Roadmap for WHO assessment of COVID-19 Vaccine (Ad26.COV2-S (recombinant)) manufactured by Janssen Cilag International NV during the COVID Public health Emergency

Preamble

In the context of the current public health emergency, regulatory alignment and collaboration are some of the key components that will help to facilitate equitable access to safe and effective vaccines that meet international quality and manufacturing standards. In addition to its procedures for prequalification (PQ) and emergency use listing (EUL) of vaccines, WHO has also developed principles for regulatory collaboration during the scientific review of any vaccine submitted to WHO for assessment. These principles are based on the framework used for prequalification of the Merck Ebola Virus disease vaccine and subsequent registration in five African countries in 2019[1]. The principles for collaboration post-introduction were also strengthened in view of the heightened need for alignment in this area. The scale of cooperation in the context of COVID is anticipated to be much greater in the context of the large number of vaccines under development and the large number of countries who could benefit from such vaccines. This roadmap is intended to serve as a model for subsequent product specific vaccine evaluations, provided there is agreement from the manufacturers and the regulators concerned.

A. Introduction

Background

Initially, when WHO's EUL procedure was developed, the main principle was to concentrate -as much as possible- on the consultation, submission of initial data and assessment during the pre-emergency phase. This was intended to allow to shorten the discussions leading to a listing recommendation considerably. Taking into consideration that the procedure would be aligned with the vaccine priorities established by the WHO R&D Blueprint, the assumption was that several vaccines would be in early stages of development for the prevention of emerging diseases.

When WHO declared a public health emergency of international concern (PHEIC) on January 30th, 2020, the etiological agent causing the new respiratory disease later called Covid-19 had just been isolated (January 7th) and the first genomic sequence had been completed on January 10th. Therefore, only after the declaration of the PHEIC, scientific/academic institutions and

[1] https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/resources/EUL_EVD_vaccines/en/

manufacturers started to work on the development of Covid-19 vaccines. This chronology of facts has challenged public health systems worldwide and regulatory bodies are no exception. Even those regulatory authorities with mechanisms in place to authorize the use of investigational products were forced to create guidelines, task forces, procedures and alliances to maximize the efficiency of assessment, review and authorizations of medical products. Vaccines are undoubtedly the most complex medical products to develop, from concept to a stage where sufficient evidence of quality, safety and efficacy are collected to provide an assurance that their use will provide more benefits than risks when used in the context of a public health emergency.

Development of COVID-19 vaccines

Although the EUL/PQ for vaccines had not been opened, WHO started discussions with manufacturers that contacted WHO to discuss the potential assessments of Covid 19 vaccines. The candidate vaccine COVID-19 vaccine (Ad26.COV2-S (recombinant)), developed by Janssen Pharmaceutica NV (Janssen) is a monovalent, recombinant, replication-incompetent adenovirus type 26 (Ad26) vectored vaccine encoding the severe acute respiratory syndrome coronavirus 2 (SRAS-CoV-2) Spike (S) protein.

For the past several years, Janssen has been building an adenoviral platform technology for the manufacturing of Ad26-based vaccines (AdVac®/PER.C6® platform, hereafter referred to as AdVac). Extensive experience has been gathered with the development of multiple vaccines that rely on the same vector platform and only differ in the inserted transgene. The Janssen Ebola vaccine Zabdeno (Ad26,ZEBOV) based on the same vector platform received its European Commission approval on July 1, 2020. The clinical experience with the Janssen Ad26®-based vaccines includes more than 110,000 subjects vaccinated to date with other vaccines based on the same platform, across 46 completed and ongoing studies with different antigens constructs.

Clinical studies Phase 1, 2 and 3 are ongoing in USA, Belgium, Japan, The Netherlands, Germany, Spain, Argentina, Brazil, Chile, Peru, Mexico, Colombia, South Africa and UK. A number of manufacturing sites worldwide are being used to produce the drug substance, the drug product and the finished product. Comparability will be established through an analytical evaluation strategy.

This roadmap outlines the steps to follow for the submission and assessment of COVID-19 vaccine (Ad26.COV2-S (recombinant)) for EUL/PQ as well as a proposed pathway for the collaboration between WHO and the NRA of record. Establishing open communication with regulatory authorities overseeing development of COVID-19 vaccine (Ad26.COV2-S (recombinant))is essential to the EUL/PQ process.

Discussions with the NRAs of record will be key in the process of granting a WHO recommendation. WHO and NRAs of record will also work together to minimize assessment timelines.

This document provides an overview of the process to ensure expedited access to this vaccine. Additionally, further clarifications on the use of the EUL procedure for vaccines against COVID-19 is available at: https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/EUL_PQ_Vaccines/en/

B. Steps and activities of assessment

a) Preliminary activities

1. Interactions and agreements with regulatory authorities of record
   Based on discussions between Janssen and WHO, and in order to accelerate the assessment process, WHO will establish agreements– or extend existing agreements where applicable- with NRAs responsible for the emergency use approval of the vaccines. Janssen has filed submissions during development of the vaccine with USFDA, EMA and PMDA. However, Janssen has confirmed that the vaccine to be submitted to WHO for assessment will have EMA as the NRA of record. WHO will discuss with EMA options to streamline the assessment process.

2. Interactions with countries to ensure expedited authorization for use
   WHO has discussed with regional offices/regulatory networks to develop a system that will facilitate rapid approval by countries once a product is listed through the EUL/PQ procedure. Countries in each region will be encouraged to rely directly on the EUL/PQ issued by WHO or on a designated reference authority in the region that has provided an authorization for use, based on the WHO recommendation for use.

b) Opening of pre-submission consultations

WHO has published a call for Expression of interest (EOI) for manufacturers of Covid-19 vaccines. According to the call for EOI, companies with candidates vaccines currently in Phase IIb/III clinical trials that expect to have an approval by their NRA within 6 months and comply with the criteria established in the document "Consideration for evaluation of Covid 19 vaccines"[2] , can express interest for potential submission of an application at WHOEUL@who.int and will be contacted by WHO for a pre-submission meeting. The

[2] https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/resources/1_EOI-Covid-19_Vaccines.pdf?ua=1

purpose of the pre-submission meeting is to discuss the assessment procedure to be used (EUL or PQ), assessment pathway, date of submission of the dossier, readiness of submission package and upcoming availability of supplemental data.

c) Assessment

An abridged review will be conducted based on the streamlined approach with the European medicines agency (EMA) as the NRA of record. A global review committee (Product Evaluation Group) will be established and include expert reviewers and regulators nominated from NRAs of potential user countries through consultation with Regional Offices.

The completeness of the submitted dossier will be key to ensure that the experts can review the information without delays due to lack of information. Should additional information be requested by WHO, the applicant should devote every possible effort to respond within a short period of time so the assessment can be completed. The extent of the assessment will be done according to the pre-determined assessment pathways as mentioned above.

d) Final assessment and recommendation

Once the product has received approval by the NRA of record, WHO will convene a Technical Advisory Group to formulate a recommendation and conditions as appropriate, based on the assessment reports and other data the committee considers necessary to make a recommendation.

C. Outcome of assessment

The outcome of the assessment includes:

a) recommendation (acceptance or non-acceptance) for emergency use or prequalification of the evaluated product;

b) supporting assessment report with i.e. executive summary, scientific review and final remarks and listing conditions.

Since vaccines assessed using the EUL procedure are still in development, the manufacturers must continue with product development and clinical trials towards registration and prequalification. The manufacturer must notify WHO of any change made to the product. In addition, they must provide updated information, so the product evaluation committee reviews and updates their assessment report (see below).

Upon making a decision whether or not to grant an emergency use listing or prequalification, WHO will (without prejudice to any confidential information of the applicant/manufacturer) publish information about the product in a public report available on a dedicated portal of the WHO

website. This may include negative assessment outcomes. In addition, WHO reserves the right to share full reports with the relevant authorities of any interested Member State and interested United Nations agencies.

D. Post recommendation activities

a) Post listing updates

The recommendation (acceptance or non-acceptance) for emergency use or prequalification of the evaluated product can be revised after the submission by the manufacturer to the WHO EUL secretariat of updated information pertaining to quality (production and quality control) and clinical data. Post listing monitoring data from ongoing clinical trials, revised RMP as required, passive and active surveillance data of the deployed vaccine (safety and effectiveness) must be submitted to WHO as the evaluation of these may have an impact on the risk-benefit assessment, thus on the listing status of the product. The WHO secretariat will transmit the data to the evaluation committee and/or relevant regulatory experts for assessment. The outcome (if accepted by WHO) will be transmitted to the manufacturer by the WHO secretariat, with UN agencies in copy. A report on the assessment of post -listing changes will be available for countries that have authorized the use of the listed vaccine.

b) Monitoring performance of the vaccine deployed to countries.

Since vaccines listed under the EUL procedure have not been licensed for use in routine immunization settings, post marketing data would not be available at the time of application. Therefore, the manufacturer should provide reports from passive surveillance of Adverse Events Following Immunization (AEFIs), any active surveillance of Adverse Events of Special Interest (AESIs) or other studies as described in the approved Risk Management Plan (RMP), including Periodic Safety Update Reports (PSURs) and Periodic Benefit Risk Evaluation Reports (PBRERs) (frequency to be determined). WHO will reassess the validity of listing based on new data generated. Additionally, qualified information collected on deployed vaccine batches by existing surveillance systems in affected countries/regions will also be analysed.

All reports on safety surveillance, efficacy/effectiveness/performance monitoring, quality complaints and other relevant data may have an impact on the validity of the listing status.

Any change in the listing status (suspension, hold, termination) will be notified to member countries and UN procurement agencies.

E. Collaboration to facilitate access in countries.

WHO will involve regulatory authorities of potential user countries in the assessment process, including evaluation of the proposed RMP, either directly or through regulatory networks at the global level during the evaluation. This will allow WHO to capture - to the highest possible extent - the requirements of the NRAs of potential user countries. WHO will also make reports from the assessment team available to countries to facilitate an expedited authorization for use of the listed products.

WHO will also facilitate a process for assisting NRAs in their decision-making process. These discussions will take place either virtually, or through face to face meetings. Timings and locations will be scheduled in accordance with EUL/PQ timelines - WHO's priority in this context is to expedite the availability of a safe, effective and quality assured vaccine, facilitate a regulatory decision by the participating countries and ease deployment of the vaccine with a high public health need.

Requirements for in country authorizations for use in target countries

The following considerations are critical for a successful WHO facilitated procedure following EUL /PQ recommendation led process:

- NRAs commit to take a regulatory decision for the product in the shortest possible time based on reliance principles;
- The reports of the assessment process by relevant experts/NRAs will be shared through a secured platform managed by WHO to countries.
- Regional platforms such as AVAREF, SEARN, PANDRH, and others may have an important role in identifying the experts from the target countries to participate in the WHO facilitated process.
- Janssen will be closely engaged with AVAREF to ensure that the vaccine is made available quickly and broadly in sub-Saharan Africa.
- Regional Reference NRAs will drive the process in their regions.

Roles and responsibilities

In the context of this roadmap, different parties will collaborate very closely, but each would have their roles and responsibilities specified as follows:

WHO/RPQ (HQ)

a) provide overall coordination of different parties' efforts;
b) develop criteria for assessment of the vaccine candidate (s)
c) collaborate with regional offices to nominate WHO and country experts;
d) collaborate with regional networks;
e) collaborate with NRAs;
f) establish agreements with the SRA to share reports or set up alternative review mechanisms that will accelerate the review process and to request the SRAs to provide support from expert reviewers
g) Implement a WHO facilitated process through virtual or face to face meetings and sharing of confidential information via secure electronic platforms to support in-country authorization for use of the vaccine in the target countries;
h) Ensure timely communication with all NRAs;
i) Implement a WHO facilitated process for post-approval activities through sharing of confidential information via secure electronic platforms to support in-country authorization for use of the vaccine in the target countries

WHO Regional offices

a) Collaborate with WHO HQ and the NRAs of target countries to identify the country experts for participation in the vaccine review;
b) Promote the principle of reliance in the EUL/PQ and the identification of reference/champion NRAs in the region to drive the decision-making process and expedite the authorization for emergency use in countries
c) Ensure timely communication with all NRAs