



RECOMMENDATION FOR AN EMERGENCY USE LISTING OF ON COVISHIELD™ SUBMITTED BY SIIPL

Abstract

The active ingredient of COVISHIELD™ [previously known as ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)] consists of a recombinant, replication-deficient simian adenovirus that encodes the SARS-CoV-2 spike protein with a tissue plasminogen activator (tPA) leader sequence. The applicant, Serum Institute of India Pvt. Ltd. (SIIPL), has submitted a Common Technical Document format application to the World Health Organization (WHO) for evaluation under the Emergency Use Listing (EUL).

The vaccine is the result of a cooperation and a technology transfer from AstraZeneca – University of Oxford to SIIPL.

COVISHIELD™ is indicated for active immunisation of individuals aged 18 years and older for the prevention of coronavirus disease 2019 (COVID-19).

The use of COVISHIELD™ under an emergency situation has been endorsed by the Drugs Controller General of India by an authorization for restricted emergency use approval issued on 3 January 2021.

This report was prepared by the product evaluation group (PEG) to be discussed by the technical advisory group for emergency use listing (TAG-EUL).

1 Introduction

1.1 Background

The current COVID-19 pandemic is unprecedented in the 21st century and the global response draws on the lessons learned from other disease outbreaks over the past several decades.

On 30 January 2020, following the recommendations of the Emergency Committee, the WHO Director-General declared that the outbreak constitutes a Public Health Emergency of International Concern (PHEIC).

Scientists around the world on COVID-19 met at the World Health Organization's Geneva headquarters on 11–12 February 2020¹ to assess what is known about the new severe acute respiratory coronavirus - 2 (SARS-CoV-2) virus, agree on critical research questions that needed to be answered urgently, and find ways to collaborate to accelerate and fund priority research to curtail the pandemic.

¹ <https://www.who.int/news/item/12-02-2020-world-experts-and-funders-set-priorities-for-covid-19-research>

The discussion led to an agreement on two main goals. The first was to accelerate innovative research to help contain the spread of the epidemic and facilitate care for those affected. The second was to support research priorities that contribute to global research platforms for the current pandemic response in order to be better prepared for the next epidemic.

The WHO Research & Development (R&D) Blueprint² aims to improve coordination between scientists and global health professionals, accelerate the research and development process, and develop new norms and standards to learn from and improve the global response. Building on the response to recent outbreaks of Ebola virus disease, SARS-CoV and MERS-CoV, the R&D Blueprint has facilitated a coordinated and accelerated response to research into diagnostics, vaccines and therapeutics for the novel disease. This led to the establishment of an unprecedented program to develop a vaccine and strengthened channels for information sharing between countries.

1.2 COVID-19 vaccines

The current global COVID-19 public health emergency underscores the need to accelerate the development of COVID-19 candidate vaccines. The vaccine prioritization agenda has a public health and a vaccine component. The strategy includes the prioritization of vaccine platform approaches and/or candidates to be considered not only for development but also for evaluation in the context of the global COVID-19 outbreak. The COVID-19 vaccine pipeline of candidate vaccines for COVID-19 is reviewed and updated continuously. The vaccine development is carefully reviewed and discussed in order to assess their value in protecting against COVID-19 and a potential recommendation of use based on a careful benefit - risk approach.

The information available on COVID-19 candidate vaccines³ and the new coronavirus (nCoV) epidemiology is closely monitored. The various technology platforms that are developed based on nucleic acids (both mRNA and DNA), viral vectored vaccine (e.g. MVA, VSV, Ad/ChAd), subunit proteins and the traditional platform of inactivated virus are reviewed. Some of the platforms may be easier and faster to manufacture at scale while other platforms may elicit a more rapid and robust protection. Technology platforms for which clinical experience, safety data and demonstrated usability already exist, could allow a more rapid advancement into final phases of clinical trials. The current epidemiological scenario is becoming increasingly complicated with the surge of virus variants due to mutations associated with increased viral transmission and the spread of COVID-19. These variants make effective changes in the virus's 'Spike' protein, which the virus uses to enter human cells and some of these variants are posing real challenges for vaccine's efficacy.

Vaccines that could exert protective immunity after a single dose are preferred, however most of the current candidate vaccines for COVID-19 require two doses.

² <https://apps.who.int/blueprint-brochure/>

³ <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>

1.3 Emergency Use Listing

The Emergency Use Listing (EUL) is a time limited risk-benefit assessment for emergency use of vaccines, medicines and in vitro diagnostics during a PHEIC when limited data are available and the products are not yet ready for licensure and WHO prequalification. As the EUL is time-limited in nature, the applicant is still expected to complete the development of the product and submit application for licensure and prequalification.

The issuance of an EUL for a product reflects WHO's recommendation for emergency use following a robust scientific risk benefit assessment. However, each WHO Member States has the sole prerogative to allow the emergency use of a product under an EUL within their country.

2 Assessment process

COVISHIELD™ manufactured by SIIPL was assessed under the WHO EUL procedure based on the review of data on quality, safety, efficacy, risk management plan (RMP) and programmatic suitability performed by WHO Vaccine Prequalification experts and evaluators from National Regulatory Authorities (NRAs) from different countries and regions.

Emphasis was placed on the risk-benefit of the vaccine and therefore on the RMP because of the need to consider the perspectives and concerns of regulators from different regions, that might otherwise not be considered by the NRA of reference for WHO – whose assessment is expected to be focused on issues related to its own jurisdiction.

The NRA of reference for WHO for this submission is the Drugs Controller General of India (DCGI) - Central Drugs Standard Control Organisation (CDSCO) of the Republic of India. The information package submitted to WHO followed the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Common Technical Document (CTD).

During the assessment of the vaccine dossier, WHO assessors were able to interact and exchange scientific opinions with scientists of Health Canada, as part of the collaboration and confidentiality agreement signed between WHO and that regulatory agency.

3 Scientific Review

3.1 Quality Overview

ChAdOx1 nCoV-19 is a recombinant replication-deficient chimpanzee adenovirus carrying a gene encoding the S protein antigen of SARS-CoV-2. The S protein antigen gene is expressed once the recombinant adenovirus enters the cells of a vaccinated individual. The recombinant adenovirus is propagated and manufactured using the T-REx-293 permissive host cell line, which was derived from a HEK293 cell line.

The ChAdOx1 vector was derived from the chimpanzee adenovirus Y25. The ChAdOx1 vector is replication-deficient as an essential gene for viral replication has been deleted. The T-Rex™-293 cell line is used as the host for the production of the virus seeds and the manufacture of the COVISHIELD™ Drug Substance (DS).⁴

As previously described, COVISHIELD™ is the result of a technology transfer from the University of Oxford / AstraZeneca (AZ) to SIIPL. Documentation on the Technology Transfer requirements along with the gap analysis (product / process / equipment / technology) is provided in the dossier. Additionally, the Technology Information Verification Report signed by AZ is also provided along with key SIIPL Personnel Training Certificates.

The Module 3 of the CTD submitted 13 January by SIIPL consists of information related to the development, production and control of ChAdOx1 nCoV-19 bulk concentrated solution and the Drug Product (DP).

The manufacturing process of the vaccine includes the manufacturing of the of ChAdOx1 nCoV-19 bulk concentrated solution which is the DS. This procedure is comprising mainly of:

1. Cell Propagation (preparation of seed for virus infection)
2. Infection with Virus Seed
3. Harvesting and Clarification
4. Purification of bulk virus harvest

The bulk obtained at the last stage of manufacturing is 0.2µ filtered and stored in Ultra Low-Density Polyethylene (ULDPE) single-use bags and stored at 2 - 8°C. Currently, SIIPL does not store the DS for more than 1 or 2 weeks because it is immediately used to formulate DP.

Submitted data support two months of stability when the DS is stored at -60 °C and -20 °C in ULDPE bags. Stability studies are on-going as per approved protocols. Once supportive data will be available, shelf-life will be defined at the approved storage condition.

The DS is manufactured at commercial scale in building SEZ-6 and building SEZ-7. Once manufactured, the DS is then transferred for formulation and filling. The day on which the filling activity is initiated is assigned as date of manufacturing to respective batch(es) of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant).

The information assessed for the DS and the DP included:

1. Pharmaceutical development;
2. Development and description of the manufacturing process, process control and critical steps and control;
3. Process validation or evaluation;
4. Comparability (process, specifications, batches)

⁴ [van Doremalen et al \(2020\) Nature 586, pages 578–582](#)

5. Specifications, justification of the specifications and quality control, including description and validation of analytical methods;
6. Reference materials;
7. Batch analysis;
8. Characterization of impurities and justification of specifications;
9. Container-closure system;
10. Stability and stability commitments;
11. Information facilities and key equipment used in the manufacturing of the vaccine.

The DP is a sterile liquid dosage form for administration by intramuscular injection, 0.5 mL per dose. It is a colourless to slightly brown, clear to slightly opaque and particle free with a pH 6.1 to 7.1.

ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) stability studies are ongoing and include several commercial scale batches. These stability studies are being performed to evaluate impact on stability indicating parameters and to establish shelf-life based on the stability results at long-term/real time and accelerated conditions. Based on the stability data (real time and accelerated) at the time of this EUL submission, the DP shelf-life is 6 months at 2 - 8°C, from the date of manufacturing.

3.2 Non-clinical overview

SIIPL has not conducted any non-clinical study beyond those conducted by AZ, whose findings are briefly addressed below.

AZ has almost completed the nonclinical studies submitted to support the EUL of AZD1222. AZD1222 was shown to be immunogenic in several animal models (mice, ferrets, pigs and non-human primates) either when administered in a single dose or in two doses, with better antigen-specific antibody (including neutralizing antibody) response and T cell responses after the latter. An important nonclinical study was a post-vaccination SARS-CoV-2 challenge in rhesus macaques in which a single administration of AZD1222 showed a significant reduction in viral load in bronchoalveolar lavage fluid and respiratory tract tissue of the vaccinated NHPs. No evidence of vaccine-associated enhanced respiratory disease (VAERD) was detected in the vaccinated NHPs.

Biodistribution studies in mice confirmed the findings of previous studies conducted with other ChAd vaccine candidates, having shown no evidence of replication of the adenovirus or presence of disseminated infection. The applicant proposed that given that AZD1222 is made with the same platform of other investigational vaccines, advantage can be taken from these toxicologic studies.

No AZD1222-related changes in arterial blood pressure, heart rate, body temperature or respiratory parameters were observed in a mouse cardiovascular and respiratory safety pharmacology study.

AZD1222 was well tolerated in a repeat dose toxicity study in CD-1 mice. Anti S glycoprotein antibodies were raised and maintained throughout the dosing and recovery periods in all the animals exposed to AZD1222. In these animals, higher spleen weights were observed but with no histological changes. At the vaccine administration sites inflammatory findings were observed, consistent with those anticipated following intramuscular injections.

No AZD1222-related effects were observed in a preliminary developmental and reproductive toxicology (DART) study conducted in mice.

In brief, AZD1222 (and similar ChAd vaccines) were well tolerated and shown to be immunogenic in several animal models. Rhesus macaques vaccinated with AZD1222 had significantly reduced viral load when challenged with SARS-CoV-2 and there is no evidence of VAERD in these animals.

3.3 Clinical overview

Clinical data submitted by SIIPL is the same presented by AZ except for the addition of an interim analysis of an ongoing bridging study which compares the immunogenicity and safety of COVISHIELD™ with AZD1222 and placebo. This study is being conducted in India by request of the Indian regulatory authority DCG(I).

3.3.1 Vaccine efficacy

AZ submitted an interim pooled analysis conducted in the primary efficacy population of one phase 2/3 clinical trial conducted in the UK (COV002) and another phase 2/3 trial conducted in Brazil (COV003). There was a median follow-up of 19 weeks after Dose 1 and 9 weeks after Dose 2. AZ claims an overall vaccine efficacy of 70.42% (95.84% confidence interval [CI]: 54.84, 80.63) against symptomatic COVID-19, calculated for two standard doses of the vaccine (SDSD regimen) or for one low dose followed by a standard dose (LSDS regimen). The vaccine efficacy when the analysis was restricted to individuals who received two standard doses of AZD1222 was 62.10% (95.84% CI: 39.96, 76.08). Vaccine efficacy estimates for the UK and Brazil were, respectively, 73.52% (95% CI: 55.50, 84.24), and 64.17 (95% CI: 30.65, 81.49). Complete protection was observed against COVID-19 hospital admission (WHO Severity Grading ≥ 4) ≥ 22 days after the first vaccine dose (0 versus 9 cases in the control group, two of which were considered severe cases and one was fatal). For the participants who received the SD regimen of AZD1222 protection was shown to begin from 22 days after the first dose and to extent at least until 12 weeks, which the applicant considers to allow flexibility for the second vaccine dose to be given 4 to 12 weeks.

Vaccine efficacy could not be reliably determined in older adults (≥ 65 years) given that the number of events was too low for that age group in the available follow-up time. Adults with pre-existing comorbidity had similar vaccine efficacy as the general population. AZ claims that the available efficacy data together with the immunogenicity data (see 3.3.3 Immunogenicity, below) support the use of an AZD1222 vaccine regimen of two standard doses (SDSD) given between 4 and 12 weeks apart in the elderly (≥ 65 years) and people with comorbidities.

3.3.2 Vaccine safety

An interim pooled analysis was conducted with data from COV001 and COV002 trials (both carried out in the UK, COV003 (conducted in Brazil) and COV005 (conducted in South Africa). The safety data base included 23 745 participants, of whom 12 021 received at least 1 dose of AZD1222, and of whom 11 723 received at least one dose of control. The median follow-up for the AZD1222 and the control groups

were, respectively, 105 and 104 days. AZD1222 was well tolerated, with most local and systemic adverse events (AEs) being mild to moderate, and even milder and less reported after the second dose compared to the first one. Among the solicited AEs (considered as adverse drug reactions - ADRs) the most commonly observed were headache, nausea, myalgia, arthralgia, fatigue, malaise, feverishness, chills, fever and local injection site reactions. According to the applicant, unsolicited AEs were consistent with those commonly observed following vaccination. Preferred terms (PTs) not commonly associated with vaccination were relatively balanced in the vaccine and control groups.

The incidence of serious adverse events (SAEs) was <1% in both the AZD1222 and the control groups, and the frequency and type of SAE also did not differ between them. A total of 6 fatal SAEs were observed (2 of them in the AZD1222 group), none of them considered by the investigators as causally related to the study interventions. Few adverse events of special interest (AESIs) were registered, 0.8% and 1.1% in the AZD1222 and the control groups, respectively. No clear imbalance in the incidence of AESIs by category or PT was observed that could suggest an association with AZD1222.

Paresthesia, hypoaesthesia, and muscular weakness were the most frequently observed PTs within the categories of neurologic events and potential immune-mediated neurologic conditions, and were less common in the AZD1222 group. Facial paralysis was reported in 3 patients in each group. Three SAEs of demyelinating events were reported, 2 in the AZD1222 group (1 case of transverse myelitis and 1 case of multiple sclerosis in a patient who already had the disease before enrolment in the study, which was unrecognized at the time).

There was no evidence of an association of AZD1222 and PTs related to possible vaccine-associated enhanced disease (VAED), which were reported in a slightly smaller percentage of participants in the AZD1222 group than in the placebo group.

The safety profile was comparable when the participants were stratified by comorbidity, country or serostatus subgroup. This was also comparable in older adults and in adults aged 18 to 64 years, but older adults reported milder and less frequent solicited reactogenic AEs.

The data from the interim analysis of the bridging study in healthy Indian subjects support that COVISHIELD™ has a similar reactogenicity and safety profile compared to AZD1222.

3.3.3 Immunogenicity

AZD1222 was highly immunogenic, with a seroconversion of binding antibodies >97% and of live virus neutralizing antibodies >80% after a single standard dose (SD) or low dose (LD), and >99% of both antibodies after a second SD. Seroconversion for both binding and neutralizing antibodies increased with increasing dose interval between the first and second vaccine dose. The applicant has interpreted this finding as supportive of the finding of increased efficacy across the dosing interval of 4 to 12 weeks.

Immunogenicity in vaccinated participants with comorbidities was similar to that observed in the general population. In older adults (≥65 years) the rates of seroconversion to binding and to live neutralising antibodies were similar to those found in younger adults, however their absolute titres tended to be lower.

The applicant took into consideration the immunogenicity data together with the efficacy data, to support their recommendations for the use of AZD1222 (see 3.3.1 Vaccine efficacy, above).

The interim analysis of the immunogenicity data of the Indian study indicates that COVISHIELD™ elicits similarly high anti-spike IgG antibody response as AZD1222.

3.3.4 Special populations

Regarding special populations, as mentioned above, efficacy in individuals over 65 years of age could not be assessed due to small numbers. AEs were generally milder and less frequent in older participants. Older adults reported milder and less frequent solicited reactogenic AEs.

Persons with severe immunodeficiency, severe underlying disease, and pregnant/lactating women were excluded from the studies, therefore efficacy, immunogenicity and safety of AZD1222 in these groups is currently unknown. Although data from Brazil and South Africa have been submitted by AZ, not all available data may be generalizable to populations in low and middle-income countries (LMIC) who have profiles that can impact on the efficacy of this vaccine (for example, ethnicity, concomitant infections and malnutrition).

3.4 Risk Management Plan

3.4.1 Product description

COVISHIELD™ is a preservative free sterile solution for injection, to be administered by an intramuscular injection of 0.5 mL. It is a colourless to slightly brown, clear to slightly opaque and particle free with a pH 6.1 to 7.1. presented in USP Type I clear glass vials (2 and 10 doses of 0.5 mL), stoppered with 13 mm grey coloured elastomeric stopper and sealed with 13 mm flip-off coloured plastic cap. Currently, there is no supporting data to assign a Vaccine Vial Monitor (VVM). Currently, the additional stability data required to support the assignment of Vaccine Vial Monitor (VVM) have not been generated yet. SIPL is committed to achieving this exercise in order to eventually assign a VVM to the vaccine.

3.4.2 Nonclinical information

Acceptable.

There are two ongoing studies, with no impact expected in the safety profile. No additional information is required.

3.4.3 Clinical information

a. Important identified risks:

Identified risks proposed by	SIIPL	WHO
None	√	√

b. Important potential risks:

SIIPL	WHO	Comments
Immune-mediated neurological conditions	Neurological System disorders, including Immune-mediated neurological conditions	Immune-mediated neurological conditions have been changed to Nervous system disorders including Immune-mediated neurological conditions in the last evaluation by CHMP Rapp team (AR dated 17.01.2021)
Vaccine-associated enhanced disease (VAED)	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	There is a theoretical concern that vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes which would manifest as VAED. Although available data have not identified VAED as a concern for AZD1222, the risk of VAED cannot be ruled out. VAED may be potentially serious or life-threatening, and requires early detection, careful monitoring, and timely medical intervention.
	Anaphylaxis	Anaphylaxis is known to be possible with any injectable vaccine. Anaphylaxis can be upgraded to an identified risk based on the outcome of the assessment of the clinical data of ongoing studies or post-marketing information. A minimum period of 15-minutes of observation is recommended for each vaccinee after vaccination, given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions
	Programmatic errors	Vaccine administration errors were a protocol deviation during clinical trials, such errors were noted to be relatively infrequent by the sponsor. However, it may be necessary to minimize this situation in advance under real use conditions.

c. Missing information:

AZ	WHO	Comments
Use during pregnancy and while breastfeeding	Use during pregnancy and while breastfeeding	Pregnant and lactating women not included in the clinical trials
Use of AZD1222 in subjects with severe immunodeficiency or requiring immunosuppressive medications.	Use in immunocompromised patients, including people living with HIV	Immunocompromised individuals not included in the clinical trials. The data in this population is limited and it is possible that immune response to the vaccine may be different and compromise the effectiveness.
Use of AZD1222 in subjects with severe and/or uncontrolled underlying disease	Use of AZD1222 in subjects with severe and/or uncontrolled underlying disease	These individuals have not been included in the clinical studies but are theoretically likely to be at risk for severe COVID-19.
	Use of AZD1222 in frail patients with comorbidities (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disease)	Frail individuals have not been included in the clinical studies, but old frail individuals have been prioritized for vaccination in practice
Interchangeability and interactions with other vaccines	Interaction with other vaccines	The safety, immunogenicity, and efficacy of this vaccine when co-administered with other vaccines (e.g. influenza) has not been evaluated.
	Interchangeability or sequential use with other vaccines	The evidence to support interchangeability or sequential use of AZD1222 with other* COVID-19 vaccines is still not available. There are proposed heterologous prime/boost studies with vaccines already approved for emergency use in some countries. *The SIIPL vaccine (COVISHIELD), which is a technology transfer of AZD1222, is not considered a different vaccine.
	Use in pediatric population <18 years of age	There are some ongoing studies in this age group, but the results are still not available and AZ1222 is currently not recommended for this population.
	Use in patients with autoimmune or inflammatory disorders	Use in patients with autoimmune or inflammatory disorders should also be considered missing information. Although patients with autoimmune or inflammatory disorders were not explicitly

		excluded from the clinical studies, the use in this subgroup of patients should be described as one of the subgroups with severe co-morbidities as recommended
	Long-term safety	Long-term safety profile of AZD1222 is currently limited and it is recognized that further follow-up for all vaccines is required. Additional activities will be needed to obtain such information.
	Vaccine effectiveness and safety in very old (e.g. 85+) individuals;	Vaccine effectiveness and safety in very old individuals (e.g. 85+) has not been demonstrated but may be addressed by observational studies [e.g. “A post-authorization/post-marketing retrospective cohort study to evaluate the effectiveness of the AZD1222 vaccine to prevent serious COVID-19 infection in conditions of usual care (D8111R00005 [EU/UK])”].
	Impact of the emergence of variants on vaccine efficacy/effectiveness and safety	AZ should provide to WHO any data on new emerging variants particularly from vaccine breakthrough cases as soon as available, irrespective of source.

3.4.4 Pharmacovigilance Plan

Routine pharmacovigilance activities: The Pharmacovigilance Plan does not provide details concerning routine pharmacovigilance measures and safety reporting.

In general, adverse reactions reporting and signal detection should be in accordance with national and international Good Pharmacovigilance (GPV) guidelines. The spontaneous reporting should be harmonized in most of the countries with the VigiBase platform. The Applicant provides a very general description of standard pharmacovigilance activities. No consideration is given to the fact that COVISHIELD™ is a novel vaccine, that vaccinations will occur during a pandemic, or to the challenges of handling an increased volume of pharmacovigilance reporting following a massive vaccination campaign. Therefore, the applicant should provide a more detailed description of pharmacovigilance activities and methods (i.e. methods for signal detection and evaluation, individual case safety reports) including challenges related to restrictions during the pandemic (e.g. limited medical resources) and plans to handle an increased volume of reporting associated with a mass vaccination campaign.

There is a general concern about the collection of AEs in low- and middle-income countries (LMICs) of certain regions, because of the need for adequate pharmacovigilance systems. The possible role of the sponsor in these activities should be explained.

The monitoring of AE of interest should consider Bell’s palsy, transverse myelitis, multisystem inflammatory syndrome following vaccination and all serious adverse events.

For signal detection a mechanism for traceability and cold chain information needs to be established. Routine pharmacovigilance activities should be implemented in all WHO regions, including at least a card with the date when the recipient needs to return for the vaccine second dose, the name of the recipient, the name of the vaccine, batch number, and a telephone number where to report side effects. The sponsor needs to inform WHO about their plans to implement the routine pharmacovigilance plan in all WHO regions.

Proposed routine pharmacovigilance activities are inadequate to address the missing data. Additional pharmacovigilance activities such as clinical or epidemiological (non-interventional or interventional studies) studies may be needed, although the applicant does not consider them necessary. However, this new vaccine requires an additional activity because of the lack of long-term safety information and the surge of new SARS-CoV-2 variants to which vaccine effectiveness could be lower. It is also important to consider vulnerable populations like pregnant women, people living with HIV, and the elderly.

AZ proposed five non-Interventional studies in the pharmacovigilance plan, listed below, are likely to provide important safety and effectiveness information applicable to COVISHIELD™: Enhanced Active Surveillance.

1. Enhanced Active Surveillance study;
2. AZD1222 Pregnancy Registry. At least one country of each WHO region would preferably be included.
3. Post-marketing observational study using existing secondary health data sources.
4. Post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency.
5. Post-marketing Effectiveness Study. If feasible, countries from the different WHO regions should be included.

However, LMICs are not well represented in these studies, and no additional pharmacovigilance activities are planned for other WHO regions.

3.4.5 Risk minimization activities

The routine risk minimization activities are sufficient to manage the safety concerns of the medicinal product. The applicant should implement these in all WHO regions and ensure the feasibility to measure these in all countries

4 Outcome of review

4.1 Quality

As a result of the assessment conducted by WHO, the interactions with the applicant during pre-submission meetings in order to address key questions, the interaction with regulators from other NRAs, as well as clarifications and additional documentation provided by SIIPL, outstanding issues have been resolved. In addition, the applicant is committed to provide more information and data as soon as these are generated. This could be very important to address some uncertainties around the specifications that

may be acceptable in the context of the EUL. Also, considering the public health crisis and urgent need, it will be unlikely that vaccines will be stored to their end of shelf life (expiration date).

The finished product specifications include a comprehensive set of relevant tests along with corresponding acceptance criteria. However, although the vaccine specifications were adopted from those developed by and for the AZ vaccine, acceptance limits should be re-assessed, and revised as appropriate, as further experience is gained (see comment above).

The currently available set of validation data for the commercial process at the different facilities (SEZ-6, SEZ-7) are reassuring. Results of performance outputs are within acceptance criteria and also the process parameters remain within their acceptance criteria or range. The data presented demonstrate process consistency, quality and comparability to batches manufactured by Oxford - AZ, sufficient to support the EUL for this product.

4.2 Clinical

This clinical assessment of the AZ COVID-19 vaccine raised a series of queries and comments from the reviewers on different aspects of the nonclinical and clinical submitted evidence, as well as on issues related to the RMP. These have either been considered covered by the AZ answers to the EMA CHMP list of questions, or have been incorporated into the recommendations listed below and in the conclusion section of this document. The assessment of the bridging study conducted by SIIPL has also raised a few clinical questions raised by WHO and by Health Canada to SIIPL, whose replies were considered acceptable.

From the clinical point of review the Product Evaluation Group (PEG) recommended that an EUL may be granted by WHO to COVISHIELD™ provided that SIIPL commits to meet the following conditions post-EUL:

1. The applicant should submit to WHO the final report of the bridging study conducted in India by SIIPL, and further interim analyses and the final clinical study reports of the ongoing studies conducted by AZ (COV001, COV002, COV003 and COV005, whose interim analyses have been presented as part of this application, as well as COV004, conducted in Kenya, D8110C00001, conducted in the United States, Chile and Peru, and D8111C00002, conducted in Japan) once they are completed.
2. The Risk Management Plan should include/address the following:
 - o Safety specifications:
 - Potential risks: add *anaphylaxis* and *programmatic error*
 - Missing information: add *people living with HIV, frail subjects, use in paediatric population <18 years of age, use in patients with autoimmune or inflammatory disorders, and long-term safety data.*
 - *Interaction with other vaccines* and *interchangeability* should be considered separately from each other.
 - o Pharmacovigilance plan
 - The monitoring of adverse events (AEs) of interest should consider Bell's palsy, transverse myelitis, multisystem inflammatory syndrome following vaccination and all serious adverse events.

- For signal detection a mechanism for traceability should be established. Routine pharmacovigilance activities should be implemented in all WHO regions, including at least a vaccination card with the date when the recipient needs to return, the name of the recipient, the name of the vaccine, batch number, and a telephone number were to report side effects. The applicant should make clear its role in pharmacovigilance activities in different LMICs in all WHO regions.
- The applicant is urged to conduct additional pharmacovigilance activities (non-interventional and interventional studies as those intended for implementation in the EEA) in other WHO regions
- o Risk minimization activities
 - A minimum period of 15-minutes of observation for each vaccinee after vaccination given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions should be recommended in the product insert.

In addition, in light of the recent evidence of vaccine escape of some emerging SARS-Cov-2 variants, the applicant is requested to closely monitor and evaluate the impact of these emerging SARS-CoV-2 variants (such as B.1.1.7, B.1.351 and P.1, and others that may appear in the future) on the effectiveness of COVISHIELD™ and to discuss with WHO in case of plans to make changes to the vaccine to address this issue.

5 Technical considerations

5.1 Vaccine characteristics

COVISHIELD™ is originally developed by Oxford University – AZ and already evaluated in Phase-II/III Clinical Trial in UK. SIIPL has signed manufacturing agreement with AZ - Oxford University to manufacture this vaccine at commercial scale for mass immunization. At SIIPL, this vaccine is manufactured essentially in line with the DS, excipients and formulation developed and used by AZ - Oxford for manufacturing of clinical trial batches and the proposed commercial batches.

Though developed without a preservative, the formulation is intended to be utilized in a multiple-dose DP but with a limited in-use time, in line with the WHO multidose vial policy (MDVP)⁵, disposing of vaccine vials within 6 hours of opening or at the end of the immunization session, whichever comes first.

The vaccine is a sterile liquid dosage form for administration by intramuscular injection, 0.5 mL per dose. It is a clear to slightly opaque solution essentially free from visible particles, with pH 6.1 to 7.1. Two presentations were subject of this EUL application, namely 2 doses and 10 doses vaccine vials. The immunogen of COVISHIELD™ is the replication-deficient simian adenovirus vector ChAdOx1, containing the full-length structural surface glycoprotein (spike protein) of SARS-CoV-2. The antigenic composition is expressed by adenovirus particles expressing COVID-19 spike protein (5×10^{10} virus particles / dose of 0.5 mL). The vaccine formulation contains excipients (e.g. histidine, L-Histidine

⁵ [WHO's multi-dose vial policy \(MDVP\)](#)

hydrochloride monohydrate, polysorbate 80, sucrose, ethanol, sodium and magnesium chloride, EDTA disodium, in water for injection as vehicle).

The vaccine formulation does not contain substances, additive or excipients of biological or animal origin.

List of presentations available to UN Agencies/COVAX Facilities – multidose vials

Presentation	Pharmaceutical form	Dose	Container	Pack Size
2 doses	solution for injection	0.5 mL	Vial: 2 mL Clear Glass (Type 1) Stopper: 13 mm, elastomeric Seal: 13 mm Aluminum flip-off plastic button	2 multidose vials (2 doses per vial - 0.5 mL per dose) Target fill volume of 1.24 to 1.28 mL
10 doses	solution for injection	0.5 mL	Vial: 5 mL Clear Glass (Type 1)	10 Multidose vials (10 doses per vial - 0.5 mL per dose) Target fill volume of 6.00 to 6.20 mL
			Stopper: 13 mm, elastomeric	
			Seal: 13 mm Aluminum flip-off plastic button	

5.2 Special precautions for storage and handling

In the absence of compatibility studies, COVISHIELD™ must not be mixed with other medicinal products. Once opened, multi-dose vials should be used as soon as practically possible and within 6 hours when kept between 2°C and 8°C. All opened multidose vials of COVISHIELD™ should be discarded at the end of immunization session or within six hours whichever comes first.

COVISHIELD™ is a colourless to slightly brown, clear to slightly opaque solution. The vaccine should be inspected visually prior to administration and discarded if particulate matter or differences in the described appearance are observed by the health care provider.

The vaccine does not contain preservative. Aseptic technique should be used for withdrawing the dose for administration.

COVISHIELD™ should be store in a refrigerator (+2° C to +8° C). Do not freeze. Do not shake the vaccine vial.

5.3 Indication, warnings and contraindications

Therapeutic indications

COVISHIELD™ is indicated for active immunisation of individuals ≥18 years old for the prevention of coronavirus disease 2019 (COVID-19)

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. [Not included in the SII product insert]

Hypersensitivity

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of COVISHIELD™.⁶

Concurrent illness

As with other vaccines, administration of COVISHIELD™ should be postponed in individuals suffering from an acute severe febrile illness. However, the presence of a minor infection, such as cold, and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, COVISHIELD™ should be given with caution to individuals with thrombocytopenia, any coagulation disorder or to persons on anticoagulation therapy, because bleeding or bruising may occur following an intramuscular administration in these individuals.

Neurological events

Very rare events of demyelinating disorders have been reported following vaccination with COVISHIELD™. A causal relationship has not been established.

As with other vaccines, the benefits and potential risks of vaccinating individuals with COVISHIELD™ should be considered. [Not included in the SII product insert]

Immunocompromised individuals

It is not known whether individuals with impaired immune responsiveness, including individuals receiving immunosuppressant therapy, will elicit the same response as immunocompetent individuals to the vaccine regimen. [This section is not in the AZ-SK insert]

Duration and level of protection

The duration of protection has not yet been established.

As with any vaccine, vaccination with COVID-19 Vaccine AZ may not protect all vaccine recipients.

Interchangeability

[There are no safety, immunogenicity or efficacy data to support interchangeability of COVISHIELD with other COVID-19 vaccines]

⁶ This text is not in the insert and is a WHO recommendation

Sodium

This medicinal product contains less than 1mmol sodium (23mg) per dose, and is considered to be essentially sodium-free. [Not included in the SII product insert]

5.4 Posology and method of administration

Posology

COVISHIELD™ vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose (see section 5.1).

It is recommended that individuals who receive a first dose of COVISHIELD™ complete the vaccination course with COVISHIELD™ (see section 4.4).

Elderly population

This sentence is not in the AZ-SK insert]

No dosage adjustment is required in elderly individuals ≥65 years of age.

Paediatric population

The safety and efficacy of COVISHIELD™ in children and adolescents (aged <18 years old) have not yet been established. No data are available.

Method of administration

COVISHIELD™ is for intramuscular (IM) injection only, preferably in the deltoid muscle.

For instructions on administration, see section 6.6.

5.5 Safety profile

Summary of the safety profile

The overall safety of COVID-19 Vaccine AstraZeneca is based on an interim analysis of pooled data from four clinical trials conducted in the United Kingdom, Brazil, and South Africa. At the time of analysis, 23,745 participants ≥18 years old had been randomised and received either COVID-19 Vaccine AstraZeneca or control. Out of these, 12,021 received at least one dose of COVID-19 Vaccine AstraZeneca.

Demographic characteristics were generally similar among participants who received COVID-19 Vaccine AstraZeneca and those who received control. Overall, among the participants who received COVID-19 Vaccine AstraZeneca, 90.3% were aged 18 to 64 years and 9.7% were 65 years of age or older. The majority of recipients were White (75.5%), 10.1% were Black and 3.5% were Asian; 55.8% were female and 44.2% male.

The most frequently reported adverse reactions were injection site tenderness (>60%); injection site pain, headache, fatigue (>50%); myalgia, malaise (>40%); pyrexia, chills (>30%); and arthralgia, nausea (>20%). The majority of adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination. When compared with the first dose, adverse reactions reported after the second dose were milder and reported less frequently.

Adverse reactions were generally milder and reported less frequently in older adults (≥65 years old). Analgesic and/or anti-pyretic medicinal products (e.g. paracetamol-containing products) may be used to provide symptomatic relief from post-vaccination adverse reactions.

Tabulated list of adverse reactions

Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) and not known (cannot be estimated from available data).

Table 1 Adverse drug reactions

MedDRA SOC	Frequency	Adverse Reactions
Nervous system disorders	Very common	Headache
Gastrointestinal disorders	Very common	Nausea
Musculoskeletal and connective tissue disorders	Very common	Myalgia, arthralgia
General disorders and administration site condition	Very common	Injection site tenderness, injection site pain, injection site warmth, injection site pruritus, fatigue, malaise, pyrexia ^a , chills
	Common	Injection site swelling, injection, site erythema

^a Pyrexia includes feverishness (very common) and fever ≥38°C (common)

Very rare events of neuroinflammatory disorders have been reported following vaccination with COVID 19 Vaccine AZ. A causal relationship has not been established.

Overall summary of the safety profile from the Indian study:

COVISHIELD™ was also safe and well tolerated in the phase II/III clinical trial in India. An interim analysis included data of all 1600 participants who received first dose [1200 in COVISHIELD™ group, 100 in Oxford/AZ-ChAdOx1 nCoV-19 vaccine group and 300 in Placebo group]. This interim analysis includes data collected until 14 Dec 2020 of all 1600 participants who received first dose and 1577 participants who received second dose. [These paragraphs are not in the AZ-SK insert]

Demographic characteristics were generally similar among participants across the three groups. Overall, among the participants who received COVISHIELD™, 87.33% were aged 18 to 59 years and 12.67% were 60 years of age or older. [This paragraph is not in the AZ-SK insert]

Overall, the incidence of solicited reactions (injection site reactions such as pain, tenderness, redness, warmth, itch, swelling and induration; and systemic reactions include fever, chills, fatigue, malaise, headache, arthralgia and myalgia), unsolicited adverse events and serious adverse events (SAEs) was comparable in the study and control groups. No causally related SAE was caused by the study vaccine. [This paragraph is not in the AZ-SK insert]

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pharmacovigilance@seruminstitute.com [Not included in the SII product insert]

6 Monitoring of performance of the vaccine in the field

AZ proposes a series of activities for post-authorization safety monitoring, focused on Europe, including a proposed effectiveness study.

These post-authorization activities do not focus on populations and special groups that may be commonly found in LMICs supplied with WHO recommended COVID-19 vaccines. Available clinical data may not fully represent all populations.

6.1 Vaccine efficacy/effectiveness

AZ is conducting a series of clinical trials with AZ1222. Part of these studies have been initiated by the University of Oxford, and others have AZ as the sponsor. An interim pooled analysis of studies COV002 (conducted in the United Kingdom) and COV003 (conducted in Brazil) has been submitted in this application to support vaccine efficacy and immunogenicity. Five other clinical trials (COV001, conducted in the UK, COV004, conducted in Kenya, COV005, conducted in South Africa, D8110C00001, conducted in the United States, Chile and Peru, and D8111C00002, conducted in Japan) are ongoing. D8110C00001, a double-blind randomized, placebo-controlled clinical trial is of major interest as it involves ~30000 participants, and its results are expected to be used to support Emergency Use Authorization and, eventually, licensure in the United States.

AZ has also indicated, in its RMP, that an effectiveness study will be conducted. Given the recent concern with new variants, case-control studies are already being conducted in the United Kingdom in order to assess whether these variants may impact on vaccine effectiveness. The fact that the UK has an excellent genomic surveillance puts that country in a unique position to conduct such assessment.

6.2 Safety Monitoring

In addition to the collection and monitoring of spontaneous reports from healthcare professionals and vaccinees, AZ has proposed, in the RMP, an Enhanced Active Surveillance, a AZD1222 Pregnancy Registry,

a post-marketing observational study using existing secondary health data sources, and a post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency.

6.3 Programmatic aspects

The programmatic suitability of vaccine candidates for WHO Prequalification (PSPQ) of COVID-19 Vaccine AZ has been assessed as per the PSPQ WHO recommendations.⁷

COVISHIELD™ meets most of the mandatory characteristics as it is to be stored at +2°C to +8°C, it does not require an intravenous route of administration and the dose volume (0.5 mL) is not more than 1 mL. However, the 10-dose presentation of the vaccine does not meet one mandatory characteristic as it is a preservative-free product.

The majority of the critical characteristics are either met (the vaccine does not require storage below +2°C, the dose volume corresponds to standardized volume) or not applicable (no constraint on vaccination visits given that the vaccine is for use in pandemic, vaccine not presented in a pre-filled device). One critical characteristic is currently not met as the vaccine does not bear a vaccine vial monitor (VVM). SIIPL mentioned that the VVM to be assigned for ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) is currently under development.

7 SAGE recommendations

The Strategic Advisory Group of Experts on Immunization (SAGE) issues recommendations for use on vaccines of public health importance, including investigational products considered for use during a public health emergency. A SAGE working group on COVID-19 vaccination was set up in spring 2020 to develop the basis for recommendations once vaccines become authorized. Based on advice provided by SAGE, the initial use of vaccine is prioritized for health workers with high and very high risk of exposure and older adults, with the intention of preserving the most essential services and reducing mortality and morbidity from disease.

On February 8, 2021, SAGE reviewed the available data on COVID-19 AZ AZD1222, also known as ChAdOx1 nCoV-19 with a specific view of addressing the above-mentioned use scenario. The resulting interim recommendations were released by WHO on 10 February 2021. WHO recommends the use of the vaccine in accordance to the prioritization roadmap in individuals above 18 years of age, without an upper age limit. A two-dose schedule should be used, with an interval of preferentially 8-12 weeks. The vaccine maintains high level of efficacy against variant B.1.1.7 strain, while preliminary findings suggest the vaccine may be less effective against B.1.351. Awaiting more data on vaccine effectiveness, in particular against severe disease, WHO recommends the use of the vaccine also in countries where variant strains are circulating. Benefit risk assessment and continued monitoring of variant epidemiology are recommended.

The interim recommendations apply to AZD1222 (ChAdOx1-S [recombinant]) vaccine against COVID-19 developed by Oxford University (United Kingdom) and AZ as well as to ChAdOx1-S [recombinant] vaccines

⁷ [Assessing the programmatic suitability of vaccine candidates for WHO prequalification, Revision 2014](#)

against COVID-19 produced by other manufacturers that rely on the AZ core clinical data, following demonstrated equivalence in their regulatory review and once emergency use listing (EUL) has been obtained from WHO.

8 Regulatory oversight

The CDSCO which approved COVISHIELD™ for restricted emergency use approval in India, is the NRA of record for this vaccine as per the EUL procedure. The WHO Vaccine Prequalification Team will continue to rely on the regulatory oversight of CDSCO and will continue fostering participation in CDSCO' decision making process, as possible and when possible.

9 Benefit/Risk Assessment

According to WHO, the COVID-19 pandemic has caused, as of 9 February 2021, over 106 million cases of the disease and over 2.3 million deaths (<https://covid19.who.int/>). COVID-19, caused by a novel coronavirus, SARS-CoV-2, transmitted easily worldwide to a naïve population and has become a major cause of morbidity and mortality given the inexistence of a vaccine and of proved specific treatment. SARS-CoV-2 transmission continues to occur with an increasing rate. Hopes that herd immunity be achieved by natural infection have not been borne out because a large proportion of the population remains seronegative, which supports the hypothesis that they are susceptible to the virus. This scenario has been complicated by the recognition of new SARS-CoV-2 variants, whose increased transmissibility has caused concern. The development of effective and safe vaccines and their deployment worldwide may decrease the spread of the disease and its morbidity and mortality.

The benefit/risk assessment for COVISHIELD™ and AZD1222 can be considered to be the same, and therefore the considerations below about AZD1222, are also applicable to COVISHIELD™.

AZD1222 has demonstrated protection against symptomatic COVID-19, and no severe cases of COVID-19 or COVID-19 hospitalisations after 10 days of the first dose were observed in two clinical trials conducted in the UK (COV002) and in Brazil (COV003). The applicant claims that AZD1222 has the potential to be a critical intervention both for the individual and for public health in preventing COVID-19 and its associated risk of severe morbidity and of mortality.

AZ also claims that the need for an effective COVID-19 vaccine is highest among older people and individuals with comorbidities, and that the available results support the use of AZD1222 in individuals with these co-morbidities. The small number of events in the available clinical data does not allow for a reliable estimate of vaccine efficacy in older adults, in particular regarding protection against severe disease. The applicant claims that there is adequate seroconversion in the elderly, but the absence of an established immunological correlate of protection limits interpretation of immunogenicity data relative to efficacy. Lower antibody titres may also translate to shorter duration of immunity. Although vaccine efficacy and its duration are yet to be established in older adults, the overall safety profile and seroconversion rates in this age group are good and suggest that the benefit of vaccine outweighs the risk. Therefore, the current benefit/risk assessment in older adults is positive.

According to the applicant the safety profiles in individuals with comorbidities and older adults were similar to those in the overall population, and that therefore the benefit-risk profile can be considered similar in the subgroups with comorbidities and/or older age as in the general adult population. However, as individuals with severe diseases were not included in the clinical trials the same inference about the benefit-risk profile is not applicable to them.

The safety database presented by AZ included data from studies COV002 and COV003, mentioned above, and also from studies COV001 (conducted in the United Kingdom) and COV005 (conducted in South Africa). No important identified risks with AZD1222 vaccination have been detected by the clinical trials so far. Very rare events of demyelinating disorders have been recognized in the AZD1222 and the control groups, however without evidence of a causal relationship between the vaccine and these disorders. AZ, however, has included immune-mediated neurological conditions as an important potential risk in the RMP, due to theoretical concerns about the association of these disorders with vaccines, notwithstanding the fact that demyelinating diseases occur more frequently with infections than with vaccination. The applicant argues that studies have not conclusively shown a causal relation between contemporary vaccines (in general) and acute demyelinating events.

AZ argues that the benefits of AZD1222, both from the individual and public health standpoints, outweigh the potential risks, including VAED/VAERD, which remain theoretical and not supported by empirical nonclinical and clinical data for this vaccine. In AZ's opinion the benefits extend to older adults from 65 years and those with comorbidities. Vaccination with AZD1222 and COVISHIELD™ are anticipated to have a major impact in the prevention of COVID-19 disease, hospitalisations and deaths, with the advantages of being a vaccine with a good safety profile and to be provided in a formulation that allows easy storage and handling.

10 Conclusion

Considering the public health need to halt COVID-19 morbidity and mortality and start immunizing the world's population to the largest extent possible, the introduction of vaccines that would protect the population from disease and, whenever possible, from SARS-CoV-2 infection is needed.

Based on the available evidence assessed, the Product Evaluation Group (PEG) finds that sufficient data has been provided by SIIPL to support the EUL application for COVISHIELD™. However, as part of the assessment process there are some actions and information that needs to be provided as post EUL commitments. These are indicated in the below sections.

10.1 Quality (CMC) perspective

Although, the data presented by SIIPL to support consistent quality of COVISHIELD™ are considered to be sufficient in the context of the EUL in the current (COVID-19) pandemic situation, the quality information of the dossier should be supplemented with additional data. The TAG however highlighted the need to finalize comparability data as soon as possible to confirm that the manufacturing at SIIPL is comparable to production elsewhere, in order to alleviate any concerns regarding the quality of the product irrespective of site of production. Therefore, several issues which have been raised and that

should be address by SIIPL as post EUL commitments in order to complete the dossier. These are the following:

- 1 Acceptance criteria are expected to be reviewed when more manufacturing experience will be gained and additional data will be available.
- 2 Confirmatory data of stability studies and evaluation of stability indicating parameters (e.g. the infectivity, viral particles) are still expected to confirm the initial shelf life claimed for the vaccine and extend it as per the stability protocols. This will ensure consistency in the quality of the product, based on manufacturing and analytical experience.
- 3 Though comparability information and data has been shown for the DS and DP, a comprehensive presentation across clinical lots, and other manufacturing scales is expected. This should also include the comparability with AZ batches. In this regard, discussion about the using different analytical methodologies should be provided as part of the comparability exercise (e.g. risk-based approach).
- 4 SIIPL shall inform WHO of any information which might influence the quality of COVISHIELD™, such as any necessary change (e.g. in the manufacturing process, control and specifications).
- 5 The applicant is committed to address all pending issues generated from the CMC review.

10.2 Clinical perspective

From the clinical point of review, the PEG recommends that an EUL may be granted by WHO to COVISHIELD™ provided that SIIPL commits to providing the following requested information post-EUL as soon as such information becomes available, and accepts/addresses the issues that regard the Risk Management Plan not in SK report:

- o The applicant should submit to WHO the final report of the bridging study conducted in India by SIIPL, and further interim analyses and the final clinical study reports of the ongoing studies conducted by AZ (COV001, COV002, COV003 and COV005, whose interim analyses have been presented as part of this application, as well as COV004, conducted in Kenya, D8110C00001, conducted in the United States, Chile and Peru, and D8111C00002, conducted in Japan) once they are completed.
- o The expectation is that the continued analysis of these studies will provide evidence of vaccine efficacy in the 65+ age group, in particular for the prevention of severe cases. Once available information (or any relevant data coming from post EUL effectiveness studies) should be shared with WHO, as this might change the benefit/risk profile of the vaccine in this population.
- o The applicant should investigate and provide to WHO, on a regular basis or whenever relevant information is available, updated data on the efficacy of the vaccine against severe disease caused by emerging SARS-CoV-2 variants such as B.1.1.7, B.1.351 and P.1. This is important information given that decreasing effectiveness may change the benefit/risk assessment in countries where these variants are predominant.
- o The text of the product insert should be aligned to the product insert of the AZ COVID-19 vaccine except for the specific information obtained in the COVISHIELD-AZD1222 bridging study.
- o The Risk Management Plan should include/address the following:
 - Safety specifications:
 - Potential risks: add *anaphylaxis* and *medication error*

- Missing information: add *people living with HIV, frail subjects, use in paediatric population <18 years of age, use in patients with autoimmune or inflammatory disorders, and long-term safety data. Interaction with other vaccines and interchangeability* should be considered separately from each other.
- Pharmacovigilance plan
 - The monitoring of adverse events (AEs) of interest should consider Bell's palsy, transverse myelitis, multisystem inflammatory syndrome following vaccination and all serious adverse events.
 - For signal detection it is necessary to establish a mechanism for traceability. Routine pharmacovigilance activities should be implemented in all WHO regions, including at least a card with the date when the recipient needs to return, the name of the recipient, the name of the vaccine, batch number, and a telephone number were to report side effects. The applicant should make clear its role in pharmacovigilance activities in different LMICs in all WHO regions.
 - The applicant is urged to conduct additional pharmacovigilance activities (non-interventional and interventional studies as those intended for implementation in the EEA) in other WHO regions.
- Risk minimization activities
 - A minimum period of 15-minutes of observation for each vaccinee after vaccination given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions should be recommended in the product insert.