NATIONAL MEDICINES REGULATORY AUTHORITY, SRI LANKA
JANUARY 22, 2021

EVALUATION REPORT FOR EMERGENCY USE PERMISSION
COVID-19 Vaccine AstraZeneca (Covishield)

Name of Manufacturer	Serum Institute of India Pvt. Ltd
Name of the Local agent	Citihealth Imports (Pvt) Ltd, 29/3, Kirimandala Mawatha, Nawala, Rajagiriya, Sri Lanka
Generic name of Vaccine	ChAdOx1 nCoV-19 – a replication-deficient simian adenoviral vector expressing the spike (S) protein of SARS-CoV-2
Trade Name (Finished product	COVISHIELD

DETAILED REVIEW COMMENTS

SECTION – 01

PHARMACEUTICAL ASSESSMENT REPORT OF COVISHIELD VACCINE MANUFACTURED BY SERUM INSTITUTE (PVT) LTD, INDIA

This report is based on the information provided by company in a rolling data submission procedure and public assessment report of the MHRA. This evaluation was performed via the reliance regulatory pathway and covers pharmaceutical aspects required for emergency use supply of COVID-19 vaccine.

Submission of the dossier

Serum Institute (Pvt.) Ltd, India who manufactures the ChAdOx1 nCoV-19 vaccine for AstraZeneca Oxford vaccine submitted the documents through the Indian High Commission in Colombo on 19th January 2021.

Legal basis for review of the submission

- Section (109) of the NMRA Act No.5 of 2015, provides the Authority legal provisions to grant permission for emergency supply of a particular medicine in special circumstances including, to control an outbreak of an infection or an epidemic.

- In terms of Regulations No. 2149/25 for the issue of Lot Release Certificate for vaccines and sera No.1 of 2019, which provides Medical Research Institute (MRI) as the National Control Laboratory (NCL) to conduct lot release on all batches that would be supplied to Sri Lanka.

Eligibility of vaccine for expedited review

This vaccine is manufactured in a country with a functional NRA for vaccines (Central Drugs Standard Control Organization, India) as per WHO's Global Benchmarking Tool (GBT) for Government-to-

Government purchase agreements. Covid 19 vaccine manufactured by AstraZeneca has received emergency use authorization by the MHRA, UK, a stringent regulatory authority, recognized as a 'reference authority' by the NMRA, Sri Lanka. Vaccine manufacturing technology has been transferred from AstraZeneca (Sending Unit) to Serum Institute of India Pvt Ltd. Pune (Receiving Unit) under a technology transfer agreement.

Manufacturing Site

Manufacturing site of Serum Institute of India Pvt Ltd, 212/2, Hadapsar, Pune -411028, India has been already approved by National Medicines Regulatory Authority (NMRA), Sri Lanka.

The following documents have been enclosed with the submission:

- Valid GMP certificate (No. 6097571 of 15th January 2021) by Food and Drug Administration, Maharashtra State, Pune, India.
- Manufacturing permission (No. Drugs/Mfg./775-20/Z-3 dated 20th August 2020) by Food and Drug Administration, Maharashtra State, Pune, India.
- Manufacturing permissions (No. MF/BIO/21/000001 dated 3rd January 2021) by Central Drugs Standard Control Organization, India.
- Emergency use authorization issued by Central Drugs Standard Control Organization, India (No. MF/BIO/21/000001 dated 3rd January 2021).

Introduction

The SARS-CoV-2 virus uses proteins on its outer surface, called spike (S) proteins, to enter the cells of the body and cause disease. The active substance of COVID-19 Vaccine AstraZeneca is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector that codes for the S glycoprotein of SARS-CoV-2 (ChAdOx1-S [recombinant]). Following vaccine administration, this vector enters into the cells of the body and produces the S glycoprotein of SARS-CoV-2 which is then expressed on the surface of the cells. Expression of the spike protein induces neutralizing antibodies and T-cells to be raised against it. Should the body then become infected with SARS-CoV-2, the immune system will recognize the SARS-CoV-2 virus and attack the pathogen.

The ChAdOx1 nCoV-19 vaccine manufacturing technology has been received from AstraZeneca (Sending Unit) by Serum Institute of India Pvt Ltd. Pune (Receiving Unit). The Technology Transfer report provides a summary of the transfer of knowledge, documentation of manufacturing process comprising of bulk, filling, packing, testing and release by sending unit (SU).

Following an extensive review of the quality, safety, immunogenicity and efficacy data, COVID-19 Vaccine manufactured by AstraZeneca, the Medicines and Health Care Products Regulatory Authority (MHRA), UK, has granted emergency use authorization (EUA) in the UK on 29 December 2020. This EUA allows temporary supply of COVID-19 Vaccine manufactured by AstraZeneca for use in UK for the following indication:

- Active immunization of individuals ≥18 years old for the prevention of coronavirus disease 2019 (COVID- 19). AstraZeneca COVID-19 Vaccine is a solution for injection stored at 2-8°C and intended for intramuscular administration (IM). A single 4 ml vial contains 8 doses (each 0.5 mL) and a single 5 mL vial contains 10 doses (each 0.5 mL).

Product Development

COVID-19, the disease caused by SARS-CoV-2, was first identified in late 2019 and spread to a global pandemic by March 2020. Oxford University developed ChAdOx1 nCoV-19 vaccine (AZD1222) against COVID-19 and entered into global license agreement with AstraZeneca Pharmaceuticals for further development and manufacturing. Serum Institute (Pvt) Ltd, India (SIIP) has a sublicense to manufacture this vaccine. ChAdOx1 nCoV-19 vaccine technology consist of replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 spike (S) surface glycoprotein with a leading tissue plasminogen activator (TPA) signal sequence. S is a type I, trimeric, transmembrane protein located at the surface of the viral envelope, giving rise to spike shaped protrusions from the virion. The S proteins subunits are responsible for cellular receptor ACE-2 binding via the receptor-binding domain and fusion of virus /to cell membranes, thereby mediating the entry of SARS-CoV-2 into the target cells. The S protein has an essential role in virus entry and determines tissue and cell tropism, as well as host range. The roles of Spike protein in receptor binding and membrane fusion make it a perfect target for vaccine and antiviral development.

Oxford University has conducted pre-clinical trials and awarded a subcontract to AstraZeneca for manufacturing and testing of ChAdOx1 nCoV-19 vaccine. Initial manufacturing in UK was by Advent.

The pre-GMP VSS starting material was transferred from Oxford to Advent. After confirming the identity and suitability of the pre-GMP starting material, Pre-GMP material, pre-GMP VSS ChAdOx1 nCoV-19 D8 Amp 4.1&.2, was amplified in the Advent GMP facility to generate lot K.0005. The detailed plan and execution of MVB is part of the development report.

Master Cell Bank (MCB HEK293TR 3G11) was generated and tested under GMP conditions by BioReliance MA, USA. This MCB was used as the starting material for virus bank manufacture and Clinical lot production.

Further, Development Report summarizes the details of development performed at the Advent to manufacture ChAdOx1 nCoV-19 vaccine. On the basis of the information shared by the Oxford University, manufacturing process was designed first at 200L scale with final harvest volume at 100L. From this batch, Master Seed Bank (MSB) was prepared by splitting the 100L batch to 10L for MSB and remaining 90L for preparation drug product. Manufacturing of AZD1222 ChAdOx1 nCoV-19 bulk concentrated solution (Drug Substance) production includes cell culture process (upstream) and purification (downstream). The formulated drug substance is aseptically filtered using 0.2µ filter and stored at 2 to 8°C. The drug substance concentration was adjusted with formulation buffer to formulate Drug Product (DP). Filling is performed in USP Type-1 glass vial under controlled environmental conditions and the DP is stored at 2 to 8°C. Stability studies are ongoing.

Quality aspects

The information is based on data submitted by Serum Institute of India with appropriate comparability and validation data of AstraZeneca UK manufacturing operation. Quality aspects of the vaccine were reviewed on a batch specific basis.

Active Substance

The active substance is clear to slightly opaque solution. Manufacture, process control and characterization of drug substance, control of materials, control of critical steps and intermediates of active substance has been done by Serum Institute (Pvt) Ltd, India under the technology transfer

from AstraZeneca -UK.
Serum Institute has provided comparative data on following,

- Seed - Virus seeds received from AstraZeneca as well as Master Virus seed
- Fermentation
- Clarification

The vaccine is produced in genetically modified human embryonic kidney (HEK) 293 cells.

Manufacturing of drug substance

The manufacturer has provided details of the responsibilities of each facility involved in manufacture and testing including responsibilities performed by contract laboratories. A description of the manufacturing process and controls has been provided for each manufacturing site, including material inputs, critical and non-critical process parameters, and process outputs. The upstream process consists of working host cell bank vial thaw, inoculum expansion, infection with working virus seed and further expansion in the production bioreactor to generate ChAdOx1-S (recombinant). The downstream process consists of lysis of the production bioreactor cell culture, nuclease digestion of the host cell DNA, clarification and further processing through a series of purification/concentration steps to remove process-related impurities and then formulation with excipients and aseptic filtration.

Validation of manufacturing process of drug substance has been submitted. The information provided has been evaluated and found to be satisfactory.

All material (raw materials, equipment and consumables) used in manufacturing of ChAdOx1-nCoV19 drug substance does not contain any materials that can be considered specified as TSE or BSE risk material. In process safety testing is performed at the end of manufacturing of every drug substance batch.

Stability of the drug substance

ChAdOx1-nCoV19 bulk concentrated solution (i.e. Drug Substance) batches are filled in sterile single use disposable bags (ULDPE) and are stored at 2-8°C in designated monitored cold rooms. The recommended storage temperature of bulk concentrated at long term storage is at or below -60 ºC. Additionally, stability of bulk concentrated at or below -20 ºC is being studied, as an additional exploratory study. The details pertaining to the batches kept on stability and the available stability data are provided in Control of materials. Stability data of commercial batches for bulk concentrated solution is given for 2.5 months.

Finished Product

The vaccine is produced in genetically modified human embryonic kidney (HEK) 293 cells. COVID-19 Vaccine AstraZeneca contains genetically modified organisms (GMOs). In addition to ChAdOx1-S (recombinant) this product also contains the excipients L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose, sodium chloride, disodium edetate dihydrate and water for injections. (There is no change in excipients used)

The finished product is packaged in multidose vials containing 5 ml of solution in a 10-dose vial (clear type I glass) with a bromobutyl rubber stopper and an aluminum overzeal with a plastic flip-off cap (in packs of 10 vials). This product is a colorless clear to slightly opaque solution. There are two pack sizes i.e. 50 multi dose vials in a pack and 300 multi dose vials in a pack. Draft labels are submitted and is acceptable.

Description of manufacturing process, characterization and process controls for the SIPI product has been provided and is satisfactory. All the processing equipment and consumables used in manufacturing of drug product do not contain any materials that considered specified TSE or BSE risk material.

The raw materials used in the manufacturing of the drug product are of synthetic origin hence does not pose TSE or BSE risk.

Packaging materials specifications (IP/Inhouse) and test data (COAs) are provided.

Stability data

Stability study protocol, test results with conclusions have been provided.

- The in-use stability results demonstrated that the vaccine in multi-dose container is physically and chemically stable for 6 hours at 2-8^{o}C after withdrawal of the first dose.
- Accelerated and real time stability data for commercial batches are ongoing and data submitted for 2 months. The manufacturer has committed to conduct stability studies for 24 months.

Lot release

Lot release certificate (CDL/2020/8154, 7th December 2020) issued by Central Drugs Laboratory India has been submitted for 12 batches under EUA granted by NRA in India.

Comparability of two products

All data provided for lot release and characterization of the drug product comparative studies meet the pre-defined comparability assessment criteria and demonstrate product manufactured by Serum Institute (Pvt) Ltd, India, clinical and commercial lots are comparable to the Oxford AstraZeneca drug product clinical as well as commercial lots.

Conclusion

Company has provided sufficient information to make a decision on the vaccine via the reliance regulatory pathway. Quality of this medicinal product submitted in the emergency context of the current COVID-19 pandemic is considered to be sufficiently consistent and acceptable. Comparability with the AstraZeneca UK product has been satisfactorily documented.

Information provided by serum Institute India assures acceptable standards are in place at all sites responsible for manufacture, analysis, and assembling and batch release of this product.

SECTION – 2

CLINICAL EVALUATION OF COVISHIELD VACCINE MANUFACTURED BY SERUM INSTITUTE (PVT) LTD, INDIA

Data from pre-clinical studies as well as phase I, II and III clinical trials were evaluated. Results of clinical studies of AZD1222 (manufactured by AstraZeneca) have been published in peer-reviewed journals. In addition to the published data, a report from ongoing bridging phase III study in India of 1600 participants submitted by Serum Institute, which contained only preliminary safety and immunogenicity data with descriptive analyses was also reviewed. COVID-19 Vaccine AstraZeneca has been given to approximately 24,000 individuals aged 18 years or older in multi-centre phase III clinical trials (results published). In pre-specified preliminary analyses, those who received the vaccine had a reduction in the rate of COVID-19 illness compared to those who received the control (30 cases of COVID19 illness in the vaccinated group compared to 101 cases in the control group). These results were observed two weeks or more after the second dose in study participants with no evidence of prior SARS-CoV-2 infection.

Overall efficacy of the vaccine is 62% with the standard dose regime. At present, there is limited data to assess vaccine efficacy and the precise level of protection in the >65 age group. However, the immune response in this age group is comparable to that of younger age groups. Limited data from the phase III study also suggests efficacy is greater when the gap between the two doses was wider, especially when the gap was more than 8 weeks (efficacy is 53·4% when dosing interval is < 6 weeks and 65.4% when it is > 6 weeks).

In vivo animal safety testing with the AZD1222 vaccine has been conducted and it was well tolerated with no adverse findings. In the animal studies, the vaccine did not cause vaccine enhanced disease.

There are no major safety concerns regarding this vaccine. The most common side effects with COVID-19 Vaccine AstraZeneca (which may affect more than 1 in 10 people) were tenderness, pain, warmth, redness, itching, swelling or bruising where the injection is given, generally feeling unwell, feeling tired (fatigue), chills or feeling feverish, headache, feeling sick (nausea), joint pain or muscle ache. In clinical studies, most side effects were mild to moderate in nature and resolved within a few days with some still present a week after vaccination.

RECOMMENDATIONS

COVID-19 Vaccine AstraZeneca (manufactured by Serum Institute – Covishield) has been shown to be effective in the prevention of COVID-19. Furthermore, the side effects observed with use of this product are considered to be similar to those seen for other vaccines. Therefore, the benefits of this vaccine are greater than the risks.

Therefore, it is recommended that permission for emergency use be granted to Covishield vaccine for temporary supply during the COVID-19 pandemic. There should be continuous monitoring of safety data.