It is primarily a vaccine used in developing countries where AEFI surveillance is poor, the press is less vigilant to report adverse events and where drug regulation is less strict. (The richer countries in the West, Europe and the USA, do not use the whole cell pertussis vaccine; so this vaccine is not marketed in those countries.) Isolated cases of unexplained deaths continue to be reported in the press. With the new AEFI classification, in the absence of 'epidemiological evidence' linking deaths to the vaccine, these deaths have been passed off as 'coincidental' SIDS deaths. Epidemiological evidence, however, is now available linking the deaths to vaccine.

To examine if deaths following pentavalent vaccine were merely coincidental SIDS deaths, a study of 45 million infants given DTP vaccination and 25 million who received pentavalent vaccine was undertaken. The study assumed that all the deaths (self-reported to the government surveillance system with 72 hours of vaccination) associated with DPT could be coincidental SIDS deaths, but any increase in the death rate after pentavalent vaccine must be assumed to have been caused by pentavalent vaccine. The odds of death after pentavalent vaccine was doubled (OR 1.98 (95% CI 1.65 to 2.38)) compared to DTP. There were 4.7 additional deaths (95% CI: 3.5-5.9) per million vaccinated with Pentavalent vaccine instead of DTP ($p<0.0001$). By the time this evidence was put together, 122 excess deaths (95% CI: 101-145) had been reported to the government, due to the switch from DPT to pentavalent vaccine. The contribution of the new AEFI classification in this delay in recognizing the problem is stark[21].

The need for revising Brighton

The revised classification have removed the categories 'probably' and 'possible' from the AEFI classification - very much like the experts who investigated the Sri Lanka deaths. This appears to be

Box 10. The vaccine that changed the definition of AEFI

The story of pentavalent vaccine

In 1949 the DTP vaccine was introduced[a] against diphtheria, tetanus, and pertussis. The first two were frequently fatal diseases. However, DTP was responsible for neurological adverse effects, seizures, encephalopathy, and hypotensive episodes (HHE)[b]. An acellular DTaP was developed and this has replaced DTP in the West.

In 1981 Hepatitis B was introduced[a]. Hepatitis B infection can cause chronic liver disease and hepatocellular carcinoma (HCC), especially if acquired at birth. Vaccine uptake was poor in developing countries. One reason was that, although Hepatitis B was common in the potentially large vaccine uptake countries like India, the incidence of HCC was very low[c]. It is now thought that newborn babies in India may be protected in the early years (where the chance of becoming a chronic carrier is worst) by passive immunity from mother to babies. This may be lost once vaccine use becomes widespread and there could be a paradoxical increase in HCC[d].

In 1987 the protein-conjugated Haemophilus influenza type b vaccine was introduced. The incidence of invasive disease with Haemophilus influenza type b in Asia is low[e] perhaps due to cross-protection from other bacteria that have cross-reactive antigens to the Hib capsular polysaccharide[f]. The uptake of Hib vaccine was poor in Asia.

It is said that the Pentavalent vaccine was introduced to improve the uptake of Hib and Hepatitis B, by combining new underused vaccines with a prior UIP vaccine like DTP as a way for the new vaccines to get a piggyback ride into the UIP[g]. The pentavalent vaccine was used only in developing countries which had not switched to DTaP.

Pentavalent vaccine has been associated with deaths. In the investigation of deaths in Sri Lanka, rather than reporting that the vaccine was 'probably' related to the vaccine, the WHO experts deleted the categories 'probable' and 'possible' from the Brighton classification. This ad-hoc improvisation was reported in medical journals. The AEFI classification was then formally revised so that reactions (deaths in this case) noticed for the first time in Phase 4 trials (post marketing trials) could all be classified as 'Inconsistent with causal association to immunization' and passed off as 'coincidental SIDS deaths'.

A new study involving 45 million infants given DTP vaccination and 25 million who received pentavalent vaccine now provides epidemiological evidence that the odds of death after Pentavalent was doubled (OR 1.98 (95% CI 1.65 to 2.38)) compared to DTP. There were 122 additional deaths (95% CI: 101-145) within 72 hours, reported to the government surveillance system, due to the switch from DPT to pentavalent vaccine. A large number of these deaths could have been avoided had the AEFI manual not been revised and the AEFI were evaluated earlier. In fact it is well documented that the combined DTP-Hepatitis B-Hib vaccine causes more local reactions and it is less effective than when they were administered separately[h]. Protection against these disease could have been better if the vaccines were administered separately.

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motivated by a laudable desire to reduce vaccine hesitancy and the attendant risk of vaccine preventable disease. The Sri Lanka report says, "Cases were classified in this review as unlikely where, in spite of not having evidence that the vaccine(s) contributed to the adverse event or the outcome of death, conclusive evidence regarding an alternate cause (or causes) of the event and outcome was lacking. This meant that we considered that classifying the AEFI in the category 'unrelated' was not fully justified (as it could not be conclusively attributed to another cause). In such cases, we go further to state that the conclusion of 'unlikely' means that the vaccine is not the major cause of death even in those cases where we discuss the possibility that the vaccine(s) or vaccination may have unmasked an underlying condition"

It seems the Sri Lankan experts were reluctant, even to classify the deaths as 'unlikely', as it could be interpreted to mean there was some likelihood of causal association. To quote from the report, "Unlikely: In defining this category, the panel took note of the fact that the WHO category 'unlikely' is often interpreted to mean that there is (conversely) some likelihood of a causal association between the adverse event and the vaccine(s) administered."

One can speculate that same reasoning and the motivation (to ally public anxiety of a causal association between AEFI and vaccination), would have provided the impetus for the revised AEFI classification.

The aftermath

That vaccines do more good than harm is taken as an article of faith, a dogma, a tenet. If the purpose of this exercise i AEFI-denialism is to prevent undermining confidence in vaccines, the

scheme does not seem to be working. Indeed, public scepticism seems to be increasing rather than diminishing with these efforts at reassurance that vaccines are safe[25,26]. Epidemics of vaccine preventable disease have resulted[27].

The response in some states in the United States has been to make vaccination mandatory for admission to public schools. Personal and religious belief exemptions for vaccination are not be allowed in California, effective July 1, 2016. The 2016 debates among US Republican Presidential aspirants suggest that there is a lack of widespread support for this measure. The Department of Health and Human Services Office for Civil Rights has now set up the Conscience and Religious Freedom Division to which individuals can complain if their conscience or religious freedom have been abridged. How these forces will interact is anyone's guess, but the present scenario augur badly for public trust in vaccines and voluntary vaccination.

Where do we go from here

The AEFI manual needs to be urgently reevaluated and revised. We need to build a better system that picks up problems and at the same time does not create a mistrust of vaccines that have been associated with a major reduction in child mortality.

Adverse reaction and deaths may not show up as significantly increased in small safety studies. However, records of all deaths and serious adverse events following vaccinations should be maintained and periodically reviewed for safety signals. The practice of discarding these records as 'inconsistent causal association to immunization' needs to change. Comparisons of the adverse events of vaccines given at the same age, as was done with DTP and pentavalent vaccine, may help to identify adverse events related to one of the vaccines. Sex specific incidence of adverse events may also act as a pointer. Till we develop a better system, it may be advisable to fall back on the time tested WHO-UMC casualty categories and the Brighton categories and to err on the side of child safety.

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David Legge helped write the initial critique published in the BMJ[13]. Prior to sending it for publishing, he wrote to the department of Immunization, Vaccines and Biologicals of the World Health Organisation in March 2016. But there was no response to this letter from the WHO.

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Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 05 July 2018

https://doi.org/10.5256/f1000research.15756.r34468

✔ **Peter Aaby**
Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

I am satisfied with the revision. Many errors and inconsistencies have been corrected. The narrative qualities have improved. The way forward is helpful.

Including the non-specific effects of vaccines as potential AEFIs is important.

In general the fact-boxes are easier to understand and helpful now. I did not understand in Box 6 how we came from the 13 fatal cases reported in Appendix 5A to the 42 deaths said to have occurred in the first 3 days.

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 06 Jul 2018

Jacob Puliyel, St Stephen's Hospital, Delhi, India

I agree the text in Box 6 needs clarification.

It read as follows
Box 6
Appendix 5A shows that 13 fatal cases were reported. There were more deaths after the first dose than after the second and third doses and the deaths after the second was more than after the third dose. This pattern is commonly seen with AEFIs that are causatively related. The appropriate denominator in all these cases is the number of babies vaccinated.

There were 42 deaths in the first three days after vaccination where there were only 16 deaths in the next 3 days. The fact that the deaths were clustered soon after vaccination suggests that the deaths may be related to the vaccination event....

It should read
Appendix 5A gives the details of 13 of the deaths after vaccination. There were more deaths after the first dose than after the second and third doses and the deaths after the second was more than after the third dose. This pattern is commonly seen with AEFIs that are causatively related. The appropriate denominator in all these cases is the number of babies vaccinated.

In all, there were 42 deaths in the first three days after vaccination where there were only 16 deaths in the next 3 days. The fact that the deaths were clustered soon after vaccination suggests that the deaths may be related to the vaccination event.

Competing Interests: None

Reviewer Report 04 June 2018

https://doi.org/10.5256/f1000research.15756.r34467

Tom Jefferson
Centre for Evidence Based Medicine, University of Oxford, Oxford, UK

The author's responses seem reasonable to me, although I do not necessarily agree with some of them. As the errors of fact have been corrected, the paper can go ahead as far as I am concerned.

Competing Interests: TJ was a recipient of a UK National Institute for Health Research grant for a Cochrane review of neuraminidase inhibitors for influenza. In addition, TJ receives royalties from his books published by Il Pensiero Scientifico Editore, Rome and Blackwells. TJ is occasionally interviewed by market research companies about phase I or II pharmaceutical products. In 2011-13, TJ acted as an expert witness in litigation related to the antiviral oseltamivir, in two litigation cases on potential vaccine-related damage and in a labour case on influenza vaccines in healthcare workers in Canada. He has acted as a consultant for Roche (1997-99), GSK (2001-2), Sanofi-Synthelabo (2003), and IMS Health (2013).In 2014 he was retained as a scientific adviser to a legal team acting on oseltamivir. TJ has a potential financial conflict of interest in the drug oseltamivir. In 2014-16, TJ was a member of three advisory boards for Boerhinger Ingelheim. TJ was holder of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews. TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine. Between 1994 and 2013, TJ was the coordinator of the Cochrane Vaccines Field. TJ was a co-signatory of the Nordic Cochrane Centre Complaint to the European Medicines Agency (EMA) over maladministration at the EMA in relation to the investigation of alleged harms of HPV vaccines and consequent complaints to the European Ombudsman. TJ is co-holder of a John and Laura Arnold

Foundation grant for development of a RIAT support centre (2017-2020) and Jean Monnet Network Grant, 2017-2020 for The Jean Monnet Health Law and Policy Network. TJ is an unpaid collaborator to the project Beyond Transparency in Pharmaceutical Research and Regulation led by Dalhousie University and funded by the Canadian Institutes of Health Research (2018-2022).

Reviewer Expertise: Clinical epidemiologist

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 03 April 2018

https://doi.org/10.5256/f1000research.14875.r31300

?

Peter Aaby
Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

The authors are to be complimented for having conducted this study. Proper handling of AEFIs is very important if we are to maintain trust between public health vaccinology and the community. However, I am missing the authors' specific suggestions for how to improve the situation. As discussed below there are also details of presentation which could be improved.

There is a rather detailed description of the changes in the definition of causality in relation to the current concept of AEFI. However, I am missing some presentation of where is the AEFIs concept coming from historically and what is the underlying theoretical biological model of why AEFI might occur and how does that affect how AEFI are observed, reported and used. Furthermore, what are the regulators requirements? Apparently the dominant thinking is that vaccines only induce disease specific memory. Presumably genetic variability may in rare cases affect how this biological process takes place and this could cause specific AEFIs. What else are the causes of other AEFIs: co-incidental infections or chronic disease, co-administration of drugs or other vaccinations? Most of such events can presumably be rejected as not "caused" directly by the vaccine.

However, the concept of vaccines may be changing. WHO experts have recognized that vaccines may have non-specific effects (NSEs) with consequences for child survival [1]. Apparently, through epigenetic and metabolic changes, vaccines can reprogram the immune system and upregulate or downregulate both the innate and the adaptive immune system [2-5]. If that is the case there is room for both beneficial and deleterious unexpected events following immunization (UEFI). Proper monitoring systems should also be able to detect beneficial UEFIs; for example, we have found that BCG reduces the risk of neonatal sepsis in low-birth weight children [6]. On the other hand, DTP consistently increases female relative to male mortality, also in societies that have no sex-differential treatment [7]. This is "unnatural" since there

was no excess female mortality in the pre-vaccination era in West Africa [8]. This being the case there should be room not only for the short-term AEFI as in the current system (14 days?) but also for much more protracted biological processes being classified as AEFI/UEFI. This would require new standards for how UEFI/AEFI are observed and registered.

Parallel with the description of the changes in the definition of AEFI, there is a series of examples where the authors apparently think there are real differences in mortality/safety issues between different vaccination groups. I have noted at least: Pentavalent vaccine and congenital heart disease; MMR and autism in African American children; Hexavac; Rotavac; HPV and chronic fatigue syndrome; Pentavalent vaccine vs DTP for SIDS. Sometimes these safety issues are mentioned in passing as examples in the discussion of the processes related to AEFI assessment. I found it sometimes unclear whether these example were presented in their own right as safety issues or whether they were only meant to illustrate problems in the assessment of AEFI, e.g. safety reports not forthcoming, etc. Sometimes the presentation was too short or unclear to be really convincing; for example, I had problems with the ROTAVAC story (box 5). It is unclear why it is said in Box 5: "Other rotavirus vaccines that do not reduce incidence of diarrhoea or increase the incidence of diarrhoea instead of decreasing it, have been published (b)". The paper which is referenced apparently reported a 40% reduction in rota-diarrhoea. If the problem is that overall diarrhea was not reduced I think this can be present more clearly.

I think the paper would be stronger/more convincing if the safety-issues that the authors believe have been documented as safety concerns were presented as safety-case stories in specific boxes; the effect of Pentavalent vaccine on SIDS is apparently such a concern. Then the text on the changes in the assessment of AEFI could refer to this or that AEFI problem which was illustrated in the safety-case stories. On the other hand if the story is about mismanagement of the assessment of AEFI, then the cases should be presented as such without implying a causal link between vaccination and AEFI; for example box 3 is an example of poor public communication but it has hardly been documented that MMR causes autism.

Abstract:
It should not be assumed that "Of course, vaccines that caused deaths in the control-trials stage would not be licensed." RTS,S malaria vaccine was recently approved by EMA but the trial data indicate that RTS,S compared with control vaccines was associated with 2-fold higher mortality for girls [9,10]. Neither the authors nor EMA apparently analysed the mortality data, overall or by sex.

The example with cardiac failure in children is not presented in the paper and should therefore not appear in the abstract unless it is fully described in the paper. The case might well warrant further presentation in the paper itself.

Introduction
Being presented with the Sri Lanka and Vietnam cases in the first paragraphs, the reader is left wondering what was the implications of the WHO experts' classifications. Was the pentavalent vaccine (Penta) reintroduced in the countries and how did that decision come about?

Causality assessment
In the long description of changes in the manual for AEFI assessment, it would be good to have an explanation of WHO's own justification for these changes.

Sometimes the text appears to have been written some years back but have been maintained unchanged in in the current 2018-version. For example in Box 3 it is said that "Thomson has now been granted

whistleblower status by the Obama administration". By now this sentence should probably be: "Thomson was granted whistleblower status by the Obama administration". Similar in the conclusion it is said that if the debates among Republican presidential aspirants "are anything to go by". By now it can no longer be "are".

Box 10: this sentence has problems: "In fact combined DTP-Hepatitis B-Hib vaccine causes more there were more local reactions and it is less effective than when they were administered separately."

Page 10: Biological plausibility.
There appears to be an increasing trend to dismiss "unexpected observations"/unpleasant observations with the argument that there is no "biological plausibility". This was one of the arguments used by WHO experts to dismiss that high-titre measles vaccine (HTMV) could be associated with excess female mortality [11]. There can obviously not be biological plausibility for a pattern just detected, that no one has ever thought about. The only relevant question is whether a pattern is repeatable – arguments about biological plausibility should not be allowed to dismiss observations of potential AEFIs. The excess female mortality was repeated in subsequent studies and WHO eventually withdrew the HTMV (1992).

I found this sentence strange: "Slate investigated of the randomised trials of human papillomavirus (HPV) vaccines and found that potential side effects were collected for only two weeks in the year long study."

Page 13: "PV" has not been defined as the abbreviation for pentavalent vaccine.

The comparison of DTP and pentavalent vaccine is frightening. Please indicate whether it is SIDS death or all-cause deaths when it is said for example: "The odds of death after pentavalent vaccine was doubled". Since it is your study I would have indicated that to the readers: "To examine if deaths following Pentavalent vaccine (PV) were merely coincidental SIDS deaths, we undertook a study of 45 million infants given DPT vaccination and 25 million who received PV". Given the scary character of this report a bit more information on methods in data collection and analysis would be appropriate. Any hypothesis of why there would be a two-fold difference in SIDS (?) mortality? Did the patterns differ for boys and girls? We have found that DTP and Penta are both associated with much higher female-than-male all-cause mortality rates [7,12].

Conclusion
I do not think the conclusion is really a conclusion to the content of the paper.

How do we proceed from here? How can we built a better system that finds even the AEFIs we do not want to see and had not expected – and at the same do not create mistrust in the vaccines (BCG, measles vaccines, OPV) which are associated with major reductions in child mortality in low-income countries. What time-frame should be used? AEFI should always be presented by sex. If there are sex-differential patterns of AEFI it might enhance the credibility of this patterns as a true AEFI since we have found sex-differential effects on mortality of most of common vaccines.

Biological plausibility should not be used to dismiss any new and unexpected pattern. There is now evidence that vaccines may reprogram both the innate and the adaptive immune system epigenetically with effect on general susceptibility to non-targeted infections [2,5]. Hence, the starting point should be that ***unlikely effects are likely*** because we have never examined the possibility.

It is standard practice in small safety study with deaths to dismiss them because we cannot see a connection. However, deaths following vaccinations should always be classified as

potential-even-though-unlikely AEFIs. Otherwise we cannot accumulate the data and detect patterns we had not imagined. For example, when DTaP was tested in an RCT in Sweden there were 4 deaths among 2847 vaccinated children but none among 954 controls [13]. Though the authors recognized that 4 deaths was too high and would have been significant if the whole Swedish population of eligible children had been used as controls, the study could find no link between the vaccine and the deaths. All properly conducted studies from low-income countries have found DTwP to be associated with increased child mortality [14-16].

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Is the topic of the opinion article discussed accurately in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Partly

Are arguments sufficiently supported by evidence from the published literature?
Partly

Are the conclusions drawn balanced and justified on the basis of the presented arguments?
Yes

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 04 May 2018

Jacob Puliyel, St Stephen's Hospital, Delhi, India

Reviewer 2

Reviewer Professor Peter Aaby

Reviewer Comment
Authors' response

The authors are to be complimented for having conducted this study. Proper handling of AEFIs is very important if we are to maintain trust between public health vaccinology and the community. I am missing the authors' specific suggestions for how to improve the situation.
We thank the reviewer for his detailed review and this compliment.

Prashant Bhushan
(TRUE COPY)

ANNEXURE: P/9

The Hindu

Probe sought into 'deaths and adverse effects' after COVID-19 vaccinations

Jagriti Chandra

NEW DELHI:, MARCH 17, 2021 15:05 IST

A group of experts have written a letter to Health Minister Harsh Vardhan and Drugs Controller General of India V.G. Somani.

A group of experts in public health, ethics, medicine, law, and journalism have written to Health Minister Harsh Vardhan and Drugs Controller General of India V.G. Somani, appealing for "time-bound and transparent investigation" following deaths and serious adverse effects after COVID-19 vaccination.

"We understand that at least 65 deaths have occurred following vaccination for COVID-19 since the vaccination campaign started on January 16. However, the National AEFI (adverse event following immunisation) Committee's investigation findings of only two of these deaths have been made public. We believe that due to the possible linkages of vaccination and blood clotting, all these deaths and adverse events should be reviewed together for a possible causal relationship with the vaccine," reads the letter.

The experts underline that even as the Indian health administration continues to be indifferent to the adverse effects of vaccination, several countries across the world such as Denmark, Iceland, Norway, Italy, France, Bulgaria, Germany, Luxembourg, Estonia, Lithuania, Latvia and Ireland have paused immunisation with Astra Zeneca vaccine pending investigation of a small number of post-vaccination deaths from intravascular clotting/ thromboembolic events. Austria has even suspended the use of certain batches.

The signatories of the letter include Amar Jesani, Editor, Indian Journal of Medical Ethics; Veena Johari, lawyer; Anand Grover, Senior Advocate and Former U.N. Special Rapporteur on the Right to Health; Brinelle Dsouza, Co-convener, Jan Swasthya Abhiyan; Imrana Qadeer, Former Professor, Centre of Social Medicine and Community Health, JNU; Sylvia Karpagam, Public Health Doctor and Researcher.

They have demanded a transparent investigation into each of the adverse incidents and sought details of all serious AEFIs till date, status of their investigation, findings of AEFI probe including cause of death by clinical diagnosis, autopsy findings, causality assessment and the process undertaken by AEFI committees to arrive at their conclusions.

"The vaccine programme should provide people complete information on the vaccines, a vaccination protocol that minimises the risk of harm, and an assurance of thorough and transparent investigation of injuries and death following immunisation. They are also owed medical care, and compensation for harm suffered post vaccination. The government has not met these obligations."

https://www.thehindu.com/news/national/probe-sought-into-deaths-and-adverse-effects-after-covid-19-vaccinations/article34090356.ece

Prashant Bhushan

(TRUE COPY)

228

ANNEXURE- P20

Phone : 2641 3344, 2641 3300, 98405 49256
Email : m.govalan@gmail.com
profcmkr@yahoo.co.in

TAMILNADU MEDICAL PRACTITIONERS' ASSOCIATION (Regd)

தமிழ்நாடு மருத்துவர்கள் சங்கம் (பதிவு)

306, Poonamallee High Road, Chennai - 600 010

April 27, 2021

Dear friends,

All of you must be concerned about the reported deaths after taking the Covid vaccine. Though the Adverse Effects Following Immunisation (AEFI) Committee comforts public and the profession by saying they're unrelated to the vaccine, we have to take it with a grain of salt.

124 cases died and 305 cases Hospitalised in India following Covid vaccination were analysed :

	Died (124)	Hospitalised (305)
Within 3 days	93	276
4th to 7th day	18	15
8th to 28th day	11	13
After 28 days	02	01

If they are due to reasons other than vaccination, they should be evenly distributed during every week following vaccination, but 75% deaths occurred and 90% were hospitalised during the first 3 days. Hence let us not take it for granted and find out if we can prevent the complications.

I feel this may be due thrombogenic property of the vaccine, which contains attenuated or dead virus. This can lead to coronary or cerebrovascular events, especially if there has been some pre-existing disease in those vessels.

Applying this logic, to all those who called me for advice before vaccination, I started anticoagulant & antiplatelet agents (rivaroxaban 10mg and aspirin 75mg) two days before the vaccination and continued for 8 days after, with no major adverse effects reported in 125 patients.

This may not be a strictly randomized, controlled study, but we are desparate in preventing post-vaccine deaths and should be ble to assure our patients about their safety. I invite comments from our colleagues, whether we should pursue this 'theory' to the next step (sending our recommendation to the ICMR & AEFI Committee for their comments and further action). Let TN Doctors take the lead in this terrible situation.

Thanking you, sincerely,

CMK REDDY

Prashant Bhushan
(TRUE COPY)

ANNEXURE:P21

The Hindu

Coronavirus | 180 deaths following vaccination reported in India

R. Prasad
CHENNAI 09 APRIL 2021 00:16 IST
UPDATED: 15 APRIL 2021 00:44 IST

Individual AEFI cases were presented and brought up for discussion by experts in the AEFI causality assessment committee.

According to a presentation made to the National AEFI Committee during a meeting held on March 31, there have been 617 severe and serious (including deaths) adverse events following immunisation (AEFI). As on March 29, a total of 180 deaths (29.2%) have been reported following vaccination across the country.

Complete documentation is available only for 236 (38.3%) cases. In all, 492 severe and serious AEFI have been classified by the AEFI Secretariat of the Immunisation Technical Support Unit (ITSU) at the Health Ministry.

Classification has been completed for 124 deaths, 305 serious events that required hospitalisation, and 63 severe events that did not require hospitalisation.

The classification by the AEFI Secretariat was on the basis of case reporting forms (CRF) and case investigation forms (CIF) submitted at the district level. In the meeting, individual AEFI cases were presented and brought up for discussion by experts in the AEFI causality assessment committee. Of the 124 deaths, more than 63 deaths (nearly 51%) have been categorised as being caused due to acute coronary syndrome (a range of conditions associated with sudden, reduced blood flow to the heart) or heart attack. Another 11 deaths (12%) of deaths are due to stroke.

As on March 17, the details of the causality assessment of only 13 AEFI including 10 deaths have already been made public by the national AEFI committee. The vaccine was not found to have caused death in any of the 10 vaccinated people.

However, in many cases post mortems have not been conducted. For example, in at least six out of 10 cases where the National AEFI Committee has completed causality assessment, no post mortem has been done, says Malini Aisola, a Public Health Researcher based in Delhi.

Virologist Dr. Jacob John, formerly of CMC Vellore, says that if deaths are not associated with vaccination, then they would be nearly evenly distributed across weeks post vaccination. However, there are 93 deaths in the first three days (31 deaths per day) and 18 deaths in four-seven days (4.5 deaths per day) after vaccination. There have been 11 deaths in 8-28 days (0.5 deaths per day) post- vaccination. "Deaths are not evenly distributed," he says. There is hence a compulsion to investigate the deaths more thoroughly for any association.

If deaths are seen on a weekly basis, there have been 111 deaths in the first week (nearly 16 deaths per day) but in the next three weeks, there have been only 11 deaths (0.5 deaths per day). "If the deaths are unrelated to vaccination, then deaths should be evenly distributed across weeks after vaccination. There are an extraordinary number of deaths in the first week but in the next two-four weeks there are only about four deaths per week," says Dr. John.

There have been 59 deaths due to sudden, reduced blood flow to the heart (acute coronary syndrome) or heart attack in the first week but only four in the second- four weeks after vaccination. Similarly, deaths due to stroke are 13 in the first week but only one death in two-four weeks after vaccination. There have been nine "sudden deaths" during the first week but only one death in two-four weeks after vaccination.

In the case of AEFI requiring hospitalisation, there have been 291 AEFI needing hospitalisation in the first week compared with only 13 in two-four weeks after vaccination. "The number of hospitalisations in the first week stands out strikingly different," Dr. John says. Again, 18 cases of reduced blood flow to the heart (acute coronary syndrome) or heart attack, 10 cases of stroke, and 46 cases of severe allergic reaction (anaphylaxis) in the first week require thorough investigation.

Weakness in one, two or all four limbs (mono/para/quadriparesis) seen in 17 people hospitalised is similar to transverse myelitis seen during the trial in the U.K., says Dr. John. About 15 cases of seizure in the first week and no such cases in the two- four weeks after vaccination is abnormal, he says. "There is something going on in the central nervous system. Also, 17 cases of mono/para/quadriparesis in four weeks needs thorough investigation," he says.

According to him, 59 cases of severe AEFI not requiring hospitalisation in the first week and four such cases in two-four weeks may be a signal.
"Since Covishield is the same vaccine as AstraZeneca, updated warnings related to these rare conditions, information for vaccine recipients and the public about when to seek medical attention, and information for health providers about how to identify and treat such occurrences needs to be done for the vaccine," says Ms. Aisola.

The European Medicines Agency (EMA) has included only six deaths from India after vaccination with Covishield for its analysis. "Due to a massive backlog in processing assessments in India, we have reported the data internationally for just a tiny fraction of the actual cases that have occurred," she says. "Timely assessment is important to formulate recommendations for vaccination for particular groups and guidance for any groups that may be identified as more susceptible to serious AEFIs. It is also important for revising and updating screening procedures and to ensure that arrangements for treatment are put in place."

"The National Committee is depending on evidence and investigations conducted at the local level. However, we observed a strong tendency by local authorities to immediately rule out any links to vaccination, even before investigation has been conducted," says Ms. Aisola. "There is an urgent need to strengthen AEFI investigation at the local level where protocols may not be adhered to and the quality of evidence being collected is often weak and inadequate."

Link: https://www.thehindu.com/news/national/coronavirus-180-deaths-following-vaccination-reported-in-india/article34274144.ece

Prashant Bhushan

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ANNEXURE- P22

VAERS COVID REPORTS

(Vaccine Adverse Events Reporting System, USA)

157,277 Reports
Through April 30, 2021
*

jump to browse reports

3837 DEATHS	**10715** HOSPITALIZATIONS	**21623** URGENT CARE
26046 OFFICE VISITS	**834** ANAPHYLAXIS	**942** BELL'S PALSY

Heart Attacks	Miscarriages	Severe Allergic Reaction	Thrombocytopenia/Low Platelet
1132	213	7463	822

* VAERS HHS releases COVID Data weekly, but they release LAST WEEK'S data. So an update will always lag a week behind. When launched, OpenVAERS used the Download date. We have switched to the "data through" date provided by VAERS.

Prashant Bhushan
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ANNEXURE: P23

EXCLUSIVE – Hospital Medical Director says level of sickness in NHS staff after Covid Vaccination is "Unprecedented"

The Daily Expose 1 month ago

The Medical Director of a hospital in the United Kingdom has bravely spoken out against the failure to report the reality of morbidity caused by the Covid-19 vaccination roll-out across the United Kingdom to NHS staff.

Dr Polyakova, who is the Medical Director of a hospital in Kent has said that the "levels of sickness after vaccination is unprecedented" among NHS staff, confirming that some are even suffering neurological symptoms which is having a "huge impact on the health service functioning".

The doctor, who progressed into medical management of the hospital over the past three years says that she is struggling with the "failure to report" adverse reactions to the Covid vaccines among NHS staff, and clarified that the young and healthy are missing from work for weeks after receiving a dose of either the Pfizer or AstraZeneca experimental vaccine.

"Some even require medical treatment" Dr Polyakova said, "Whole teams are being taken out as they went to get the vaccine together". In response to the arising question of making Covid-19 vaccination compulsory for NHS staff, Dr Polyakova said –
"Mandatory vaccination in this instance is stupid, unethical and irresponsible when it comes to protecting our staff and public health. We are in the voluntary phase of vaccination, and staff are being encouraged to take an unlicensed product that is impacting on their immediate health.

"I have direct experience of staff contracting Covid after vaccination and probably transmitting it. It is clearly stated that these vaccine products do not offer immunity or stop transmission.

"So why are we doing it? There is no longitudinal safety data available and these products are only under emergency licensing. What is to say that there are no longitudinal adverse effects that we may face that may put the entire health sector at risk?"

Both the Pfizer and AstraZeneca jab are only licensed for emergency use only, as confirmed by Dr Polyakova. This means that the manufacturer of the vaccine, in this case either Pfizer or AstraZeneca, are not liable for any injury or ill-effect that may occur in the recipient of their product.

The Medical Director didn't stop their though as she went on to attack the coercion and mandating of experimental medical treatments for NHS staff, comparing it to a Nazi dystopia –
"Flu is a massive annual killer, it inundates the health system, it kills young people, the old the comorbid, and yet people can chose whether or not they have that vaccine (which had been around for a long time). And you can list a whole number of other examples of vaccines that are not mandatory and yet they protect against diseases of higher consequence.

"Coercion and mandating medical treatments on our staff, of members of the public especially when treatments are still in the experimental phase, are firmly in the realms of a totalitarian Nazi dystopia and fall far outside of our ethical values as the guardians of health.

"I would never debase myself and agree, that we should abandon our liberal principles and the international stance on bodily sovereignty, free informed choice and human rights and support unprecedented coercion of professionals, patients and people to have experimental treatments with limited safety data. This and the policies that go with this are more of a danger to our society than anything else we have faced over the last year.

What has happened to "my body my choice?" What has happened to scientific and open debate? If I don't prescribe an antibiotic to a

patient who doesn't need it as they are healthy, am I anti-antibiotics? Or an antibiotic-denier? Is it not time that people truly thought about what is happening to us and where all of this is taking us?"
We couldn't have said it better ourselves.

Prashant Bhushan
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ANNEXURE-P24

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Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial

Raches Ella, Krishna Mohan Vadrevu, Harsh Jogdand, Sai Prasad, Siddharth Reddy, Vamshi Sarangi, Brunda Ganneru, Gajanan Sapkal, Pragya Yadav, Priya Abraham, Samiran Panda, Nivedita Gupta, Prabhakar Reddy, Savita Verma, Sanjay Kumar Rai, Chandramani Singh, Sagar Vivek Redkar, Chandra Sekhar Gillurkar, Jitendra Singh Kushwaha, Satyajit Mohapatra, Venkat Rao, Randeep Guleria, Krishna Ella, Balram Bhargava

Summary

Background To mitigate the effects of COVID-19, a vaccine is urgently needed. BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine formulated with a toll-like receptor 7/8 agonist molecule adsorbed to alum (Algel-IMDG) or alum (Algel).

Methods We did a double-blind, multicentre, randomised, controlled phase 1 trial to assess the safety and immunogenicity of BBV152 at 11 hospitals across India. Healthy adults aged 18–55 years who were deemed healthy by the investigator were eligible. Individuals with positive SARS-CoV-2 nucleic acid and/or serology tests were excluded. Participants were randomly assigned to receive either one of three vaccine formulations (3 μg with Algel-IMDG, 6 μg with Algel-IMDG, or 6 μg with Algel) or an Algel only control vaccine group. Block randomisation was done with a web response platform. Participants and investigators were masked to treatment group allocation. Two intramuscular doses of vaccines were administered on day 0 (the day of randomisation) and day 14. Primary outcomes were solicited local and systemic reactogenicity events at 2 h and 7 days after vaccination and throughout the full study duration, including serious adverse events. Secondary outcome was seroconversion (at least four-fold increase from baseline) based on wild-type virus neutralisation. Cell-mediated responses were evaluated by intracellular staining and ELISpot. The trial is registered at ClinicalTrials.gov (NCT04471519).

Findings Between July 13 and 30, 2020, 827 participants were screened, of whom 375 were enrolled. Among the enrolled participants, 100 each were randomly assigned to the three vaccine groups, and 75 were randomly assigned to the control group (Algel only). After both doses, solicited local and systemic adverse reactions were reported by 17 (17%; 95% CI 10·5–26·1) participants in the 3 μg with Algel-IMDG group, 21 (21%; 13·8–30·5) in the 6 μg with Algel-IMDG group, 14 (14%; 8·1–22·7) in the 6 μg with Algel group, and ten (10%; 6·9–23·6) in the Algel-only group. The most common solicited adverse events were injection site pain (17 [5%] of 375 participants), headache (13 [3%]), fatigue (11 [3%]), fever (nine [2%]), and nausea or vomiting (seven [2%]). All solicited adverse events were mild (43 [69%] of 62) or moderate (19 [31%]) and were more frequent after the first dose. One serious adverse event of viral pneumonitis was reported in the 6 μg with Algel group, unrelated to the vaccine. Seroconversion rates (%) were 87·9, 91·9, and 82·8 in the 3 μg with Algel-IMDG, 6 μg with Algel-IMDG, and 6 μg with Algel groups, respectively. $CD4^+$ and $CD8^+$ T-cell responses were detected in a subset of 16 participants from both Algel-IMDG groups.

Interpretation BBV152 led to tolerable safety outcomes and enhanced immune responses. Both Algel-IMDG formulations were selected for phase 2 immunogenicity trials. Further efficacy trials are warranted.

Funding Bharat Biotech International.

Introduction

Spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections has led to a global COVID-19 pandemic. Vaccines from multiple manufacturers will be needed to address the global need for SARS-CoV-2 vaccines and thus far, 194 vaccine candidates are in development.[1]

A desirable characteristic for any COVID-19 vaccine candidate is the ability to induce T-helper-1 cell (Th1) responses.[2] Whole-virion inactivated vaccines are usually formulated with Alum, which does not have the ability to induce cell-mediated responses.[3,4] An imidazoquinoline molecule, which is a toll-like receptor (TLR) 7/8 agonist, has been used to stimulate cell-mediated responses.[5,6] Algel-IMDG (an imidazoquinoline molecule chemisorbed on alum [Algel]) has been designed to traffic vaccine antigen directly to draining lymph nodes without diffusing into the systemic circulation. BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine adjuvanted with Algel-IMDG.

Preclinical studies in mice, rats, and rabbits showed appropriate safety profiles and humoral and cell-mediated responses.[7] Two live viral challenge protective efficacy studies in hamsters and non-human primates were done.

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See Comment page 581

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For the **WHO COVID-19 dashboard** see https://covid19.who.int/

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Research in context

Evidence before this study

We searched PubMed on Jan 15, 2020, for published research articles using the search terms "SARS-CoV-2", "COVID-19", "vaccine", and "clinical trial", with no language or date restrictions. We found several publications on COVID-19 vaccine clinical trials from mRNA, adenovirus, protein subunit, and inactivated vaccines.

As of Jan 15, 2020, nine vaccines have received emergency use authorisation to be administered to prevent COVID-19. Inactivated vaccines have been approved for decades with well established safety profiles. Immune responses from two other inactivated vaccines have been reported; however, with few results on cell-mediated responses. Bharat Biotech has developed a vero cell-based whole-virion inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine (BBV152) formulated with alum and a TLR7/8 agonist producing a T-helper-1 cell skewed response. This vaccine candidate reported protection in two live viral non-human primate and hamster challenge models.

Added value of this study

We report the preliminary analyses for the safety and immunogenicity of the vaccine candidate BBV152 in 375 vaccinated adults. All vaccine groups had similar reactogenicity and serological outcomes to the control group. BBV152 led to enhanced immune responses; the 3-µg and 6-µg Algel-IMDG vaccines induced T-cell responses that were biased to T-helper-1 cells.

Implications of all the available evidence

Findings from other inactivated SARS-CoV-2 vaccine candidates are corroborating. However, to the best of our knowledge, ours is the only reported inactivated COVID-19 vaccine candidate inducing cell-mediated responses and humoral neutralising responses. Both Algel-IMDG formulations will be assessed in a phase 2 immunogenicity trial.

In both studies, protection was evident by rapid clearance of virus in the lower and upper respiratory tract, and absence of lung pathology (after viral challenge).[8,9] Here, we report the interim findings from the randomised, controlled, double-blind phase 1 trial on the safety and immunogenicity of three different formulations of BBV152 and one control group containing Algel (without antigen). This phase 1 trial was done with the intention of selecting two formulations for progression to the phase 2 trial.

Methods

Study design and participants

This is a randomised, double-blind, multicentre, phase 1 trial to assess the safety, reactogenicity, tolerability, and immunogenicity of the whole-virion inactivated SARS-CoV-2 vaccine (BBV152) in healthy adult volunteers, at 11 hospitals across nine states of India (appendix pp 5, 13). Participants were aged 18–55 years and deemed healthy by the investigator at the time of enrolment. At the screening visit, participants were tested with both SARS-CoV-2 nucleic acid (TRUPCR SARS-CoV-2 RT-PCR; 3B BlackBio Biotech, Bhopal, India) and serology (chemiluminescence immunoassay; LIAISON SARS-CoV-2 S1/S2 IgG; DiaSorin, Saluggia, Italy) tests (conducted at Dr Dangs Lab [New Delhi, India] using commercially available assays; appendix p 3). If found positive for any one test, they were excluded from the trial. The median time between the screening visit and vaccination visit was 4 days (range 3–6). Other key exclusion criteria were an axillary temperature of more than 37·0°C and known allergy to any vaccine component. Participants were screened for eligibility on the basis of their health status, including their medical history, laboratory findings (haematology, biochemistry, and urine tests), vital signs, and physical examination results, and were enrolled after providing signed and dated informed consent forms. Full inclusion and exclusion criteria are in the protocol.

See Online for appendix

The trial was approved by the National Regulatory Authority (India) and the respective ethics committees and was conducted in compliance with all International Council for Harmonization Good Clinical Practice guidelines.

Randomisation and masking

The master randomisation list was uploaded on the interactive web response system, which contained the randomisation number and intended allocation. The depot manager uploaded the kit code list and assigned the kits to the sites that had the kit codes and the allocation groups. At the site level, the system would set the randomisation number and the allotment of the kit without displaying the true group allocation, and the system would allocate the same treatment group for the second visit. For the first 50 participants, a block size of five with ten blocks was generated for the 3 µg with Algel-IMDG and control groups at a ratio of 4:1. In the remaining participants, the number of blocks was 20. For the first 15 blocks, a block size of 16 was used to randomly assign participants (3:5:5:3) to 3 µg with Algel-IMDG, 6 µg with Algel-IMDG, 6 µg with Algel, or Algel-only control. The next five blocks were size 17, and used to randomly assign participants (3:5:5:4) to 3 µg with Algel-IMDG, 6 µg with Algel-IMDG, 6 µg with Algel, or Algel-only control. An unmasked contract research organisation, Sclin Soft Technologies, generated the randomisation list for the study.

Participants, investigators, study coordinators, study-related personnel, and the funder were masked to treatment group allocation (excluding an unmasked member of the contract research organisation, who was

tasked with the dispatch and labelling of vaccine vials and the generation of the master randomisation code). Participants were assigned a computer-generated randomisation code that maintained masking. The masked study nurse was responsible for vaccine preparation and administration. Each vial contained a unique code that ensured appropriate masking. The appearance, colour, and viscosity were identical across all vaccine and control formulations.

Procedures

The virus strain (NIV-2020-770) containing the Asp614Gly mutation, isolated from a COVID-19 patient and sequenced at the Indian Council of Medical Research National Institute of Virology, was provided to Bharat Biotech.[10] Biosafety level 3 manufacturing facilities and a well established Vero cell manufacturing platform (with proven safety in other licensed live and inactivated vaccines) were used for the rapid development of BBV152.[11–16]

BBV152 (manufactured by Bharat Biotech) is a whole-virion β-propiolactone-inactivated SARS-CoV-2 vaccine. The NIV-2020-770 strain contains the Asp614Gly mutation, which is characterised by aspartic acid to glycine shift at the amino acid position 614 of the spike protein.[10]

The candidates were formulated with two adjuvants: Algel (alum) and Algel-IMDG, an imidazoquinoline class molecule (TLR7 and TLR8 agonist) adsorbed onto Algel. After their eligibility was established, participants were assigned to the four groups. The control group contained only a sterile phosphate-buffered solution and Algel. Both the vaccine and control were stored at 2–8°C.

The vaccine (BBV152) and the control were provided as a sterile liquid that was injected intramuscularly (deltoid muscle) at a volume of 0·5 mL/dose in a two-dose regimen on day 0 (day of randomisation) and day 14. This accelerated schedule was chosen given the context of the ongoing pandemic. No onsite dose preparation was required. Each glass vial contained a single dose of either vaccine or control formulation that required no additional dilution steps. No prophylactic medication (ibuprofen or acetaminophen) was prescribed either before or after vaccination.

The follow-up visits were scheduled on days 7, 28, 42, 104, and 194 after vaccination. The study was done in a dose-escalation manner after completing vaccination in the first 50 participants with 3 µg with Algel-IMDG (the lowest antigen concentration) and the control; these participants were monitored for 7 days for safety. The independent data safety monitoring board reviewed masked safety data and decided whether the trial was allowed to continue with enrolment of the remaining participants into all groups.

Outcomes

The primary outcome was the number and proportion of participants with solicited local and systemic reactogenicity events at 2 h and 7 days after vaccination and throughout the full study duration, including serious adverse events. The secondary outcomes was immunogenicity, in terms of geometric mean titres (GMTs) and four-fold seroconversion rate of neutralising antibodies, from baseline to days 14, 28, 42, 104, and 194.

Safety assessments

The unsolicited adverse events were recorded for 28 days after vaccination. Laboratory values (serum chemistry, haematology, and urine) were compared before vaccination (day 0) and after vaccination (day 28).

Participants were observed for 2 h after vaccination to assess reactogenicity. They were instructed to record local and systemic reactions within 7 days (days 0–7 and days 14–21) after vaccination using a diary card. The diary card contained fields for symptom onset, severity, time to resolution, concomitant medication, and was collected during the next visit to the site. Routine telephone calls were scheduled after the first 7 days after each vaccination.

Solicited local adverse events were pain at the injection site and swelling, and systemic adverse events, including fever, fatigue or malaise, myalgia, body aches, headaches, nausea or vomiting, anorexia, chills, generalised rash, and diarrhoea. All unsolicited adverse events were reported by participants throughout the study. Adverse events were graded according to the severity score (mild, moderate, or severe) and whether they were related or not related to the investigational vaccine, as detailed in the protocol (appendix p 6).

Immunogenicity assessments

IgG responses against the spike (S1) glycoprotein, receptor-binding domain, and nucleocapsid protein of SARS-CoV-2 were assessed by an in-house-developed ELISA and are expressed as GMTs. Neutralising antibody titres were assessed by wild-type virus neutralisation assays: a microneutralisation assay (MNT_{50}) and a plaque-reduction neutralisation test ($PRNT_{50}$), at Bharat Biotech. These assays were based on the Asp614Gly strain (appendix p 4). To establish interlaboratory comparability, a subset of randomly selected serum samples (n=50) was analysed by MNT_{50} at the National Institute of Virology. Additionally, three laboratory strains were used in vitro for $PRNT_{50}$ at the National Institute of Virology: the BBV152 strain NIV-2020-770 homologous, and two heterologous strains from the O clade (nCoV-Q111 and nCoV-Q100). Genomic analyses of strains were reported by Potdar and colleagues.[17] Only the NIV-2020-770 strain contained the Asp614Gly mutation.[10]

To compare vaccine-induced responses to natural SARS-CoV-2 infections, 41 convalescent serum samples (collected within 1–3 months after nucleic acid test-based diagnosis) were tested by MNT_{50}. These serum samples were collected from both self-reported symptomatic (n=25) and asymptomatic (n=16) patients with COVID-19 at Nizam's Institute of Medical Sciences (NIMS;

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Hyderabad, India). The age of these participants was 23–62 years. For symptomatic patients, ascertainment of severity grading and requirement of supplemental oxygen was not obtainable. A participant who achieved seroconversion was defined as having a post-vaccination titre at least four-fold greater than their respective pre-vaccination titre. Serum samples were analysed in a masked manner at Bharat Biotech and the National Institute of Virology.

Cell-mediated responses were assessed in a subset of participants at one site (NIMS). The contract research organisation generated a random code containing randomisation numbers, which was provided to the staff to identify participants. Blood (3–5 mL) was collected from those participants who consented to the additional volume on days 0 and 28. Peripheral blood mononuclear cells were collected to assess IFN-γ by ELISpot (13 in vaccinated groups and six in the control group). Intracellular cytokine staining was used to assess T-cell responses in the remaining samples that contained an adequate number of cells. To ensure equal distribution, eight samples in each vaccine group were selected. These assays were done at Indoor Biotechnologies (Bangalore, India) and Bharat Biotech. All samples were analysed in a masked manner. The details of all assay methods are in the appendix (p 5).

Statistical analysis

Using a two-sided 5% significance level, power was calculated for several levels of the absolute difference between seroconversion rates for vaccine formulations, and we decided on the power to find a statistically significant difference between rates if the true underlying absolute difference was at least 20%. The allocation ratio was 1:1:1 for three vaccine formulations and 4:1 for the vaccine (all formulations combined) to placebo. The placebo group was not included in the sample size calculations. For a sample size of 90 for each formulation, the power to find a statistically significant absolute difference for a true underlying difference of 20% was at least 80% if the lower seroconversion rate for two formulations was at least 52%, which is lower than the seroconversion rate we expected for an effective vaccine. The sample size chosen was 100 per vaccine formulation, to allow for loss of data because of withdrawals or loss to follow-up. We did not incorporate an adjustment for multiple comparisons, because this phase 1 study was not a pivotal study for licensure, and we planned to

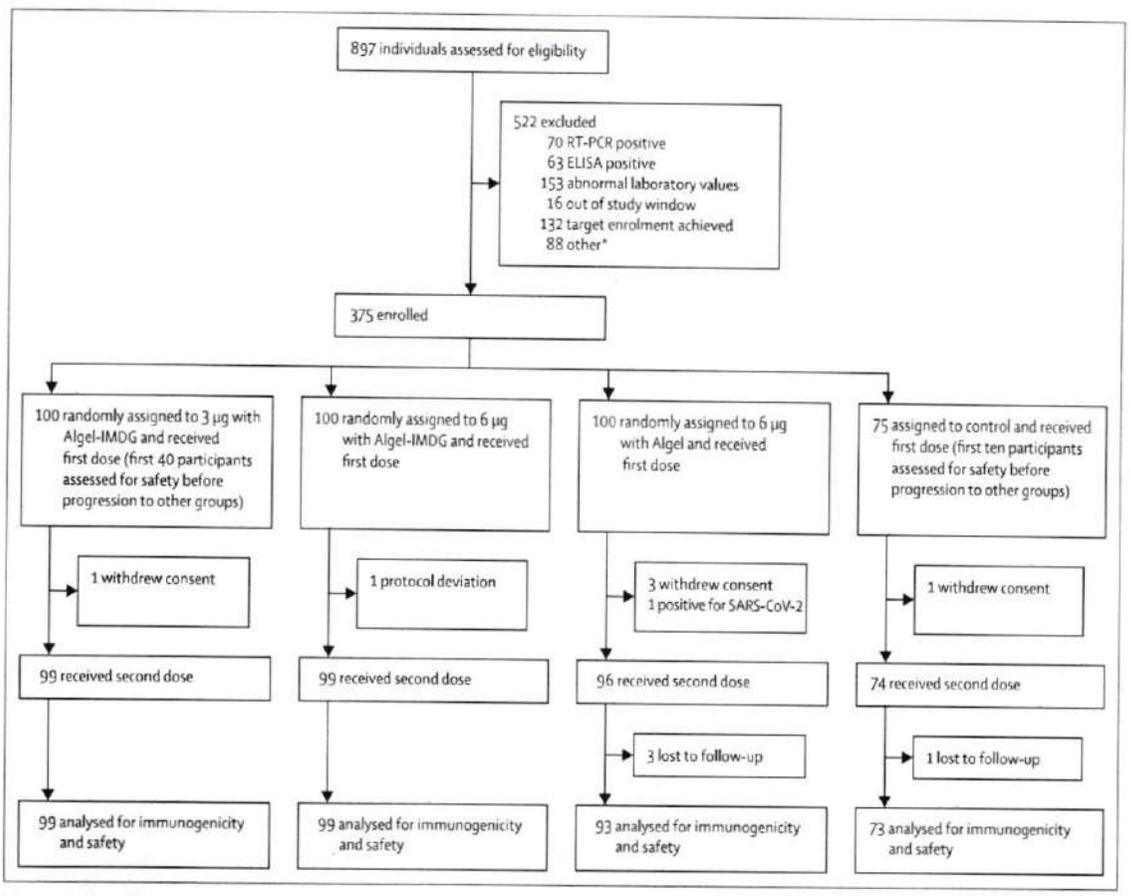

Figure 1: **Trial profile**
SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *Unable to contact the participant for vaccination or withdrawal of consent.

choose two vaccine formulations from the phase 1 study for further assessment. Sample size estimation was done using PASS 13 software, version 13.0.17.

Safety endpoints are described as frequencies (%). GMTs with 95% CI are used for immunological endpoints. For continuous variables (<20 observations), medians and IQRs are reported. The exact binomial calculation was used for the CI estimation of proportions. The Wilson's test was used to test differences in proportions. CI estimation for the GMT was based on the $\log_{10}$ (titre) and the assumption that the $\log_{10}$ (titre) was normally distributed. A comparison of GMTs was done with t tests on the means of the $\log_{10}$ (titre). Significance was set at $p<0{\cdot}05$ (two-sided). This preliminary report contains results regarding immunogenicity (days 0–28) and safety outcomes (days 0–42). Descriptive and inferential statistics were assessed using SAS, version 9.2. The trial was registered at ClinicalTrials.gov (NCT04471519).

Role of the funding source

The funder of the study had no role in data collection, data analysis, data interpretation, or writing of the statistical report, but was involved in study design. Data cleaning and analysis was conducted by a third party contract research organisation (Sclin Soft Technologies). Masked laboratory assessments were done at the respective laboratories and masked data sheets were sent to the contract research organisation for decoding and analysis. The unmasked randomisation list was not shared with the sponsor. All authors had full access to masked data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 13 and 30, 2020, 897 individuals were screened and 375 were enrolled. Of the 522 initially screened individuals who were excluded, 133 participants were excluded because they were positive for SARS-CoV-2 by nucleic acid test or serology and 153 were excluded because of abnormal laboratory values (figure 1). The first 50 participants enrolled were monitored for 7 days after vaccination, and on the basis of the independent data safety monitoring board review of masked safety data, the trial was allowed to continue with enrolment of the remaining participants into all groups. Among the enrolled participants, 100 each were randomly assigned to the three vaccine groups, and 75 were randomly assigned to the control group (Algel only). Demographic characteristics of the participants were similar across groups (table 1).

After dose 1, solicited local adverse reactions were reported by five (5%; 95% CI 1·9–11·8) participants in the 3 µg with Algel-IMDG group, five (5%; 1·9–11·8) in the 6 µg with Algel-IMDG group, one (1%; 0·05–6·2) in the 6 µg with Algel group, and three (3%; 1·04–12·03), in the Algel-only control group. Solicited systemic adverse reactions were reported by five (5%; 1·9–11·8) participants in the 3 µg with Algel-IMDG group, 14 (14%; 8·1–22·7) in the 6 µg with Algel-IMDG group, eight (8%; 3·8–15·6) in the 6 µg with Algel group, and seven (7%; 4·2–18·9) in the Algel-only group (table 2; appendix p 14). The most common solicited adverse events were injection site pain (17 [5%] of 375 participants), headache (13 [3%]), fatigue (11 [3%]), fever (nine [2%]), and nausea or vomiting (seven [2%]). All adverse events were mild or moderate in severity and resolved within 24 h of onset. After both doses, solicited local and systemic adverse reactions were reported by 17 (17%; 95% CI 10·5–26·1) participants in the 3 µg with Algel-IMDG group, 21 (21%; 13·8–30·5) in the 6 µg with Algel-IMDG group, 14 (14%; 8·1–22·7) in the 6 µg with Algel group, and ten (10%; 6·9–23·6) in the Algel-only group. All adverse events were mild

	BBV152 3 µg with Algel-IMDG (n=100)	BBV152 6 µg with Algel-IMDG (n=100)	BBV152 6 µg with Algel (n=100)	Algel only (n=75)
Age, years				
Median (IQR)	32·5 (25·0–40·0)	35·0 (25·0–40·0)	32·0 (25·0–40·0)	29·0 (24·0–38·0)
≥18 to ≤25	29 (29%)	28 (28%)	31 (31%)	22 (29%)
≥26 to ≤40	47 (47%)	47 (47%)	45 (45%)	37 (49%)
>40 to ≤55	24 (24%)	25 (25%)	24 (24%)	16 (21%)
Sex				
Men	78 (78%)	82 (82%)	76 (76%)	61 (81%)
Women	22 (22%)	18 (18%)	24 (24%)	14 (19%)
Body-mass index*, kg/m²	24·8 (3·5)	25·8 (4·2)	24·9 (3·7)	24·6 (3·5)
Vital signs				
Systolic blood pressure, mm Hg	122·9 (8·5)	123·5 (7·9)	121·6 (8·3)	123·6 (8·5)
Diastolic blood pressure, mm Hg	79·4 (5·9)	79·3 (6·5)	79·2 (5·3)	79·4 (6·4)
Pulse rate, beats per min	77·4 (7·3)	78·1 (8·2)	78·0 (5·9)	78·3 (7·6)
Respiratory rate, breaths per min	16·9 (2·3)	16·7 (2·6)	17·1 (2·6)	16·9 (2·2)
Temperature, °C	36·6 (0·4)	36·5 (0·6)	36·5 (0·4)	36·6 (0·4)
Sites				
All India Institute of Medical Sciences, New Delhi	3 (3%)	6 (6%)	3 (3%)	4 (5%)
All India Institute of Medical Sciences, Patna	25 (25%)	9 (9%)	6 (6%)	7 (9%)
Gillukar Multispeciality Hospital	10 (10%)	14 (14%)	19 (19%)	12 (16%)
Institute of Medical Sciences and SUM Hospital	4 (4%)	5 (5%)	9 (9%)	5 (7%)
Jeevan Rekha Hospital	1 (1%)	1 (1%)	2 (2%)	0
Nizam's Institute of Medical Sciences	11 (11%)	14 (14%)	15 (15%)	7 (9%)
Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences	22 (22%)	10 (10%)	15 (15%)	16 (21%)
Prakhar Hospital	8 (8%)	10 (10%)	11 (11%)	10 (13%)
Rana Hospital and Trauma Centre	1 (1%)	3 (3%)	2 (2%)	2 (3%)
Redkar Hospital	7 (7%)	14 (14%)	13 (13%)	9 (12%)
SRM Hospital and Research Center	8 (8%)	14 (14%)	5 (5%)	3 (4%)

Data are n (%) or mean (SD) unless otherwise stated. The intention-to-treat population included all participants who received at least one dose. *Calculation was based on the bodyweight and height measured at the time of screening. No data on race were collected; all participants were south Asian.

Table 1: Demographic characteristics of the participants in the intention-to-treat population

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	Dose 1				Dose 2			
	3 µg with Algel-IMDG (n=100)	6 µg with Algel-IMDG (n=100)	6 µg with Algel (n=100)	Algel only (n=75)	3 µg with Algel-IMDG (n=100)	6 µg with Algel-IMDG (n=100)	6 µg with Algel (n=100)	Algel only (n=75)
Local reactions								
Pain at injection site								
Mild	4 (4%; 1·1–9·9)	4 (4%; 1·1–9·9)	1 (1%; 0·0–5·5)	2 (3%; 0·3–9·3)	2 (2%; 0·2–7·0)	1 (1%; 0·03–5·5)	1 (1%; 0·0–5·5)	0
Moderate	1 (1%; 0·0–5·5)	1 (1%; 0·0–5·5)	0	0	0	0	0	0
Swelling								
Mild	0	0	0	1 (1%; 0·0–7·2)	0	0	0	0
Moderate	0	0	0	0	0	0	0	0
Systemic reactions								
Fever								
Mild	0	1 (1%; 0·0–5·5)	1 (1%; 0·0–5·5)	0	2 (2%; 0·2–7·0)	1 (1%; 0·0–5·5)	1 (1%; 0·0–5·5)	0
Moderate	0	1 (1%; 0·0–5·5)	2 (2%; 0·2–7·0)	0	0	0	0	0
Body ache								
Mild	0	1 (1%; 0·03–5·5)	0	0	0	0	0	0
Moderate	0	1 (1%; 0·0–5·5)	1 (1%; 0·0–5·5)	0	1 (1%; 0·0–5·5)	0	0	0
Fatigue								
Mild	1 (1%; 0·0–5·4)	0	0	0	1 (1%; 0·03–5·4)	0	3 (3%; 0·6–8·5)	0
Moderate	2 (2%; 0·2–7·0)	3 (3%; 0·6–8·5)	0	0	1 (1%; 0·0–5·5)	0	0	0
Headache								
Mild	1 (1%; 0·03–5·5)	2 (2%; 0·2–7·0)	0	5 (7%; 2·2–14·9)	0	0	0	0
Moderate	0	3 (3%; 0·6–8·5)	2 (2%; 0·2–7·0)	0	0	0	0	0
Nausea or vomiting								
Mild	1 (1%; 0·03–5·5)	2 (2%; 0·2–7·0)	2 (2%; 0·2–7·0)	2 (3%; 0·3–9·3)	0	0	0	0
Moderate	0	0	0	0	0	0	0	0

Data are n (%; 95% CI). The safety set includes all participants who received one dose of the vaccine (n=375). Dose 1 events are from days 0–7 and dose 2 events are days 14–21. The grading scale for most adverse events was based on the US Food and Drug Administration (FDA) guidance document for toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. For adverse events where grading was not mentioned in the FDA guidance document, we have used the common terminology criteria for adverse events grading. There were no severe adverse events.

Table 2: **Solicited adverse events in the safety set**

(43 [69%] of 62) or moderate (19 [31%]) and were more frequent after the first dose than the second. No significant differences were observed between the vaccinated and control groups.

44 unsolicited adverse events were reported by 24 (6%) of 375 participants (appendix p 6). Biochemical, haematological, and urine parameters outside of the normal ranges had no corroborating clinical manifestations (appendix pp 7–9).

One serious adverse event was reported in the 6 µg with Algel group. The participant was screened on July 25 and vaccinated on July 30. 5 days later, the participant reported fever and headache (initially reported as a solicited adverse event), and on Aug 8 tested positive for SARS-CoV-2 (by a nucleic acid test). The symptoms were initially mild in nature, with the onset of relapsing fever requiring admission to hospital on Aug 15. The participant had stable vital signs (except body temperature) during their hospital stay and did not require supplemental oxygen. The participant was discharged on Aug 22 after a negative nucleic acid test result. The event was not causally associated with the vaccine. No other symptomatic SARS-CoV-2 infections were reported between days 0 and 75. However, follow-up of routine SARS-CoV-2 nucleic acid testing was not done on any scheduled or illness visit.

IgG titres (GMTs) to all epitopes (spike protein, receptor-binding domain, and nucleocapsid protein) increased rapidly after the administration of both doses (figure 2A–C; appendix pp 3–4). Both 3 µg and 6 µg with Algel-IMDG groups reported similar anti-spike, anti-receptor binding, and anti-nucleoprotein IgG titres (GMTs), adding to the dose-sparing effect of the adjuvant. Binding antibody titres to the whole-virion inactivated antigen are shown in the appendix (p 15). The mean isotyping ratios (IgG1/IgG4) were greater than 1 for all vaccinated groups, which was indicative of a Th1 bias (figure 2D).

Seroconversion rates (after the second dose), based on MNT_{50} were 87·9% (95% CI 79·8–94·3) in the 3 µg with Algel-IMDG group, 91·9% (84·6–96·0) in the 6 µg with Algel-IMDG group, and 82·8% (73·7–89·2) in the 6 µg with Algel group (figure 3A). Seroconversion (at day 28) in the control group was reported in six (8% [3·6–17·2]) of 75 participants, suggestive of asymptomatic infection. The post-second-dose GMTs (MNT_{50}) were 61·7 (49·5–76·9) in

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the 3 µg with Algel-IMDG group, 66·4 (53·4–82·4) in the 6 µg with Algel-IMDG group, and 48·0 (37·7–61·1) in the 6 µg with Algel group. Responses in the Algel-IMDG groups were not significantly different to the response in the 6 µg with Algel group. The vaccine-induced responses were similar to those observed in the convalescent serum collected from 41 patients who had recovered from COVID-19 (figure 3B). On these 41 patients, the median titre of symptomatic patients (n=25; median 142·2 [IQR 56·6–350]) was significantly higher than that of the asymptomatic patients (n=16; 22·6 [9·0–56·5]; appendix p 16). Seroconversion rates analysed by $PRNT_{50}$ (after the second dose) were 93·4% (95% CI 83·7–97·8) in the 3 µg with Algel-IMDG group, 86·4% (75·1–93·2) in the 6 µg with Algel-IMDG group, and 86·6% (74·3–93·6) in the 6 µg with Algel group (figure 3C).

MNT_{50} wild-type neutralising antibody responses for a subset of paired serum samples (n=50) were analysed at the National Institute of Virology and Bharat Biotech (on day 28, 2 weeks after the second vaccination in all groups). Additionally, neutralising antibodies were analysed by $PRNT_{50}$ at Bharat Biotech and the National Institute of Virology. Similar results were obtained for MNT_{50} and $PRNT_{50}$ assays at both laboratories (appendix p 17). Randomly selected serum samples from day 28 were analysed by $PRNT_{50}$ at the National Institute of Virology with homologous and heterologous strain assessments. Neutralisation responses, regardless of the challenge strain, were observed (figure 3D).

In a subset of randomly selected blood samples at one site, IFN-γ ELISpot responses against SARS-CoV-2 peptides peaked at about 100–120 spot-forming cells per million peripheral blood mononuclear cells in all vaccinated groups on day 28. Both the Algel-IMDG groups elicited $CD3^+$, $CD4^+$, and $CD8^+$ T-cell responses that were reflected in the IFN-γ production, albeit in a small number of samples. However, there was a minimal detection of less than 0·5% of $CD3^+$, $CD4^+$, and $CD8^+$ T-cell responses in the 6 µg with Algel group and the Algel only group (appendix p 16).

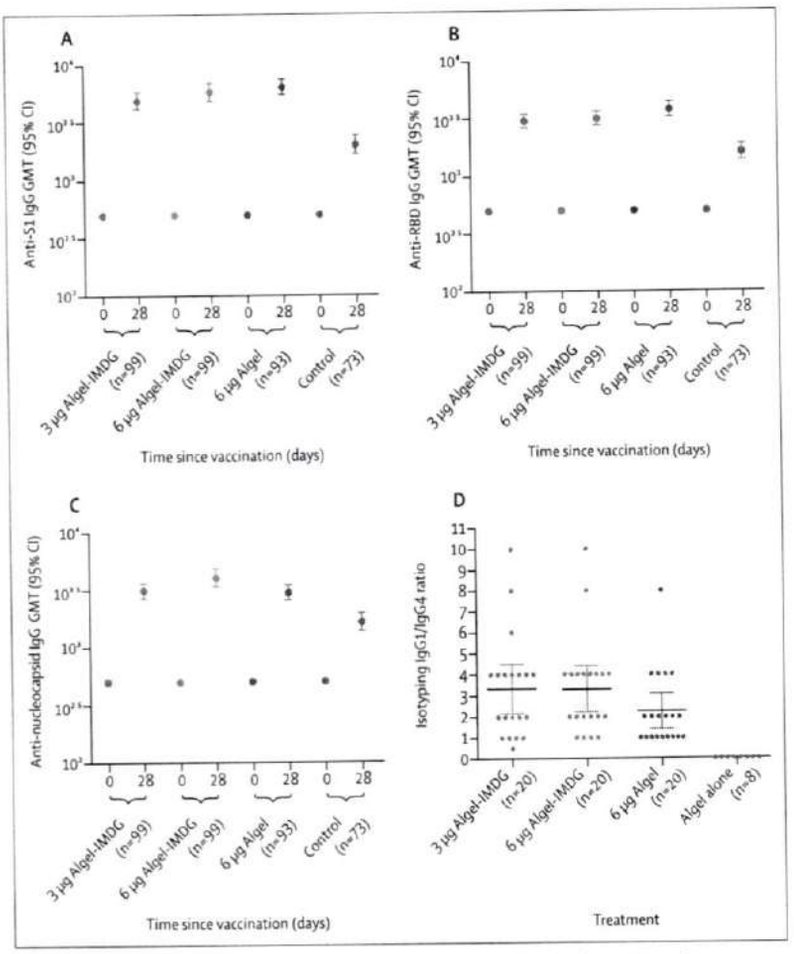

***Figure 2*: SARS-CoV-2 IgG titres against anti-spike protein (A), receptor-binding domain (B), and nucleocapsid IgG (C) and anti-spike protein IgG1/IgG4 ratio (D)**

ELISA results at baseline (day 0) and 2 weeks after the second vaccination (day 28). In A–C, error bars show 95% CIs. The cutoff for detectable antibodies was 1/500. Some samples were positive for SARS-CoV-2 in the control group, as evident by the antibody titres on day 28. Endpoint titre dilution for day 28 sera samples was established with baseline (day 0), interpolated from the absorbance of the corresponding day 0 sample. Cutoff (mean ± 3 SD) for day 0 was calculated considering the absorbance of all sera dilutions (1/500 to 1/32000) tested, except the lowest dilution (1/500). ELISA titres (endpoint titres) on day 14 were not analysed. In D, the isotyping ratio was calculated (in a randomly selected subset) as IgG1/IgG4; dots show the individual datapoints and horizontal bars show means with error bars for 95% CIs. Endpoint titre=the highest sera dilution at which the absorbance was above the cutoff. GMT=geometric mean titre. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Discussion

We report the interim findings from the phase 1 clinical trial of BBV152, a whole-virion inactivated SARS-CoV-2 vaccine. The vaccine was well tolerated in all dose groups with no vaccine-related serious adverse events. Both humoral and cell-mediated responses were observed in the recipients of the Algel-IMDG-based vaccines.

The most common adverse event was pain at the injection site, followed by headache, fatigue, and fever. The overall incidence of solicited local and systemic adverse events in this study was 14–21% in all vaccine-treated groups, which is noticeably lower than the rates for other SARS-CoV-2 vaccine platform candidates[18–23] and similar to the rates for other inactivated SARS-CoV-2 vaccine candidates[24,25] One serious adverse event (positive for SARS-CoV-2 by a nucleic acid test) in an individual in the 6 µg with Algel group was not related to vaccination. Because the event occurred in the 5 days after vaccination, the development of a protective immune response was not likely.

BBV152 induced binding and neutralising antibody responses that were similar to those induced by other SARS-CoV-2 inactivated vaccine candidates.[24,25] Titres from the Anti-spike IgG ELISA assay correlated positively with live virus microneutralisation assay titres (R^2=0·51). We assessed an accelerated schedule (vaccination 2 weeks apart) and did not include a routine schedule (vaccination 4 weeks apart). It has been reported that a routine schedule for another SARS-CoV-2 vaccine candidate offers better immune responses, as is to be expected.[26] The 4-week schedule for BBV152 3 µg and 6 µg with

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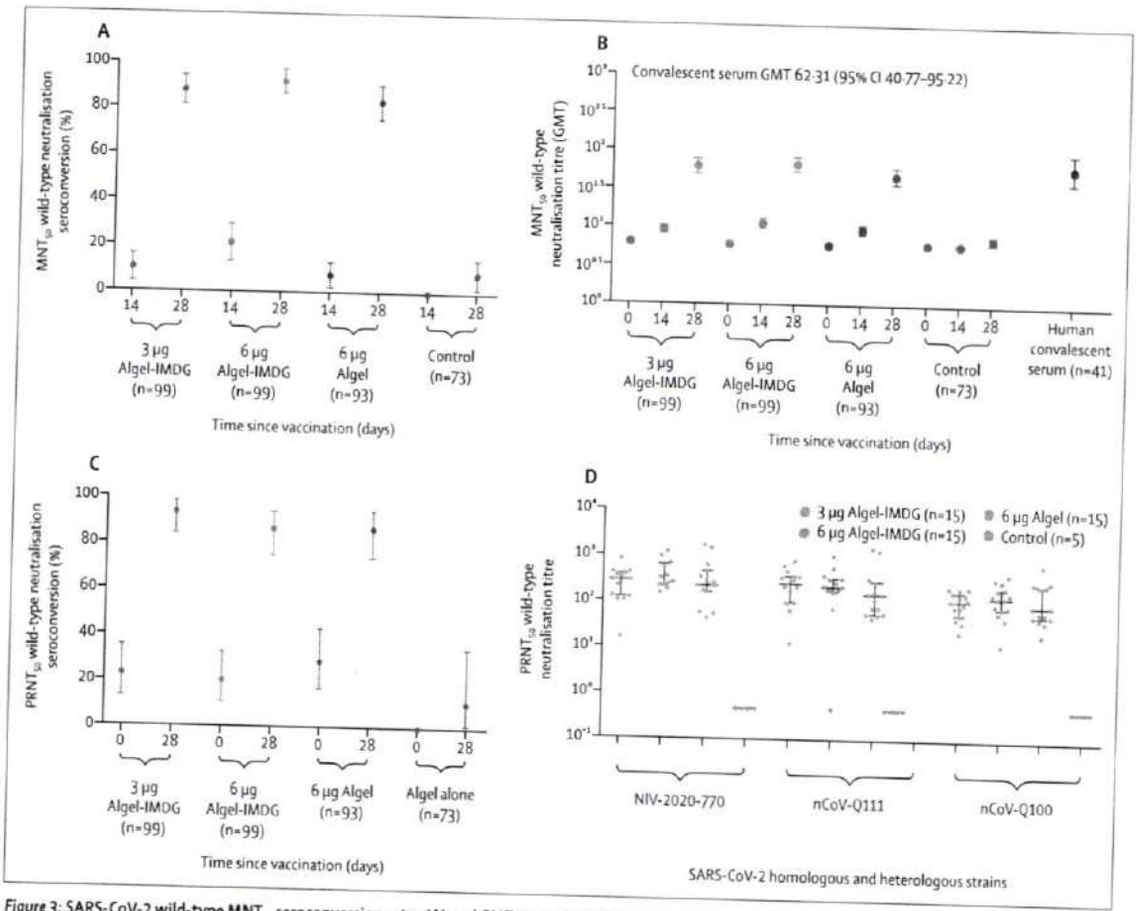

Figure 3: **SARS-CoV-2 wild-type MNT_{50} seroconversion rates (A) and GMT (B) and $PRNT_{50}$ seroconversion rates (C) and medians (D)**
Results at baseline (day 0), 2 weeks after the first vaccination (day 14), and 2 weeks after the second vaccination in the immunogenicity cohort. Seroconversion rates were defined by the proportion of titres achieving at least four-fold greater than baseline. In A–C, error bars show 95% CIs. In B, the human convalescent serum panel included specimens from participants with PCR-confirmed symptomatic or asymptomatic COVID-19, obtained at least 30 days after diagnosis (41 samples for MNT_{50}). In D, randomly selected serum samples from day 28 were analysed by $PRNT_{50}$ at the National Institute of Virology for homologous (NIV-2020-770) and heterologous (nCoV-Q11 and nCoV-Q100) assessments; dots show individual datapoints and horizontal bars show medians with error bars for IQRs. GMT=geometric mean titre. MNT_{50}=microneutralisation assay. $PRNT_{50}$=plaque-reduction neutralisation test. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Algel-IMDG is being assessed in a phase 2 trial in 380 volunteers (NCT04471519). Here, we showed that all vaccine formulations were Th1 skewed with IgG1/IgG4 ratios greater than 1. Furthermore, the Algel-IMDG formulations were associated with an increase in the frequency of $CD4^+$ $INF\text{-}\gamma^+$ T cells compared with the 6 µg with Algel formulation, which is indicative of a Th1 bias. Additionally, cell-mediated responses from other SARS-CoV-2 inactivated vaccine candidates have not been reported thus far.

A few animal studies of SARS-CoV and Middle East respiratory syndrome-CoV inactivated or vectored vaccines adjuvanted with alum have shown Th2 responses resulting in eosinophilic infiltration in the lungs.[27–29] Adverse events might be associated with the induction of weakly neutralising or non-neutralising antibodies that lead to antibody-dependent enhancement or enhanced respiratory disease, thus prompting the attempt to develop SARS-CoV-2 vaccines that induce a $CD4^+$ Th1 response with a minimal Th2 response.[2,10–12] Whole-virion inactivated vaccines are mostly developed with Algel (alum) as the adjuvant. The response generated by alum is primarily Th2 biased, with the induction of strong humoral responses by neutralising antibodies.[13] To circumvent this concern of antibody-dependent enhancement, we have assessed this vaccine with Algel and a TLR7/8 agonist that results in immune responses that are biased to Th1. Previous studies have shown that the toll-like receptors play an integral role in bridging the innate and adaptive immune responses, leading to the differentiation of $CD4^+$ T cells into Th1 cells, which produce IFN-γ.[14] Geeraedts and colleagues[15] reported that the stimulation of TLR7 by an influenza whole-virion inactivated vaccine was a significant determinant of a greater immune response and Th1 polarisation. Thus, it is imperative to develop such whole-virion inactivated vaccines with adjuvants that can synergistically

contribute to the full potential. Algel-IMDG contains an imidaquizoquinoline class TLR7/8 agonist adsorbed to Algel. Preclinical studies on BBV152 adjuvanted with this molecule reported a Th1-biased response in mice.[7] Furthermore, in a non-human primate and hamster live viral challenge studies, Algel-IMDG formulations led to higher neutralising antibodies, which might have resulted in improved upper and lower airway viral clearance (after challenge).[8,9]

This study was done at a time of rapidly increasing daily diagnoses of COVID-19. Among all 897 individuals screened for this trial, 70 (8%) had positive SARS-CoV-2 nucleic acid test results and 63 (7%) had positive SARS-CoV-2 serology results. Seroconversion (at day 28) in the control group was reported in six (8%) of 75 participants from five separate study sites. Because substantial SARS-CoV-2 was observed at enrolment and some of the control group recipients seroconverted, post-vaccination titres from the vaccinated recipients might be slightly inflated, in the event of natural exposure to SARS-CoV-2. No symptomatic COVID-19 cases were reported in the control group.

Because this is an interim report, we are not reporting any data on the persistence of vaccine-induced antibody responses or long-term safety outcomes. The results reported here do not permit efficacy assessments. The analysis of safety outcomes requires more extensive phase 2 and 3 clinical trials. Pre-vaccination laboratory values were similar to values after vaccination. However, transient laboratory abnormalities might have been resolved by day 28. The analysis of T-cell responses by Th2 cytokines was not done and is planned for phase 2. We were unable to assess other immune responses of convalescent serum because of insufficient number of samples. The proportion of samples collected from asymptomatic individuals was high (39%), and no additional data on the severity of disease from symptomatic individuals was obtained. This study population did not have ethnic diversity and most of the participants were men, further underscoring the importance of assessing BBV152 in other populations.

However, this study has several strengths. To ensure generalisability, this study was conducted with participants from diverse geographic locations within India (appendix p 13), enrolling 375 participants across 11 hospitals. The first 50 participants were enrolled into the 3 µg with Algel-IMDG and control groups. Before granting the recommendation to proceed with the enrolment of other cohorts, masked safety data was reviewed by the data safety monitoring board. As a result, no operational bias was introduced. Despite enrolment occurring during a national lockdown, which led to several operational challenges, the overall participant retention rate was 97%. The sample size was intentionally large to enable the inference of meaningful conclusions regarding neutralising responses. With several reports questioning the efficacy of SARS-CoV-2 vaccines against antigenically divergent strains, we report neutralising responses to homologous and heterologous strains. The BBV152 vaccine strain, based on the Asp614Gly mutation, has been reported to have differential sensitivity to neutralisation by vaccine-elicited antibodies or by antibodies produced by natural infection.[36,37] The increase in Asp614Gly infectivity results in the virus being more susceptible to neutralising antibodies,[38] which is corroborated by marginal reductions in neutralising titres in the $PRNT_{50}$ assays with heterologous strains, which are devoid of the Asp614Gly mutation.

BBV152 induced binding and neutralising antibody responses and with the inclusion of the Algel-IMDG adjuvant, this is the first inactivated SARS-CoV-2 vaccine that has been reported to induce a Th1-biased response. BBV152 is stored at 2–8°C, which is compatible with immunisation cold-chain requirements. Both Algel-IMDG formulations were selected for the phase 2 immunogenicity trials. Further efficacy trials are warranted.

Contributors

RE and KMV accessed and verified the data. HJ, BG, PY, and GS led the immunogenicity experiments. KMV, SPr, VS, and RE contributed to the analysis and manuscript preparation. SR was the study coordinator and helped immensely with the protocol design and interim report generation. PA, SPr, NG, and BB contributed various neutralising antibody assays and participated in the writing of this manuscript. SPa reviewed the manuscript. PR, SV, SKR, CS, SVR, CSG, JSK, SM, VR, and RG were involved with the scientific review of this manuscript. KE was responsible for overall supervision of the project and review of the final paper.

Declaration of interests

RE, HJ, BG, KMV, SPr, VS, KE, and SR are employees of Bharat Biotech, with no stock options or incentives. KE is the Chairman and Managing Director of Bharat Biotech. PY, GS, PA, NG, SPa, and BB are employees of The Indian Council of Medical Research. All other authors declare no competing interests.

Data sharing

Deidentified individual participant data will be made available when the trial is complete, upon requests directed to the corresponding author; after approval of a proposal, data can be shared through a secure online platform.

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ANNEXURE- P25

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Safety and immunogenicity clinical trial of an inactivated SARS-CoV-2 vaccine, BBV152 (a phase 2, double-blind, randomised controlled trial) and the persistence of immune responses from a phase 1 follow-up report

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Abstract:

Background:

BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine (3 µg or 6 µg) formulated with a Toll-like receptor 7/8 agonist molecule adsorbed to alum (Algel-IMDG). Earlier, we reported findings from a phase 1 (vaccination regimen on days 0 and 14) randomised, double-blind trial on the safety and immunogenicity of three different formulations of BBV152 and one control arm containing Algel (without antigen). Two formulations were selected for the phase 2 (days 0 and 28) study. Here, we report interim findings of a controlled, randomised, double-blind trial on the immunogenicity and safety of BBV152: 3 µg and 6 µg with Algel-IMDG.

Methods:

We conducted a double-blind, randomised, multicentre, phase 2 clinical trial to evaluate the immunogenicity and safety of BBV152. A total of 380 healthy children and adults were randomised to receive two vaccine formulations (n=190 each) with 3 µg with Algel-IMDG and 6 µg with Algel-IMDG. Two intramuscular doses of vaccines were administered (four weeks apart). Participants, investigators, and laboratory staff were blinded to the treatment allocation. The primary outcome was seroconversion (≥4-fold above baseline) based on wild-type virus neutralisation ($PRNT_{50}$). Secondary outcomes were reactogenicity and safety. Cell-mediated responses were evaluated. A follow-up blood draw was collected from phase 1 participants at day 104 (three months after the second dose).

Findings:

Among 921 participants screened between Sep 7-13, 2020, 380 participants were randomised to the safety and immunogenicity population. The $PRNT_{50}$ seroconversion rates of neutralising antibodies on day 56 were 92·9% (88·2, 96·2) and 98·3% (95·1, 99·6) in the 3 µg and 6 µg with

Algel-IMDG groups, respectively. Higher neutralising titres (2-fold) were observed in the phase 2 study than in the phase 1 study ($p<0.05$). Both vaccine groups elicited more Th1 cytokines than Th2 cytokines. After two doses, the proportion (95% CI) of solicited local and systemic adverse reactions were 9.7% (6·9, 13·2) and 10.3% (7·4, 13·8) in the 3 μg and 6 μg with Algel-IMDG groups, respectively. No significant difference was observed between the groups. No serious adverse events were reported in this study. Phase 1 follow-up immunological samples at day 104 showed seroconversion in 73·5% (63·6, 81·9), 81·1% (71·4, 88·1), and 73·1% (62·9, 81·8) of individuals in the 3 μg with Algel-IMDG, 6 μg with Algel-IMDG, and 6 μg with Algel groups, respectively.

Interpretation:

In the phase 1 trial, BBV152 produced high levels of neutralising antibodies that remained elevated in all participants three months after the second vaccination. In the phase 2 trial, BBV152 led to tolerable safety outcomes and enhanced humoral and cell-mediated immune responses. The safety profile of BBV152 is noticeably lower than the rates for other SARS-CoV-2 vaccine platform candidates. The 6 μg Algel-IMDG formulation was selected for the phase 3 efficacy trial.

Funding:

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Clinicaltrials.gov: NCT04471519

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel human coronavirus [1], has spread worldwide. To date, 194 vaccine candidates are being developed to prevent coronavirus disease 2019 (COVID-19) [2]. Several such vaccines have been given an Emergency Use Authorization [3-6]. The virus strain NIV-2020-770 was isolated from a COVID-19 patient, sequenced at the Indian Council of Medical Research-National Institute of Virology (NIV), and provided to Bharat Biotech [7]. Bio-safety level 3 manufacturing facilities and a well-established Vero cell manufacturing platform aided in the rapid development of BBV152.

Preclinical studies in mice, rats, and rabbits demonstrated appropriate safety profiles and humoral and cell-mediated responses [8]. Live viral challenge protective efficacy studies in hamsters and nonhuman primates demonstrated rapid viral clearance in the lower and upper respiratory tracts and the absence of lung pathology (after viral challenge) [9,10].

Earlier, we reported interim findings from a phase 1 controlled, randomised, double-blind trial on the safety and immunogenicity of three different formulations of BBV152 and one control arm containing Algel (without antigen). This phase 1 trial was successfully conducted with the intention of selecting two formulations for progression to a phase 2 trial. The formulations selected were 3 µg and 6 µg with Algel-IMDG. Here, we report interim findings from a phase 2 controlled, randomised, double-blind trial on the immunogenicity and safety of two formulations of BBV152. Additionally, this paper reports follow-up immunological endpoints from the phase 1 trial (day 104), three months after the second dose.

Methods

Trial Design and Participants

This was a randomised, double-blind, multicentre phase 1 trial that was seamlessly followed by a phase 2 trial to evaluate the safety, reactogenicity, tolerability, and immunogenicity of a whole-virion inactivated SARS-CoV-2 vaccine (BBV152) in healthy male and nonpregnant female volunteers across 11 hospitals. Participants were ≥12-<65 years of age at the time of enrolment. At the screening visit, participants were evaluated with both SARS-CoV-2 nucleic acid and serology tests (conducted at a central laboratory using commercially available assays). If individuals were positive for either test, they were excluded from the trial. The median time between the screening visit and vaccination visit was 3 (range: 2-4) days. Participants were screened for eligibility based on their health status, including their medical history, vital signs, and physical examination results and were enrolled after providing signed and dated informed consent forms. Details of the inclusion and exclusion criteria can be found in the protocol.

The trial was conducted across nine sites in nine states in India. The trial was approved by the National Regulatory Authority (India) and the respective Ethics Committees and was conducted in compliance with all International Council for Harmonization (ICH) Good Clinical Practice guidelines. The trial was registered on clinicaltrials.gov: NCT04471519.

Trial Vaccines

BBV152 (manufactured by Bharat Biotech) is a whole-virion ß-propiolactone-inactivated SARS-CoV-2 vaccine. The vaccine strain NIV-2020-770 contains the D614G mutation, which is characterised by an aspartic acid to glycine shift at amino acid position 614 of the spike protein [7].

The candidates were formulated with Algel-IMDG, an imidazoquinoline class molecule (a Toll-like receptor (TLR)7/TLR8 agonist abbreviated as IMDG) adsorbed to Algel. After their eligibility was determined, participants were randomised into two groups: the 3 µg with Algel-IMDG and 6 µg with Algel-IMDG groups. Both vaccines were stored between 2°C and 8°C. All vaccines were stored in a single-use glass vial at a volume of 0·5 mL per dose. The appearance, colour, and viscosity were identical across all formulations.

Trial Procedures

Vaccines were provided as a sterile liquid that was injected through an intramuscular route (deltoid muscle) at a volume of 0·5 mL/dose in a two-dose regimen on days 0 and 28. No on-site dose preparation was required. Each glass vial contained a single dose of one of the vaccine formulations and required no additional dilution steps. No prophylactic medication (ibuprofen/acetaminophen) was prescribed either before or after vaccination. The follow-up visits were scheduled on days 42, 56, 104, and 194.

In the phase 1 trial, at day 104 (three months after the second dose), 97 (97%), 95 (95%), 92 (92%), and 69 (92%) participants were followed up in the 3 µg with Algel-IMDG, 6 µg with Algel-IMDG, 6 µg with Algel, and Algel alone (control) groups, respectively.

Randomisation

The master randomisation list was uploaded to the Interactive Web Response System, which contained the randomisation number and intended allocation. The depot manager uploaded the kit code list and assigned the kits to the sites that had the kit codes and the allocation groups. At the site level, the system set the randomisation number and the allotment of the kit without displaying the true group allocation, and the system allocated the same treatment arm for the second visit. A block size of four was utilised. An unblinded Contract Research Organization (CRO), Sclin Soft Technologies, was involved in randomisation for the study.

Blinding

Participants, investigators, study coordinators, study-related personnel, and the sponsor were blinded to the treatment group allocation (excluding an unblinded CRO that was tasked with the dispatch and labelling of vaccine vials and the generation of the master randomisation code). Participants were assigned a computer-generated randomisation code that maintained blinding. The blinded study nurse was responsible for vaccine preparation and administration. Each vial contained a unique code that ensured appropriate blinding.

Immunogenicity Assessments

Anti-IgG responses against the spike (S1) protein, receptor-binding domain (RBD), and nucleocapsid (N) protein of SARS-CoV-2 were assessed by enzyme-linked immunosorbent assay (ELISA) and are expressed as geometric mean titres (GMTs). The primary outcome was neutralising antibody titres evaluated by wild-type virus neutralisation assays, namely, (i) a plaque-

reduction neutralisation test ($PRNT_{50}$) and (ii) a microneutralisation assay (MNT_{50}), at Bharat Biotech. Details of these assays are provided in the Supplementary Appendix.

To compare vaccine-induced responses to natural SARS-CoV-2 infections, 50 convalescent serum samples (collected either one to two months after a nucleic acid test-based diagnosis) were tested by $PRNT_{50}$ and MNT_{50}. These serum samples were collected from self-reported symptomatic (n=35) and asymptomatic (n=15) COVID-19 patients and were provided by the NIV, Pune. For symptomatic patients, the ascertainment of severity grading and the requirement for supplemental oxygen was not available. Seroconversion was defined as a postvaccination titre ≥4-fold above the pre-vaccination titre in a participant. All serum samples were analysed in a blinded manner at Bharat Biotech by $PRNT_{50}$ and MNT_{50}. To ensure the validity of our assay, a subset of serum samples (n=50) were randomly selected and tested by $PRNT_{50}$ and MNT_{50} at NIV.

Cell-mediated responses were assessed in a subset of participants at three sites on day 42. Serum was used to evaluate Th1 and Th2 dependent antibody isotypes and peripheral blood mononuclear cells (PBMCs) were used to assess the Th1 & Th2 cytokines. The CRO generated a random code containing randomisation numbers, which was provided to the staff to identify participants. Blood (3-5 mL) was collected from participants who consented to have additional blood volume collected on day 42. PBMCs were collected from 58 participants (n=29 each in the 3 µg and 6 µg with Algel-IMDG groups). Pre-vaccination samples collected on day 0 (n=10, from both groups) served as the control. PBMCs collected on day 42 were tested at Indoor Biotechnologies, India, whereas Day 56 PBMCs were tested at Bharat Biotech using Luminex based multiplex assay and Cytokine Bead Array Multiplex Assay (CBA, BD Biosciences, USA), respectively. Luminex based

multiplex assay to assessed Th1 (IFN-γ, TNF-α and IL-2) and Th2 (IL-5, IL-10 and IL-13) cytokines. In PBMCs collected on day 104 of the phase 1 trial, T cell memory responses ($CD4^+$ $CD45RO^+$ T cells and $CD4^+$ $CD45RO^+$ $CD27^+$ T cells) were evaluated at Bharat Biotech. After antigen stimulation of day 104 PBMCs, culture supernatant was collected on day 3, to assess cytokines and secreted SARS-CoV-2 IgG antibodies (by ELISA) on day 6. All samples were analysed in a blinded manner. The details of all assay methods can be found in the Supplementary Appendix.

Safety Assessments

The secondary outcome was the number and percentage of participants with solicited local and systemic reactogenicity within two hours and seven days after vaccination. Unsolicited adverse events were recorded within 28 days after vaccination.

Participants were observed for two hours postvaccination to assess reactogenicity. They were instructed to record local and systemic reactions within seven days (days 0 to 7 and days 28 to 35) postvaccination using a memory aid. The memory aid contained fields for symptom onset, severity, time to resolution, and concomitant medications and was collected during the next visit to the site. Routine telephone calls were scheduled following the first seven days after each vaccination. Solicited local adverse events included pain at the injection site and swelling, and systemic adverse events included fever, fatigue/malaise, myalgia, body aches, headache, nausea/vomiting, anorexia, chills, generalised rash, and diarrhoea. All unsolicited adverse events were reported by participants throughout the study. Adverse events were graded according to the

severity score (mild, moderate, or severe) and whether they were related or unrelated to the investigational vaccine, as detailed in the protocol.

Sample Size

We assumed that we would observe seroconversion rates (SCRs) of 85% for 3 μg with Algel-IMDG and 95% for 6 μg with Algel-IMDG and a standard deviation (SD) of 0.5 for $\log_{10}$ titre. The required sample size for 90% power to find a significant difference (between vaccine formulations differing in the GMT by a ratio of 2) in a trial with a 1:1 allocation using a two-sample z-test at the two-sided 5% significance level was 171 per group. Assuming 10% loss during the study, the number was 190 per group. Sample size estimation was performed using PASS 13 software (Number Cruncher Statistical Systems, USA).

Statistical Analysis

Safety endpoints are described as frequencies (%). GMTs with 95% confidence intervals (CIs) are presented for immunological endpoints. For continuous variables (below 20 observations), medians and IQRs are reported. The exact binomial calculation was used for the CI estimation of proportions. Wilson's test was used to test differences in proportions. CI estimation for the GMT was based on the $\log_{10}$ (titre) and the assumption that the $\log_{10}$ (titre) was normally distributed. A comparison of GMTs was performed with t-tests on the means of the $\log_{10}$ (titre). Significance was set at $p < 0{\cdot}05$ (2-sided). This preliminary report contains results regarding immunogenicity and safety outcomes (captured on days 0 to 56). Descriptive and inferential statistics were performed using SAS 9·2.

Role of The Funding Source

The sponsor of the study had no role in data collection, data analysis, data interpretation, or writing the report. The CRO was responsible for data analysis and generating the report. The first and corresponding authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

Results

Among the 921 potential participants screened between Sep 7 and Sep 11, 2020, 380 participants were randomised. Among the 541 initially screened individuals who were excluded, 48 and 123 participants were found to be positive for SARS-CoV-2 with a nucleic acid test and serology, respectively. Due to competitive recruitment, some screened participants (n=188) were eligible but not enrolled and randomised (Figure 1). Other notable exclusions (n=168) were due to inconclusive RT-PCR results. Among enrolled participants, 190 individuals were randomised to each group. The retention rates at day 56 were 96.8% and 93.2% in the 3 μg and 6 μg with Algel-IMDG groups, respectively. Demographic characteristics of participants are presented in Table 1.

Immune Responses

Phase 2: Binding Antibody Titres

Binding antibody Anti-IgG titres (GMTs) to all epitopes (S1 protein, RBD, and N protein) increased rapidly after the administration of both doses. Both the 3 μg and 6 μg with Algel-IMDG groups reported comparable anti-S1 protein, -RBD, and -N protein GMTs. The Anti-S1 isotype ratios (IgG1/IgG4) were 2.4 (1.9, 2.9) and 2.1 (1.7, 2.6) in the 3 μg and 6 μg with Algel-IMDG groups, respectively (Table 2).

Phase 2: Neutralising Antibody Titres (at day 56, four weeks after the second dose)

GMTs ($PRNT_{50}$) were 100·9 (74·1, 137·4) and 197·0 (155·6, 249·4) in the 3 µg and 6 µg with Algel-IMDG groups, respectively. The GMT in the 6 µg with Algel-IMDG group was higher and found to be significantly different than that in the 3 µg with Algel-IMDG group. The 6 µg with Algel-IMDG-induced responses were comparable to those observed in convalescent serum collected from patients who had recovered from COVID-19 (Figure 2A). The proportions of participants who experienced seroconversion based on $PRNT_{50}$ (95% CI) were 92·9% (88·2, 96·2) and 98·3% (95·1, 99·6) in the 3 µg and 6 µg with Algel-IMDG groups, respectively (Figure 2B). GMTs (MNT_{50}) were 92·5 (77·7, 110·2) and 160·1 (135·8, 188·8) in the 3 µg and 6 µg with Algel-IMDG groups, respectively (Figure 2C). The proportions of participants who experienced seroconversion based on MNT_{50} (95% CI) were 88·0% (82·4, 92·3) and 96·6% (92·8, 98·8) in the 3 µg and 6 µg with Algel-IMDG groups, respectively (Figure 2D and Table S2 in the Supplementary Appendix). The $PRNT_{50}$ and MNT_{50} GMTs in the 6 µg with Algel-IMDG group were higher and significantly different than those in the 3 µg with Algel-IMDG group.

$PRNT_{50}$ wild-type neutralising antibody responses for a subset of paired serum samples (n=50) were analysed at NIV and Bharat Biotech (on day 42, 2 weeks after the second vaccination in both groups). In comparisons of $PRNT_{50}$ assays between laboratories, a strong agreement was observed. Seroconversion in any three age groups was always found to be above 90%. No significant differences were observed in seroconversion and GMTs across the three age groups and between both sexes, but small numbers of samples were included in the ≥12-<18 and ≥55-<65 age groups (Table S3 in the Supplementary Appendix).

Phase 1: Neutralising Antibody Titres (at day 104, three months after the second dose)

GMTs (MNT_{50}) were 39·9 (32·0, 49·9), 69·5 (53·7, 89·9), and 53·3 (40·1, 71·0) in the 3 μg with Algel-IMDG, 6 μg with Algel-IMDG and 6 μg with Algel groups, respectively (Figure 3A). The proportions of participants who experienced seroconversion based on MNT_{50} (95% CI) were 73·5% (63·6, 81·9), 81·1% (71·4, 88·1), 73·1% (62·9, 81·8) in the 3 μg with Algel-IMDG, 6 μg with Algel-IMDG, and 6 μg with Algel groups, respectively (Figure 3B). SCRs and GMT responses in the 6 μg with Algel-IMDG group were higher and were significantly different than those in the 3 μg with Algel-IMDG and 6 μg with Algel groups (Table S4 in the Supplementary Appendix). In the 6 μg with Algel-IMDG group, there were no significant differences in SCRs and GMTs between day 42 (two weeks after the second dose) and 104 (three months after the second dose). The phase 2 neutralisation GMTs were higher and significantly different than those in phase 1 (Figure 3C). At four weeks after the second dose of 6 μg with Algel-IMDG, the MNT_{50} GMT ratio between Phase 1 and 2 was 1.9 (95%CI: 1·5, 2·6).

Cell-mediated Responses

Phase 2 (at day 42, two weeks after the second dose)

The ratios of Th1/Th2 cytokines (IFN-γ + TNF-α + IL-2 /IL-5 + IL-13 + IL-10) were biased to a Th1 response (Figure 4A). Th2 responses were detected at minimal levels in both formulations, as observed by IL-5, IL-10 and IL-13 responses (Figure 4B).

Phase 2 (at day 56, two weeks after the second dose)

We observed a profound increase in the levels of Th1-biased cytokines, such as IFN-γ, IL-2 and TNF-α responses on day 56, performed by the CBA method (Supplementary Figure S1).

Phase 1 (at day 104, three months after the second dose)

In the phase 1 trial, PBMCs from a subset of participants at one site were collected to evaluate T cell memory responses at day 104. Formulations with Algel-IMDG generated a T cell memory response, as shown by an increase in the frequency of effector memory $CD4^+$ $CD45RO^+$ T cells and $CD4^+$ $CD45RO^+$ $CD27^+$ T cells compared to pre-vaccination samples (Figure 4C & D). Placebo samples also showed a T cell memory response. We also detected secreted IgG antibodies in the cell culture supernatant by ELISA, and the antibody titre ranged from neat (undiluted) to 1:64 (Supplementary Table S5). Further effector function of activated and differentiated T cells was demonstrated by the measurement of Th1 mediated cytokines (Supplement Table S6).

Reactogenicity

After dose 1, the proportions of solicited local adverse reactions (95% CI) reported were 4·7% (2·2, 8·8) and 4·2% (1·8, 8·1) in the 3 μg and 6 μg with Algel-IMDG groups, respectively. The proportions of solicited systemic adverse reactions (95% CI) were 4·7% (2·2, 8·8) and 7·4% (4·1, 12·1) in the 3 μg and 6 μg with Algel-IMDG groups, respectively (Table 3). After both doses, the most common solicited adverse events were injection site pain, at 2·6% (0·9, 6·0) and 3·2 (1·2, 6·8) in the 3 μg and 6 μg with Algel-IMDG groups, respectively. The majority of the adverse events were mild and resolved within 24 hours of onset. After both doses, the proportions (95% CI) of solicited local and systemic adverse reactions were 9·7% (6·9, 13·2) and 10·3% (7·4, 13·8) in the 3 μg and 6 μg with Algel-IMDG groups, respectively. No significant differences were observed between the groups.

Safety

A total of 6 (28·6%) out of 21 unsolicited adverse events were reported to be related to the vaccine. No significant difference was observed between the groups (Supplementary Table S7). The evaluation of severity grading and the relationship to the vaccine are described in Supplementary Table S8. No symptomatic SARS-CoV-2 infections were reported between days 0 and 75. However, the follow-up of routine SARS-CoV-2 nucleic acid testing was not conducted at any scheduled or illness visit. No serious adverse events were reported until day 56.

Phase 1 (at day 104, three months after the second dose)

No new solicited/unsolicited adverse events that occurred after day 42 were considered to be related to the vaccine by the investigators. No new serious adverse events were reported.

One case of symptomatic COVID-19 was reported in the Algel alone (control/placebo) group. The participant was screened on July 15th and vaccinated on July 17th. The participant was unable to be contacted for the second vaccination visit and was considered to be lost to follow-up. The participant visited the site on November 27th with complaints of chronic anosmia and a history of a positive SARS-CoV-2 rapid antigen test on August 16th.

Discussion

We report interim findings from the phase 2 clinical trial of BBV152, a whole-virion inactivated SARS-CoV-2 vaccine. Both humoral and cell-mediated responses were observed. No neutralising antibody differences were observed between sexes and across age groups, albeit small numbers of

participants were included in the ≥12-<18 and ≥55-<65 age groups. The vaccine was well tolerated in both dose groups with no serious adverse events.

The most common adverse event was pain at the injection site, followed by headache, fatigue, and fever. No severe or life threatening (Grade 4 and 5) solicited adverse events were reported. After any dose, the combined incidence rate of local and systemic adverse events in this study is noticeably lower than the rates for other SARS-CoV-2 vaccine platform candidates [4,11-15] and comparable to the rates for other inactivated SARS-CoV-2 vaccine candidates [5,16].

BBV152 induced binding (to both spike- and nucleocapsid protein epitopes) and neutralising antibody responses that were similar to those induced by other SARS-CoV-2 inactivated vaccine candidates [5,16]. The current literature reports the variable persistence of humoral and cell-mediated responses acquired from natural infection [17,18]. In the phase 1 trial, we evaluated an accelerated schedule (vaccination occurring two weeks apart). At day 104 (three months after the second vaccination dose), we observed detectable humoral and cell-mediated responses. Serum neutralising antibodies were detected in all the participants on day 104. These findings are in accordance with those on the mRNA-1273 vaccine, which will be licensed soon [19]. A sizeable T cell memory population was also observed at this time point. A routine schedule (vaccination occurring four weeks apart) was evaluated in the phase 2 trial for 3 µg and 6 µg with Algel-IMDG. Here, immune responses were significantly higher than those in the phase 1 trial, which concurs with reports that a routine schedule offers higher immune responses [20]. It is hypothesised that the humoral and cell-mediated responses reported in this study may persist until at least 6-12 months after the second vaccination dose.

An imidazoquinoline molecule (IMDG), which is a TLR7/8 agonist, has been used to augment cell-mediated responses [21,22]. BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine adjuvanted with Algel-IMDG. Both formulations were Th1-skewed with IgG1/IgG4 ratios above 1. The ratio of Th1/Th2 cytokines was clearly biased to a Th1 response with increased IFN-γ generation.

In the present study, BBV152 induced T cell memory responses, which was demonstrated by an increased frequency of antigen-specific $CD4^+$ T cells expressing the memory phenotype marker $CD45RO^+$. The increase in the $CD4^+CD45RO^+CD27^+$ population also demonstrates the activation of the co-stimulatory marker CD27 and confirms the antigen recall memory T cell response. Further, the effector function of these cells was supported by the Th1-biased cytokine secretion observed on day 3. These results further corroborate our phase 1 results, where we reported an increased frequency of $CD4^+$ T lymphocytes producing IFN-γ in Algel-IMDG recipients. The ability to secrete spike-specific IgG antibodies further demonstrates the long-lived memory response generated by BBV152. Similar findings supporting long-term immunity were reported by Sekine et al. in convalescent COVID-19 patients [23]. Cell-mediated responses to other SARS-CoV-2 inactivated vaccine candidates have not been reported thus far.

This study was conducted in a time of rapid increases in daily diagnoses of COVID-19 cases. Among all participants who were screened, 48 (5.2%) and 63 (13.4%) reported positive SARS-CoV-2 nucleic acid tests and serology, respectively. In the phase 1 Algel alone (control arm) recipients, seroconversion was reported in 8·2% (1·9, 14·5), 18·1% (10·1, 29·3), and 32·9% (22·3, 44·9) on days 28, 42, and 104, respectively. At day 104, a total of 39 (52%) participants

(receiving Algel alone) reported a 2-fold change in neutralising antibody titres. This suggests that both phase 1 and 2 trials are being conducted during a period of high ongoing SARS-CoV-2 circulation. In phase 2, no COVID-19 cases were reported from either group, while there was one cases of symptomatic COVID-19 in the control group of the phase 1 trial.

The results reported here do not permit efficacy assessments. The evaluation of safety outcomes requires extensive phase 3 clinical trials. We were unable to assess other immune responses (binding antibody and cell-mediated responses) of convalescent serum due to the limited quantity. No additional data on the severity of disease from symptomatic individuals were obtained. Last, this study population lacked ethnic diversity, further underscoring the importance of evaluating BBV152 in other populations. Longitudinal follow-up is important and is ongoing.

However, this study had several strengths. To ensure generalizability, this study was conducted with participants from diverse geographic locations, enrolling 380 participants across nine hospitals. The study enrolled participants with a wide range of ages and found no differences in immune responses across age groups. The overall participant retention rates were 96·8% and 93·2% in the 3 µg and 6 µg with Algel-IMDG groups, respectively.

Based on follow-up data from the phase 1 trial, at day 104 (three months after the second dose), despite a marginal expected decline in neutralising antibody titres, BBV152 has exhibited the potential to provide durable humoral immunity and cell-mediated immunity. From the phase 2 trial, the 6 µg with Algel-IMDG formulation was selected for the phase 3 efficacy trial, which is being carried out in 25,800 volunteers (NCT04641481).

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Author Contributions

All listed authors met the criteria for authorship set forth by the International Committee for Medical Editors and have no conflicts to disclose. E.R. and K.M.V. accessed and verified the data (the CRO was responsible for generating the report). J.H., D.D., D.R., U.P., B.G., P.Y., and G.S. performed the immunogenicity experiments. K.M.V., P.S., S.R., V.S., and E.R. contributed to the analysis and manuscript preparation. S.R. was the study coordinator and helped immensely with the protocol design and interim report generation. P.A., S.P., A.P., N.G., and B.B. of NIV and

ICMR, India, contributed various neutralising antibody assays and participated in writing this manuscript. All principal investigators were involved in the scientific review of this manuscript.

Competing Interests

This work was supported and funded by Bharat Biotech International Limited. E.R., J.H., B.G., K.M.V., S.R., D.D., D.R., U.P., P.S., V.S., K.E., and V.S. are employees of Bharat Biotech, with no stock options or incentives. Co-author- K.E. is the Chairman and Managing Director of Bharat Biotech. P.Y., G.S., P.A., N.G., S.P., and B.B. are employees of The Indian Council of Medical Research. P.R., S.V., S.K.R., C.S., S.V.R., C.S.G., J.S.K., S.M., V.R., and R.G. were principal investigators representing the study sites.

Table 1: Demographic Characteristics of the Participants in the Intention-to-Treat Population

Variable			3 µg with Algel-IMDG n=190	6 µg with Algel-IMDG n=190
Age (years)		Median (IQR)	34 (26, 41·8)	35 (27, 44)
Age Group (years) n (%)		≥12-<18	10 (2·6%)	4 (1·1%)
		≥18-<55	173 (45·5%)	176 (46·3%)
		≥55-≤65	7 (1·8%)	10 (2·6%)
Sex (Male)		n (%)	140 (73·7%)	145 (76·3%)
Body Mass Index‡		Means ± SD	25·1±3·4	24·9±2·8
Vitals				
Blood Pressure	Systolic (mm Hg)	Means ± SD	124·7±6·3	124·8±6·6
	Diastolic	Means ± SD	79·5±6·3	79·9±5·8

(mm Hg)			
Pulse Rate (Beats/min)	Means ± SD	80·5±6·4	80·29±6·8
Respiratory Rate (Breaths/min)	Means ± SD	17·8±1·6	17·9±1·7
Temperature (°F)	Means ± SD	98·1±0·5	98·0±0·5
Sites		**n (%)**	**n (%)**
Nizam's Institute of Medical Sciences, Hyderabad		30 (15·8%)	30 (15·8%)
All India Institute of Medical Sciences, New Delhi		25 (13·2%)	25 (13·2%)
Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak		25 (13·2%)	25 (13·2%)
All India Institute of Medical Sciences, Patna		25 (13·2%)	25 (13·2%)
Redkar Hospital, Goa		25 (13·2%)	25 (13·2%)
Jeevan Rekha Hospital, Belgaum		9 (4·7%)	4 (2·1%)
Gillukar Multispecialty Hospital, Nagpur		7 (3·7%)	9 (4·7%)
Prakhar Hospital, Kanpur		25 (13·2%)	25 (13·2%)
SRM Hospital and Research Centre, Chennai		19 (10%)	22 (11·6%)

The intention-to-treat population included all participants who received at least one dose. ‡ The body mass index is the weight in kilograms divided by the square of the height in metres. The calculation was based on the weight and height measured at the time of screening.

Figure 1: CONSORT

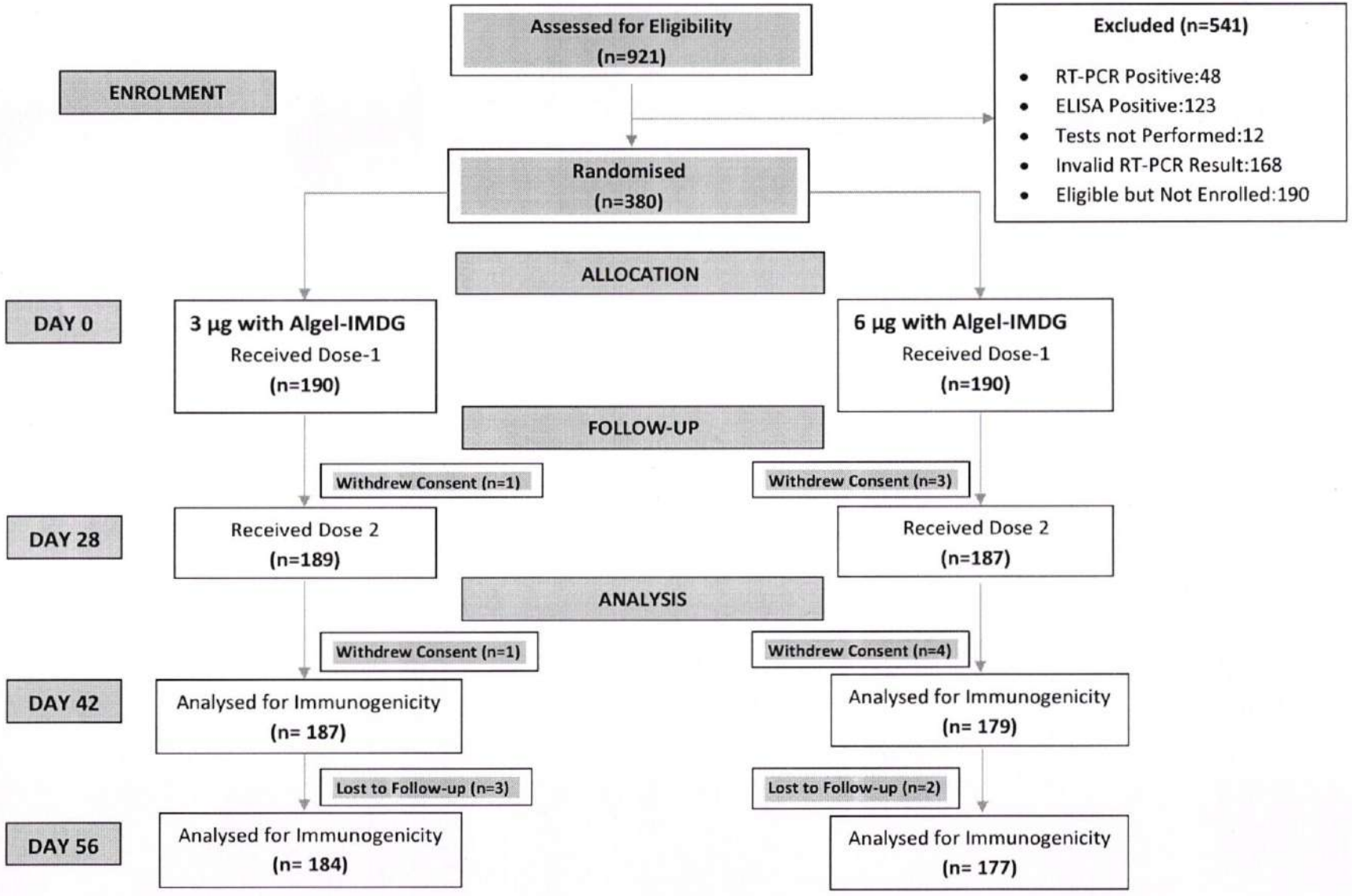


Table 2: SARS-CoV-2 Binding Antibody Responses (Anti-S1, -RBD, and -N IgG)

ELISA (Anti-S1, -RBD, and -N IgG)			3 µg with Algel–IMDG (n=190)	6 µg with Algel-IMDG (n=190)
GMT (95% CI)	S1-Protein	Day 0	500 (500,500)	500 (500,500)
		Day 28	2574·2 (2228·9, 2973·1)	2240·5 (1942·4, 2584·5)
		Day 42	11528·8 (10002·7, 13287·8)	10040·0 (8667·0, 11630·5)
		Day 56	10413·87 (9142·4, 11862·2)	9541·6 (8245·9, 11041·0)
	RBD-Protein	Day 0	500 (500,500)	500 (500,500)
		Day 28	1962·7 (1726·2, 2231·6)	2031·6 (1777·3, 2322·3)
		Day 42	5572·3 (4897·5, 6339·9)	4980·8 (4366·7, 5681·3)
		Day 56	5874·0 (5194·8, 6642·0)	5558·0 (4859·9, 6356·5)
	N-Protein	Day 0	500 (500,500)	500 (500,500)
		Day 28	2734·1 (2375·1, 3147·5)	2490·4 (2161·7, 2869·2)
		Day 42	8957·2 (7778·6, 10314·3)	9211·2 (7939·3, 10686·8)
		Day 56	8626·0 (7528·6, 9883·4)	8754·0 (7589·4, 10097·4)
SCR (95% CI)	S1-Protein	Day 28	71·20% (64·1, 77·6)	65·0% (57·5, 72·0)
		Day 42	98·4% (95·3, 99·7)	98·3% (95·1, 99·7)
		Day 56	98·4% (95·3, 99·7)	96·6% (92·8, 98·8)
	RBD-Protein	Day 28	58·7% (51·2, 65·9)	58·2% (50·6, 65·6)
		Day 42	94·0% (89·6, 97·0)	93·2% (88·5, 96·5)
		Day 56	96·2% (92·3, 98·5)	94·4% (89·9, 97·3)

	N-Protein	**Day 28**	72·3% (65·2, 78·6)	71·2% (63·9, 77·7)
		Day 42	97·3% (93·8, 99·1)	95·5% (91·3, 98·0)
		Day 56	97·3% (95·3, 100·0)	96·6% (92·8, 98·8)
Isotype Mean (95% CI)	**Day 28**		1·7 (1·3, 2·1)	1·9 (1·5, 2·8)
	Day 42		2·4 (1·9, 2·9)	2·2 (1·7, 2·6)

Binding antibody results at baseline (day 0), 4 weeks after the first vaccination (day 28), 2 weeks after the second vaccination (day 42), and 4 weeks after the second vaccination (day 56) for the 3 µg (n=190) and 6 µg (n=190) with Algel-IMDG groups are shown. IgG titres against anti-S1, anti-RBD, anti-N, and the anti-S1 IgG1/IgG4 ratio. The cut-off for detectable antibodies was set at 1:500. Endpoint titre dilution for day 28 serum samples was determined with baseline (day 0) and interpolated from the raw optical density (OD) data of the corresponding day 0 sample. The cut-off (mean±3 SD) for day 0 was calculated based on the absorbance of all serum dilutions (1:500 to 32000) tested, except the lowest dilution (1:500). Isotyping titres on day 56 were not analysed. SCRs were defined based on the proportion of titres that increased ≥4-fold compared to baseline.

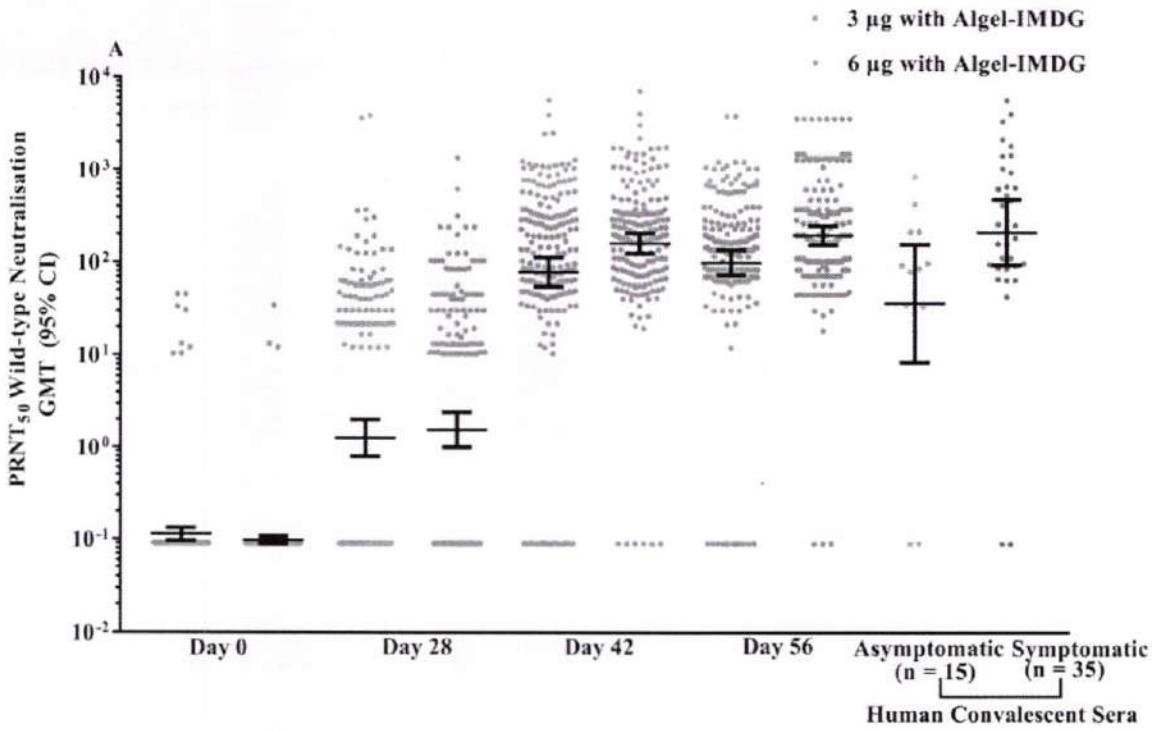
Table 3: Solicited Adverse Events After Two Doses in the Safety Set

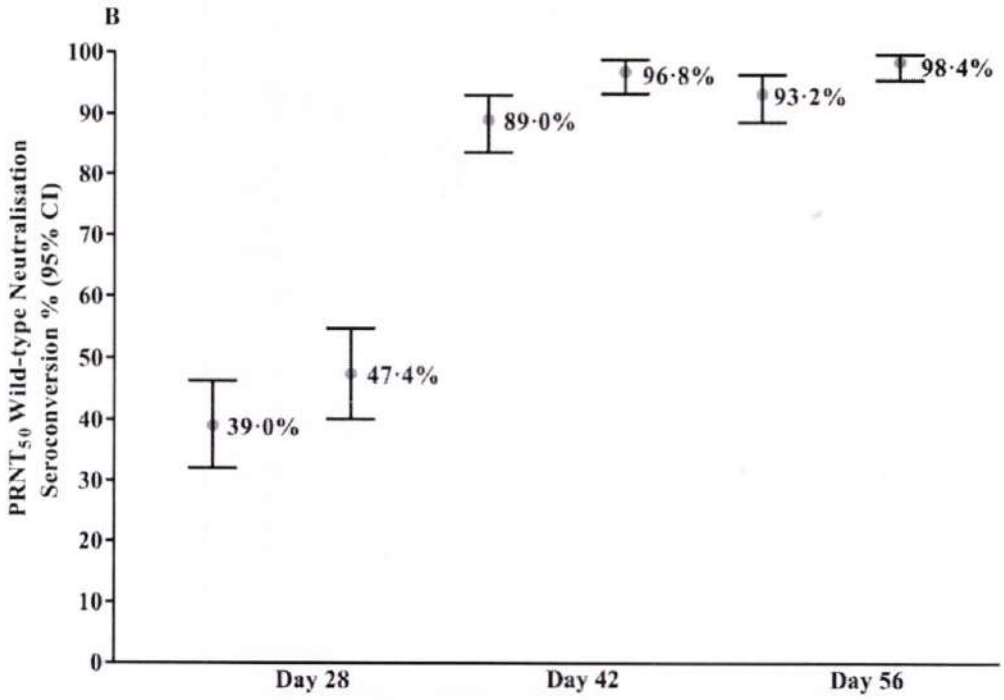
Symptoms	**Dose Group**	**Severity**			
		Dose 1		**Dose 2**	
		Mild (n)	**Moderate (n)**	**Mild (n)**	**Moderate (n)**
Local					
Pain	3 µg with Algel-IMDG	(5) 2·6% (0·9, 6·0)	(1) 0·5% (0·01,2·9)	(6) 3·2% (1·2, 6·8)	-
	6 µg with Algel-IMDG	(6) 3·2% (1·2, 6·8)	-	(4) 2·1% (0·6, 5·5)	(1) 0·5% (0·01, 2·9)
Redness	3 µg with Algel-IMDG	(1) 0·5% (0·01, 2·9)	-	-	-
	6 µg with Algel-IMDG	(1) 0·5% (0·01, 2·9)	-	-	-
Itching	3 µg with Algel-IMDG	(1) 0·5% (0·01, 2·9)			
	6 µg with Algel-IMDG	(1) 0·5% (0·01, 2·9)		(1) 0·5% (0·01,2·9)	
Stiffness in the Upper Arm	3 µg with Algel-IMDG	(1) 0·5% (0·01, 2·9)	-	-	-
	6 µg with Algel-IMDG	-	-	-	-
Weakness in the Right Arm	3 µg with Algel-IMDG	-	-	(1) 0·5% (0·01,2·9)	-
	6 µg with Algel-IMDG	-	-	-	-

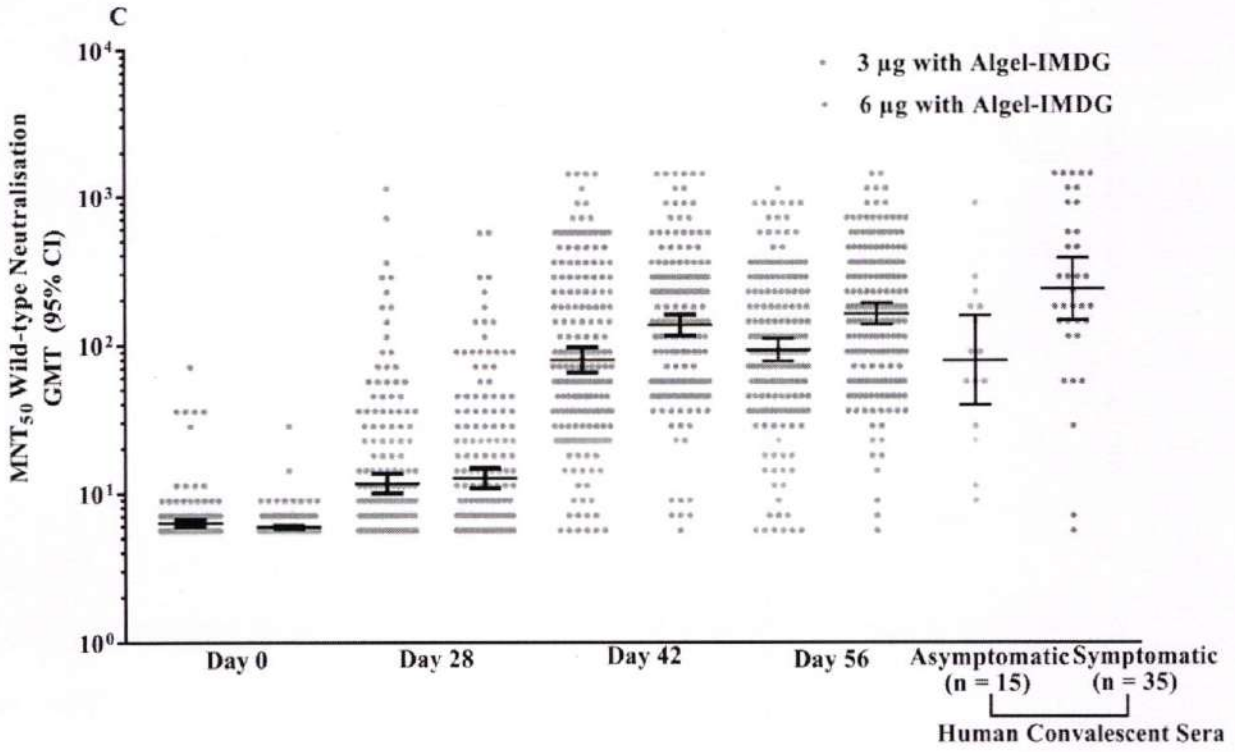
Systemic					
Body Ache	3 µg with Algel-IMDG	-	-	(1) 0·5% (0·01, 2·9)	-
	6 µg with Algel-IMDG	(2) 1·1% (0·1, 3·8)	(1) 0·5% (0·01, 2·9)	(2) 1·1% (0·1, 3·8)	-
Fever	3 µg with Algel-IMDG	(2) 1·1% (0·1, 3·8)	(1) 0·5% (0·01, 2·9)	(5) 2·6% (0·9, 6·0)	-
	6 µg with Algel-IMDG	(5) 2·6% (0·9, 6·0)	(3) 1·6% (0·3, 4·5)	(4) 2·1% (0·6, 5·5)	-
Headache	3 µg with Algel-IMDG	(2) 1·1% (0·1, 3·8)	-	(1) 0·5% (0·01, 2·9)	-
	6 µg with Algel-IMDG	(1) 0·5% (0·01, 2·9)	-	(2) 1·1% (0·1, 3·8)	(1) 0·5% (0·01, 2·9)
Malaise	3 µg with Algel-IMDG	(4) 2·1% (0·6, 5·5)	-	(3) 1·6% (0·3,4·5)	-
	6 µg with Algel-IMDG	(1) 0·5% (0·01, 2·9)	-	-	-
Weakness	3 µg with Algel-IMDG	-	-	(1) 0·5% (0·01, 2·9)	-
	6 µg with Algel-IMDG	-	(1) 0·5% (0·01, 2·9)	(2) 1·1% (0·13, 3·8)	-
Rashes	3 µg with Algel-IMDG	-	-	(1) 0·5% (0·01, 2·9)	-
	6 µg with Algel-IMDG	-	-		-
Total		(33) 8·7% (6·1, 11·9)	(7) 1·8% (0·7,3·8)	(34) 8·9% (6·3, 12·3)	(2) 0·5% (0·13, 3·8)

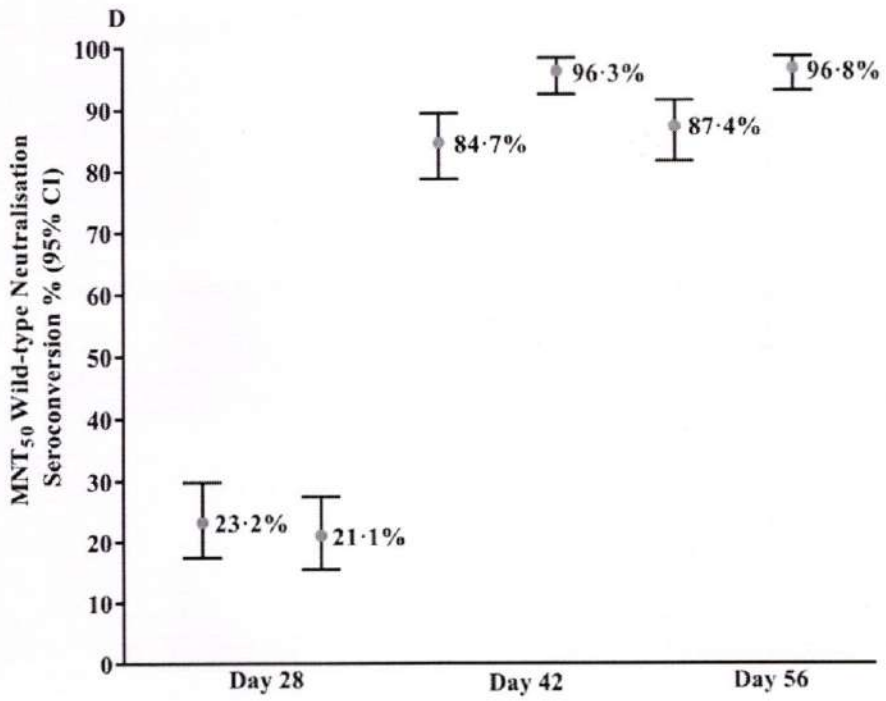
The groups received 3 µg with Algel-IMDG or 6 µg with Algel-IMDG. Data are shown as the number of participants who experienced an event (%) after receiving either dose 1 (0-7) or dose 2 (28-35 days). The grading scale for most adverse events was based on the FDA guidance document for the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. For adverse events where grading was not described in the FDA guidance document, we used the Common Terminology Criteria for Adverse Events (CTCAE) grading.

Figure 2: SARS-CoV-2 Neutralising Antibody Responses



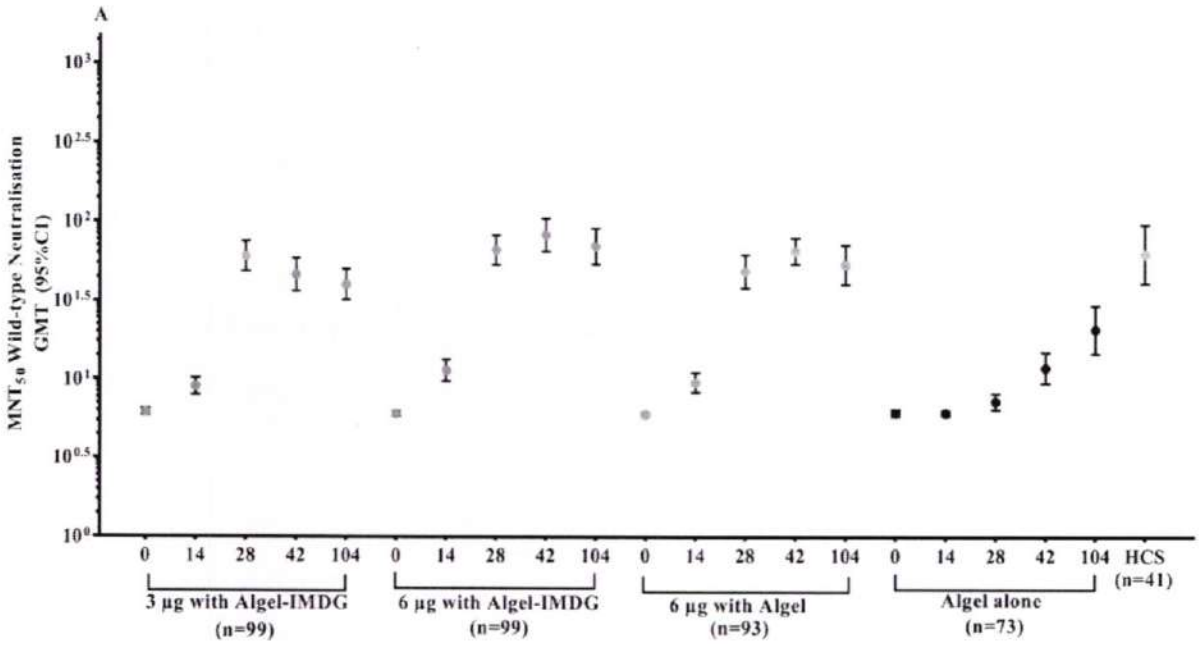


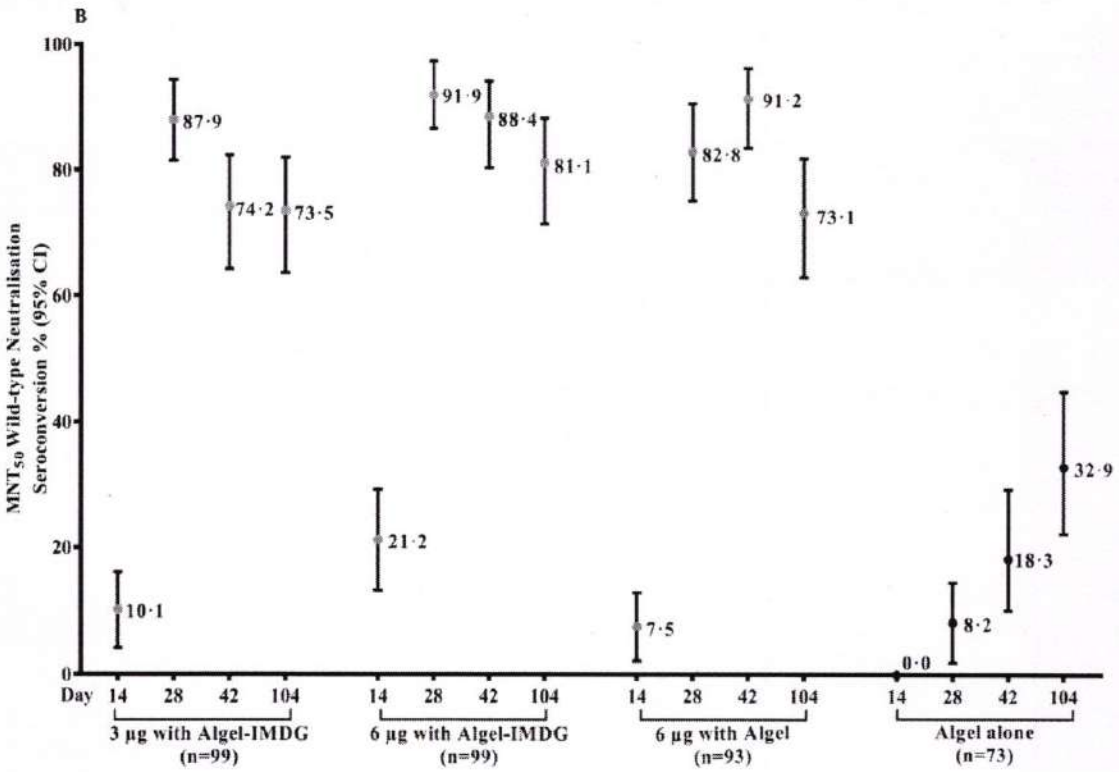


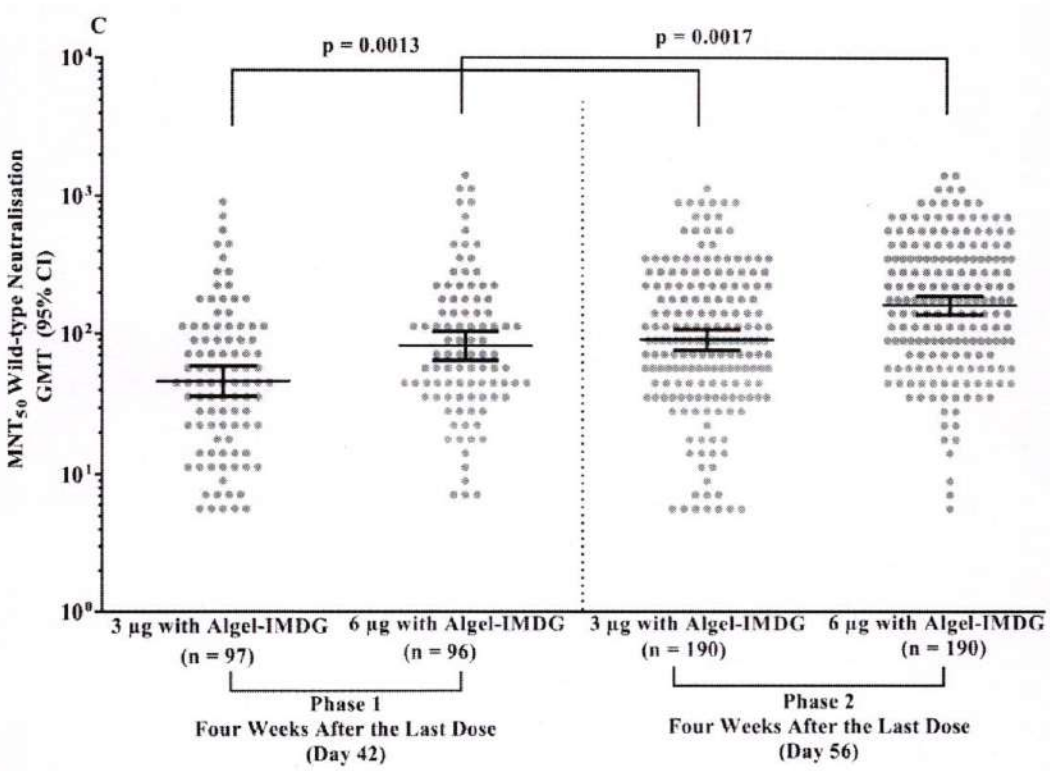


Titres of the wild-type SARS-CoV-2 neutralisation assay ($PRNT_{50}$ and MNT_{50}) at baseline (day 0), 4 weeks after the first vaccination (day 28), 2 weeks after the second vaccination (day 42), and 4 weeks after the second vaccination (day 56) for the 3 µg (n=190) and 6 µg (n=190) with Algel-IMDG groups are shown. SCRs were defined based on the proportion of titres ≥4-fold above baseline. The dots and horizontal bars represent the SCR and 95% CI, respectively (panels A&C). In panels B&D, the dots and horizontal bars represent individual data points and the geometric mean (95% CI). The human convalescent serum (HCS) panel included specimens from PCR-confirmed symptomatic/asymptomatic COVID-19 participants obtained at least 30-60 days after diagnosis (n=50 samples).

Figure 3: Neutralising Responses from Phase 1 and 2 Trials

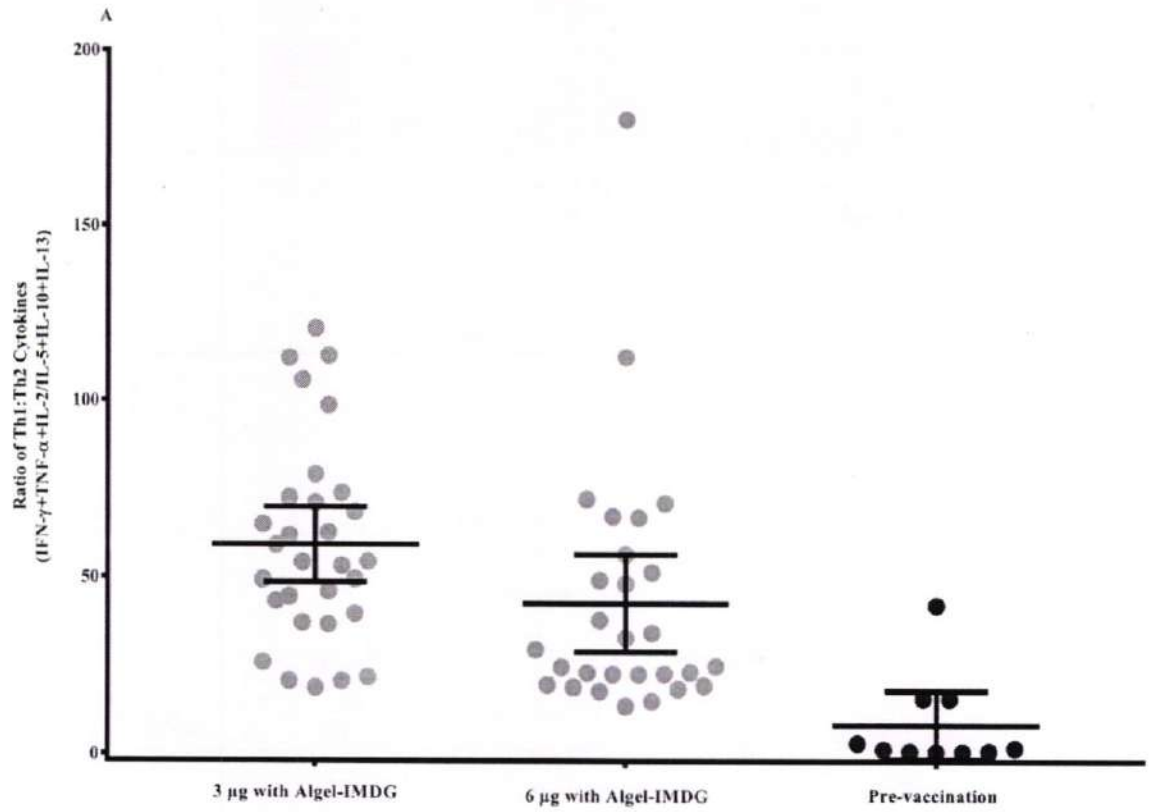


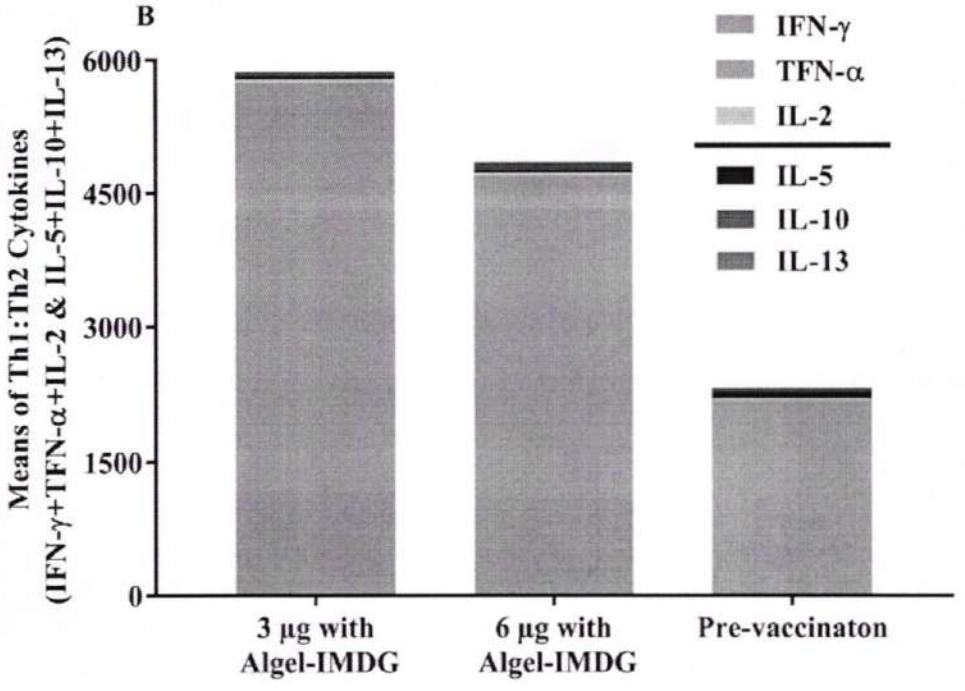


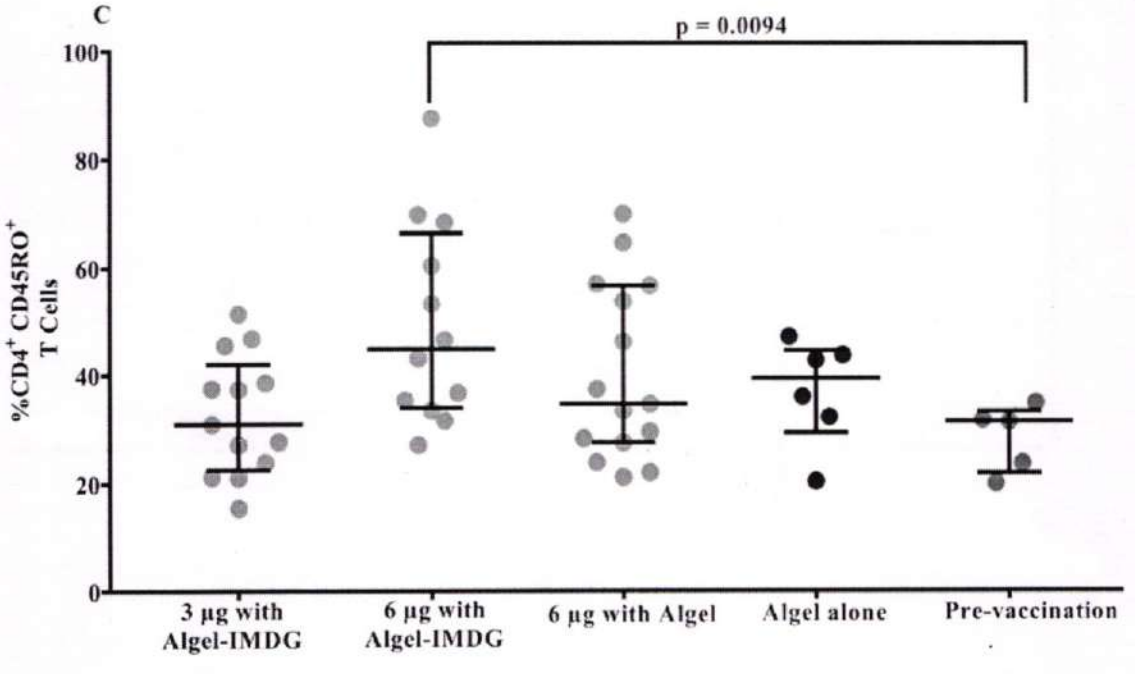


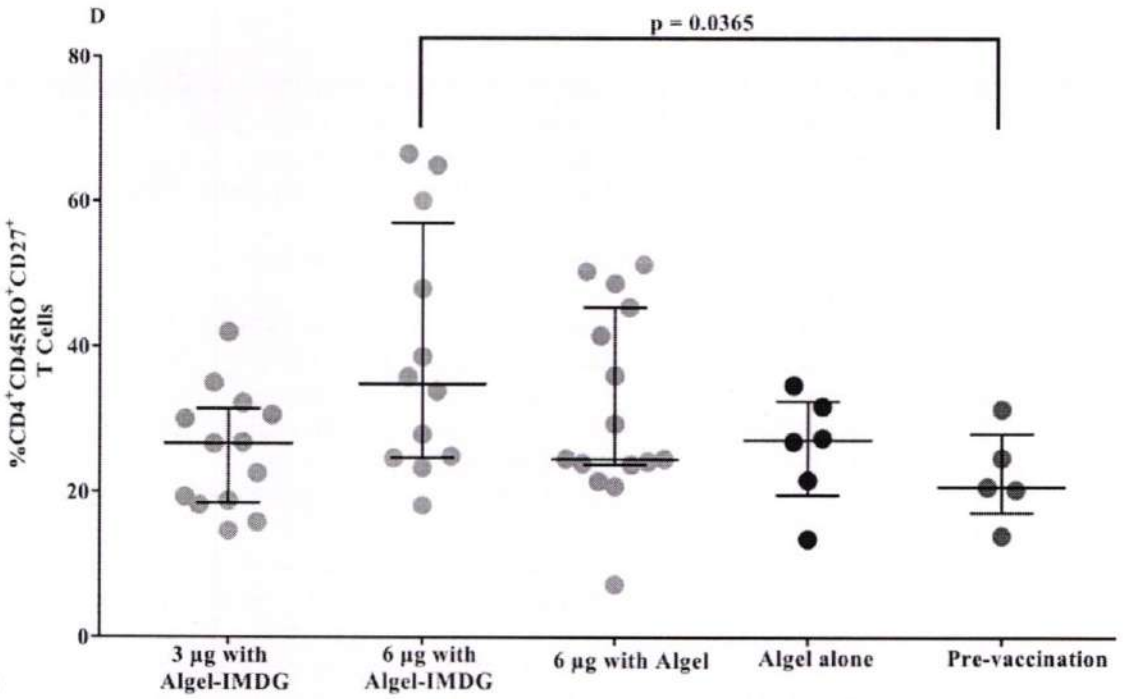
Panels A & B show phase 1 GMTs of the wild-type SARS-CoV-2 MNT_{50} at baseline (day 0), 2 weeks after the second vaccination (day 28), 4 weeks after the second vaccination (day 42), and 3 months after the second vaccination (day 104) for the 3 µg and 6 µg with Algel-IMDG groups, the 6 µg with Algel group, and the Algel-only control arm. In the phase 1 trial, the dosing schedule was days 0 and 14 for the first and second doses of the vaccine, respectively. SCRs were defined based on the proportion of titres ≥4-fold above baseline. The HCS panel included specimens from PCR-confirmed symptomatic/asymptomatic COVID-19 participants obtained at least 30 days after diagnosis (41 samples for MNT_{50}). In the phase 2 trial, the dosing schedule was days 0 and 28 for the first and second doses of the vaccine, respectively. Panel C shows phase 1 and 2 GMT) of the wild-type SARS-CoV-2 MNT_{50}. GMTs in phase 2 were significantly higher than those in phase 1.

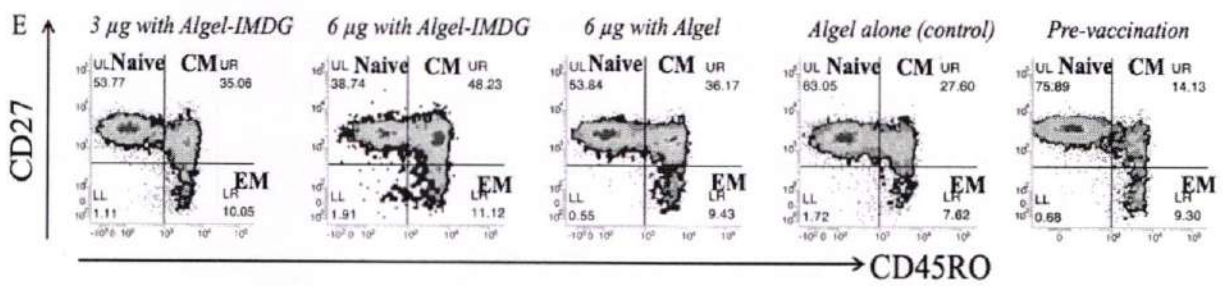
Figure 4: SARS-CoV-2 Cell-mediated Responses











Cytokine levels in day supernatants from 58 participants (n=29 in each of the 3 µg and 6 µg with Algel-IMDG groups) and controls (n=10 pre-vaccination samples from both groups) with proliferative responses to BBV152 vaccination whose PBMCs were evaluated after stimulation with SARS-CoV-2 peptides are shown. Samples were collected two weeks after the second vaccination (day 42) for the 3 µg and 6 µg with Algel-IMDG groups. Error bars show the mean (95% CI) of the ratio of Th1/Th2 cytokines: [interferon-gamma (IFN-γ) + IL-2]/[IL-5+IL-13] (panel A). Th1 and Th2 cytokines are represented by stacked bars (panel B). Panels C & D: Scatter plot represents the frequencies of antigen-specific T cell memory responses 3 months after the second vaccination (day 104) for the 3 µg and 6 µg with Algel-IMDG groups, 6 µg with Algel group, and the Algel-only control arm from the phase 1 trial participants are shown. Dots represent an individual data point with medians and IQR. Panel E: Representative dot plots from one participant, representative of the group mean value. Gating was done on $CD4^+$ T cells illustrating the frequencies of naïve effector memory ($_{EM}$) T_{EM}, CD45RO- $CD27^+$, central memory ($_{CM}$) T_{CM}, $CD45RO^+CD27-$, and T_{EM}, $CD45RO^+CD27^+$ $CD4^+$ T cells.

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ANNEXURE-P26

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COVID-19 Information

Public health information (CDC)

Research information (NIH)

SARS-CoV-2 data (NCBI)

Prevention and treatment information (HHS)

Español

NIH U.S. National Library of Medicine

ClinicalTrials.gov

An Efficacy and Safety Clinical Trial of an Investigational COVID-19 Vaccine (BBV152) in Adult Volunteers

⚠ The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04641481

Recruitment Status ⓘ : Active, not recruiting
First Posted ⓘ : November 23, 2020
Last Update Posted ⓘ : March 19, 2021

Sponsor:
Bharat Biotech International Limited

Collaborators:
Indian Council of Medical Research
Iqvia Pty Ltd

Information provided by (Responsible Party):
Bharat Biotech International Limited

Study Description

Go to

Brief Summary:

The BBV152 vaccine is being developed to prevent COVID-19, the disease resulting from Severe Acute Respiratory Syndrome coronavirus (SARS-CoV-2) infection. The study is designed to primarily evaluate the efficacy, safety, and immunogenicity of BBV152 to prevent COVID-19 for up to 1 year after the second dose of BBV152.

Condition or disease	Intervention/treatment	Phase
Covid19 SARS-CoV Infection	Biological: BBV152 Biological: Placebo	Phase 3

Detailed Description:

This is a phase 3 Event-Driven, randomized, double-blind, placebo-controlled, multicentre study to Evaluate the Efficacy, Safety, and Immunogenicity of BBV152, a Whole-Virion Inactivated SARS-CoV-2 Vaccine in Volunteers aged 18 years and above.

A total of 25,800 subjects will be enrolled and randomized in a 1:1 ratio to receive the BBV152 vaccine and control. All participants will be assessed for efficacy and safety endpoints and provide a Nasopharyngeal(NP) swab and blood sample before the first dose of IP. The NP swab and blood collected will be subject to RT-PCR and Anti-SARS-CoV-2 IgG antibodies. The results of this will not affect the enrollment of the participant. Participants who are found to be positive for either RT-PCR Or Anti-SARS-CoV-2 IgG antibodies will be excluded from the primary efficacy analysis. A safety follow-up will be done for all.

In addition, sites will be segregated based on the study objectives:

Category 1 (Symptomatic): In addition to administering the IP, a series of post-dose telephonic follow-up visits will be scheduled to detect suspect symptomatic COVID-19 infections. If a suspect is identified, a nasopharyngeal sample will be collected from the participant for detecting the presence of COVID-19 infection. Telephonic follow-up will occur at 15 Day intervals.

Category 2 (Symptomatic/Asymptomatic): In addition to administering the IP, a series of post-dose Nasopharyngeal samples for detecting an incidence of asymptomatic COVID-19 infection at 1-Month intervals will be collected.

Category 3 (Symptomatic/Asymptomatic+Immunogenicity): In addition to administering the IP and collecting NP samples, a series of blood samples will be collected for analyzing serum for immunological assessments.

The Phase 3 study will follow randomized study participants for efficacy until virologically confirmed (RT-PCR positive) symptomatic COVID-19 participants will be eligible for the primary efficacy analysis. After reaching the target number (n=130) of symptomatic COVID-19 cases, the study will continue to assess safety until the

completion of the study duration. It is planned to continue the Phase 3 trial until 130 study participants in the per-protocol population develop PCR-confirmed symptomatic COVID-19 disease during follow-up beginning 14 days after the second dose of vaccine or placebo. We estimate that approximately 25,800 participants should be randomized to accrue these 130 events. The Lot-to-Lot consistency (Immunogenicity) study will be nested within the Phase 3 (Efficacy) study (in three selected sites). The Immunogenicity study will assess the immune response of a 2-dose regimen of BBV152B vaccine through geometric mean titers (GMTs) by neutralizing antibody, S-protein, and RBD specific anti-IgG binding titer in a subset of 600 (450 vaccine: 150 placebo) participants, across three consecutive manufacturing Lots. Data generated through Day 56 (Month 2) will be unblinded only to the biostatistician for evaluation of immune responses in the Immunogenicity subset.

Formal interim analyses are planned when approximately 1/3 and 2/3 of the target number of participants with confirmed symptomatic COVID-19 have been accrued, to determine whether the sample size and/or length of follow-up should be increased. This interim report containing safety and immunogenicity data will be submitted to CDSCO.

Study Design

Go to

Study Type :

Interventional (Clinical Trial)

Actual Enrollment :

25800 participants

Allocation:

Randomized

Intervention Model:

Parallel Assignment

Masking:

Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Masking Description:

All vaccine and placebo formulations are at a volume of 0.5mL per dose filled into a single-use glass vial. The appearance, color, and viscosity are identical across all vaccine and control formulations.

Participants, investigators, study coordinators, study-related personnel, and the sponsor will be blinded to the treatment group allocation (excluding an unblinded CRO, who is tasked with the dispatch and labeling of vaccine vials and the generation of the master randomization code). Participants will be assigned a computer-generated randomization code that maintains blinding. The blinded study nurse is responsible for vaccine preparation and administration. Each vial contains a unique code that ensured appropriate blinding.

Primary Purpose:

Prevention

Official Title:

An Event-Driven, Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate Efficacy, Safety, Immunogenicity, Lot-to-Lot Consistency of BBV152, a Whole-Virion Inactivated SARS-CoV-2 Vaccine in Adults≥18 Yrs of Age

Actual Study Start Date :

November 16, 2020

Actual Primary Completion Date :

January 8, 2021

Estimated Study Completion Date :

December 2022

Resource links provided by the National Library of Medicine NIH NLM

Genetic and Rare Diseases Information Center resources: Severe Acute Respiratory Syndrome

U.S. FDA Resources

Arms and Interventions

Go to

Arm	Intervention/treatment
Experimental: Study vaccine BBV152B (6µg-Algel-IMDG)	Biological: BBV152 BBV152 (6µg-Algel - Imidazoquinoline)
Placebo Comparator: Placebo Phosphate buffered saline with Alum (without antigen)	Biological: Placebo Placebo (PBS+Alum, without antigen)

Outcome Measures

Go to

Primary Outcome Measures :

1. First occurrence of Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19.
   [Time Frame: Day 42 to Month 12]

   (RT-PCR positive) symptomatic cases of COVID-19.

Secondary Outcome Measures :

1. First occurence of Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19 based on the case definition for the secondary efficacy symptomatic endpoint. [Time Frame: Day 42 to Month 12]

   (RT-PCR positive) symptomatic cases of COVID-19.

2. Virologically confirmed (RT-PCR positive) severe cases of COVID-19 [Time Frame: Day 42 to Month 12]

   (RT-PCR positive) severe symptomatic cases of COVID-19.

3. Virologically confirmed COVID-19 cases of any severity occurring among participants 18 through 59 years of age and ≥60 years of age. [Time Frame: Day 42 to Month 12]

   (RT-PCR positive) symptomatic cases of COVID-19

4. Virologically confirmed COVID-19 asymptomatic and symptomatic cases occurring from two weeks after the second vaccination. [Time Frame: Day 42 to Month 12]

   (RT-PCR positive) asymptomatic/symptomatic cases of COVID-19.

5. Reactogenicity and Safety [Time Frame: Day 42 to Month 12]

   Solicited, Unsolicited, Serious Adverse Events

6. The occurrence of enhanced respiratory disease episodes. [Time Frame: Day 42 to Month 12]

   Reported by participant/documented in hospital records throughout the trial.

7. Immunogenicity: Lot-to-Lot consistency of three consecutive GMP Lots [Time Frame: Day 0 to Day 42]

   Assessed based Wild-type SARS-CoV-2 Specific Neutralizing Antibody (nAb)

8. Geometric Mean Titer (GMT) of SARS-CoV-2 Specific Neutralizing Antibody (nAb) [Time Frame: Day 0 to Month 12]

   Specific Neutralizing Antibody (nAb)

Eligibility Criteria Go to

Information from the National Library of Medicine NIH NLM

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:

18 Years to 99 Years (Adult, Older Adult)

Sexes Eligible for Study:

All

Accepts Healthy Volunteers:

Yes

Criteria

Inclusion Criteria:

- Ability to provide written informed consent and availability to fulfill the study requirements.
- Participants of either gender of aged 18 years and above.
- Participants with good general health as determined by the discretion of the investigator, or participants with stable medical conditions. A stable medical condition is defined as a disease not requiring significant change in therapy or hospitalization or worsening disease during the 3 months before enrolment.
- For a female participant of child-bearing potential, planning to avoid becoming pregnant (use of an effective method of contraception or abstinence) from the time of study enrolment until at least eight weeks after the last vaccination.
- Male subjects of reproductive potential: Use of condoms to ensure effective contraception with the female partner and to refrain from sperm donation from first vaccination until at least 3 months after the last vaccination.
- Agrees not to participate in another clinical trial at any time during the study period.
- Agrees not to take any COVID-19 licensed vaccination for the entire duration of the study.
- Agrees to remain in the study area for the entire duration of the study.
- Willing to allow storage and future use of biological samples for future research

Exclusion Criteria:

- History of any other COVID-19 investigational or licensed vaccination.
- Known history of SARS-CoV-2 infection, as declared by the subject.

- For women, positive urine pregnancy test before the first dose of vaccination, or any time during the study period.
- Temperature >38.0°C (100.4°F) or symptoms of an acute self-limited illness such as an upper respiratory infection or gastroenteritis within three days prior to each dose of vaccine.
- Resident of COVID-19 infection in the same household.
- Known case of HIV, hepatitis B, or hepatitis C infection.
- Receipt of any licensed/experimental vaccine within four weeks before enrolment in this study.
- Receipt of immunoglobulin or other blood products within the three months before vaccination in this study.
- Immunosuppression as a result of an underlying illness or treatment with immunosuppressive or cytotoxic drugs, or use of anticancer chemotherapy or radiation therapy within the preceding 36 months.
- Immunoglobulins, anti-cytokine antibodies, and blood products within 6 months prior to study vaccination, during, and 21 days following the last dose of vaccination.
- Pregnancy, lactation, or willingness/intention to become pregnant during the first 6 months after enrolment.
- Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, an endocrine disorder, and neurological illness (mild/moderate well-controlled comorbidities are allowed)

Re-Vaccination Exclusion Criteria

- Pregnancy.
- History of virologically (RT-PCR) confirmed SARS-CoV-2 infection
- Anaphylactic reaction following administration of the investigational vaccine.

Contacts and Locations

Go to

Information from the National Library of Medicine NIH NLM

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT04641481***

Locations

India

Pt BD SHARMA,PGIMS/UHS

Rohtak, Haryana, India, 124001

Sponsors and Collaborators

Bharat Biotech International Limited

Indian Council of Medical Research

Iqvia Pty Ltd

Investigators

Principal Investigator:	Dr Chadramani Singh	All India Institute of Medical Sciences Patna
Principal Investigator:	Dr Sanjay Kumar Rai	All India Institute of Medical Sciences Delhi
Principal Investigator:	Dr Azhar Ali Khan	Baba Raghav Das Medical Gorakhpur
Principal Investigator:	DrAnil Kumar Pandey	ESIC Medical College and Hospital Faridabad
Principal Investigator:	Dr Simmi Dube	Gandhi Medical College, Bhopal
Principal Investigator:	Dr Anjan Jyoti Talukdar	Gauhati Medical College & Hospital Assam
Principal Investigator:	Dr Priti Meshram	Grant Government Medical College and Sir J.J. Group of
Principal Investigator:	Dr Laxmi S Kumari	Guntur Medical College ,Guntur
Principal Investigator:	Dr Shiva Narang	Guru Teg Bahadur Hospital
Principal Investigator:	Dr E Venkat Rao	Institute of Medical Sciences and SUM Hospital Odisha
Principal Investigator:	Dr P Venugopal	King George Hospital Visakhapatnam
Principal Investigator:	Dr. N.T. Awad	Lokamanya tilak Municipal Medical College and General
Principal Investigator:	Dr Pajanivel Ranganadin	Mahatma Gandhi Medical College& Research Institute P(
Principal Investigator:	Dr Prabhakar Reddy	Nizam's Institute of Medical Sciences Hyderabad
Principal Investigator:	Dr Raghavendra Gumashta	Peoples university Bhopal
Principal Investigator:	Dr Tapan Kumar Saikia	Prince Aly Khan Hospital Mumbai
Principal Investigator:	Dr Savita Verma	Pt BO Sharma,PGIMS/UHS. Rohtak, Haryana
Principal Investigator:	Dr Manish Multani	Rahate Surgical Hospital ,Nagpur
Principal Investigator:	Dr Sagar Vivek Redkar	Redkar Hospital and Research Centre Goa
Principal Investigator:	Dr Meghana Murthy	Vagus Super speciality hospital,Bangalore
Principal Investigator:	Dr Akshata	Vydehi Institute of Medical Sciences and Research Centr
Principal Investigator:	Dr T S Selvavinayagam	Directorate of Public Health and Preventive Medicine,Che
Principal Investigator:	Dr Suman Kanungo	ICMR-National Institute of Cholera and Enteric Diseases,
Principal Investigator:	Dr Mohammad Shameem	Aligarh Muslim University,Uttar Pradesh
Principal Investigator:	Dr Parul Bhatt	Gmers Medical College and Civil Hospital,Ahmedabad

More Information

Go to

Responsible Party:

Bharat Biotech International Limited

ClinicalTrials.gov Identifier:

NCT04641481 History of Changes

Other Study ID Numbers:

BBIL/BBV152-C/2020

BBIL/BBV152-C/2020 (Other Identifier: Bharat Biotech International Ltd)

First Posted:

November 23, 2020 Key Record Dates

Last Update Posted:

March 19, 2021

Last Verified:

March 2021

Individual Participant Data (IPD) Sharing Statement:

Plan to Share IPD:

No

Studies a U.S. FDA-regulated Drug Product:

No

Studies a U.S. FDA-regulated Device Product:

No

Additional relevant MeSH terms:

Severe Acute Respiratory Syndrome

Coronavirus Infections

Coronaviridae Infections

Nidovirales Infections

RNA Virus Infections

Virus Diseases

Respiratory Tract Infections

Respiratory Tract Diseases

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ANNEXURE: P27

File No. Z 60011/06/2020 CVAC
Government of India Ministry of Health and Family Welfare
CVSE Department

Nirman Bhawan, New Delhi
Dated 9th March, 2021

To,
Sh. Anurag Sinha,
OTR No. 10 PO Swang Bokaro Jharkhand, Gomia, 829128
Jharkhand

Subject: Information Sought under RTI Act, 2005

Sir,
Your RTI MoHFW/R/E/21/00630 was received on 27.02.2021 seeking information under the RTI Act, 2005.

S. No.	Questions Asked by the Applicant	Answers
1.	Is taking the vaccine for Corona voluntary or compulsory?	Taking the Corona vaccine is voluntary.
2.	Will not taking the vaccine result in stoppage of government facilities like pension?	The words written in the application are baseless. The vaccine has nothing to do with any government facility, citizenship, job, etc.
3.	Will not taking the vaccine disentitle one from jobs, taking the bus, the metro?	
4.	If any IAS/IPS/Health Personnel threatens someone to take the vaccine, what recourse do they have? Can they go to court?	
5.	Will you not get schools, colleges, universities, gas connections, water, electricity connections, rations, etc., if you do not take the vaccine?	

6.	If one doesn't take the vaccine, can they be dismissed from their jobs, can their salaries be stopped, in both private and government departments?	

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ANNEXURE- P28

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सत्यमेव जयते

Select Language

Eng

Public Authorities Available

RTI Online

Version 2.0

An Initiative of Department of Personnel & Training, Government of India

Home Submit Request Submit First Appeal View Status View History User Manual FAQ

Online RTI Status Form

Note:Fields marked with * are Mandatory.

Enter Registration Number	MOHFW/R/E/21/01681
Name	Rakesh Singh
Date of filing	21/04/2021
Public Authority	Department of Health & Family Welfare
Status	REQUEST DISPOSED OF
Date of action	02/05/2021

Reply :- Your queries -

1. Is corona Vaccine (Covid- 19 vaccine) compulsory ?

2. Can private company force its employees to take Covid 19 vaccine ?

3. Will I be debarred from public services like Metro rail, indian railway, Bus services, hospital, electricity, internet, food and inter and intra-city movement, if I dont take covid-19 vaccine ?

4. What can I do if my senior officer forces me to take Covid 19 vaccine /

5. What are my rights if a police officer beats me publically for not accepting forced Covid 19 vaccine ?

6. Can police and group of health workers break the house door and barge into my house, beat my family members (Old age parents, kids and other members) and forcefully vaccinate them by COVID 19 Jab ?

7. Can a government health worker be suspended for not taking Covid 19 vaccine ?

8. Does government or its any associate body have any reliable data of covid 19 vaccine research so that citizens can trust efficacy of vaccine ?

Reply _

1- Vaccination for COVID-19 is voluntary.

However, it is advisable to receive the complete schedule of COVID-19 vaccine for protecting oneself against this disease and also to limit the spread of this disease to the close contacts including family members, friends, relatives and co-workers.

2 to 8 - In view of reply as Sl. No.1, these questions have no relevance

CPIO Details :-	Satyendra Singh Phone: 011-23062959 singh.satyendra80@gov.in
First Appellate Authority Details :-	Sarita Nair Phone: 011-23061554 sarita.nair@gov.in
Nodal Officer Details :-	
Telephone Number	011-23061831
Email Id	r[dot]attri54[at]nic[dot]in

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ANNEXURE-P29

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2:40

← **Thread**

Letter by the Civil Surgeon (equivalent to CMO/CMHO) in Koderma in Jharkhand mandating local govt health workers to take Vaccine for COVID-19, or otherwise their salary will be withheld.

कार्यालयः जिला स्वास्थ्य समिति, कोडरमा।

आदेश

कार्यालय आदेश ज्ञापांक 90 रा0 अ0 कोडरमा दिनांक 15.01.2021 के निर्देशानुसार, जो सरकारी सेवक कोविड–19 का टीका नहीं लगाये हैं, वे शीघ्र कोविड –19 टीका लगाये। कोविड–19 का टीकाकरण नहीं लेने की स्थिति में अगले आदेश तक संबंधित सरकारी सेवकों का वेतन अवरूद्ध रहेगा। लिये गये टीकाकरण का प्रमाण पत्र प्रस्तुत करने के पश्चात् ही वेतन भुगतान किया जायेगा।

16/01/21

जिला प्रतिरक्षण पदाधिकारी
कोडरमा।

16/01/21

मुख्य चिकित्सा पदाधिकारी सह
मुख्य कार्यपालक पदाधिकारी
जिला स्वास्थ्य समिति कोडरमा।

ज्ञापांक 38 (1) कोडरमा, दिनांक 16/01/2021

प्रतिलिपिः संबंधित सभी सरकारी सेवकों/अन्य व्यक्तियों को सूचनार्थ एवं अनुपालनार्थ प्रेषित।
प्रतिलिपिः कोडरमा जिला अंतर्गत सभी प्रभारी चिकित्सा पदाधिकारियों को सूचनार्थ एवं आवश्यक कार्रवाई हेतु प्रेषित।
प्रतिलिपिः उपाधीक्षक, सदर अस्पताल कोडरमा को सूचनार्थ प्रेषित।
प्रतिलिपिः स्वास्थ्य विभाग अंतर्गत निकासी एवं व्ययन पदाधिकारी को सूचनार्थ प्रेषित।
प्रतिलिपिः उपायुक्त, कोडरमा को सूचनार्थ।

16/01/21

जिला प्रतिरक्षण पदाधिकारी
कोडरमा।

मुख्य चिकित्सा पदाधिकारी सह
मुख्य कार्यपालक पदाधिकारी
जिला स्वास्थ्य समिति कोडरमा।

Prashant Bhushan
(TRUE COPY)

ANNEXURE: P 30

GOVERNMENT OF MAHARASHTRA
Department of Revenue and Forest, Disaster Management,
Relief and Rehabilitation, Mantralaya, Mumbai- 400 032
No: DMU/2020/CR. 92/DisM-1, Dated: 13th April, 2021

ORDER
Break The Chain

Reference:

1.The Epidemic Diseases Act, 1897.

2. The Disaster Management Act, 2005

3. Revenue and Forest, Disaster Management, Relief and Rehabilitation Department Order No. DMU-2020/C.R.92/DMU-I, dated 2nd May 2020, 3rd May 2020, 5th May 2020, 11th May 2020, 15th May 2020, 1 7th May 2020, 19th May 2020, 21st May 2020, 31 May 2020, 4th June 2020, 25th June 2020, 29th June 2020, 6th July 2020, 7th July 2020, 29th July 2020, 4th August 2020, 19th August 2020, 31st August 2020, 30th September, 2020 and 14th October 2020, 23rd October, 2020, 29th October, 2020, 3rd November, 2020, 14th November, 2020, 23rd November, 2020, 27th November, 2020, 27th November, 2020, 21st December, 2020, 24th December, 2020, 29th December, 2020, 14th January, 2021, 19th January, 2021, 29th January, 2021, 24th February, 2021, 15th March, 2021, 27th March, 2021, 4th April, 2021 and 5th April, 2021

4. Ministry of Home Affairs (MHA) Order No. 40-3/2020-PM-1 (A) Dated 1st May 2020, 11th May 2020, 17th May 2020, 20th May 2020, 30th May 2020, 29th June 2020, 29th July 2020, 29th August 2020, 30th September 2020 and 27th October 2020, 25th November, 2020, 28th December, 2020, 27th January, 2021 and 23rd February, 2021

Whereas, in exercise of the powers, conferred under the Disaster Management Act 2005, the undersigned, in his capacity as Chairperson, State Executive Committee has issued an Order dated 30th September, 2020 and 14th October, 2020 (extended by order dated 29th October, 2020, 27th November, 2020, 29th December, 2020 and 29th January, 2021 and 24th February, 2021, 15th March, 2021, 17th March, 2021, 27th March, 2021, 4th April, 2021 and 5th April, 2021) for containment of COVID 19 in the State for theperiod upto 30th April, 2021 and issued revised guidelines by including certain activities from time to time vide above mentioned orders.

Whereas the State Government is satisfied that the State of Maharashtra is threatened with the spread of COVID-19 virus, and therefore it is imperative to take certain emergency measures to prevent and contain the spread of virus, the Government in exercise of the powers conferred under Section 2 of the Epidemic Diseases Act, 1897, read with all other enabling provisions of

The Disaster Management Act, 2005, finds it is expedient to enforce the following measures throughout the State from 8 PM on 14th April, 2021 till 7 AM on 1st, May, 2021 to break the chain of transmission.

Now, therefore, in exercise of the powers conferred under Section 2 of the Epidemic Diseases Act, 1897 and the powers, conferred under The Disaster Management Act, 2005, the undersigned, in his capacity as Chairperson, State Executive Committee, hereby issues the following directions, that will remain in force throughout the state of Maharashtra from 8 PM on 14th April, 2021 till 7 AM on 1st, May, 2021 –

1. **Imposition of Section 144 and Night Curfew**

   a. Section 144 to be imposed in the State.

   b. No one to move in public place without valid reasons mentioned herein below.

   c. All the establishments, public places, activities, services shall remain closed, save as explicitly mentioned herein below.

   d. Services and activities mentioned in Essential Category herein below are exempted and their movements and operations are to be unrestricted.

   e. Services and activities mentioned in Exceptions Category herein below are exempted from 7 AM to 8 PM on working days and their movements and operations are to be unrestricted during these periods.

   f. Decision regarding inclusion of domestic help/ drivers/ attendants to work in Exceptions Category be taken by the local authorities based on local conditions.

2. **Essential Category includes the following**:

   1) Hospitals, diagnostic centers, Clinics, vaccinations, Medical insurance offices, Pharmacies, Pharmaceutical companies, other medical and health services including supporting manufacturing and distribution units along with their dealers, transport and supply chain. Manufacturing and distribution of vaccines, sanitizers, masks, medical equipment, their ancillaries, raw material units and support services.

   2) Veterinary Services/ Animal Care shelters and pet food shops

3) Groceries, Vegetables Shops, fruit vendors, dairies, bakeries, confectionaries, all type of food shops.

4) Cold Storage and Warehousing services

5) Public Transport: Airplanes, Trains, Taxis, Autos and public buses.

6) Services related to functioning of offices of Diplomats of various countries

7) Pre Monsoon Activities by local authorities

8) All Public Services by local authorities.

9) Reserve Bank of India and services designated by RBI as essential

10) All offices of SEBI recognized market infrastructure institutions such as Stock Exchanges, depositories, clearing corporations etc and other intermediaries registered with SEBI

11) Services required for restoration/ maintenance of telecom services

12) Transport of Goods

13) Water Supply Services

14) Agriculture related activities and all allied activities required to ensure seamless continuity of the agricultural sector including availability of farming input, seeds, fertilizers, equipment's and repairs thereof.

15) Export – Import of all commodities

16) E-Commerce (only for the supply of essential goods and services)

17) Accredited Media

18) Petrol Pumps and Petroleum related products; including offshore / onshore production

19) All cargo services

20) Data Centers/ Cloud Services/ IT services supporting critical infrastructure and services

21) Government and Private Security Services

22) Electric and gas supply services

23) ATM's

24) Postal Services

25) Ports and related activities

26) Custom House Agents/ Licensed Multi Modal Transport Operators associated with movement of vaccines/ lifesaving drugs/ pharmaceutical products.

27) Units producing raw material/ packaging material for any essential services

28) Units that are engaged in production of materials for impending rainy season for individuals as well as for organisations .

29) Any Services designated as essential services by local disaster management authority.

Implementing agencies must follow these general principles about above mentioned services:

1. All enforcing authorities to note that fundamentally strict restrictions relate to movement of people but not to goods and commodities as a matter of principle.

2. All the requirements of movement for performance of services mentioned in this section are valid reasons for travel under 1(b).

3. Incidental activities that are required for performance of these services by concerned personnel or organization are to be considered as essential themselves. Principle is 'essential for essential is essential'.

3. Shops falling under essential services as mentioned in this order shall follow following guidelines:

a. Essential services shops to operate while ensuring Covid Appropriate Behavior (CAB) by owners, staff working there at as well as customers in the shop premises.

b. Essential shops owners and person working at all shops to get vaccinated at the earliest, as per criteria of GOI. All shops are advised to follow safety measures like interaction with customers through a transparent glass or other material shields, electronic payment etc.

c. Any essential shop owner, person working there at or any customer found defaulting on above requirements shall be punishable by a fine of Rs. 500/- and if the shop is found serving a customer who is defaulting on Covid Appropriate Behavior, the shop will be fined Rs.1000/-. In case of repeated defaults, a shop may be ordered to be closed till end of notification of Covid 19 as a disaster.

d. Movement of personnel to perform duties related to essential shops shall constitute a valid reason for the purposes of 1(b).

e. For Groceries, Vegetables Shops, fruit vendors, dairies, bakeries, confectionaries, all type of food shops etc. mentioned in 2(3) above, local authority should study the locations where these are densely located or where people may come together in large numbers and plan out their staggering in terms of locations and if need be in terms of periods of operations. Open public spaces may also be identified for shifting their operations, in case of non-permanent structures. Local authorities are expected to take all the measures to ensure these essential operations do not become a place that facilitates spread of COVID 19. If so deemed necessary, local authorities may also declare some locations as closed for these operations.

f. All shop owners that are closed for now are advised to get all persons working with them to get vaccinated as per criteria of GOI as well as prepare themselves with measures like interaction with customers through a transparent glass or other material shields, electronic payment etc. so that government can expedite reopening of the same without fear of COVID 19 transmission.

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4. **Public Transport - Public transport will be fully operational with following restrictions:**

Auto Rickshaw	Driver + 2 passengers only
Taxi (4 wheelers)	Driver + 50% vehicle capacity as per RTO
Bus	Full seating occupancy as per RTO passing. However, no standing passengers will be allowed.

a) All persons using public transport to compulsorily wear mask in a proper manner barring which fine of Rs 500 will be imposed on the offenders.

b) In 4 wheeler taxi, if any one person is not wearing mask, the offender and the driver of the taxi will be fined an amount of Rs 500 each.

c) All vehicles to be sanitised after every trip.

d) All public transport - drivers and other staff coming into contact with the public to get vaccinated at the earliest, as per criteria of GOI and must display exemplary Covid Appropriate Behaviour. For taxis and autos, driver should be encouraged to isolate himself or herself through use of a plastic sheet or otherwise.

e) Movement of personnel to perform duties related to public transport shall constitute a valid reason for the purposes of 1(b).

f) In the case of out-station trains, railway authorities to ensure that there are no standing passengers in the general compartment and all passengers use masks.

g) Fine of Rs 500 to be levied in all trains for non-compliance with Covid Appropriate Behaviour.

h) Public transport that has been allowed with some conditions also includes all incidental services that are essential for the smooth functioning of all modes of public transport. This also includes all incidental activities that are required at the airport including handling of cargo, ticketing etc.

i) Persons arriving/ departing by any bus/ train/ flight from or towards place of residence may travel on basis of a valid ticket through public transport.

5. **Exemption Category:**

a) Offices:

- Following Offices shall belong to exemption category.
    i. Offices of Central, State and Local governments, including of their statutory authorities and organisations
    ii. Cooperative, PSU and Private Banks
    iii. Offices of companies providing essential services
    iv. Insurance/ Mediclaim Companies
    v. Pharmaceutical company offices needed for management of production/ distribution
    vi. RBI regulated entities and intermediaries including standalone primary dealers, CCIL, NPCI, payment system operators and financial market participants operating in RBI regulated markets.
    vii. All Non Banking Financial Corporations
    viii. All micro finance institutions
    ix. Offices of advocates if operations of Courts, Tribunals or Commissions of Enquiries are on.
- These should work with minimum staff required and in no case with more than 50% of normal capacity, except for government offices that are concerned with response to Covid 19 pandemic.
- Movement for attending these offices shall constitute valid reasons under 1(b)
- Local disaster management authorities may add exceptions to offices if needed.
- There should be no visitors to the offices and all meetings with anyone apart from office staff which is present in the same campus must only be conducted online.
- For both private and government offices, personnel to get vaccinated at the earliest, as per criteria of GOI, so that government may reopen expeditiously offices without fear of spread or acceleration of Covid 19.

b) **Private Transport**:

- Private Vehicles including private buses can ply for the purposes of emergency, essential services or for valid reasons as specified in this order.
- Any default will be punishable with the fine of Rs. 1000/-.
- Private buses, in addition will be subjected to following:
    i. To ply with only seating capacity. Standing passengers are strictly not allowed.
    ii. Staff must get vaccinated at per GOI criteria and must display exemplary Covid Appropriate Behaviour.

c) **Restaurants, Bars, Hotels**

a. All Restaurants and bars to remain closed for in-dining, except for those inside the campus and which form an integral parts of hotels.

b. Only home delivery services shall be allowed and there shall be no visiting any restaurant or bar for ordering purposes or pickup.

c. Restaurants and bars inside hotels are to be open only for in-house guests. In no circumstance should outside guests be allowed. For outsiders, they will follow the same restrictions as any other restaurant and bar as mentioned above. Guests of the hotel may move out only for the valid reasons or for performance of duty required for essential services or for exceptions made for offices mentioned in this order.

d. All personnel belonging to home delivery services to be vaccinated at the earliest as per GOI guidelines.

e. All the home deliveries to buildings housing more than one family should be restricted to the entrance of the building and internal movement of the delivery should be by dedicated staff of the building. It is also expected that all the interactions of home delivery staff and the building personnel are disciplined and COVID appropriate.

f. Any default on Covid Appropriate Behaviour will attract a fine of Rs 1000/- on the offender and fine of Rs 10,000 will be levied on the establishment. Repeated offence may be lead to withdrawal of licenses or permissions for operations till notification for COVID 19 epidemic remains in force.

g. All staff working in these restaurants and bars are advised to get vaccinated at the earliest, as per GOI guidelines, so that reopening of these may be expedited.

d) Manufacturing Sector:

a. Following units shall continue to operate and may operate in various shifts as required:

i. All the units that manufacture items needed for essential services as per this order to remain operational with full capacity.

ii. Export oriented units that need to fulfill export obligation.

iii. Units that require processes that are of such a nature that these cannot be stopped immediately and cannot restart without considerable time requirement, may continue with maximum of 50% of workforce at any given point of time. Industry department, Government of Maharashtra should ensure that no unit misuses this provision and follows all reasonable precautions that are needed. These processes however must not be net consumers of oxygen, unless producing items that are needed for essential services. It is expected that these industries will try to house their labourers in the campus or if they are housed outside, then to ensure that their movement is within an isolation bubble, to the extent possible.

b. All the units that provide accommodation to the their labour, working either in the same campus or in an isolated facility from where movement may happen in an isolated bubble, with only 10% of managerial staff coming from outside may continue to work. Movement of the staff outside the premises is not allowed till the end of this notification. Such units may operate in various shifts as required.

c. All staff - managerial as well as shop floor and others - without exception - every one engaged in the activity to get vaccinated at the earliest, as per criteria of GOI. These units, if falling in eligibility criteria of GOI for workplace vaccination, must organize these vaccinations at the earliest possible opportunity.

d. Factories and manufacturing units that are operating under these conditions must subscribe to following discipline:

i. To scan body temperature of labourers pre- entry and confirm to Covid Appropriate Behavior of all concerned.

ii. If a labourers/ worker found positive, other laborers who have come into active contact with him to be quarantined with pay.

iii. Factories/ Units with more than 500 workers to set up their own quarantine facilities. Such Quarantine Centers to have all basic facilities and in case of such a facility being set up outside the campus of the industry, the affected persons should be moved to the said facility while ensuring that there is no contact with any other person during the transit.

iv. In case of any worker found to be positive, unit to be closed until completely sanitised.

v. Lunch and tea breaks to be staggered for avoiding crowding. No common eating places

vi. Common toilet facilities to be sanitised frequently.

e. If a worker is found positive he or she would be allowed medical leave and cannot be discontinued during this absence for this reason. He or she will be entitled for full wages that he or she might have earned had he or she not contacted corona.

f. All the factories/ industries not specifically allowed herein must stop their operations till the end of period specified in these orders. In case of any doubt, authority to take decision rests with department of industry.

e) Roadside Eatable Vendors:

- There will be no serving of food for eating at the location. Parcels or home deliveries are allowed from 7 AM to 8 PM on every day. Reasonable movement for this constitutes a valid reason under 1(b).
- Waiting customers to wait away from counter with adequate social distancing.
- Every one engaged in the activity to get vaccinated at the earliest, as per criteria of GOI.
- Local authority to have a close watch over such places through deployment of adequate personnel/ CCTV. Any customers engaging in irresponsible behaviour

violating COVID 19 protocols to be fined Rs. 500/-. Any vendor serving any customer engaging in such behaviour shall be fined Rs. 500/-.

- Violation would lead to shutting down of the vendor till end of pandemic.
- However if the local authority feels that such behaviour is repetitive and is not possible to contain with the imposition of fines, then they may order closure of the location either temporarily or till the end of the pandemic.

f) Newspapers/ magazines/ periodicals:

- Newspapers/ magazines/ periodicals can be printed and circulated.
- Only Home Delivery is allowed.
- All persons engaged in the activity to get vaccinated at the earliest, as per criteria of GOI.

6. **Recreation, Entertainment, shops, malls, shopping centres etc.:**

Without prejudice to generality of section (1) it is declared that -

a) Cinema halls, to remain closed.

b) Drama theatres and auditoriums to remain closed.

c) Amusement Parks/ Arcades/ Video Game Parlours to remain closed.

d) Water Parks to remain closed

e) Clubs, Swimming Pools, Gyms and Sports Complexes to remain closed.

f) All persons connected with these establishments should get vaccinated at the earliest, as per GOI guidelines so that reopening of these may be achieved at the earliest without fear of spread or acceleration of Covid 19.

g) Shooting for Films/ Serials/ Advertisement to be closed.

h) All shops, malls, shopping centers not performing essential services shall be closed.

i) Public places like beaches, gardens, open spaces etc. shall remain closed. In case of any public arena that may belong to any of the uses mentioned herein, local authority may decides about continuation or discontinuation of its use during the operation of this order.

7. **Religious Places of Worship**

a) Religious Places of Worship to remain closed.

b) All the personnel engaged in the service of the place of workshop shall continue to perform their duties though no outside visitor shall be allowed.

c) All staff that may work in these places are advised to get vaccinated at the earliest, as per GOI guidelines, so that reopening of these may be expedited.

8. **Barber Shops/ Spa/ Salon/ Beauty Parlors**

a) Barber shops/ Spa's / Salons and Beauty Parlors to remain closed.

b) All staff that may work in these establishments are advised to get vaccinated at the earliest, as per GOI guidelines, so that reopening of these may be expedited.

9. **Schools and colleges:**

a) Schools and Colleges to remain closed.

b) Rule is hereby relaxed for std 10th and 12th students to the extent of exams. All the staff that may be used for conduct of exams must be either vaccinated or should carry a negative RT-PCR/ RAT/ TruNAT/ CBNAAT certificate, valid for 48 hours.

c) For exams that are being conducted by any board, university or authority outside the state, denial of which may lead to hardships for students residing in Maharashtra may be allowed by concerned department under intimation to concern disaster management authority.

d) Students who have to attend any exam physically, may be allowed to travel along with one adult, on basis of a valid hall ticket for the same.

e) All private coaching classes of any kind to remain closed.

f) All staff that may work in these establishments are advised to get vaccinated at the earliest, as per GOI guidelines, so that reopening of these may be expedited.

10. **Religious, Social, Political, Cultural Functions**

a) No religious, social, cultural or political functions of any kind to be allowed.

b) In case of districts where elections are scheduled to be held, the permission may be granted by the District Collector for any political gatherings subject to the following conditions-

   a. The District Collector can authorize the Returning Officer to give permission for any political gathering for the purpose of campaigning within the guidelines of the Election Commission of India subject to no more than 200 people or 50% occupancy whichever is less being allowed in any enclosed space and 50% of the capacity be allowed in open spaces subject to complete adherence to all laid down COVID 19 protocols as per the Central Government guidelines.

   b. There should be personnel deputed by the Collector for overseeing any such event to ensure scrupulous adherence to all protocols.

   c. In case of violation of the said protocols, the owner of the premises should be held accountable and may be penalised under the Disaster Management Act, 2005. In case of serious breaches, the space may be sealed until the end of the pandemic.

   d. Incase of more than 2 such violations in gatherings of any candidate, no further permissions for holding any political gatherings be granted by the Collector to the said candidate.

   e. For any other event like rallies, corner meetings etc, all COVID 19 protocols must be adhered to.

   f. All guidelines must be applied equally without fear or favour to all participants in the election process and there should be no room for any grievance arising from selective or partisan application of the said guidelines.

   g. After 8 PM on the day of polling, all the provisions of this order will come into effect in totality for the said area.

c) Marriages will be allowed only with maximum of 25 people present.

   a. All the staff at any marriage hall or at any location serving visitors have to be vaccinated and till completely vaccinated they have to carry a valid negative RT-PCR/ RAT/ TruNAT/ CBNAAT certificate.

b. In case if any of the above are found to be without negative RTPCR/ RAT/ TruNat/CBNAAT Certificate/ without being vaccinated as above, a fine of Rs 1000/- will be levied on the offender and fine of Rs 10,000 will be levied on the establishment.

c. Repeated offence in respect of a premise would lead to sealing of the same and withdrawal of permission to conduct any gathering therein till operation of notification of Covid 19 epidemic.

d. In case of marriage being conducted inside a place of worship, it will be allowed to do so with adherence to the above rules.

d) Funerals to be allowed a maximum of 20 people. All the staff should get vaccinated at the earliest and should carry a valid negative RT-PCR/ RAT /TruNAT/ CBNAAT certificate. Funerals may also be performed at places of worship with strict adherence to the said rules.

11. **Oxygen Producers -**

A) Any industrial process that is a net consumer of oxygen as a raw material is to be disallowed. Development Commissioner, however may allow the process either in case of process being essential for any of the essential activities or for exceptional circumstances for reasons to be recorded in writing.

B) All industrial producers of oxygen shall reserve a percentage of their production (actual as well as capacity) for medical or pharmaceutical purposes as specified by Public Health Department. They should declare their customers and end use of the oxygen supplied from 10th April 2021 onwards.

12. **E-Commerce**

a. E-Commerce will be only allowed for the delivery of essential goods and services as mentioned in Section 2 of this order

b. Every one engaged in the activity of home delivery or activity involving interaction with staff engaged in activity of home delivery to get vaccinated at the earliest, as per criteria of GOI and if an Organization running e-commerce falls in the eligibility criteria of GOI for workplace vaccination it must organise these vaccination camps at the earliest. For the staff not engaged in home delivery or in the activity of requiring interaction with staff engaged in home delivery shall follow the discipline laid down in (5) concerning offices.

c. All the home deliveries to buildings housing more than one family is expected to be restricted to the entrance of the building and internal movement of the delivery should be by dedicated staff of the building. It is also expected that all the interactions of home delivery staff and the building personnel are disciplined and COVID appropriate.

d. Any default on Covid Appropriate Behaviour while performing home delivery shall lead to a fine of Rs. 1000/- . Repeated offence may lead to withdrawal of license to operate till the end of notification of COVID 19 epidemic.

13. **Cooperative Housing Societies:**

a) Any Cooperative Housing Society having more than 5 active Corona positive cases will be treated as an micro containment zone. These will follow strictly the SOP laid down for micro containment zones.

b) Such societies shall put up a board at the gate informing visitors and deny them entry.

c) All restrictions of micro-containment zones like control over ingress and egress shall be monitored by the society.

d) In case of default the society may be fined Rs.10000/- in the first instance. Later instances may attract higher fines as decided by local authorities. This fine may be used to employ supervising personnel to ensure compliance of SOP and these orders by the society.

e) All CHS's are advised to ensure that all persons coming into the building on a regular basis get their RTPCR/ RAT/ TruNat/ CBNAAT test done till they are vaccinated as per Government norms.

14. **Construction Activity**

a) To be allowed only for sites where labourer's are living on site. Movement to and fro from outside must be avoided, except for the purpose of material movements.

b) Every one engaged in the activity to get vaccinated at the earliest, as per criteria of GOI and organisations engaged in these activities should go for workplace vaccinations as per GOI guidelines at the earliest.

c) Defaults will lead to a fine of Rs.10000/- for the developer of the construction site and repeated defaults may lead to closure of the site till existence of notification of COVID 19 epidemic.

d) If a worker is found positive he or she would be allowed medical leave and cannot be discontinued during this absence for this reason. He or she will be entitled for full wages that he or she might have earned had he or she not contacted corona.

e) Local authorities may decide to allow any construction activity in view of impending rainy season for reasons of public safety or safety of the structures.

15. **Penalties:**

All the fines so collected shall be used by the concerned disaster management authority towards better containment and treatment of the Covid 19 disaster.

The said rules will remain in force till 1st May, 2021 – 7 AM for containment of COVID-19 epidemic in the State. This order is in supersession of the 'Break the Chain' orders issued by the State Government and clarifications/ additions issued thereof to the tune of all clauses that have been mentioned in this order. For any other clause not specifically mentioned in this order the other 'Break the Chain' orders mentioned earlier prevail.

BY ORDER AND IN THE NAME OF THE GOVERNOR OF MAHARASHTRA

13/4/21

(SITARAM KUNTE)
CHIEF SECRETARY
GOVERNMENT OF MAHARASHTRA

Copy to :

1. Principal Secretary to Hon'ble Governor of Maharashtra, Mumbai.
2. Hon'ble Chairman, Maharashtra Legislative Council.
3. Hon'ble Speaker, Maharashtra Legislative Assembly.
4. Additional Chief Secretary to Hon'ble Chief Minister, Government of Maharashtra.
5. Principal Secretary to Hon'ble Chief Minister, Government of Maharashtra,
6. Secretary to Hon'ble Deputy Chief Minister, Government of Maharashtra,

7. Private Secretary to Leader of Opposition, Legislative Council / Assembly,
8. Private Secretaries of All Hon'ble Minister/Minister of State, Mantralaya,
9. All Additional Chief Secretaries / Principal Secretaries / Secretaries of Government of Maharashtra.
10. Director General of Police, Maharashtra State, Mumbai,
11. Principal Secretary, Public Health Department, Mantralaya,
12. Secretary, Medical Education, Mantralaya,
13. All Divisional Commissioners in the State
14. All Commissioners of Police in the State
15. All Commissioners of Municipal Corporations in the State
16. All District Collectors
17. All Chief Executive Officers, Zilla Parishad
18. All District Superintendents of Police in the State

Prashant Bhushan

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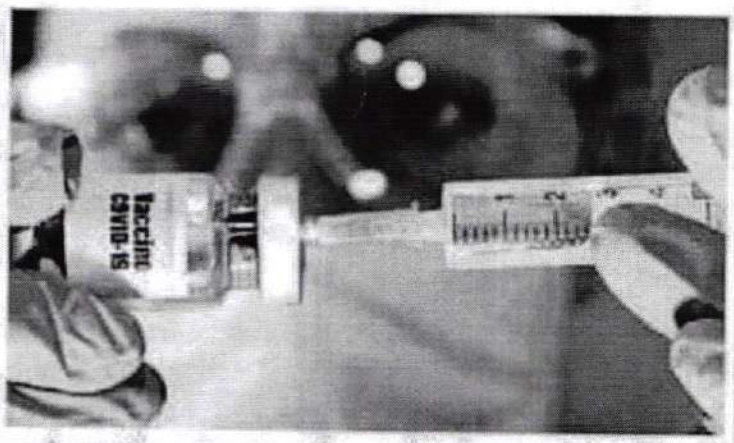
ANNEXURE:P31

Lokmat Times

Only vaccinated citizens can step out of homes after May 1

AMC mulling imposing strict restrictions in city to contain Covid spread



LOKMAT NEWS NETWORK
AURANGABAD, APRIL 18

"The Maharashtra Government has imposed strict restrictions until May 1 to break the coronavirus chain. After that, the Aurangabad Municipal Corporation (AMC) will not allow unvaccinated traders and general people, aged 45 and above, to step out of home. So, citizens eligible for vaccination should get vaccinated as soon as possible," said AMC administrator Astik Kumar Pandey.

On Facebook Live, the AMC administrator said, "As coronavirus is going to stay, vaccination is the only option to stop its spread. People aged 45 and above are being vaccinated presently. The municipality is seriously considering allowing only vaccinated people move out and vaccinated traders do their business after May 1. A final decision in this regard would soon be taken."

At present, 6,000 people are being vaccinated every day. The aim is to increase this number to 10,000. "I think the vaccination of 3 lakh people will be completed in 30 days and then Aurangabad will be safe," Pandey said.

The AMC has started vaccination centres in every ward. There are 115 centres in 115 wards and 26 private centres. From Monday onwards, 11 more vaccination centres will be set up for traders, 10 for bank officials and employees and two for industrial workers.

He appealed to citizens to take advantage of this and get vaccinated.

Aurangabad First
Page No. 1 Apr 19, 2021
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ENGLISH தமிழ் বাংলা മലയാളം हिंदी मराठी

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The Indian EXPRESS

Monday, May 03, 2021

ANNEXURE:P32

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Gujarat: Row over two circulars making Covid shot mandatory for school teachers

The circular has been received by the Primary Health Centres (PHCs) under the taluka.

Written by **Aditi Raja** , **Ritu Sharma** | Vadodara |
February 11, 2021 2:03:21 am

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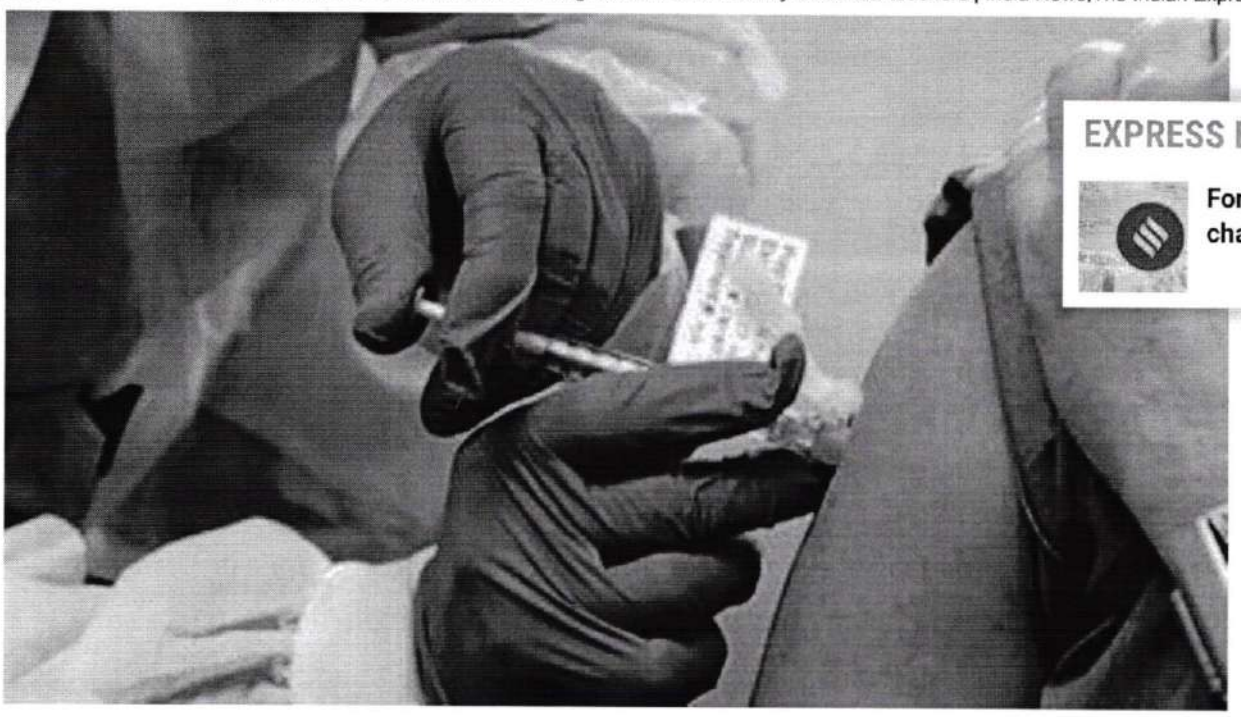

The government plans to inoculate medical workers first, then people aged 65 or above, those with health conditions, and workers at elderly care facility workers. (File)

Two circulars issued by different authorities making vaccination against Covid-19 in the ongoing drive, compulsory for teachers, has run into controversy with the authorities issuing revised circulars. One of the circulars was issued by the Garudeshwar taluka education officer for school teachers in the district that shifted the onus of "any student testing Covid-19 positive" on to teachers who refused to take the vaccine shot. While the district administration later called it a "draft copy" that was issued "by mistake", officers in charge of the nodal supervision of the vaccination drive for teachers said the decision to make teachers "accountable" was taken because many had refused to take the shot.

The second circular was issued by the Ahmedabad Municipal Corporation School Board that made it compulsory for its teachers and other staffers to get themselves vaccinated. Municipal school teachers told The Indian Express, on conditions of anonymity, they were asked to not sign the muster roll if they did not take the vaccine.

The circular from Garudeshwar taluka, falling in the tribal Narmada district, cites a video-conference held by the district primary education officer (DPEO) on February 8, and was issued to two nodal officers in the taluka on February 9. It said, "Teachers of the government primary schools, who have to interact with students and work among the students, have to mandatorily take the Covid-19 vaccine, which must be ensured. If any teacher refuses to take the vaccine or remains

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absent during the vaccination drive, and if any student thereafter contracts Covid-19 from the teacher, the entire responsibility of the same will be on the teachers."

Read | Gujarat: Weeks after getting first dose of vaccine, doctor tests positive on Rapid Antigen Test

Teachers who refuse to take the vaccine shot will have to submit a certificate in writing, citing reasons for the same, the circular added. "Female teachers, who are pregnant or lactating are exempted from the vaccine, provided they submit a proof to the observer beforehand," it stated.

The circular has been received by the Primary Health Centres (PHCs) under the taluka.

The Garudeshwar taluka education officer, Parimal Vyas, told The Indian Express, "We had drafted the letter as per the instructions handed out by the district primary education department during the video-conference to plan the vaccination drive for teachers on February 8. Not just Garudeshwar, but other talukas of the district have also issued similar letters. However, when the draft was prepared and it appeared to make the vaccinations mandatory, we had decided to change it, since vaccination is a voluntary exercise. However, it seems that the draft was issued by mistake before it could be changed."

The taluka education officer issued another circular on February 9, for the vaccination drive to be held Wednesday, which did not have the controversial reference to "shifting onus" on the teachers refusing the vaccination. However, the circular continues to direct the supervising officers to "ensure" that all teachers take the vaccine.

Vyas added, "Those persons with high-risk comorbidities, pregnant and lactating teachers have been exempted. The others can choose to decline but they must give us a reason so that we know why they refused."

We are proud to announce that Jharkhand CM @HemantSorenJMM will be the Chief Guest of the discussion 'Decoding India's internal migration' on February 12 at 2pm.
Register here to join: https://t.co/ngDRKfgS9T
pic.twitter.com/7DLIk0HZju
— The Indian Express (@IndianExpress) February 9, 2021

Dilip Chaudhary, the nodal officer of Songam PHC, told The Indian Express the circular had been issued with "good intentions". Chaudhary said, "We have received the directive and are not forcing teachers to take the vaccine or submit certificates. But it has been issued with the intention of encouraging the teachers. There has to be some responsibility fixed because the government is giving these vaccines for free. If a teacher is healthy and does not have any comorbidity, that is contra-indicated, why should they refuse the vaccine? They must understand that ultimately when they interact with students, it would be to the benefit of the society if they are vaccinated. Teachers have been frontline workers during this pandemic and it is for their benefit. There is no side-effect and so many people have taken it in the hope of beating the virus. We are ensuring that those with diabetes or other ailments do not take the jab."

When contacted, Vinod Rao, Secretary (Primary and Secondary Education), said the vaccination drive is voluntary. "We cannot force the teachers to take the shot. No department has been instructed to issue such circulars making the vaccination mandatory. If any district department has issued such a circular, it is illegal and against the voluntary nature of the drive, and it should be immediately withdrawn."

Ahmedabad, meanwhile, more than 100 teachers were summoned by the administrative authorities to their respective zonal offices on Wednesday and asked to submit "proof" about their health condition which they had cited for e themselves from the inoculation drive.

A school teacher, who did not wish to be identified, told The Indian Expr were not allowed to sign the musters today morning when we reached the school. The reason cited by the school principal was that it was 'as directed by higher authorities' since we have declined to get vaccinated."

Another teacher said, "When we protested, the principal locked the muster register." But the teachers were marked present in the online attendance system, the teacher added.

In a fresh circular Wednesday, the AMC School Board directed 416 primary school teachers to be present "without fail" with their supervisors at the Pandit Deendayal Auditorium in Bodakdev on Thursday to get vaccinated. "If any employee has any medical reason, a decision will be taken based on the advice of the health experts present at the site. Principals have to ensure that no teacher remains absent," the circular stated.

When contacted, AMC School Board administrative officer L D Desai told The Indian Express, "I am not aware about the musters. But yes, we have asked teachers to get vaccinated... Those who left yesterday's (vaccination) sites (Mangal Pandey Hall in Nikol and Pandit Deendayal Auditoirum in Bodakdev) without taking the vaccine were asked to be present at the zonal offices."

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Desai had said Tuesday that the school board had "exempted" around 480 teachers, including teachers who were pregnant or had heart or skin conditions, from taking the vaccine on medical grounds. Of the over 4,200 teachers under the school board, Desai had claimed nearly 700 were yet to be vaccinated.

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"When doctors, AMC officers, school board officers, government officials, and 98 per cent of teachers have taken the vaccine then why should not all teachers too. So, I request all teachers without medical reasons to get vaccinated," Des

TAGS: Ahmedabad Municipal Corporation Coronavirus Vaccine COVID-19 Pandemic

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Prashant Bhushan

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LIVE BLOG

UP Panchayat Election Results 2021 Live Updates: Final results likely by Monday afternoon

21 mins ago

Coronavirus India Live Updates: India reports 3.68 lakh new Covid-19 cases as

3/9

ANNEXURE: P33

OFFICE OF THE DISTRICT EDUCATION OFFICER (Edu. Cir.), TARN TARN

To

All BEEOs, Tarn Tarn

Letter No. G-1/2021/36650 dated 23.04.2021

Sub: COVID-19 VACCINATION

Ref. Meeting held in the D.C. Office on 22.04.2021

This has a reference to the meeting held by the Deputy Commissioner on 22.04.2021 regarding the COVID Vaccination and the instructions were issued and received by this office on the mandatory COVID Vaccination of all the officers/employees. It is clearly stated that if any officer/employee is unwilling or refuses to be vaccinated, the concerned DEOs shall not draw the salary of such officers/employees. In this concern, you are hereby informed that you ensure the vaccination of the entire office staff and the teaching staff are vaccinated. If, due to any reason, any employee is not vaccinated, its report should be sent to the concerned office for onward submission for information and necessary action to the office of the DC.

Note: A list of 30 employees from each block be sent daily to the nearest Govt. Hospital or CHC for mandatory vaccination and its progress report must be forwarded on the WhatsApp group of the office daily by 3 p.m.

Sd/-

District Education Officer (Ed. Cir.)

23.04.2021

Copy being sent to the DC, Tarn Tarn, Office for info, & N.A.

S/d District Education Officer,

23.04.2021 Tarn Tarn

Prashant Bhushan

(TRUE COPY)

ANNEXURE: P34

Gmail cancer Naturally Healing Nisha Koiri <cancernaturallyhealing@gmail.com>

MEMO TO ALL: Vaccination against COVID

1 message

Nisha K <nisha.k@bholanath.in> Mon, May 3, 2021 at 12:23 PM
To: cancernaturallyhealing@gmail.com

From: Administration <administration@whistlingwoods.net>
Sent: Thursday, April 29, 2021 3:49:01 PM
To: Chaitanya Chinchlikar <chaitanya.c@whistlingwoods.net>; Saumya Dixit <saumya.dixit@whistlingwoods.net>
Subject: MEMO TO ALL: Vaccination against COVID

Dear All,

The pandemic has impacted almost every corner of life, which includes, changing the way we work and interact with one another. The only way to transition out of this phase of the pandemic and get back to normal is to **get vaccinated.**

One major potential barrier that we all must overcome is the negative opinion of the vaccine. Please know that your health and safety is our priority as well. COVID-19 vaccines are procured and supplied only after they meet WHO's established safety and efficacy criteria. Please consult the doctor in case you have any existing ailments. Please read the attached pdf for more information on the vaccines available in India.

You may register yourself on the CoWIN website https://www.cowin.gov.in/home or download the Arogya Setu app from Play Store for your vaccination. The registration began yesterday on 28th April for everybody above the age of 18 years. We would like everyone who plans to come to campus post lockdown to be vaccinated, this will help us build a safer workplace. Please ensure that you have your dozes of vaccines **before end of July 2021** so we can start our operations full force as soon as the restrictions are over.

After getting vaccinated, kindly send your vaccination certificates at hr@whistlingwoods.net.

The nature of the COVID-19 virus is under study. So, until we get all the answers, for your own safety and that of your loved ones, please continue wearing masks and follow all sanitation measures even after getting vaccinated.

Let's end this pandemic for good!

May The Force be with you!

Chaitanya Chinchlikar

Vice President & Business Head, Whistling Woods International
Chief Technology Officer & Head of Emerging Media, Whistling Woods International

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Get Vaccinated.pdf
1732K

Prashant Bhushan

(TRUE COPY)

Government of Punjab
Department of Home Affairs & Justice
(Home -4 Branch)

To

1. All Divisional Commissioners and Commissioners in the State
2. All the Zonal IGPs, Commissioners of Police, DIGs and SSPs in the State

No.7/56/2020/2H4/2142
Dated: Chandigarh, the 30th day of April,2021.

Sub: ConsolidatedGuidelines regarding Covid appropriate behaviour and restrictions to be implemented w.e.f.1st May 2021 till 15th May 2021.

1. Inorder to consolidate all earlier instructions on the subject matter,the following guidelines are issued in relation to restrictions imposed to contain and manage the Covid-19 pandemic. These are to be strictly and meticulously enforced throughout the State w.e.f.1st May, 2021 till 15th May, 2021

(i.) Daily Night Curfew from 6 pm to 5 amand Weekend curfew from 6.00 pm on Friday upto 5.00 am on Mondaythroughout the state strictly prohibiting all non-essential activities; but all essential activities including those enumerated hereinafter in the paragraph 2 titled 'Exemptions' to continue to remain exempted from curfew restrictions.

(ii.) Number in public transport (buses, taxis, autos) to be restricted to 50% of the capacity.

(iii.) All bars, cinema halls, Gyms, spas, swimming pools, coaching centres, sports complexes to remain closed.

(iv.) All restaurants (including in hotels), Cafes, Coffee Shops, fast food outlets, Dhabas etc. to remain closed for dine-in and may function only for take-away. Home delivery allowed till 9pm. No seating inside Restaurants, Fast Food Joint, Coffee Shops etc. to be allowed.

(v.) All shops including those in malls and multiplexes etc. to close everyday by 5.00 pm.

(vi.) All Weekly markets (such as apni mandis) to be closed.

(vii.) There shall be a complete ban on all social, cultural or sports gatherings and related functions.

(viii.) No gathering of people more than 20 to be allowed; including for weddings/cremations/funerals; every gathering of over 10 persons to be with prior approval of District administration, except for cremations.

(ix.) There shall be a complete ban across the State on all political gatherings. For any gathering organised in violation of these orders, FIRs will be registered against the organisers and participants as well as against the owners of the venue and the tent houses under the

Disaster Management Act and the Epidemic Diseases Act. Such venues shall also be sealed for next 3 months.

(x.) Persons who have attended large gatherings anywhere (religious/ political/social) to be mandatorily home quarantined for 5 days and tested as per protocol.

(xi.) All educational institutions i.e. schools and colleges to remain closed but the teaching and non-teaching staff of Govt schools to attend duty.

(xii.) All the medical and nursing colleges may continue to remain open.

(xiii.) All recruitment exams to be postponed.

(xiv.) All Private Offices, including Service Industry, such as offices of Architects, Chartered Accountants, Insurance Companies etc., allowed to 'Work from Home' only.

(xv.) In Government offices – Health/ frontline workers and employees over 45 years who have not got at least one vaccine dose in last 15 days or more, should be encouraged to take leave and stay home until then. Employees under 45 years to be allowed only on basis of negative RT-PCR not more than 5 days old or else should take leave and stay home.

(xvi.) Micro-containment zones in high positivity areas to be increased and strictly enforced. Special Monitors to be designated for enforcement.

(xvii.) Grievance redressal by all the government offices shall be preferred through virtual/on-line modes. Public dealings be discouraged as far as possible and allowed only where deemed unavoidable. Revenue Department shall also endeavour to limit appointments to public to bare minimum for execution of Conveyance Deeds for sale and purchase of properties.

2. **Exemptions**:

The following activities/establishments shall, subjecthowever to observing Covid appropriate behaviour by all concerned, remain exempted from Covid restrictions in Para 1 above:-

(i) Hospitals, veterinary hospitals and all establishments both in public and private sector related to manufacture and supply of all medicines and medical equipment. Transportation of all personnel of these establishments shall be allowed subject however to production of identity cards.

(ii) E-commerce and movement of all goods.

(iii) Chemist shops and shops dealing with supply of essential goods, milk, bread, vegetables, fruits,dairy and poultry products like eggs, meat etc.

(iv) 'To and fro' movement of passengers travelling by air, trains and buses on production of travel documents.

(v) Construction activities in both urban and rural areas.

(vi) Agricultural including procurement, horticultural, animal husbandry and veterinary services.

(vii) Vaccination out-reach camps.

(viii) Activities of Manufacturing industry,and servicesgiven below including movement of all their employees/workers and vehicles carrying them upon production of requisite permission from their employers :-

a) Telecommunication, internet services, broadcasting and cable services. IT and IT enabled services.

b) Petrol pumps and petroleum products, LPG, petroleum and gas retail and storage outlets.

c) Power generation, transmission and distribution units and services.

d) Cold storage and warehousing services.

e) All Banking/RBI services, ATMs, Cash Vans and cash handling/ distribution services.

3. District authorities shall continue to ensure strict implementation of all the extant directives of MHA/State Government onCovid appropriate behaviour including social distancing norm of minimum 6 feet distance, no crowds in market places and public transport, and imposition of penalties prescribed for violation of Covid appropriate behaviour like wearing of face masks etc.

Additional Chief Secretary(Home)
30.04.2021

CC:

1. CPS/CM
2. CS
3. PSCM
4. All administrative Secretaries/Registrar - Punjab & Haryana High Court
5. DGP Punjab
6. ADGP-Law & Order

Prashant Bansal
(TRUE COPY)

ANNEXURE:P36

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Government of Punjab
Department of Home Affairs & Justice
(Home -4 Branch)

To

1. All the Divisional Commissioners and the Deputy Commissioners in the State
2. All the Zonal IGPs, Commissioners of Police, DIGs and SSPs in the State

No.7/56/2020/2H4/2143
Dated: Chandigarh, the 2nd day of May, 2021.

Sub: Additional restrictions regarding COVID-19 applicable w.e.f. 02.05.2021 to 15.05.2021.

1. In continuation to this office letter No. 7/56/2020/2H4/2142 dated the 30th April 2021 in the subject matter which shall continue to be enforced till 15.05.2021.

2. In addition to the restrictions as imposed vide letter referred to hereinabove, the following additional restrictions shall be strictly and meticulously enforced:-

i. All shops selling non-essential items to remain closed

Essential items include Chemist shops and shops dealing with supply of essential goods, milk, bread, vegetables, fruits, dairy and poultry products like eggs, meat, mobile repair etc.

No restriction on laboratories, nursing homes and all other medical establishments.

ii. Nobody to enter the State whether by air, rail or road without either
   a. Negative Covid report not more than 72 hours old, or
   b. Vaccination certificate (at least one dose) over 2 weeks old.

iii. All Government offices as well as banks will work at 50% strength other than those where officials are involved in Covid management. Deputy Commissioners are authorised to draft services of any official for Covid management and related duties.

iv. All Four-Wheeler Passenger vehicles, including Cars and taxis, not allowed to seat more than 2 passengers. Vehicles carrying patients to hospitals exempted. No Pillion riders on scooters and motorcycles except those belonging to the same family and living in the same house.

v. No gathering of more than 10 persons to be allowed; including for weddings/cremations/funerals.

vi. Villages will organise Thikri Pehras to ensure that 'Night Curfew'and 'Weekend Curfew' Orders are complied with.

vii. Social Distancing to be maintained in SabziMandis, which would be open only to Fruit and Vegetable Wholesalers.

viii. Appeals to Kisan Unions and Religious leaders not to hold gatherings and restrict number of protestors to token presence at Toll Plazas, Petrol Pumps, Malls etc.

ix. Religious Places to be closed at 6 pm daily. No overcrowding at Gurudwaras, Mandirs, Masjids, Churches etc.

x. Action by District Administrations against those hoarding Oxygen Cylinders etc.

xi. RT-PCR testing of Road and Streetwise vendors, such as Rehriwallahs etc. to be carried out.

3. **Implementation to be stepped up**

i. Daily Night Curfew from 6 pm to 5 am and Weekend curfew from 6.00 pm on Friday upto 5.00 am on Monday throughout the state. No vehicle to ply except for medical purposes. with curfew pass

ii. Number in public transport (buses, taxis, autos) to be restricted to 50% of the capacity. Transport and civil officials, along with police personnel, to constitute flying squads to enforce.

iii. All bars, cinema halls, Gyms, spas, swimming pools, coaching centres, sports complexes to remain closed.

iv. All restaurants (including in hotels), Cafes, Coffee Shops, fast food outlets, Dhabas etc. to remain closed for dine-in and may function only for take-away. Home delivery allowed till 9pm. No seating inside Restaurants, Fast Food Joint, Coffee Shops etc. to be allowed.

v. All Weekly markets (such as apnimandis) to be closed.

vi. There shall be a complete ban on all social, cultural or sports gatherings and related functions, including government functions, such as inaugurations, foundation stone laying ceremonies, etc unless prior permission of Deputy Commissioner has been obtained.

vii. There shall be a complete ban across the State on all political gatherings. For any gathering organised in violation of these orders, FIRs will be registered against the organisers and participants as well as against the owners of the venue and the tent houses under the Disaster Management Act and the Epidemic Diseases Act. Such venues shall also be sealed for next 3 months.

viii. Persons who have attended large gatherings anywhere (religious/ political/social) to be mandatorily home quarantined for 5 days and tested as per protocol.

ix. All educational institutions i.e. schools and colleges to remain closed but the teaching and non-teaching staff of Govt schools to attend duty.

x. All the medical and nursing colleges may continue to remain open.

xi. All recruitment exams to be postponed, unless it relates to recruitment of Covid management related manpower.

xii. All Private Offices, including Service Industry, such as offices of Architects, Chartered Accountants, Insurance Companies etc., allowed to 'Work from Home' only.

xiii. In Government offices – Health/ frontline workers and employees over 45 years who have not got at least one vaccine dose in last 15 days or more, should be encouraged to take leave and stay home until then. Employees under 45 years to be allowed only on basis of negative RT-PCR not more than 5 days old or else should take leave and stay home.

xiv. Micro-containment zones in high positivity areas to be increased and strictly enforced. Special Monitors to be designated for enforcement.

xv. Grievance redressal by all the government offices shall be preferred through virtual/on-line modes. Public dealings be discouraged as far as possible and allowed only where deemed unavoidable. Revenue Department shall also endeavour to limit appointments to public to bare minimum for execution of Conveyance Deeds for sale and purchase of properties.

4. District authorities shall also continue to ensure strict implementation of all the extant directives of MHA/State Government on Covid appropriate behaviour including social distancing norm of minimum 6 feet distance (Do Gaz Ki Doori), regulating crowds in market places and public transport, and imposition of penalties prescribed for violation of Covid appropriate behaviour like wearing of face masks and spitting in public places etc.

Additional Chief Secretary (Home)
02.05.2021

CC:

1. CPS/CM
2. CS
3. PSCM
4. All administrative Secretaries/Registrar - Punjab & Haryana High Court
5. DGP Punjab
6. ADGP-Law & Order

Prashant Bhushan
(TRUE COPY)

GUJARAT TECHNOLOGICAL UNIVERSITY

(Established by Government of Gujarat Under Gujarat Act No.: 20 of 2007)

ગુજરાત ટેકનોલોજીકલ યુનિવર્સીટી

(ગુજરાત સરકારના ગુજરાત અધિનિયમ ક્રમાંક : ૨૦૦૭ દ્વારા સ્થાપિત)

ESTD - 2007

Ref. No: GTU/Winter/2021/Vaccine/ 1978 **Date: 22/04/2021**

Circular

Regarding Covid-19 Vaccination before Winter - 2021 Exam Form Filling

Government has announced "liberalized and accelerated Phase 3 strategy" of Covid-19 vaccination. The nation's entire adult population, i.e, all citizens above the age of 18 years will be allowed to receive the vaccination from May 1, 2021. This is a major step in controlling the second wave of Covid-19. India is vaccinating people at world record pace and it is our moral duty to continue this with even greater momentum.

All the students who have attained age of 18 years as on 01/05/2021 are hereby informed that it is mandatory to get Covid-19 vaccination before filling Winter 2021 exam forms. Along with the prevailing GTU norms, Institutes will have to allow only the students who have taken Covid-19 vaccination to fill their Winter - 2021 exam forms.

All the affiliated Institutes are hereby informed to convey this Circular to its all students, faculties and staff members.

Registrar 22/4/21

Prashant Bhushan

(TRUE COPY)

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ANNEXURE-P38

W.P.(C) No. 36065 of 2017 - G

Parents Teachers Association v. State of Kerala

2017 SCC OnLine Ker 36408

In the High Court of Kerala at Ernakulam
(BEFORE K. VINOD CHANDRAN, J.)

Parents Teachers Association (P.T.A.), Government Higher Secondary School, Kokkur, Kokkur (P.O.), Malappuram District, Represented by its President, Mujeeb Kokkur, Aged 45 years, S/o Mohammed Kutty, Kanichath Valappil, Kokkur (P.O.), Malappuram District-679 591 ..... Petitioner

By Adv. Sri. K. Rajesh Kannan

v.

1. State of Kerala, Represented by the Secretary to Government, Department of Health & Family Welfare, State Secretariat, Thiruvananthapuram-695 001.
2. The District Collector, Malappuram District, Collectorate, Malappuram-676 001.
3. The District Medical Officer, Malappuram District, Office of the District Medical Officer, Malappuram-676 505.
4. The Superintendent of Primary Health Centre, Alamcode, Primary Health Centre, Alamcode (P.O.), Malappuram-679 585.
5. Government Higher Secondary School, Kokkur, Represented by its Headmaster, Kokkur (P.O.), Malappuram District-679 591.
6. Alamcode Grama Panchayath, Represented by its Secretary, Alamcode (P.O.), Malappuram-679 585 ..... Respondent(s)

R1 to R5 by Government Pleader Sri. Kannan

W.P.(C) No. 36065 of 2017 - G
Decided on November 10, 2017

The Judgment of the Court was delivered by

K. VINOD CHANDRAN, J.:— The petitioner, a Parent Teacher Association (PTA), has filed the above writ petition, seeking implementation of Ext.P5 Vaccination Form, with respect to the children, studying in the 5th respondent school, before administering the vaccination. It is also prayed that there shall be no administration of vaccination to the children, without the consent from the parents of the children, studying in the 5th respondent school.

2. There can be no such orders passed in an application, filed by the PTA, especially since the vaccination, as a policy measure is taken up by the Government in a massive scale, with the intention of averting spread of endemic and communicable disease. The present campaign initiated by the State of Kerala is a measure for eradicating the specific disease "Measles - Rubella". A campaign as such is undertaken by the State to vaccinate the children so as to ensure a healthy life and total eradication of the communicable disease. The petitioners are here, pointing out certain instances, resulting in adverse consequences after vaccination was administered. This cannot lead to a blanket order, with respect to the children of the petitioner's school. If at all any parent has an objection, it has to be necessarily brought before the authorities

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and there need not be any vaccination administered to such children, whose parents object to the vaccination. The learned Government Pleader also submits that no forceful vaccination is attempted.

3. As for the implementation of Ext.P5 Vaccination Form, the learned Government Pleader submits on instructions that a vial of vaccine, contain 10 dozes and once opened, it has to be used within a period of four hours. The specific vaccination used, the time when the bottle is opened and the various dozes are administered are recorded in a Register. The Register should also contain the manufacturer's name and batch number of the vaccination, which shall be shown to the parent of the child, on whom the vaccination is administered, if specifically requested for.

4. In such circumstance, recording the submission of the learned Government Pleader, the writ petition would stand closed. No costs.

———

Prashant Bhushan
(TRUE COPY)

ANNEXURE: P39

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* **IN THE HIGH COURT OF DELHI AT NEW DELHI**

\+ **W.P.(C) 343/2019 & CM Nos.1604-1605/2019**

MASTER HARIDAAN KUMAR MINOR THROUGH AND ORS. ..... Petitioners

Through: Mr Anubhav Kumar and Mr Abhinav Mukherji, Advocates.

versus

UNION OF INDIA AND ANR. ..... Respondents

Through: Mr Ramesh Singh, Standing Counsel, GNCTD with Mr Chirayu Jain and Ms Nikita Goyal, Advocates for GNCTD.

Mr Sushil Kumar Pandey, Senior Panel Counsel with Ms Neha Sharma, Advocates for UOI with Dr Pradeep Haldar (Deputy Commissioner (IMM) Incharge).

AND

\+ **W.P.(C) 350/2019 & CM Nos.1642-1644/2019**

BABY VEDA KALAAN AND ORS. ..... Petitioners

Through: Ms Diya Kapur, Ms Shyel Trehan and Mr Rishabh Sharma, Advocates.

versus

DIRECTORATE OF EDUCATION AND ORS. ..... Respondents

Through: Mr Ramesh Singh, Standing Counsel, GNCTD with Mr Santosh Kumar Tiwari, ASC, Mr Chirayu Jain and Ms Nikita Goyal, Advocates for GNCTD.

Ms Monika Arora, CGSC for R-2/UOI with Mr Harsh Ahuja and Mr Praveen Singh, Advocate for UOI.

CORAM:
HON'BLE MR. JUSTICE VIBHU BAKHRU

ORDER

% 22.01.2019

1. The petitioners have filed the above-captioned petitions, *inter alia,* impugning the notification No. DE.23 (386)/Sch.Br./2018 dated 19.12.2018 (hereafter 'the impugned notification') issued by the Directorate of Education (DoE), Government of National Capital Territory of Delhi. By the impugned notification, the Directorate of Education (DoE) has directed the Chairman/Manager/Principal to direct all schools (whether Government, Government Aided and Private Unaided Recognised schools) to comply with certain guidelines relating to implementation of the Measles and Rubella (MR) vaccination campaign. Under the said campaign, MR vaccines are to be administered to all children aged between nine months and fifteen years (the beneficiaries). The said guidelines, *inter alia,* provide that no consent would be required from the beneficiaries / their parents for implementing the MR Campaign.

2. The petitioners are, essentially, aggrieved by the decision of the respondents to forcibly administer MR vaccination without the consent of the parents/guardians or family members of the beneficiaries (children aged between nine months to fifteen years). The petitioners in W.P.(C) 350/2019 pray that the impugned notification be set aside and further directions be issued that no vaccination be administered in cases where there is parental objection to such vaccination. The petitioners in W.P.(C) 343/2019, *inter*

alia, pray that an order be issued to the respondents restraining them from forcibly administering vaccinations to children without the consent of their parents/guardians.

3. On 15.01.2019, this Court had observed that the contention of the petitioners, that children cannot be administered vaccination forcibly and without the parental consent, is merited. Mr Singh, learned counsel appearing for DoE and Government of NCT of Delhi (respondent nos. 1 and 2) did not dispute the said proposition that readily accepted that vaccination cannot be administered forcibly and without the consent of the parents.

4. He, however, submitted that an express affirmative consent from parents / guardians of the beneficiaries ought not to be a pre-condition for administering the said vaccine. He contended that such consent of the parents / guardians should be inferred unless they expressly state in the negative. He referred to the same as "*opt-out consent*".

5. Plainly, in order for any parent or guardian to give his/her consent (whether expressly or by inference), it would be necessary for such parent or guardian to have complete information with regard to the proposed vaccination campaign. Clearly, for any parent or guardian to take an informed decision, it would be necessary for such parent to be aware of (a) the vaccine proposed to be administered; (b) contraindications or side effects of such vaccine; (c) the date on which such vaccine administered to the ward/children; and (d) the personnel who would administer the same.

6. Mr Raj Shekhar Rao and Ms Diya Kapur, learned counsel advanced arguments on behalf of the petitioners and Mr Ramesh Singh advanced

arguments on behalf of respondent nos. 1 and 2. It was apparent from the said arguments that learned counsel for both the sides were *ad idem* that vaccination could not be administered to children without consent of their parents / guardians. Mr Pandey, learned counsel appearing for the Union of India, did not advance any submissions apart from stating that the MR Campaign was successfully implemented in twenty-six states of the country.

7. In view of the above, impugned notification, to the extent it provides that no consent is required for the beneficiaries and/or their parents, is quashed.

8. Mr Singh, also readily agreed, on instructions, that information with regard to MR campaign would require to be disseminated. He also handed over a tabular statement indicating the names of daily newspapers in English, Hindi, Urdu and Punjabi, which would carry the advertisements. It was also submitted that advertisements would be of a quarter page and would indicate the material information. It was also agreed that the said information would be put up on the website of DoE.

9. In view of the above, the controversy between the parties was narrowed down, essentially, on two issues, (a) whether an express consent of the parents/guardians was necessary or whether the same could be inferred by silence on the part of the concerned parents/guardians; and (b) whether the respondents were required to indicate the contraindications and the side effects of the vaccines in the newspaper advertisements as well as in other literature to be provided to parents/guardians of the beneficiaries.

10. Insofar as the first issue is concerned – that is, whether an express

consent from parents/guardians is necessary – Mr Singh contended that the vaccination campaign is required to cover at least 95% of the beneficiaries within a short span of time for the same to be successful and, therefore, there would not be enough time for respondents to elicit a positive express response from the parents/guardians. He had further submitted that there are a large number of students from EWS categories and it would be very difficult to ensure a response from the parents of such students. He further submitted that the respondents would also have no opportunity to counsel such parents.

11. Ms Diya Kapur countered the aforesaid submissions. She submitted that she had contacted certain schools and the data indicated that parents of EWS students, in most cases, had responded to the consent forms sent by the concerned schools. She referred to the case of one such school (Bal Bharti), where consent forms were sent to 856 students from the EWS category and 812 such consent forms were received back. Out of the aforesaid, 394 had not agreed for administration of the MR vaccine. She further contended that the contention of the respondents, that it is difficult to contact students from EWS category, is without basis. She further referred to various newspaper reports, which had reported incidents where the children had fallen sick after administration of the MR vaccine. She contended that it was, thus, necessary for parents to take an informed decision.

12. Mr Singh, countered the aforesaid submissions and submitted that vaccination was a necessary measure for eradication of the diseases in question and those children, who are not vaccinated, may act as a disease vector putting the general health of others at risk. He contended that in

larger public interest, it was necessary that the MR campaign be supported by all measures.

13. Undisputedly, there is an urgent need to disseminate information regarding the MR campaign and the assumption that children could be vaccinated forcibly or without consent is unsustainable. This Court is of the view that all efforts are required to be made to obtain the decision of the parents before proceeding with the MR campaign. In this regard, it would be apposite to ensure that the consent forms/slips are sent to each and every student. Since the time period for implementing the campaign is short, the response period should be reduced and parents / guardians of students must be requested to respond immediately and, in any case, in not more than three working days. If the consent forms/slips are not returned by the concerned parent, the class teacher must ensure that the said parents are contacted telephonically and the decision of such parent is taken on phone. The concerned teacher ought to keep full records of such decisions received telephonically. In respect of those parents/guardians that neither return the consent slips nor are available telephonically despite efforts by the concerned teacher, their consent can be presumed provided respondent nos. 1 and 2 ensure that full information regarding the commission is provided to all parents.

14. The contention that indication of the side effects and contraindications in the advertisement would discourage parents or guardians from consenting to the MR campaign and, therefore, the same should be avoided, is unmerited. The entire object of issuing advertisements is to ensure that necessary information is available to all parents/guardians in order that they

can take an informed decision. The respondents are not only required to indicate the benefits of the MR vaccine but also indicate the side effects or contraindications so that the parents/guardians can take an informed decision whether the vaccine is to be administered to their wards/children.

15. In view of the above, it is directed as under:

(1) Directorate of Family Welfare shall issue quarter page advisements in various newspapers as indicated by the respondents, namely, The Hindustan Times, The Times of India, The Hindu, The Pioneer, The Indian Express, Delhi Tribune, Mail Today, The Asian Age, Navbharat Times, Dainik Jagran, Punjab Kesari, Hindustan, Amar Ujala, Navodaya Times, Hamara Samaj, Pratap, Daur-e-Jadeed, Jathedar, Jan Ekta. The advertisements shall also indicate that the vaccination shall be administered with Auto Disable Syringes to the eligible children by Auxiliary Nurse Midwifery. The advertisement shall also clearly indicate the side effects and contraindications as may be finalised by the Department of Preventive Medicine, All India Institute of Medical Sciences.

(2) The Head of Department of Preventive Medicine, All India Institute of Medical Sciences is directed to finalise the list of contraindications and risks associated with the vaccine being included in the aforesaid advertisements. Advertisements in two of the newspapers (one in English and the other in Hindi language) will also indicate the dates on which MR vaccine will

be administered in respective schools. The website of DoE shall also clearly set out the above information.

(3) The School shall issue consent forms to parents of all students admitted in their schools up to Class X with instructions that the forms be returned to the school within a period of two working days. The class teacher/nodal teacher shall contact parents/guardians of students who have not returned the consent forms within a period of one working day thereafter and elicit their consent or objection to administration of such vaccines. The class teacher/nodal teacher shall keep a record of the decision of the parents so contacted. In the event the class teacher/nodal teacher is unable to reach parents despite best efforts, the record of the efforts made shall be duly noted by her.

(4) MR vaccines will not be administered to those students whose parents/guardians have declined to give their consent. The said vaccination will be administered only to those students whose parents have given their consent either by returning the consent forms or by conforming the same directly to the class teacher/nodal teacher and also to students whose parents/guardians cannot be contacted despite best efforts by the class teacher/nodal teacher and who have otherwise not indicated to the contrary.

16. It will be open for the DoE/Department of Health to approach the parents directly to inform them and educate them regarding the MR vaccine

campaign in order to elicit their consent.

17. Mr Singh had submitted that under the present MR Vaccination campaign, DoE is targeting 55 lakh children in the age group of nine months to fifteen years. Of these 55 lakh children, approximately 34 lakh children are attending recognised schools; approximately 10-11 lakh children are attending unrecognised private/ pre-nursery schools; and the remaining 10-11 lakh children are either not attending any school or are below the age of 3 years and are living with their parents/guardians.

18. It is made clear that the directions set out above relate only to students attending recognized schools. In respect of the remaining children, the respondents seek time of two to three weeks to submit the modalities of obtaining consent. Once these have been submitted, the court shall consider the conditions on which the MR campaign in respect of the remaining unrecognised private/ pre-nursery schools and children not attending school shall proceed.

19. List for further proceedings on 01.02.2019.

VIBHU BAKHRU, J

JANUARY 22, 2019
RK

Prashant Bhushan

(TRUE COPY)

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VAKLATNAMA

(S.C.R.Order IV Rule 18)

In The Supreme Court of India

ORIGINAL/CRIMINAL/CIVIL/ JURISDICTION

Writ Petitiion (Civil) No. _____ of 2021

IN THE MATTER OF:

DR. JACOB PULIYEL — PETITIONER

VERSUS

UNION OF INDIA & ORS. — RESPONDENTS

I, DR. Jacob Puliyel, S/o of Late Shri P.M. Mammen, R/o 6A, 7 Raj Narayan Marg, Delhi-110054, the Petitioner

In the above petition/Appeal do hereby appoint and retain

PRASHANT BHUSHAN Advocate on Record

of the Supreme Court to act and appear for me/us in the above Petition/Appeal and on my /our behalf to conduct and prosecute (or defend) or withdraw the same and all proceedings that may be taken in respect of any application connected with the same or any degree or order passed there in, including proceeding in taxation and application for review, to file and obtain return of document and to deposit and receive money on may/our behalf in the said petition/appeal Reference and application, Review Petition and to represent me/us and to take all necessary steps on may /our behalf in the above matter, I. We agree to rectify all acts done by the aforesaid advocate on record in pursuance of this authority.

Dated- 11th May, 2021 (Signed)

Accepted, Identified & Certified

Prashant Bhushan

ADVOCATE

(DR. JACOB PULIYEL)

(For the Petitioner)

To,
The Registrar,
Supreme Court of India,
New Delhi,

MEMO OF APPEARANCE

Sir,

Please enter my appearance on behalf of the Appellant(s)/Petitioner(s)/ Respondent(s) opposite Parties/intervener in the matter mentioned above:

New Delhi dated this the- 12th day of May, 2021

Yours faithfully,

Prashant Bhushan

(PRASHANT BHUSHAN)

Counsel for the Petitioner