ALL INDIA DRUG ACTION NETWORK

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

Shri Rajesh Bhushan
Secretary, Ministry of Health and Family Welfare
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)

1 January 2021

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

Consideration of Serum Institute of India's application for emergency approval for COVISHIELD in light of the UK MHRA's approval of the AstraZeneca/Oxford University COVID-19 vaccine

In our letter dated 8 December 2020 (attached for your reference) we had expressed our concerns regarding the application submitted by the Serum Institute of India (SII) to CDSCO for emergency approval of its vaccine candidate, COVISHIELD. Our concerns stemmed from the fact that the application had been made prematurely and was deficient in data that would be essential for the regulator and experts to consider for granting approval, as well as the lack of transparency in the handling of the serious adverse event that occurred in October in SII's trial.

As noted by the SEC on 31 July 2020[1] and reiterated on 9 December 2020[2], clinical data generated in SII's bridging study in India is to be considered along with data from clinical trials of the AstraZeneca/Oxford vaccine candidate in other countries, for grant of market authorisation.

Therefore, the SEC on 9 December 2020 instructed SII to submit the following data and information:

> "1. Updated safety data of the Phase II/III clinical trial in the country.
> 2. Immunogenicity data from the clinical trial in UK and India.
> 3. The outcome of the assessment of UK-MHRA for grant of EUA."

[1] https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/common_download.jsp?num_id_pk=MTE2Mg==

[2] https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/common_download.jsp?num_id_pk=MTI3NQ==

On 30 December 2020, the UK's MHRA provided temporary authorisation (under Regulation 174 of the Human Medicine Regulations 2012 which allows for rapid emergency regulatory approvals) to AstraZeneca/Oxford University's COVID-19 vaccine[3] for immunisation of individuals ≥18 years.

The SEC is meeting today to review the emergency approval application of SII, in addition to applications of two other companies. It has been reported that the SEC had sought additional information from SII regarding the data on the basis of which the MHRA made its assessment, the conditions of the temporary authorisation, factsheets related to the vaccine and prescribing information[4].

The UK's MHRA assessed the efficacy of the vaccine based on 131 events in 11,636 people (94% of whom were under 65 years of age) merging data across two trials from the UK and Brazil. In these data there are wide variations in the duration of the interval between dosing (ranging 4 weeks - 26 weeks) and also differences in the strength of the vaccine doses. There were also differences in the trial designs of the UK and Brazil trials.

The SEC and DCGI, will also be reviewing efficacy data from the UK and Brazil trials, alongside the safety and immunogenicity data of the Indian trial. Yet there are important differences of SII's Indian trial and the foreign trials of the AstraZeneca/Oxford vaccine. Further, we are unclear if SII has submitted the interim safety and immunogenicity data for all participants which is critical for assessment of the vaccine candidate in an Indian population and the purpose of the bridging study.

As you know, the COVISHIELD trial in India to assess safety and immunogenicity involves two standard doses of the vaccine candidate given 28 days apart[5]. There is in fact no corresponding efficacy analysis reported for such a dosing regimen in the published data of the UK and Brazil trials for the AstraZeneca/Oxford vaccine[6]. However an efficacy analysis for two standard doses administered at an interval of less than 6 weeks shows efficacy of 53·4% (95% CI: −2·5 to 78·8) based on analysis of 28 cases (in 3400 persons aged 18 – 55 years) in the UK and Brazil trials (Table 3 in the *Lancet* publication). While this efficacy estimate may not be particularly robust due to the small sample, it would fail to meet the criteria set out by the WHO for evaluation of COVID-19 vaccines for either prequalification or for Emergency Use Listing (EUL)[7] and draft guidelines of the CDSCO[8]. Even while the vaccine efficacy in participants with less than a 6 week interval between doses did not differ statistically from the vaccine efficacy in participants with more than a 6 week interval between doses (65.4%; 95% CI: 41.1 to 79.6; p interaction = 0·56), it certainly raises the need for more data.

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3 https://www.gov.uk/government/news/oxford-universityastrazeneca-vaccine-authorised-by-uk-medicines-regulator

4 https://economictimes.indiatimes.com/industry/healthcare/biotech/healthcare/sec-to-reconvene-on-january-1-to-consider-emergency-use-authorisation-for-covid-vaccines/articleshow/80026394.cms?utm_source=contentofinterest&utm_medium=text&utm_campaign=cppst

5 http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=46186&EncHid=&userName=CTRI/2020/08/027170

6 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32661-1/fulltext

7 https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/WHO_Evaluation_Covid_Vaccine.pdf

8 https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadPublic_NoticesFiles/Regulatory_guidelines_for__development_of_Vaccine_20.9.20.pdf

We therefore urge that:

- **The SEC and DCGI must undertake a thorough scientific examination of the efficacy data from foreign studies to determine congruence with Indian data and applicability to the Indian dosing regimen. In making its decision, the experts and regulator must also review the complete interim data for safety, immunogenicity of all participants from the SII Indian trial.**

- **In granting any restricted emergency use (REU) approval or emergency authorisation:**
  - **provide the legal provisions under which such approval is being granted**
  - **share the restrictions/conditions attached to the emergency approval**
  - **make public the data, evidence and information that was reviewed and the data and analysis on the basis of which approval was given**
  - **require SII and ICMR to publish interim data from the Indian trial**

Further, we reiterate our earlier requests to:

- Disclose the detailed clinical trial protocol for the Phase 2/3 bridging trial for COVISHIELD along with all amendments made to the protocol.
- 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
- 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. In this regard, we would like clarity regarding the draft guidelines of the CDSCO[9] which have not yet been notified.

India would play a very important role in terms of global supply of vaccines and meeting the needs of other countries, particularly in the developing world. It is important in this context that there is adequate transparency about the vaccines candidates being progressed in the regulatory approval process, on the trials and the data being generated.

We look forward to your urgent consideration of our concerns and recommendations.

Sincerely,

All India Drug Action Network

9 https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadPublic_NoticesFiles/Regulatory_guidelines_for__development_of_Vaccine_20.9.20.pdf

Copy to:

Dr. Balram Bhargava, Director General, ICMR
Ms. S. Aparna, Secretary, DOP, Ministry of Chemicals and Fertilizers
Dr. Renu Swarup, Secretary, Department of Biotechnology
Dr. Sunil Kumar, DGHS
Dr. Randeep Guleria, Director, AIIMS, New Delhi
Dr. Samiran Panda, Director, ICMR-National AIDS Research Institute
Shri Ajay Prakash Sawhney, Secretary, Ministry of Electronics & Information Technology
Dr. Shekhar C. Mande, Secretary, DSIR and DG, Council of Scientific & Industrial Research
Shri Dammu Ravi, Additional Secretary (Europe and COVID-19), Ministry of External Affairs
Dr. S. Eswara Reddy, Joint Drugs Controller (India), CDSCO
Shri A. K. Pradhan, DDC (I), CDSCO
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

For further information, contact:

Malini Aisola, 7838381185, malini.aisola@gmail.com
Chinu Srinivasan, 9998771064, chinusrinivasan.x@gmail.com
Siddhartha Das, das.seed@gmail.com