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Serum Institute of India's application for emergency approval for COVISHIELD | *All India Drug Action Network*

To,

Dr. Vinod K. Paul
Member, Niti Aayog
Chair, National Expert Group on Vaccine Administration for COVID-19

Shri Rajesh Bhushan
Secretary, MOHFW
Co-Chair, National Expert Group on Vaccine Administration for COVID-19

Dr. V. G. Somani
Drugs Controller General (India)
Central Drugs Standard Control Organization (CDSCO)

8 December, 2020

Dear Dr. Paul, Shri Bhushan, and Dr. Somani,

Serum Institute of India's application for emergency approval for COVISHIELD

We are writing to express our concerns over media reports that the Serum Institute of India (SII) has submitted an application to the CDSCO on 6 December 2020 for emergency approval of the COVISHIELD vaccine candidate. It has been reported that interim data from four clinical trials – two in the UK, one in Brazil and one in India – have been submitted.

As you know, not only India but several developing countries have been eagerly awaiting the development and approval of COVISHIELD not only as an affordable vaccine but also one that will be well suited for rollout in developing country conditions. Precisely because of the hope that is being placed on this vaccine candidate, the conduct of clinical trials to determine its safety, quality and efficacy as well as the regulatory standards to review data and the approval process must be above reproach. However, the manner and timing of SII's application and handling of a serious adverse event that was reported in the public domain have raised serious concerns and questions.

1. **What interim data were submitted from the Indian Phase 2/3 bridging trial?**

As you are aware, SII and ICMR are conducting a Phase 2/3 bridging clinical trial to determine the safety and immunogenicity of COVISHIELD, the AstraZeneca/Oxford vaccine candidate being manufactured in India by SII.

It is unclear what data SII would have submitted in its application to the regulator from the Indian trial because as per the timelines and criteria set out for interim analyses in the clinical trial protocol, the data for immunogenicity and safety could not be available for Phase 3 participants (i.e., 1500 participants out of total 1600 participants) at this time.

According to SII's clinical trial protocol:

"Two interim analyses are planned as below:

1. Safety data of 28 days post second vaccination (Day 57) of all study participants.
2. Immunogenicity data by IgG ELISA at 28 days post second vaccination (Day 57) of participants in immunogenicity cohort and safety data of 28 days post second vaccination (Day 57) of all study participants."

We note also that while assessing the SII-ICMR trial, the COVID-19 SEC directed that:

"interim analysis of Immunogenicity cohort may be carried out only after day 58 both for safety & immunogenicity" (on 28 July 2020) [1]

and

"the committee opined that Market authorization of the vaccine will be based on clinical data generated in the said trial as well as the data from other countries, as available" (on 31 July 2020). [2]

The date of first enrollment in the clinical trial, as per the CTRI entry[3], is 24 August 2020. The final enrollment in the trial was completed on 31 October 2020 according to a press release issued by SII[4]. Given these dates, it is unclear how SII could have conducted interim analyses involving all of the trial participants by the time of its application.

That is, as per the criteria of the planned interim analyses, data on safety or immunogenicity for 1500 participants enrolled in Phase 3 (out of 1600 trial participants enrolled in Phase 2/3 trial) would not be available as yet. This includes data from the non-inferiority study being conducted in 400 participants that compares COVISHIELD, SII's vaccine candidate with the AstraZeneca/Oxford vaccine candidate.

It is a concern that SII does not appear to have waited until meaningful data from interim analyses were available from the bridging study in Indian population.

2. **AstraZeneca/Oxford vaccine candidate has not obtained Emergency Use Authorisation**

Previously, it had been indicated that DCGI may consider granting emergency authorisation to SII's vaccine candidate if the AstraZeneca/Oxford vaccine candidate obtained an EUA in the UK.[5]

However, the AstraZeneca/Oxford vaccine candidate has not yet been granted any EUA. The UK Medicines and Healthcare products Regulatory Agency (MHRA) is currently undertaking a rolling review of AstraZeneca's application[6], having been instructed by the UK Government to review the AstraZeneca/Oxford vaccine candidate[7].

The results of the interim analyses of the AstraZeneca/Oxford vaccine candidate based on subgroups from UK and Brazil trials, which were initially shared through a press release on 23 November 2020 were received with criticism for not disclosing crucial details.[8] The interim analysis from the UK, Brazil and South Africa trials have only been published today in the Lancet and the merging of data appears to have been followed even in this publication.

We are not aware of what data have been submitted by SII to CDSCO in respect of trials in the UK and Brazil. The Indian government had indicated that it would only consider Phase 3 interim data of the UK and Brazil trials for the two full-dose regimen.[9]

Given that the UK's MHRA is still examining the data for the AstraZeneca/Oxford vaccine candidate and that it is evident that interim data for all study participants from SII's trial could not possibly have been submitted, SII's application appears to be premature and most likely incomplete. For a company with such a considerable international reputation, the least to be expected would be for it to seek approval only on the basis of a complete and well considered application.

As is the case with the interim data from the UK, Brazil and South Africa trials, we urge that the interim data from the Indian trial should also be published in a peer-reviewed journal when it is available.

3. **Persisting concerns over adverse events in AstraZeneca/Oxford and SII clinical trials**

At this point, there are three known cases of serious adverse events (SAEs) related to neurological symptoms in healthy trial participants of the AstraZeneca/Oxford and SII vaccine candidates. Regarding the SAE that occurred in October in the COVISHIELD trial, it is unfortunate that ICMR, SII and other authorities did not report the same to all the sites where the trial was being conducted.

The details of the said incident were disclosed by the participant and his family almost a month and half after the occurrence of the SAE. Unfortunately, no public details are available till date through the CDSCO or the trial sponsors, SII and ICMR, regarding the handling of the adverse event, and how it was determined that the incident is not related to the vaccine candidate.

Neither the process nor timelines have been shared through which the SAE was investigated and determination of causality was made, including the role of the site PI, Institutional Ethics Committee, DSMB, DCGI and Independent Expert Group.

We understand that the trial participant has not been contacted by the DCGI or trial sponsors to convey and discuss the conclusions reached in respect of the SAE or his current medical condition. If the participant is the most important person in the trial, it is rather strange that the participant has not been contacted and was not involved in the process of determination of the SAE.

Moreover, when the participant, whose health deteriotated during the trial sent a notice claiming damages, SII's immediate response to attempt to intimidate the trial participant with a threat of a Rs.

100 crore defamation suit is shocking. ICMR being the co-sponsor of the trial ought to have stopped such intimidating tactics by the company. Such threats damage the entire clinical trial system and would discourage people from participating in trials. A participant takes the maximum health risk, and then being threatened with such a lawsuit is unacceptable, highly damaging and should not be tolerated by the government agencies involved in the trial and authorization process.

We have learned that the final report of the DSMB, dated 30 November 2020, concluded that:

"After a thorough review of this event which is acute encephalopathy it is noted that there are anti-smith antibodies which are strongly positive suggestive of autoimmune aetiology of this encephalopathy and the participant also has nutritional deficiency, and at present there is no indication that the event is caused by the study vaccine."

We would like to know if information of the similar SAEs that had occurred in the UK trial of the AstraZeneca/Oxford vaccine candidate was also reviewed in this process.

We urge that for adverse events reviewed by the DSMB and the DCGI, the conclusions regarding relatedness with the vaccine and the reasoning in arriving at the conclusions should be shared in the public domain.

We request that the specific findings of the IEC, DSMB, recommendations of the Independent Expert Group, and the DCGI's review of the SAE of the participant who developed acute encephalopathy and the recommendations regarding compensation be shared with the trial participant and that the information is also provided to the public.

4. **Agreements between SII and ICMR for the conduct of clinical trials on COVISHIELD**

SII has entered into a strategic alliance through which ICMR is jointly conducting and funding ongoing clinical trials of COVISHIELD in India.[10] As public funds are being invested in bringing COVISHIELD to the market, the agreement between SII and ICMR should be made public. In addition, the details of instructions and feedback given by the ICMR to SII and the mechanisms in place at the ICMR-end for the monitoring of SII's conduct and performance should also be available in the public domain. We therefore request you to place the agreements that ICMR and the government has entered into with all the private companies with regard to development of a vaccine against SARS-COV-2, in the public domain.

Need for transparency on agreements between SII and various national, international and commercial entities regarding COVISHIELD

SII's COVISHIELD is based on a licensing and technology transfer agreement with UK multinational company AstraZeneca. SII also has entered into a partnership with the Gates Foundation, GAVI and the COVAX facility that will impact production and supply of SII's vaccine candidates not just in India but globally as well.[11] It is unclear whether any of these agreements have been scrutinised by the government to determine the quantity of vaccine doses that will be available in India and by what dates, how much will be exported and what SII's legal obligations are towards its international partners.

It is evident that SII on its own will not be able to manufacture and meet the demands in India or even internationally. In this regard, it is important for the government to consider options for disseminating the technologies for the production of these vaccine candidates to ensure that more companies can also manufacture these vaccines and ensure better and more sustainable supply.

These agreements between SII and AstraZeneca as well as with the other international entities should be in the public domain and subject to public scrutiny to ensure that public interest is not being undermined by commercial interests during this pandemic. It may be noted that the agreement between AstraZeneca and Fiocruz in Brazil has been put in the public domain.[12]

The Government of India needs to ensure that Indian companies retain their role as suppliers of safe, effective and affordable health technologies to the developing world for COVID-19; global solidarity is essential to address this and other pandemics. However secret deals and agreements between various entities should not be the basis for this global solidarity and this must be done transparently to ensure that national or international public interest is not undermined or restricted through commercial terms.

6. **Lack of clarity and transparency on 'Restricted Emergency Use' for COVID-19 vaccine candidates**

Over the course of the pandemic, the CDSCO has issued 'restricted emergency use' or accelerated approvals for some COVID-19 therapies which are now being sought for COVID-19 vaccine candidates. However there has been no clarity regarding the basis for REU approvals and the specific conditions and restrictions attached to each such approval.

In relation to COVID-19 vaccine candidates, we are unaware of the parameters that need to be met for seeking REU approval from CDSCO. If an REU for a COVID-19 vaccine is granted, kindly make public the basis of approval, including evidence reviewed; the restrictions/conditions linked to the approval; and at what point full market authorisation may be given.

For COVISHIELD, it is reasonable to surmise that REU could translate into 'use' as the production numbers give an impression that there is likely to be large scale rollout of this vaccine. Media reports indicate that the vaccine may even be available in the private market for purchase. If REU is going to be treated as "full marketing approval" and given the scale at which this vaccine is likely to be used and made publicly available, we urge the government to consider approval based on final rather than interim data.

Recommendations

In the interest of transparency and with a view to building public confidence, we request you to:

1. ***With regard to SII's COVISHIELD application for emergency approval:***

Disclose the detailed clinical trial protocol for the Phase 2/3 bridging trial for COVISHIELD along with all amendments made to the protocol.

1. Clarify whether SII's application will be considered prior to the grant of an EUA in the UK to AstraZeneca/Oxford's vaccine candidate

iii. Disclose information about which interim data from each of the clinical trials will be considered and reviewed by the SEC

1. Require SII and ICMR to make public any interim data from the Indian trial on the basis of which SII is seeking emergency approval.
2. While preserving the privacy and confidentiality of the participant, provide the conclusions of the DSMB and DCGI regarding relatedness of the SAE with the vaccine candidate and the reasoning behind the decisions. Provide also details of the protocol, process and timelines that were followed in investigating this SAE
3. Disclose the details of the strategic alliance between SII and ICMR and share the MoU/agreement in the public domain

vii. Disclose the licensing and technology transfer agreement between AstraZeneca and SII.

viii.Disclose the agreements between SII and the Gates Foundation, GAVI and COVAX and any other international agencies or bodies that impact the production and supply of COVISHIELD and other vaccine candidates in India and abroad.

1. ***With regard to the regulatory approval processes:***

Clarify the exact processes and parameters for REU approval of COVID-19 vaccine candidates in India and whether and under what conditions interim results can be sufficient for seeking such an approval.

1. If an REU for a COVID-19 vaccine is granted, kindly make public the basis of approval, including evidence reviewed; the restrictions/conditions linked to the approval; and at what point full market authorisation may be given.

iii. Provide details of the protocol, process and timelines followed in investigating any reported SAEs.

1. Clarify the Government's stand on indemnifying vaccine manufacturers.
2. Clarify if the Government has or is planning to put in place a mechanism to compensate individuals who suffer serious adverse events post-licensure
3. Make public all relevant documents and details related to COVID-19 vaccine trials. This includes
4. details of the composition of the COVID-19 SEC. We also urge that the composition and reports of any committees or bodies set up in relation to COVID-19 vaccine trials such as Drug Safety Monitoring Boards, Independent Expert Groups be made public.
5. monitoring reports of all Institutional Ethics Committees (IECs)
6. details of all adverse events (AEs) and severe adverse events (SAEs) and the redacted documents placed before the committees for analysis of SAEs reported from the trial sites

For a vaccine that is intended for large scale national rollout as well as international supply to multiple developing countries, rushed approval applications can undermine public confidence in the vaccinec candidate and its safety and efficacy. SII is looking to supply up to 200 million doses of vaccine candidate, upon gaining regulatory approval and WHO Prequalification, to low and middle income countries as part of the Gavi COVAX AMC mechanism in 2021.[13] It is all the more important to instill national and international confidence in the trial being conducted by SII in

collaboration with ICMR, for there to be transparency and public scrutiny of the data, and the CDSCO to follow a rigorous approach in the regulatory approval process.

In the midst of a pandemic that continues to spread rapidly, that is taking countless lives and causing long-term morbidity, the approval of a safe, effective and affordable vaccine will take the joint work, collaboration and scrutiny of industry, government, experts and the public. It is also a responsibility and an obligation of the government and its agencies to conduct itself in an open and transparent manner to regain the trust and confidence of the people of the country and assure that there are no pressures on the authorities to give quick approvals without considering the safety and efficacy of the vaccine candidates that may be approved.

We request a meeting to discuss the issues and concerns discussed above and look forward to hearing from you.

Sincerely,

All India Drug Action Network

Copy to:

Ms. S. Aparna, Secretary, DOP, Ministry of Chemicals and Fertilizers

Dr. Renu Swarup, Secretary, Department of Biotechnology

Dr. Balram Bhargava, Director General, ICMR

Dr. Sunil Kumar, DGHS

Dr. P K Mishra, Principal Secretary to Hon'ble PM

Shri P. K. Sinha, Principal Advisor to Hon'ble PM

Shri S. Gopalakrishnan, Additional Secretary to Hon'ble PM

Ms. P. Amudha, Joint Secretary to Hon'ble PM

[1]

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[8] https://www.nytimes.com/2020/11/25/business/coronavirus-vaccine-astrazeneca-oxford.html ; https://www.defense.gov/Newsroom/Releases/Release/Article/2428796/this-week-in-operation-warp-speed-nov-27-2020/

[9] https://timesofindia.indiatimes.com/india/india-to-consider-clinical-trials-data-of-two-full-doses-of-astrazeneca-vaccine/articleshow/79437239.cms

[10] "The strategic alliance between SII and the ICMR will advance India's role in the global race to develop COVID-19 vaccines. ICMR is providing continuous support to SII in conducting and funding the ongoing clinical trials of COVISHIELD across 15 centres in India." https://www.seruminstitute.com/news_sii_icmr_partnership.php

[11] https://www.seruminstitute.com/news_gavip_partnership_annoucement.php

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