GUIDELINE ON EMERGENCY USE AUTHORIZATION (EUA) OF COVID-19 VACCINES IN BANGLADESH

Directorate General of Drug Administration
Health Services Division
Ministry of Health and Family Welfare
Government of the People's Republic of Bangladesh

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Goverment of the people's Republic of Bangladesh

MESSAGE FROM THE DIRECTOR GENERAL

Directorate General of Drug Administration (DGDA) is responsible to ensure quality, safety and efficacy of all medical products including medicines, medical devices, vaccines, Biologicals, alternative medicines etc. It has major functions like national regulatory system, registration and marketing authorization, pharmacovigilance (PV), market surveillance & control, regulatory inspection, licensing of premises, lab access, clinical trial oversight, and lot release of vaccines. During the pandemic access to quality assured COVID-19 vaccine is a big challenge where the vaccine has limited safety and efficacy data.

COVID-19 has rapidly spread throughout the world. After the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic on March 11, 2020, it has posed a challenge to public health systems globally. In Bangladesh, the first COVID-19 case was detected on March 8, 2020, and the first reported death occurred on March 18, 2020. Starting in February 2021, the Government of Bangladesh started COVID-19 vaccine deployment for the people of Bangladesh to overcome the pandemic.

The Directorate General of Drug Administration (DGDA) is solely responsible for providing Emergency Use Authorization (EUA)/ No Objection Certificate (NOC) for COVID-19 vaccines and overall quality and safety monitoring of vaccines through post-marketing surveillance (PMS). Because vaccines are crucial to ending the pandemic, DGDA has a keen interest to develop comprehensive procedures on PMS and EUA for COVID-19 and non-COVID vaccines.

DGDA has developed one standard operating procedure (SOP: NRA-MA-011) on the issuance of EUA for imported COVID-19 Vaccines in Bangladesh; however, the SOP is intended for internal use only. For common regulatory understanding and promoting effectiveness and compliance of regulatory system for EUA, DGDA needs a comprehensive guideline for EUA in Bangladesh.

DGDA has developed "the guideline for emergency use authorization (EUA) of COVID-19 vaccines" in Bangladesh in consultation with expert committee. I expect that this guideline will help DGDA, importer, manufacturer, marketing authorization holder's (MAH), and all other relevant stakeholders for emergency use authorization of COVID-19 vaccine, that will promote standard regulation and better access to quality assured vaccines to combat COVID-19 pandemic.

I appreciate all members of the public health emergency committee, USAID funded PQM+ program for technical support to develop the guideline for EUA of COVID-19 Vaccines in Bangladesh.

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Acronyms

AEFI	adverse events following immunization
BMRC	Bangladesh Medical Research Council
CMA	conditional marketing authorization
CMC	chemistry, manufacturing, and controls
CTD	common technical document
DG	director general
DGDA	Directorate General of Drug Administration
EMA	European Medicine Agency
EUA	emergency use authorization
EUL	Emergency Use Listing
GCP	good clinical practice
GMP	good manufacturing practice
icddr,b	International Centre for Diarrhoeal Disease Research, Bangladesh
MCB	Master Cell Bank
MOHFW	Ministry of Health and Family Welfare
NCL	National Control Laboratory
NOC	No Objection Certificate
NRA	National Regulatory Authority
PIL	product information leaflet
PHEC	Public Health Emergency Committee
PQ	Prequalification
PQM+	Promoting the Quality of Medicines Plus
PV	Pharmacovigilance
RMP	Risk Management Plan
RU	Receiving Unit
SmPC	summary of product characteristics
SRA	Stringent Regulatory Authority
SU	Sending Unit
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization

Definition of Terms

Emergency use authorization: EUA is a special procedure for regulation of medical products (including medicines, vaccines, biologicals, medical devices, and in-vitro diagnostics) in case of any public health emergency when optimized assurance of the safety and efficacy of products are accepted—considering the risk-benefit assessment—given the epidemiological situation of the disease and the absence of or shortfalls in treatment and/or prevention options[8].

Regulatory flexibility: Reducing time for regulatory approval by defining emergency pathways and modifying procedures, such as reviewing the submissions and other rele¬vant evidence on a rolling basis[8].

Regulatory reliance: Applying principles of reliance and recognition to decisions and evidence made available by WHO Emergency Use Listing (EUL) Prequalification (PQ) procedures and by Stringent Regulatory Authorities (SRAs) to allow efficient use of resources[8].

Regulatory cooperation: Establishing links and cooperation agreements to support the regulatory process by joint review and sharing the tasks with neighbouring National Regulatory Authorities

(NRAs) and/or supporting NRAs[8].

Regulatory recognition: A routine acceptance of the regulatory decision of another regulator or trusted institutions. Recognition indicates that the evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B[8].

Regulatory agility: Adopting proactive search, review, and use of published evi¬dence on COVID-19 vaccines with the aim of supporting regulatory decisions, in particu¬lar, decisions based on reliance and recognition[8].

Executive Summary

This guidance document addresses the process and the criteria to evaluate COVID-19 vaccines submitted to Directorate General of Drug Administration (DGDA) for emergency use authorization (EUA). This guideline is intended to direct manufacturers, importers (local agents/distributors/ other importing entities), and/or other interested parties for submission of applications to the DGDA for EUA of Covid-19 vaccines. The guideline is formulated to establish eligibility criteria, essential information requirements, and procedures for evaluating COVID-19 vaccines in Bangladesh. As an endeavor, the Government of Bangladesh has published several gazette notifications for strengthening the regulatory framework and formed several expert groups to facilitate regulatory operations of DGDA for EUA of COVID-19 medical products and/or commodities. DGDA defined the EUA pathways based on the source of the COVID-19 vaccines, and the pathways are:

1. Reliance and recognition pathway
2. Critical review pathway

DGDA classified the sources of vaccines into five categories to formulate the specific steps and evaluation mechanism. These are:

- Imported Covid-19 finished vaccine
- Local manufacturing of Covid-19 vaccine from imported bulk
- Local manufacturing of Covid-19 vaccine through technology transfer
- Local production of Covid-19 vaccine from Master Cell Bank (MCB) which is approved in other countries with WHO Maturity Level 3 in terms of vaccine manufacturing capacity.
- Indigenous Covid-19 vaccine development and local production

The eligibility criteria set in this guideline were aligned and harmonized with global best practices and DGDA's regulatory contexts. DGDA explicitly defined the set of essential data requirements as well as the submission and review procedure. The screening and evaluation procedure for applications is formulated based on the four sources of vaccines with a well-defined evaluation method. The criteria for evaluating COVID-19 vaccines are demonstrated in this guideline to facilitate the evaluation procedure irrespective of the sources of vaccines. The special case considerations are also defined when DGDA is required to impose conditions during issuing EUA, determining validity, and withdrawal, cancellation, revoke, and/or suspension of EUA. Post-authorization activities, such as lot release, risk management plan (RMP) implementation, market surveillance, and safety surveillance are also addressed. Coordinating, monitoring, and evaluating COVID-19 vaccines are emphasized for evidence generation, regulatory decision making, and actions for public health protection.

1. Introduction

The COVID-19 pandemic has created a significant threat and impact to global health. The World Health Organization (WHO) declared the novel coronavirus (2019-nCoV) outbreak a public health emergency of international concern on January 30, 2020 and classified the outbreak as a pandemic on March 11, 2020. Transitioning regulatory pathways and practices from a traditional and reactive control system to a proactive and risk-based approach is an important aspect of emergency preparedness for the medicine regulatory authorities during this pandemic.

The DGDA is committed to safeguarding Bangladeshi citizens from unsafe and infective medical products used in health care, including those intended for use in the treatment of emerging infectious diseases (such as COVID-19). DGDA poses sole responsibility for establishing the requirements, procedures, and times when the vaccine manufacturers and importers request authorization for the introduction and use of their products in Bangladesh. DGDA is also responsible for ensuring that the vaccines and manufacturing facilities meet established standards, including manufacturing, quality control, and distribution, for their clinical study as well as ensuring better access. DGDA needs to develop a time limited EUA guideline to expedite the availability of vaccines that are needed in public health emergency situations, based on an essential set of available quality, safety, and efficacy/immunogenicity/performance data. It is vital to clarify, however, that an EUA is not the same as, or an alternative for, a full marketing authorization. The EUA decision should be reviewed periodically and converted to regular marketing authorization when feasible. Given the disease's prevalence, severity and the scarcity of treatment, diagnosis and detection, and prevention alternatives, the EUA delivers a special procedure for conditionally licensing vaccines like Covid-19. The procedure's purpose is to provide unlicensed vaccines with a time-limited and conditional approval in an emergency where minimal data are available, and the vaccines are not yet ready for a full marketing authorization application.

The first COVID-19 case in Bangladesh was discovered on March 8, 2020, and the first death was recorded on March 18, 2020. On January 27, 2021, Bangladesh started administering COVID-19 vaccines, and mass immunization commenced on February 7, 2021(3,4). From January through April 2021, the only COVID-19 vaccine approved for emergency use was the Oxford–AstraZeneca vaccine(5). Bangladesh purchased vaccines from the Serum Institute of India; however, only half of the doses were delivered. In late April 2021(6), the DGDA approved eight vaccines for emergency use following standard operating procedures (an internal document) in order to minimize the scarcity of lifesaving Covid-19 vaccines in Bangladesh. These vaccines include Sinopharm COVID-19 vaccine (vero cell), Sputnik-V, Sinovac Vaccine, Pfizer COVID-19 vaccine, AstraZeneca AZD1222 Vaccine, Covishield vaccine, Johnson & Johnson Vaccine, and Moderna Vaccine. It is also reported that the locally developed vaccine called Bangavax, which was developed by Globe Biotech Ltd., was listed in the Draft Landscape and Tracker of COVID-19 Candidate Vaccines by WHO(7). It needs common understanding for relevant stakeholders and DGDA for import, development, manufacturing, marketing, promotion and overall regulation. This guideline is intended to minimize those gaps for standard regulatory practice regarding Covid-19 vaccines in Bangladesh.

Currently, Bangladeshi manufacturers are manufacturing some vaccines. They are manufacturing fill finish vaccines and vaccines from master cells.

2. Country Regulatory Framework

Regulatory preparedness is key to a rapid response during a pandemic like COVID-19 and minimizes the time available to reach a final decision on the potential inclusion of products and the consequent importation and national deployment procedures. Delays in regulatory readiness will affect access to medical products. The legal framework for DGDA's regulatory functions is based on The Drug Act 1940, Bengal Drug Rule 1946, Drug (Control) Ordinance 1982, and Drug Policy 2016.

The Drug Rule 1945; Part-IV, Rule-36 under The Drug Act 1940 rolled out the legislative basis of issuing a No Objection Certificate (NOC). The Drug Control Ordinance 1982 rolled out the constitution of a drug control committee with specific functions of regular registration of medical products along the obligation of registration of manufactured/imported/distributed/sold medicines to the licensing authority based on the recommendation of the drug control committee.

The National Drug Policy 2016 placed a strong emphasis on pharmaceutical governance and regulatory systems. As per clause 4.2 of National Drug Policy 2016, the government will ensure equitable access to all drugs, including essential drugs, at all levels by taking drug safety, efficacy, and affordability into account. All drugs required for the prevention, control, and eradication of Malaria, Kalaazar, Nipah virus, SARS, tuberculosis, AIDS, and Dengue, as well as other contagious diseases, will be made accessible. Access to all types of vaccines and other drugs required for better maternal and child health care will be ensured on an equitable basis.

On May 17, 2020, the Bangladesh Government issued a gazette notification to include action to combat the COVID-19 pandemic in Clause 4.2 of the National Drug Policy 2016. This gazette notification authorized DGDA as a licensing authority to issue NOC/EUA in the event of a need for manufacturing, importing, distributing, and ensuring access to essential drugs, investigational drugs, and medical devices in the country for detection of Corona virus and diagnosis, treatment, and prevention of COVID-19 (Government Gazette Notification No: 45.00.0000.182182.99.017.08-110). As per Clause 4.5 (L) of National Drug Policy 2016, DGDA/Government can enforce the registered manufacturers to produce any medicine in case of public health emergency, and manufacturers will be obliged to obey the order of the government.

The Ministry of Health and Family Welfare (MOHFW) established a technical committee on June 4, 2020, for the evaluation of medicines, investigational drugs, vaccines, and medical devices related to the treatment/prevention of the COVID-19 public health emergency by a gazette notification. The Public Health Emergency Committee (PHEC) makes recommendations to the director general (DG) of DGDA and DGDA officials regarding medical products, including vaccines, to be used/authorized for treatment and prevention related to the COVID-19 pandemic.

To ensure the quality, safety, and efficacy of COVID-19 vaccines in Bangladesh, the Government formed a committee, the Quality Assurance Committee for Vaccines, on December 14, 2020, headed by the DG of DGDA. This committee is enabled to take necessary measures to ensure the quality, safety, and efficacy of COVID-19 vaccines in Bangladesh.

According to the Government Notification No: 45.00.0000.182.89.001.21.93, dated April 24, 2021, the Covid-19 vaccine must have EUA/EUL from the United States, United Kingdom, Switzerland, Germany, France, Australia, Japan, and/or the European Medicine Agency (EMA), or WHO to issue the EUA/NOC. But in special cases, the DGDA can issue EUA/NOC of the medicines, vaccines, investigational drugs, and medical devices having EUA at other countries/regulatory bodies than those mentioned above prior to evaluating the dossier—clinical and chemistry, manufacturing, and controls (CMC) data—by the PHEC.

In general, the DGDA performs as Bangladesh's National Pharmacovigilance Center and is linked to the WHO-Upsala Monitoring Center, a global pharmacovigilance (PV) platform. Since the government's

COVID-19 vaccination campaign began, the DGDA has devised a 'Pharmacovigilance Protocol for COVID-19 Vaccine with the goal of ensuring its safety, quality, and efficacy. This protocol has been approved by MOHFW. After receiving EUA from the DGDA, this protocol provides instructions for passive and active PV activities in Bangladesh relating to reporting, investigation, causality assessment, and management of adverse events following immunization (AEFI) from COVID-19 vaccines. For effective regulatory decision making, the protocol describes the monitoring, evaluation, and management of AEFI and serious adverse events cases following COVID-19 immunization. DGDA, DGHS and EPI consulted the district or city corporation AEFI Committee, Divisional AEFI Casualty Assessment Committee, and the National AEFI Advisory Committee for COVID-19 vaccines as a three-layer committee. The National AEFI Advisory Committee for COVID-19 is being supported by the PV and COVID-19 safety surveillance cell of DGDA. With technical assistance from WHO and the USAID-funded Medicines, Technologies, and Pharmaceutical Services program, the DGDA has established an online system for adverse event reporting of COVID-19 vaccines[9].

The Bangladesh MOHFW formulated a National Deployment and Vaccination Plan(10) for COVID-19 vaccines with an aim to present the Bangladesh plans for the deployment, implementation, and monitoring of potential COVID-19 vaccine(s). The National Deployment and Vaccination Plan emphasizes the following areas: planning and coordination; regulatory preparedness; advocacy, communication, and demand promotion; vaccine deployment; human resources, vaccine, cold chain, and logistics planning; vaccine safety; and monitoring and evaluation. Planning and coordination committees oversee the planning, implementation, and monitoring of the deployment and introduction of COVID-19 vaccine(s) in the country. The Government has established vaccination working groups at different levels to support development of a deployment plan— planning, implementing, monitoring the implementation of vaccine deployment—in coordination of various sectors as per national guidelines. The DGDA is responsible for establishing regulatory pathways of COVID-19 vaccine authorization and utilizing the necessary regulatory instruments and resources ahead of time for regulatory decision making and safeguarding vaccines. The approval and import procedures are based on the origin of vaccines and the purchasing methods. An RMP has been put in place to protect against any potential adverse effect from vaccine use. The Government, along with the National Immunization Technical Advisory Group, has developed a deployment plan to ensure equitable allocation of limited doses. Initially focusing on high-risk groups, a phase-by-phase rollout of COVID-19 vaccines has been implemented.

3. Scope of EUA Guideline of COVID-19 Vaccines

The EUA Guideline is intended to provide a time-limited authorization for unlicensed COVID-19 vaccines in an emergency context when limited data are available.

This document is intended to establish eligibility criteria, essential information requirements, and procedures for evaluating COVID-19 vaccines based on a critical set of quality, safety, efficacy/immunogenicity/performance data, regardless of whether COVID-19 vaccines are imported or produced locally. It is also intended to adapt global best practices and guidelines in a national context through aligning with the national regulatory framework.

This guideline is intended to assist manufacturers, importers (local agents/distributors), and other interested parties in submitting applications to the DGDA in order to get an EUA for applicable COVID-19 vaccines in Bangladesh.

4. Eligibility Criteria of COVID-19 Vaccines for EUA

In context of the COVID-19 vaccines, the imported/locally manufactured vaccines shall be eligible for an EUA in Bangladesh if they meet the following criteria:

All Phases of clinical trials (Pre-clinical, Phase-I phase-II & phase-III/non-inferiority trial) as appropriate to be

determined by DGDA should have been completed for local production. Manufacturer should submit further trial data on rolling basis, when available.

Must have registration/EUA by the NRA of the country of origin with satisfactory clinical and pre-clinical data and complete CMC data evaluated and recommended by PHEC; or

Registration/EUA in any of the seven countries—United States, United Kingdom, Switzerland, Germany,

France, Australia, Japan—and/or the EMA or WHO EUL.

The EUA of Covid-19 vaccines is applicable based on decision from PHEC or DGDA. The decision will depend on the end of pandemic (following declaration from WHO), sufficiency of supply versus demand, transition from

EUA system to full marketing authorization in other countries, or any guidance from WHO.

5. EUA Pathways

One of the key challenges in ensuring access to life-saving vaccines in Bangladesh is establishing pathways

for authorizing COVID-19 vaccines for emergency use in a timely manner. Covid-19 vaccine EUA will be carried out following a critical review pathway, either adopting reliance and recognition or through critical review. In Bangladesh, DGDA has two distinct regulatory EUA pathways, which are depicted below:

5.1. Reliance and recognition pathways

Regulatory reliance has emerged as an exciting and viable way to avoid duplication of review efforts, ease the burden on under-resourced regulatory agencies, and still deliver new medicines to patients who need them. DGDA may totally or partially rely upon the evaluations performed by another NRA or trusted institution in reaching its own decision. The DGDA remains responsible and accountable for decisions taken even when it relies on the decisions and information of others. With strong collaboration among regulatory agencies, it may be possible to build upon existing frameworks and global standards, building trust and sharing resources and experiences. The basis of applying this pathway for those imported Covid-19 vaccines that got EUA/conditional marketing authorization (CMA) registration in any of the seven countries (United States, United Kingdom, Switzerland, Germany, France, Australia, and Japan) or EMA and/or WHO EUL. Imported bulk for fill-finish or for technology transfer pre-clinical and clinical parts of dossier will go under reliance pathway with the aforementioned criteria. The reliance and recognition pathways require submission of satisfactory evidence of required documents as per requirements of DGDA

5.2 Critical review pathway

The PHEC will review the submitted documents (Referred to section 7) and make a recommendation to DGDA. Based on this recommendation, the PHEC and the DG of DGDA will take the decision of EUA, regardless of whether the application will be granted. The proposed Covid-19 vaccines or bulk for vaccine or master cell bank for vaccines should go through the critical review pathway:

a) The imported Covid-19 vaccines that are not listed by the aforementioned regulatory bodies/countries or WHO EUL

b) Local manufacturing through imported bulk

c) Local manufacturing through technology transfer (either from bulk or master seed)

d) Local production of Covid-19 vaccine from Master Cell Bank (MCB) which is approved in other countries with WHO Maturity Level 3 in terms of vaccine manufacturing capacity.

e) Indigenous Covid-19 vaccine development and local production

6. Registration and Marketing Authorization Department for Vaccines and Biologics and Public Health Emergency Committee

Upon receipt of an application from applicant, Registration and Marketing Authorization Department of Vaccines and Biologics will process the application, and the evaluation report will be reviewed by PHEC if the DG of DGDA decides.

6.1. Registration and Marketing Authorization Department for Vaccines and Biologics

For the evaluation of COVID-19 vaccines, the Registration and Marketing Authorization Department for vaccines and biologics" will:

- ✓ Scrutinize the EUA application and communicate through official letter to the applicant if any further documents required
- ✓ Prepare a summary report based on the review of the submitted common technical document (CTD) dossier

The Registration and Marketing Authorization Department for Vaccines and Biologics may invite members of the following departments and experts from relevant fields to review the respective part of the CTD dossier:

- Clinical trial oversight
- NCL-Vaccine Wing
- Regulatory Inspection
- PV

6.2 Public Health Emergency Committee for evaluation of COVID-19 vaccines

The PHEC will review technical documents and provide its recommendation to the DG of DGDA on the conditions under which the Covid-19 vaccine may be granted under the EUA procedure or may not be granted. PHEC will adopt a proactive search, review, and use of the published evidence on COVID-19 vaccines with the aim of supporting regulatory decisions. The PHEC will:

- Review the summary report of the eligible vaccine from Registration and Marketing Authorization Department for Vaccines and Biologics
- Review the published guidelines, requirements/recommendations, and international guidance materials available from WHO and any other regulatory authorities relevant to the evaluation of COVID-19 vaccines
- Explore relevant publications that support scientific consensus on a product's safety, immunogenicity, or clinical efficacy
- After evaluation of the applied vaccine, the PHEC will evaluate the risk-benefit ratio for issuance or rejection of the EUA application and will recommend to the DG of DGDA.
- Members of the PHEC will sign “confidentiality undertaking and declaration of interest (DOI).”

7. Submission and Review Processes

7.1. Essential data requirements for EUA

Imported Covid-19 finished vaccine (for reliance and recognition)	Imported Covid-19 finished vaccine (for full/critical review)
01. Evidence of EUA by the NRA in the country of origin 02. Evidence of EUA/EUL/CMA any of the 7 countries (USA, UK, Switzerland, Germany, France, Australia, and Japan, and/or EMA or WHO EUL 03. The review report of the referring regulatory authority for reliance 04. The CTD dossier to be submitted to DGDA (if it is required by DGDA) 05. RMP for applied Covid-19 vaccine to be submitted by local agent/manufacturer 06. Proper labeling and product Information leaflet (PIL) 07. Summary of product characteristics (SmPC) should be submitted	01. Preclinical study report 02. Phase I, phase II, and phase III full study report 03. Dossier in CTD format with complete CMC data 04. Evidence of EUA/registration by the NRA in the country of origin 05. RMP for applied Covid-19 vaccine to be submitted by local agent/manufacturer 06. Proper labeling and PIL 07. SmPC should be submitted

Note: In case of importing same finished vaccine from same company but different source of production/ same finished vaccine from different company, the importer should submit a new application for EUA

Covid-19 vaccine from imported bulk (for critical review)
1. Source validation certificate 2. Evidence of EUA/registration by the NRA in the country of origin 3. Lot release certificate from NRA/NCL of country of origin 4. Preclinical study report 5. Phase I, phase II, and phase-III full study report 6. Dossier in CTD format with complete CMC data 7. MP for applied Covid-19 vaccine to be submitted by the manufacturer. 8. Proper labeling and PIL 9. SmPC should be submitted

Locally manufactured Covid-19 vaccine through technology transfer

1. Agreement copies of technology transfer between innovator and receiving manufacturer
2. Evidence of transfer of starting materials including cell bank and seeds, manufacturing process, analytical methods
3. Evidence of demonstration of analytical comparability at commercial scale – "process performance qualification" batches
4. Evidence of comparability of commercial scale batches with clinical batches to demonstrate safety and efficacy (a comparability study between the vaccine of tech-transfer plant and vaccine of sending unit with a reasonable number of subjects)
5. Product performance qualification from two different sites of sending unit and receiving unit
6. WHO TRS 961 Annex 7, can also be referred
7. Research license (Form 17 of Bengal Drug Rules 1946), if produced from master cell bank.
8. Audit report of Innovator
9. Evidence of EUA by the NRA in the country of origin
10. EUA/registration from any of the 7 countries (USA, UK, Switzerland, Germany, France, Australia, and Japan and EMA or WHO EUA (if any)
11. Preclinical study report
12. Phase I phase, II, and phase-III full study report
13. Complete dossier in CTD format
14. RMP for applied Covid-19 vaccine to be submitted by the receiving manufacturer
15. Proper labeling and PIL
16. SmPC should be submitted

Locally produced Covid19 vaccine from Master Cell Bank (MCB) which is approved in other countries with WHO Maturity Level 3 in terms of vaccine manufacturing capacity

1. Agreement copies of Master Cell Bank (MCB) transfer between innovator & receiving manufacturer.
2. Research license from DGDA for developing vaccines using master cell bank.
3. Permission documents (NOC) for importing master seed/ cell line for target vaccine.
4. Evidence of EUA of the vaccine (Reference Vaccine) by the NRA which contains same Cell Line
5. Preclinical study report of the MCB provider/ Innovator/ carried out by local developers
6. Clinical trial protocol to be approved by DGDA, having prior ethical clearance from BMRC.
7. Comparative Immunogenicity Clinical Trial between Reference vaccine vs Locally produced vaccine (Non-inferiority study design)
8. Complete Dossier in CTD format with full CMC data
9. RMP for applied Covid-19 vaccine to be submitted by the receiving manufacturer
10. Proper labeling and PIL
11. SmPC should be submitted

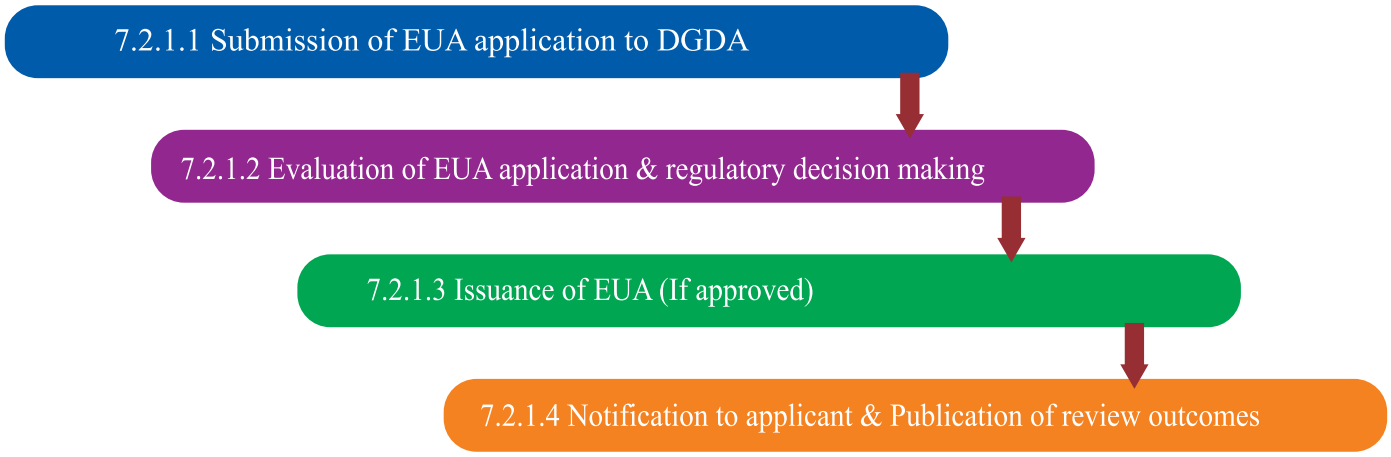
Indigenous Covid-19 vaccine (for critical review)

1. Permission documents (NOC) for importing master seed/cell line for target vaccine
2. Research license of the manufacturer from DGDA (Form 17 of Bengal Drug Rule 1946)
3. Preclinical study report.
4. Clinical trial protocol to be approved by DGDA, having prior ethical clearance from Bangladesh Medical Research Council
5. Phase I, phase II, and phase III satisfactory full study report
6. Complete Dossier in CTD format with full CMC data
7. RMP for applied Covid-19 vaccine to be submitted by the manufacturer.
8. Proper labeling and PIL
9. SmPC should be submitted

Note: In case of age group extension and changing dose regimen after approval of EUA with specific dose for specific age group, the EUA holder should submit safety and efficacy data for claimed age group in favor of applied new dose.

7.2. Submission procedure and processing of the EUA application

7.2.1. General steps involved in submission and process of issuing EUA[11]



7.2.1.1. Submission of EUA application

- The manufacturer/importer must submit an application to DGDA as per Annex 1 along with proof of the submission of government fees.
- The application letter should be submitted along with required essential documents mentioned in Section 8.1.
- Applicant must submit the documents following CTD format (Annex 2).

7.2.1.2. Evaluation of EUA application and regulatory decision making

7.2.1.2.1. Screening by Registration and Marketing Department of Vaccines and Biologics of DGDA

- The Registration and Marketing Authorization Department for Vaccines and Biologics of DGDA will scrutinize the EUA application.
- The Registration and Marketing Authorization Department for Vaccines and Biologics will communicate through official letter to applicant if any EUA application, whether rejected or any further documents are required to be submitted (Annex 3).
- Relevant department of DGDA will review the relevant section of the CTD application.
- This department will also prepare a summary report to present to the DG of DGDA (Annex 4).

7.2.1.2.2. Determination of regulatory approval pathway

- The head of Registration and Marketing Authorization Department for Vaccines and Biologics will present the summary report of the proposed Covid-19 vaccine for EUA to the DG of DGDA.
- Based on the submitted documents (according to section 7.1), the DG of DGDA will instruct the pathway of EUA approval toward either reliance and recognition pathway or critical review pathway.

7.2.1.2.3. Review, evaluation, and recommendation

- For the critical review pathway, Registration and Marketing Authorization Department for Vaccines and Biologics will place the documents and summary report to the PHEC. PHEC will review the documents along with summary report and will submit its recommendation to DG of DGDA
- In case of reliance and recognition pathway, DG of DGDA may award EUA of the vaccine with the intimation to the PHEC.

7.2.1.2.4. Decision of DGDA

- Based on the recommendation of PHEC, the decision (approval/rejection) for EUA will be taken by the DG of DGDA.
- In case of approval, DGDA will issue EUA.
- In case of rejection, DGDA will communicate the decision to the applicant with necessary justification.

7.2.1.3. Issuance of EUA (If approved)

- DGDA will issue EUA for Covid-19 vaccine upon satisfactory review (Annex 5).
- DGDA may impose conditions along with the issuance of EUA, such as rolling safety and effectiveness data submission or any other risk-based conditions.
- The EUA holder will be bound to follow and comply with the imposed conditions.
- If any non-compliance is evidenced after issuance of EUA, DGDA may cancel, revoke, and/or suspend the EUA.

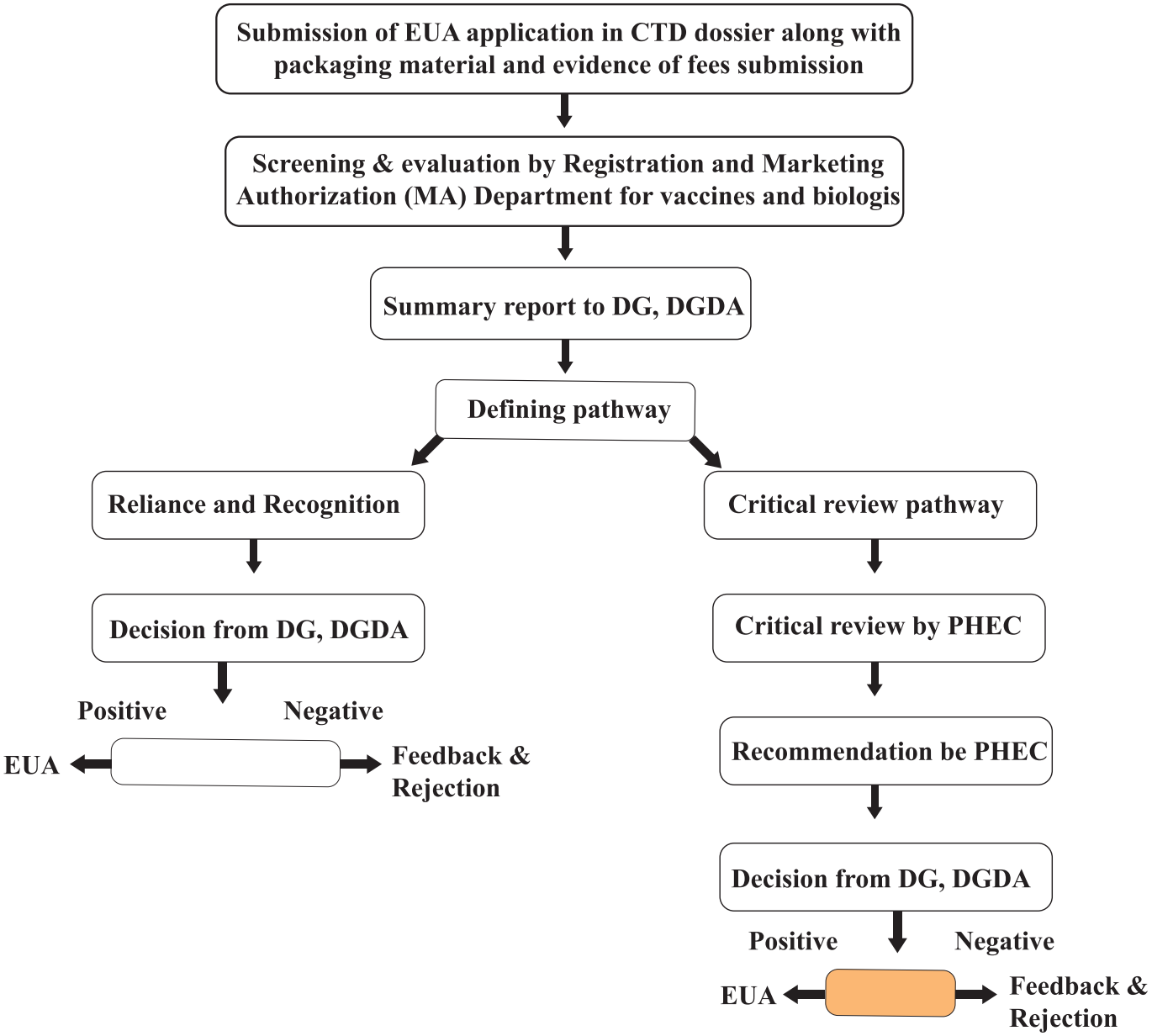
7.2.1.4. Notifications to manufacturer and publication of review outcomes and communications

- Upon issuance of EUA, DGDA will notify the applicant and publicize through its website and other relevant media.

7.3 Specific steps involved in submission and evaluation of EUA

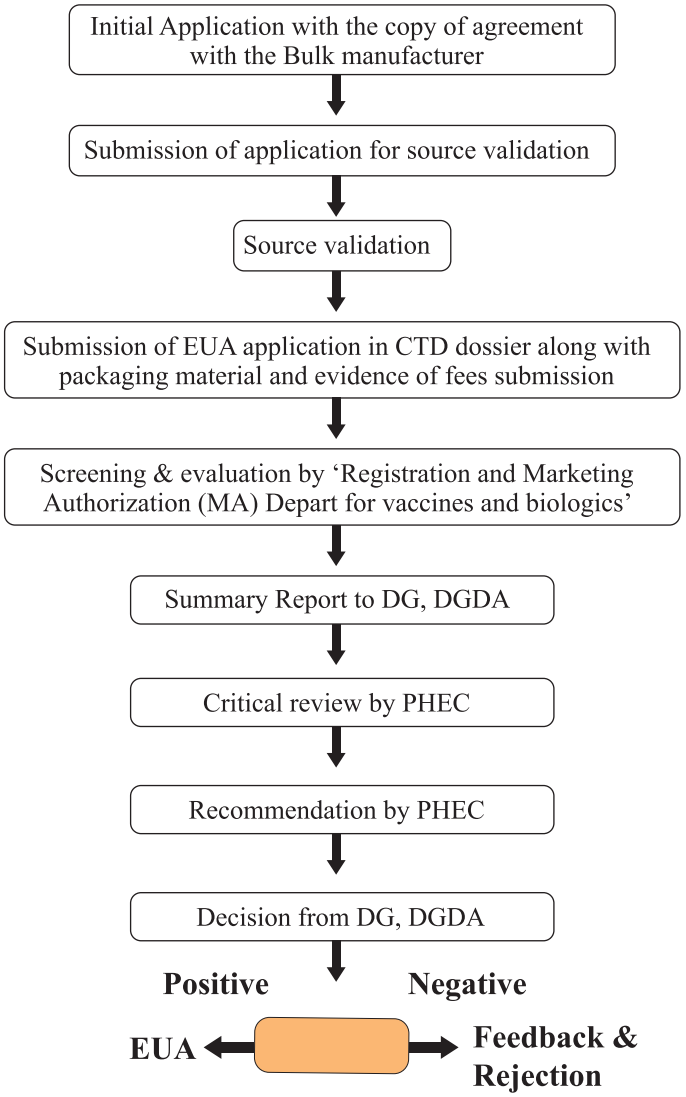
7.3.1. Imported finished Covid-19 vaccine

- Criteria for finished Covid-19 vaccine importers:
- If an innovator/manufacturer by itself applies for EUA in Bangladesh, it must have a registered local office in Bangladesh.
- The innovator/manufacturer may appoint a local agent to apply for EUA. The local agent must be a registered entity in Bangladesh.
- If any registered local company/agent applies for EUA of a Covid-19 vaccine in Bangladesh, it must have a valid agreement with the innovator/manufacturer.
- The importer/manufacturer/local agent must have a proper cold chain system and distribution facility across Bangladesh.


Submission of EUA application in CTD dossier along with packaging material and evidence of fees submission
Screening & evaluation by Registration and Marketing Authorization (MA) Department for vaccines and biologis
Summary report to DG, DGDA
Defining pathway
Reliance and Recognition
Critical review pathway
Decision from DG, DGDA
Critical review by PHEC
Positive
Negative
EUA
Feedback & Rejection
Recommendation be PHEC
Decision from DG, DGDA
Positive
Negative
EUA
Feedback & Rejection

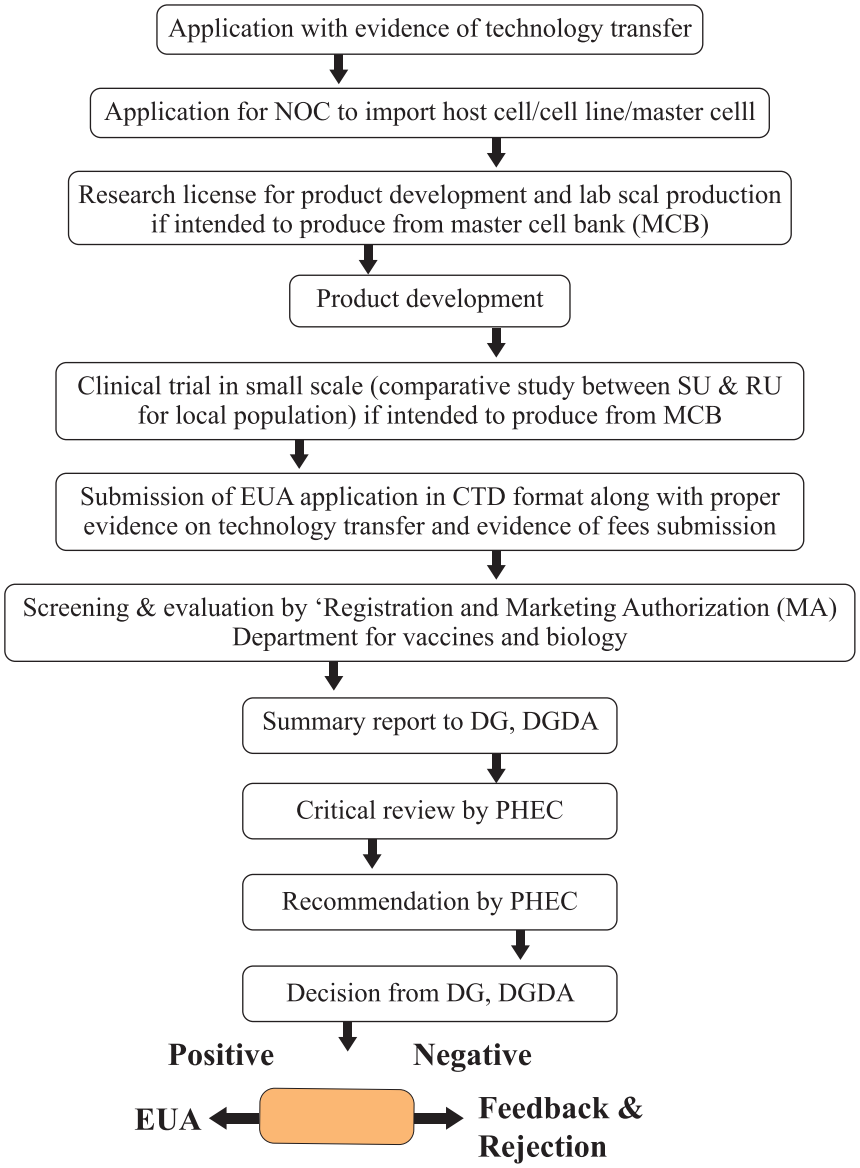
7.3.2 Local manufacturing of Covid-19 vaccine from imported bulk

After making an agreement with the manufacturer, an applicant must submit an initial application to DGDA to initiate further steps under an expedited EUA procedure. The application for source validation must be submitted as per the checklist of required documents (Annex 6) prior to applying for EUA. Upon completing the source validation, the applicant can submit an EUA application to DGDA, along with evidence of paid submission fees. The steps involved in the regulatory pathway for local manufacturing of Covid-19 vaccines from imported bulk are given below:



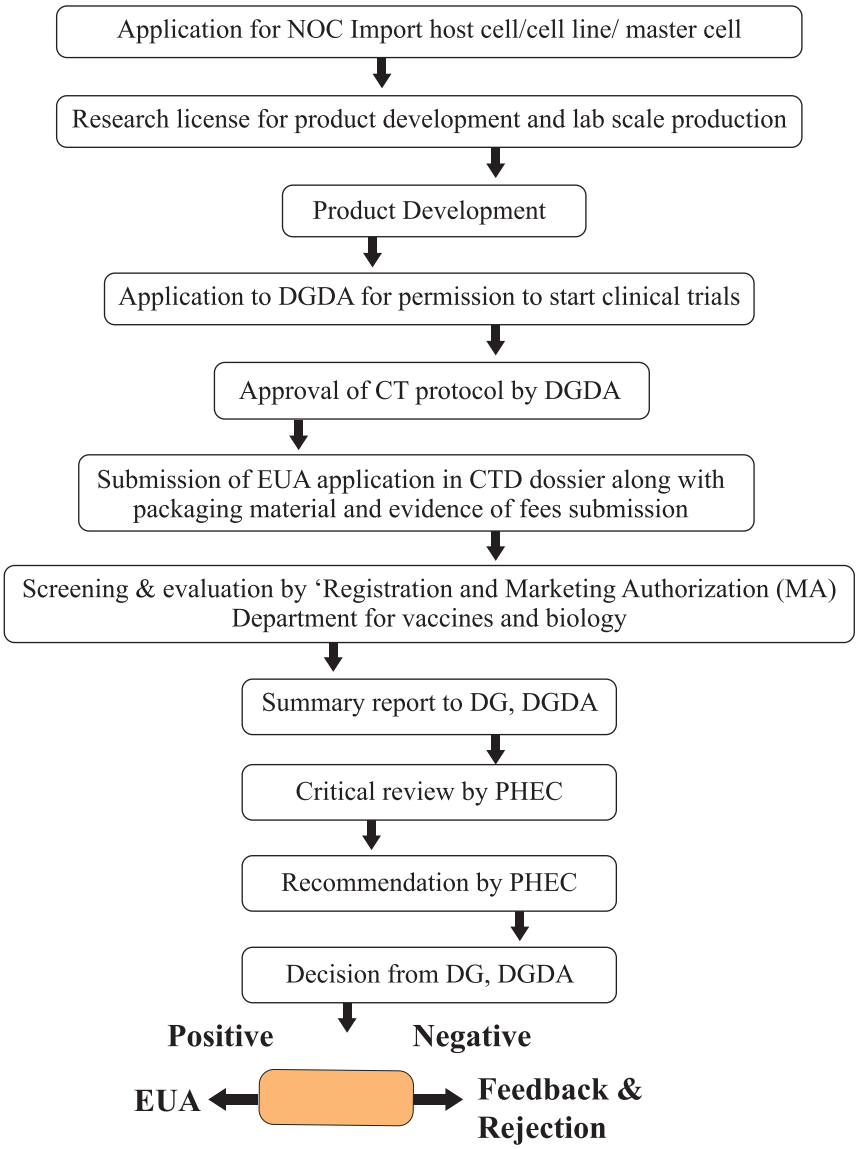
7.3.3. Local Manufacturing of Covid-19 vaccines through technology transfer

Generally, a technology transfer should include relevant documentation, information, and knowledge from the sending unit in order to enable the receiving unit to effectively execute the specified process or procedure in, for example, production and quality control. A successful transfer of technology should result in documented evidence that the receiving unit can routinely reproduce the transferred product, process, or proceed in compliance with a predefined set of specifications as agreed between the sending unit and the receiving unit. In the case of technology transfer of Covid-19 vaccines in Bangladesh, an applicant is required to submit appropriate evidence of technology transfer as per required documents mentioned in Section 7.1



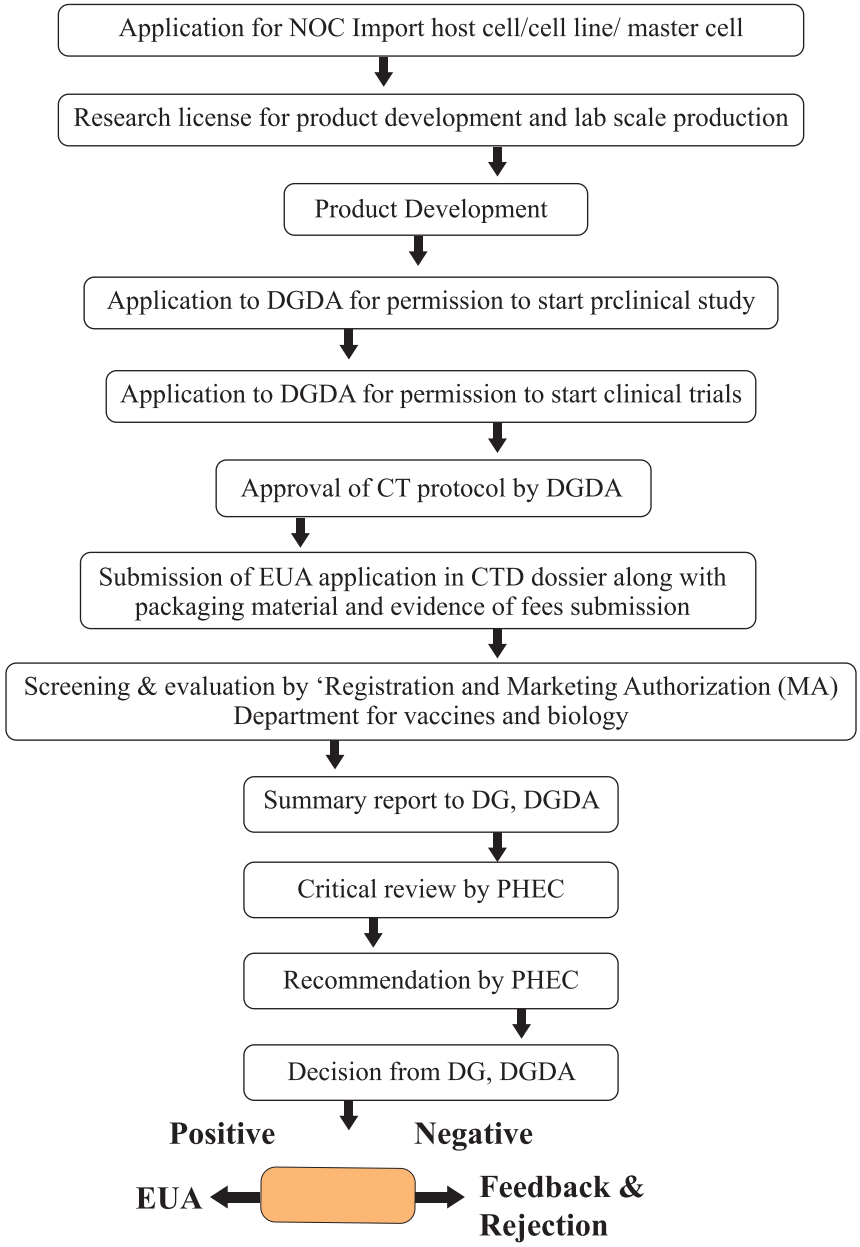
7.3.4 Locally produced Covid 19vaccines from Master Cell Bank (MCB) which is approved in

The steps involved in the regulatory pathway for locally manufactured vaccine produced from Master Cell Bank (MCB) which is approved in other countries are given below:



7.3.5 Indigenous or locally developed Covid-19 vaccines

The steps involved in the regulatory pathway for indigenous or locally developed Covid-19 vaccines are given below:



8. Risk-based Approach of Applying Regulatory Cooperation Mechanism upon Issuing EUA

If it is required, any neighboring NRA/WHO listed authorities or any other regulatory network that is willing to cooperate with DGDA in establishing an integrated regulatory cooperative mechanism/link for jointly evaluating the COVID-19 vaccines or task sharing, it is also required to establish the mechanism through a cooperation agreement between/among DGDA and cooperating NRA(s).

9. Risk-based Approach of Determining Validity of EUA

- The EUA of Covid-19 vaccine will have the validity until the date after 6 months of transition from EUA to full marketing authorization. After the transition of EUA to full marketing authorization notice, the EUA holder should apply for full marketing authorization, to get within 6 months.
- The transition decision will depend on the end of the pandemic (following declaration from WHO), sufficiency of supply versus demand, transition from EUA system to full marketing authorization in other countries, or any guidance from WHO even during the pandemic period.
- The validity of EUA may be ended upon decision of DGDA at any time based on guidelines from WHO, WHO listed authorities/SRA/other NRA to be relied on.

10. Withdrawal and Suspension of Emergency Use Authorizations

EUA of a Covid-19 vaccine may be canceled, revoked, or suspended based on following issue(s):

- Unacceptable post-EUA safety and efficacy data as recommended by the relevant committee(s)
- Decision of WHO for delisting the vaccine from WHO EUL
- Published safety/alert/signal by the WHO
- Any other relevant data that supports the cancelation, revocation, and suspension.

11. Criteria for the Evaluation of COVID-19 Vaccines

General Considerations

Format and content of an application	The application should be formatted according to the International Council for Harmonization CTD guidelines. Annex 2 refers the Vaccine Prequalification Dossier.
Screening of applications	A vaccine's CTD is expected to contain sufficient information to support the product's quality, effectiveness, immunogenicity, and safety, as well as evidence that such information justifies the vaccine's wide use. At this point, queries may be issued to the applicant, and acceptance of the application for review will be conditional upon satisfactory responses.

Additional non-clinical information

The CTD dossier requires the presentation of a summary table of non-clinical studies. Additional information on non-clinical studies may be requested by the clinical reviewers whenever necessary, and if this is anticipated by the applicant, such information should be included in the application. If novel adjuvants are used, relevant non-clinical data, as recommended in the WHO guidelines on the non-clinical evaluation of vaccine adjuvants, must be submitted.

Assays for vaccines with multiple components or adjuvants should be measured with either a multiplex assay or separate single assays. The assays used for immunogenicity evaluation should be validated for their intended purpose and calibrated against WHO international standards where available.

Clinical Assessment

Clinical development program	The applicant should provide a tabulated summary of the clinical development study in one or more table(s) in the CTD dossier. A tabular synopsis of the clinical development study in one or more tables should be included in the CTD dossier by the applicant.
Requirement for the protocols of clinical trials that support application	The English version of the protocols of the clinical trials supporting the application must be provided by the applicant. The protocols should be the final approved versions, incorporating all amendments.
Evidence of Ethical Committee approval of clinical trials	The summary is expected to include evidence of the clinical trial's approval by competent ethical committees, as well as information regarding their contact information in CTD. If the clinical trial has been conducted in Bangladesh, it is required to provide sufficient evidence of approval from DGDA and ethical clearance from the Bangladesh Medical Research Council.
Evidence of good clinical practices (GCPs) for each trial conducted	In absence of a certificate of GCP compliance from the responsible NRA, applicants must submit evidence of GCP compliance for each trial, such as independent monitoring of trial conduct, sponsor audits, available NRA inspection reports, or Data and Safety Monitoring Board reports, as well as information regarding their contact information. If the clinical trial has been conducted in Bangladesh it is required to provide the sufficient evidence of compliance of GCPs and/or a certificate from DGDA regarding GCP compliance.

Evidence for registration of each clinical trial	The applicant should provide a tabulated summary of the clinical development study in one or more table(s) in the CTD dossier. A tabular synopsis of the clinical development study in one or more tables should be included in the CTD dossier by the applicant.
Clinical trial design	The English version of the protocols of the clinical trials supporting the application must be provided by the applicant. The protocols should be the final approved versions, incorporating all amendments.
Statistical considerations	The summary is expected to include evidence of the clinical trial's approval by competent ethical committees, as well as information regarding their contact information in CTD. If the clinical trial has been conducted in Bangladesh, it is required to provide sufficient evidence of approval from DGDA and ethical clearance from the Bangladesh Medical Research Council. In absence of a certificate of GCP compliance from the responsible NRA, applicants must submit evidence of GCP compliance for each trial, such as independent monitoring of trial conduct, sponsor audits, available NRA inspection reports, or Data and Safety Monitoring Board reports, as well as information regarding their contact information. If the clinical trial has been conducted in Bangladesh it is required to provide the sufficient evidence of compliance of GCPs and/or a certificate from DGDA regarding GCP compliance.
Clinical trial endpoint assays—relevance, validation, and accreditation	Any serological correlate of protection used in the analyses must be justified and supported with the best scientific evidence available. Assays should consider the assessment of a functional antibody response along with immunoglobulin serum titre unless the immunoglobulin measured is clearly demonstrated as an immune correlate of protection. Evidence should be provided of endpoint immunogenicity assay relevance and standardization. Assay results should be reported in international units wherever possible. The laboratory should be identified and evidence of competence or accreditation to conduct these assays should be provided. The assays should be validated and run in a central laboratory, if possible.

Vaccine lots used in clinical studies and lot-to-lot consistency studies	Manufacturing consistency for vaccine candidate lots used in clinical trials should be shown and documented thoroughly. CMC consistency data must be submitted if clinical lot-to-lot consistency has not been shown.
Follow-up in clinical trials	As immune responses to the vaccine wane, study participants should be followed for COVID-19 outcomes for as long as possible (at least one to two years), to assess duration of protection and the potential for vaccine-associated enhanced disease. The condition for immunogenicity outcomes follow-up usually covered by protocol approval process and decision for the timeline "at least one to two years" is provided by clinical trial advisory committee of DGDA.
Requirement for RMP, or equivalent document as part of the CTD	RMPs, including PV plans, are part of modern risk management strategies required for vaccines. This plan should include actions designed to address all important identified and potential risks.
Specific data should be submitted to answer the questions	Please find the list of questions in Annex 8.

Manufacturing and Quality Control

Information on CMC: a list of each site where the product is manufactured, including relevant information about each site and the current status of the manufacturing site(s) with respect to current good manufacturing practice (GMP) requirements should be provided.

Information during application	The complete information of CTD Module 3 must be submitted during the application.
Drug substance	● **Manufacturer(s)** □ The manufacturer and manufacturing sites ● **Description of manufacturing process and process controls** □ A flow diagram depicting the manufacturing process from starting materials (Master and Working Cell Banks, Master and Working Seeds, and biologically derived starting materials) to the drug substance should be provided. □ Relevant information for each stage of the upstream and downstream processes should be included. Critical steps and critical intermediates for which specifications are established should be identified. A description of each process step in the flow diagram should be provided, including major equipment and process controls, including in-process tests and operational parameters, with acceptance criteria. Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided. If applicable, reprocessing procedures with criteria for reprocessing of any intermediate or the drug substance should be described. A description of the filling procedure for the drug substance, process controls (including in process tests and operational parameters), and acceptance criteria should be provided. ● **Cell banking system, characterization, and testing** □ A complete characterization of the cell banks should be supplied, including viral safety tests, in accordance with applicable WHO guidelines and should include viral safety studies. Information on the cell banking system should include quality control activities and cell line stability during production and storage (including procedures used to generate the Master and Working Cell Bank(s). ● **Characterization of master and working seed** □ Full characterization of master and working seed and complete history of the virus used to prepare the virus seed.

Information during application	The complete information of CTD Module 3 must be submitted during the application.
	● **Controls of critical steps and Intermediates** □ Tests and acceptance criteria for all critical steps (with justification including experimental data) should be provided for all critical steps of the manufacturing process to ensure that the process is controlled. ● **Process validation and/or evaluation** □ Process validation (based on quality risk-based approach) and demonstration of consistency of production at the production scale used for the lots to be distributed should be provided. □ Sufficient information should be provided on validation and evaluation studies to demonstrate that the manufacturing process is suitable for its intended purpose and to substantiate selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g., cell culture, harvesting, purification, and modification). ● **Analytical method validation** □ If novel test methods have been developed for potency tests and other critical assays, full description of the test development and qualification/ validation must be provided. □ The analytical procedures and corresponding validation should be cross-referenced or provided as part of justifying the selection of critical process controls and acceptance criteria. ● **Manufacturing process development** □ A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, clinical, scale-up, pilot, and, if available, production scale batches. ● **Control of drug substance** □ The specification for the drug substance should be provided and justified. □ Analytical procedures for testing of the drug substance should be validated and standard testing procedures must be provided. □ Description of batches and results of batch analyses should be provided to demonstrate lot consistency. ● **Reference standards or materials** □ Information on reference standards or reference materials should be provided

Information during application	The complete information of CTD Module 3 must be submitted during the application.
	● **Container closure system** □ A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. ● **Stability** □ This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life, where relevant. The post-approval stability protocol should be included.
Drug product	● **Manufacture** □ Manufacturer(s) of drug product, filler/packagers must be indicated for the vaccine that will be submitted for EUA. ● **Pharmaceutical development** □ The pharmaceutical development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. □ This section should also identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance, and drug product quality. ● **Components of the drug product** □ **Drug substance** 1. The compatibility of the drug substance with excipients/ stabilizers/a djuvants listed should be discussed. 2. If the manufacturer of the drug substance is different from the manufacturer of the drug product, it should be indicated. □ **Excipients, stabilizers, adjuvants** 1. The choice of excipients/stabilizers/adjuvants listed, their concentration, and their characteristics that can influence the drug product performance should be discussed relative to their respective functions.

Information during application	The complete information of CTD Module 3 must be submitted during the application.
	● **Formulation development** □ A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. ● **Manufacturing process development** □ The selection and optimization of the manufacturing process, in particular its critical aspects, should be explained. Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in finished product that can influence the performance of the product should be discussed. ● **Container closure system** □ The suitability of the container closure system used for the storage, transportation (shipping) and use of the drug product should be discussed. ● **Compatibility of diluents** □ If the vaccine is lyophilized, the compatibility of the drug product with reconstitution diluent(s) or dosage devices—if applicable—should be addressed to provide appropriate and supportive information for the labeling. ● **Batch formula** □ A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards. ● **Description of manufacturing process and process controls** □ A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests, or final product controls are conducted should be identified. A narrative description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. □ Equipment should, at least, be identified by type and working capacity, where relevant. □ Steps in the process should have the appropriate process parameters identified.

Information during application	The complete information of CTD Module 3 must be submitted during the application.
	● **Controls of critical steps and intermediates** □ Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps of the manufacturing process, to ensure that the process is controlled. Information on the quality and control of intermediates isolated during the process should be provided. ● **Process validation and/or evaluation** □ Process validation (based on quality risk-based approach) and demonstration of consistency of production at the production scale used for the lots to be distributed should be provided. In relevant cases, Process validation protocol with commitment letter should be submitted to conduct process validation of first 03 commercial lot (after getting EUA/annexure approval with condition). □ Use of multiple sites for production of drug product should be supported by demonstration of analytical comparability. ● **Control of drug product** □ The specification(s) for the drug product and the analytical procedures used for testing the drug product should be provided. □ Justification for the proposed drug product specification(s) should be provided. ● **Control of excipients, stabilizers, adjuvants** □ The specifications for excipients and the analytical procedures used for testing the excipients should be provided, where appropriate. □ Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate. □ Justification for the proposed excipient specifications should be provided, where appropriate. □ For excipient(s) and adjuvants used for the first time in a drug product or by a new route of administration, full details of manufacture, characterization, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance format. ● **Reference standards or materials** □ Information on the reference standards or reference materials used for testing of the drug product should be provided.

Information during application	The complete information of CTD Module 3 must be submitted during the application.
	● **Stability** □ The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life. □ Generated complete stability data with commercial lots should be submitted after EUA. ● **Post-approval stability protocol and stability commitment** □ The post-approval stability protocol and stability commitment should be provided. As data for real-time stability will be limited at the time of submission, updated information will be part of the post-listing commitments
Changes	If changes in the manufacturing process are introduced before the assessment is finalized or after the listing, these must be reported and all information provided for evaluation before the final report is prepared. Post-listing changes must also be reported.
Inspection reports	Inspection report(s) from the responsible NRA showing compliance with GMP requirements should be provided. In cases where an inspection was deemed not required, a valid GMP certificate for the facility should be provided.
Labeling	● **Vial label, carton label, and package insert should follow the models provided by WHO.** □ Summary of product characteristic (information for health care provider) □ Patient information leaflet □ Container labelling □ Any other instructional materials provided to the user □ A plan to help assure that prospective recipients and health care providers are adequately informed about the uncertainties regarding both the potential benefits and risks □ Storage condition should be mentioned on the vial and packaging

12. Post-authorization Activities

12.1. Lot release

Vaccines should be manufactured in accordance with GMP and tested by the vaccine manufacturer for quality and safety. Such vaccines should also undergo quality control testing (with a certificate of analysis) and be released by the responsible NCL in accordance with WHO's Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities (and should be accompanied by lot release certificate).

DGDA will adopt a reliance-based approach in case of vaccines coming from reliable sources and will only test physical parameters and review basic required documents. The lot release certificate of the responsible NRA/NCL of the producing country shall be duly recognized. The required documents for expedited lot release are:

- Summary lot protocol
- Q-tag or data logger reading
- Certificate of Analysis
- Lot release certificate of NCL or Official Medicines Control Laboratory from country of origin

In case of local manufacturing from bulk and indigenous vaccine/tech transfer vaccine, a full laboratory test report from any WHO functional laboratory is required for the first three batches or numbers of batches decided by DGDA/NCL, and physicochemical parameters, sterility, and endotoxin tests will be performed by the DGDA NCL vaccine wing. Further full laboratory testing will be decided on a case-by-case basis, based on the outcome of the risk-based assessment. The procedures adopted should ensure that vaccines are deployed as quickly as possible.

12.2. Monitoring of vaccine storage facilities

DGDA will form the following vaccine monitoring teams to monitor COVID-19 vaccine storage conditions:

- An inspection team to inspect the storage facilities where the vaccine will be stored
- An inspection team to receive vaccines and check the data logger and physical parameter of the vaccines at the airport
- Formation of a team with DGDA officers on a risk-based approach at the district level to receive/monitor vaccine and data logger

12.3 Post-authorization monitoring

12.3.1 Risk management plan

To safeguard against any harm linked with the usage of products, an RMP should be in place. The manufacturer will submit the RMPs, which outline a series of activities aimed at identifying, characterizing, preventing, or minimizing the risk associated with the product; evaluating the vaccination's effectiveness; and communicating the risk information to the national EPI program and other relevant stakeholders. Based on available adverse events of special interest, the RMP could be developed and implemented.

12.3.2 Pharmacovigilance and safety surveillance

In general, the DGDA performs as Bangladesh's National Pharmacovigilance Center and is linked to the WHO-Upsala Monitoring Center, a global PV platform. Since the government's COVID-19 vaccination campaign began, the DGDA has devised a PV protocol for the COVID-19 vaccine, with the goal of ensuring its safety, quality, and efficacy. PV activities of COVID-19 vaccines will be performed based on

13. Post-authorization data submission requirement

12.3.2 Pharmacovigilance and safety surveillance

Emergency Use Authorization (EUA) once authorized with limited data in specific area of requirements like clinical trial, safety surveillance & pharmacovigilance, process validation of three consecutive production batches and real time study report, the EUA holder should submit following data to DGDA on timely manner:

13.1 Further clinical trial study data (if conducted)

13.2 Continuous safety monitoring data

13.3 Real time stability data

13.4 Evidence data/ document due to change control

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20 DCVMN. Workshop by CEPI: Best Practices for Tech Transfer. Accessed Oct. 19, 2021, at https://www.dcvmn.org/Workshop-by-CEPI-Best-Practices-for-Tech-Transfer

Annexes

Annex 1: Application Format for Emergency Use Authorization

[Must be Submitted in Official Pad with full address]

Reference no: ……..... Date: ……

To

Director General
Directorate General of Drug Administration
Aushad Bhaban, Mohakhali, Dhaka-1212

Subject: Application for Emergency Use Authorization of COVID-19 vaccine [name of vaccine] in Bangladesh

COVID-19 Vaccine: [name of the vaccine]

Dear Sir,

We ……. hereby submit our applications for the below:

Name of COVID-19 vaccine:

Type of the vaccine and presentation:

The target indication for [name of vaccine] is:

Description of intended use of Vaccine:

Category of applied vaccine for EUA application-

Imported Covid-19 finished vaccine

- Indigenous Covid-19 vaccine development and local production
- Local manufacturing of Covid-19 vaccine from imported bulk
- Local manufacturing of Covid-19 vaccine through technology transfer
- Local production of Covid-19 vaccine from Master Cell Bank (MCB) which is approved in other countries
-

We are submitting the following documents for your perusal:

Imported Covid-19 finished vaccine (for reliance and recognition)

Documents	Yes	No
Evidence of European Medicine Agency (EUA) by the NRA in the country of origin		
Evidence of EUA/EUL/CMA any of the 7 countries (USA, UK, Switzerland, Germany, France, Australia, and Japan and/or EMA or WHO EUL		
The review report of the referring regulatory authority for reliance		
The CTD dossier to be submitted to DGDA (if it is required by DGDA).		
RMP for applied Covid-19 vaccine to be submitted by local agent/ manufacturer.		
Proper Labeling and PIL		
SmPC should be submitted		

Documents	Yes	No
Preclinical study report		
Phase I phase II, and phase-III full study report		
Dossier in CTD format with complete CMC data		
Evidence of EUA /Registration by the NRA in the country of origin.		
Risk Management Plan (RMP) for applied Covid-19 vaccine to be submitted by local agent/ manufacturer.		
Proper labeling and PIL		
SmPC should be submitted.		

Indigenous or locally developed Covid-19 vaccine

Documents	Yes	No
Permission documents (NOC) for importing master seed/ cell line for target vaccine.		
Research license of the manufacturer from DGDA. (Form 17 of Bengal Drug Rule 1946)		
Preclinical study report.		
Clinical trial protocol to be approved by DGDA, having prior ethical clearance from BMRC.		
Phase-I phase-II & phase-III satisfactory full study report.		
Complete Dossier in CTD format with full CMC data		
Risk Management Plan (RMP) for applied Covid-19 vaccine to be submitted by the manufacturer.		
Proper labeling and PIL		
SmPC should be submitted		

Locally manufactured Covid-19 vaccine through technology transfer

Documents	Yes	No
Agreement copies of technology transfer between sending & receiving company		
Transfer of starting materials including cell bank and seeds, manufacturing process, analytical methods.		
Evidence of demonstration of analytical comparability at commercial scale – "process performance qualification" batches		
Evidence of comparability of commercial scale batches with clinical batches to demonstrate safety and efficacy (A comparability study between the vaccine of tech-transfer plant and vaccine of sending unit with a reasonable number of subjects).		
Product performance qualification from two different sites of sending unit and receiving unit.		
WHO TRS 961 Annex-7, can also be referred.		
Research license (Form 17 of Bengal Drug Rules 1946)		
Audit report of Sending Unit		
Evidence of EUA by the NRA in the country of origin. EUA/ registration from any of the 7 countries (USA, UK, Switzerland, Germany, France, Australia, and Japan, and/ or EMA or WHO EUL (if any).		
Preclinical study report		
Phase-I phase-II & phase-III full study report		
Complete Dossier in CTD format		
RMP for applied Covid-19 vaccine to be submitted by the manufacturer.		
Proper labeling and PIL		

Locally produced Covid 19 vaccine from Master Cell Bank (MCB) which is approved in other countries

Documents	Yes	No
Agreement copies of Master Cell Bank (MCB) transfer between innovator & receiving manufacturer		
Research license from DGDA for developing vaccines using master cell bank		
Permission documents (NOC) for importing master seed/ cell line for target vaccine.		
Evidence of EUA of the vaccine (Reference Vaccine) by the NRA which contains same Cell Line		
Preclinical study report of the MCB provider / Innovator/carried by local developer		
Clinical trial protocol to be approved by DGDA, having prior ethical clearance from BMRC.		
Comparative Immunogenicity Clinical Trial between Reference vaccine vs Locally produced vaccine (Non-inferiority study design)		
Complete Dossier in CTD format with full CMC data		
Risk Management Plan (RMP) for applied Covid-19 vaccine to be submitted by the manufacturer.		
Proper Labelling and Product Information Leaflet (PIL).		

Other Documents

Sl.	Documents		Yes	No
	Proof of deposit of applicable fees as per DGDA requirements			
	Contact person: [name of applicant's contact person] Title Tel:			

Signature:

Name:

Title:

Date:

Annex 2: Vaccine Prequalification Dossier/ICH CTD Format

(Adopted from: https://www.who.int/immunization_standards/vaccine_quality/VaccinePQ-dossier_Dec2017.pdf?ua=1)

Vaccine Prequalification Dossier
Introduction

The current process for prequalification of vaccines states that once a product is eligible for prequalification evaluation the manufacturer must submit a product summary file (PSF) according to the Procedure for Prequalification of Vaccines (WHO Technical Report Series 978/WHO TRS 978), http://www.who.int/immunization_standards/vaccine_quality/TRS_978_61st_report_Annex_6_PQ_vaccine_procedure.pdf?ua=1, in either Microsoft Word or PDF format, which should be fully up to date and written entirely in English.

The procedure also states that the common technical document (CTD) format can be accepted so long as (a) a detailed cross-referencing of contents is presented; and (b) those aspects required by WHO but not included in the CTD requirements are presented. The global use of CTD format has increased significantly since the last revision of the vaccine prequalification procedure. Most manufacturers have a prepared dossier in CTD format that they have used to register the product in one or more countries, and many countries that import prequalified medicines require submission of a CTD format dossier for registration of the products. The Prequalification team vaccine assessment group [PQT/VXA] has decided to adopt a CTD based format for the Vaccine Prequalification dossier. This should reduce the regulatory burden on companies as they do not need to maintain dossiers in multiple formats. Modules 2,3,4 and 5 will have common format and content to that maintained for submission to other authorities [see Summary headings and link to the International Council for Harmonization (ICH) guidance later in this document]. Module 1 contains information not included in the other modules but required to assess the product for prequalification purposes.

The Dossier should be submitted in English. Until the end of the grace period (to be announced)

Content of the Vaccine Prequalification Dossier

Module 1: Administrative and Product information

1.1 Table of Contents

The overall table of contents should include all modules from 1 to 5

1.2 Correspondence

1.2.1 Copy of the letter from the manufacturer indicating the intention to submit an application for prequalification of the vaccine and of the acknowledgement from WHO of the acceptability for submission.

1.2.2 Agreed minutes of any pre-submission meetings between WHO/PQT and the applicant.

1.3 Site Master file

(Consistent with WHO Guidance document: WHO Technical Report Series, No 961, Annex 14, 2011)

1.4. Compliance information

1.4.1. Certificate of Establishment Licensing, if required and provided by the National Regulatory Authority (NRA) of the country of manufacture.

1.4.2. Copy of GMP certificate, or other evidence of GMP compliance issued by the NRA of the country of manufacture. Report (English translation if required) of the last GMP inspection (which included in its scope the production of the product submitted for prequalification) by the NRA of the country of manufacture

1.4.3. Copy of marketing authorizations for all formulations and presentations in the Country of Manufacture and/or the Country of Reference of the vaccine submitted for prequalification, or the EMA scientific opinion for article 58 products

1.4.4. Policy for assignment of date of manufacture of each component as well as the final product and diluents.

1.4.5 If the vaccine contains or consists of genetically modified organisms (GMOs), supply a copy of the Environmental Risk Assessment (GMO means an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.1
Environmental risk assessment means the evaluation of the risk to human health and the environment (which includes plants and animals) connected with the release of GMOs or products containing GMOs.)1

1.5. Vaccine composition, presentations and scheduling information

1.5.1. Description of presentations available to UN agencies, including diluent (if applicable), combination products, forms, dose sizes and type of containers and indicate Vaccine Vial Monitor (VVM) type and location.
a). Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the d eliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC
b). Council Directive 90/220/EEC of 23 April 1990

1.5.2 Vaccine temperature stability profile
Additional to stability information in 3.2.P.8, please provide any additional stability data required to support the assignment of VVM type or to support any on-label claim for elevated temperature storage according Extended Controlled Temperature Conditions guideline (http://who.int/biologicals/areas/vaccines/ectc/en/).

1.5.3 Description of immunization /administration devices to be delivered with the vaccine

1.5.4 Recommended schedule and route of administration

1.5.5 Artworks or mockups of labels of primary containers and secondary packaging for the product (including diluents. If applicable). Artworks and mockups may be submitted in English for review of the content.

1.5.6 Samples of package inserts (in English) to be used for supply through UN agencies. After finalization of the review of the English version, translation to other languages required by UN procurement agencies (currently French, Portuguese, Russian and Spanish) should be provided.

1.5.7 Template of lot summary protocol to be provided to UN agencies, in compliance with WHO- recommended format.

1.5.8 Self-assessment against programmatic suitability for prequalification (PSPQ) criteria http://apps.who.int/iris/bitstream/10665/148168/1/WHO_IVB_14.10_eng.pdf

1.6. Supplemental pre-clinical and clinical Information (Pre- and post-marketing)
Note: Where data is not already included in the NRA submission or modules 2-5 submitted for Prequalification

1.6.1 List of pre-clinical studies sponsored by applicant – not included in Module 2.6 and Module 4 of the application- including any conclusion(s) including preclinical studies performed after initial licensure of product (and the reasons for these studies)

1.6.2 List of all clinical trials sponsored by the applicant relevant for the application – not included in Module 5.2 of the application - which must contain:

- Location of study sites
- Number and age of subject
- Date of study
- Evidence of registration in clinical registry (part of ICTRP)
- Indication of whether the study complied with GCP
- Rational of each study must be included in the summary table
- Statement of final conclusions on safety and immunogenicity (and/or efficacy)

1.6.3 Cross reference to the final approved protocol by ERC and NRA1.6.4 List of any clinical trials that are known to be currently ongoing with the vaccine candidate, not relevant to the current PQ application including the summary of details of the study plan and expected date of result (for example, clinical trials being conducted for a different use indication and/or with a different age group, etc.).

1.6.5 List of other studies with applicant product – not included in Module 5 - for which the applicant is not the sponsor.
The applicant should make every effort to provide a list of all trials and, where applicable, observational studies relevant to the application that were not sponsored by the applicant but in which the product was evaluated. This list should be compiled from publications identified using an extensive literature search (details of which should be provided) and, in the case of co-licensure agreements, from any other company that holds a license for or a right to market the same product.

1.6.6 Complementary Clinical summary supporting the use of the product worldwide by UN agencies
Provide a detailed summary and interpretation of the safety and efficacy data obtained from the pre- licensure clinical studies and all studies performed in the post-licensure period that support the current prescribing information. The summary should pay particular attention to any data that are relevant to the use of the product worldwide in WHO recommended schedules (e.g. co-administration of other vaccines). In the absence of such data, the summary should provide a preclinical and/or clinical justification for the extrapolation of the existing data to the likely circumstances of use after prequalification. This summary should complement, and not replace, the summary written by an independent clinical expert described in

1.6.8.

Consistency of manufacturing for the vaccine lots used in clinical trials should be demonstrated and well documented. It is ideal that at least three lots with the same formulation intended for marketing are used in the late stages of the clinical development programme. However, a formal lot-to-lot consistency clinical study is considered only on a case-by-case basis, in particular when assessing vaccine formulations with inherent variability.

It is important to note that there are a number of important issues to consider in the event that the manufacturer decides to perform a lot-to-lot consistency clinical study to fulfil the requirements for vaccine licensure of a NRA. Vaccines used in clinical-consistency trials must have been manufactured at commercial scale. The study should be designed (and analysed) as an equivalence trial and have a pre-defined criteria and choice of parameters to conclude comparability.

Changes to the batch size used to produce the clinical lots will require additional information to support the change (e.g. scale-up). Depending on the manufacturing consistency data, additional clinical studies to support comparability to the clinical lots may be required. These issues should be decided in consultation with the WHO Prequalification Secretariat.

1.6.7 Assessment Report from the NRA(s)

Whenever possible, the applicant should provide the reference NRA assessment reports from the country of origin and/or country where the vaccine is initially licensed. Assessment reports for both initial licensure and any subsequent variations to the licence for changes relevant to clinical data are requested1.6.8. Clinical Independent expert report

Provide an independent clinical expert report on the clinical studies (evidence of expertise and independence should be provided). If the application for prequalification is based on the extrapolation of the existing clinical data to the likely circumstances of use after prequalification, and if the data are old or there is a doubt regarding the ethical or regulatory oversight of the trial, the report should discuss the degree of compliance with WHO GCP recommendations and current guidance regarding preclinical and clinical trials with vaccines.

1.6.9 Post-marketing Safety documentation

Safety data should be submitted both in the case of the initial application for prequalification evaluation and for reassessment purposes.

1.6.9.1 Outline of the post-marketing pharmacovigilance plan for the product or Risk Management Plan.

1.6.9.2. Initial evaluation of vaccines that have been in the market for more than five years or reassessment of already prequalified vaccines (The latest PSUR may be provided)

- Outline of the applicant's procedures for the collection, onward notification and assessment of adverse events.
- Listing of all reported AEFIs for the vaccine in question in the last five years or since the last WHO reassessment. As far as is possible from the reports received, applicants should list the type of reaction, lot number, date and place of immunization, patients' initials and age and, for immunization series, the dose number. A judgment of seriousness and whether or not the event was expected (in the light of the prescribing to the vaccine made by a clinician and, where relevant, by the applicant company or its independent clinical expert, should be included.

1.6.9.3 List of ongoing clinical studies for vaccines licensed within the last five years. Add a cross reference to Module

5 and any studies that may not be part of the CTD

This includes Phase IV studies or any active monitoring of safety profile of the vaccine.

1.7. Regulatory actions

1.7.1 Information on refusals, withdrawals, suspensions, including those initiated by the manufacturer

1.7.2. List of lots rejected by an NRA, if applicable

1.7.3. Restrictions on distributions and recalls of lots, including those initiated by the manufacturer

1.7.4. Clinical trial suspensions

1.7.5. Dosage or schedule changes since the initial marketing authorization in the country of manufacture and/or the country of reference 1.7.6. Changes in target populations since the initial marketing authorization in the country of manufacture and/or the country of reference.

1.8. Distribution information

1.8.1. Quantity of finished product distributed in the domestic market of the country of manufacture and/or the country of reference and exported in the last three years, by presentation. Clearly indicate if numbers refer to vials or doses.

1.8.2. List of countries where the product has received a Marketing Authorization, indicating if product has been s upplied in those countries.

1.8.3. Description of the release process by the NRA/NCL and recording system for distribution.

1.8.4 Summarize the packaging procedures for international shipments for UN agencies and the validation (according to relevant, current WHO guidelines) of this packaging.

The content of Modules 2, 3, 4, and 5 should be according to the major heading shown below, as described at http://www.ich.org/products/ctd.html

Module 2: Common Technical Document Summaries (As per ICH guidelines M4Q, M4S, M4E)

2.1 Common Technical Document Table of Contents (Modules 2–5)

2.2 CTD Introduction

2.3 Quality Overall Summary 2.4 Nonclinical Overview

2.5 Clinical Overview

2.6 Nonclinical Written and Tabulated Summaries Pharmacology Pharmacokinetics Toxicology

2.7 Clinical Summary Biopharmaceutic Studies and Associated Analytical Methods Clinical Pharmacology Studies Clinical Efficacy Clinical Safety Literature References Synopses of Individual Studies

Module 3: Quality (as per ICH M4Q)

3.1 Table of Contents of Module 3

3.2 Body of Data

3.3 Literature References

3.2. Appendices

Module 4: Nonclinical Study Reports (as per ICH M4S)

4.1 Table of Contents of Module 4

4.2 Study Reports

4.3 Literature References

Module 5: Clinical Study Reports (as per ICH M4E)

5.1 Table of Contents of Module 5

5.2 Tabular Listing of All Clinical Studies

5.3 Clinical Study Reports

5.4 Literature References

Annex 3: Communication Format if Any EUA Application Cannot Be Processed or Any Further Documents Required to Be Submitted

Government of the People's Republic of Bangladesh
Directorate General of Drug Administration
Ministry of Health and Family Welfare
Mohakhali, Dhaka-1212

Memo no: ……. Date: ……

To
Name of the applicant & address
……

Subject: Regarding documents required to continue further steps of Emergency Use Authorization of COVID-19 vaccine – [Vaccine Name]

In response to your letter number- …….. dated…….. for Emergency Use Authorization (EUA) for manufacturing/ importing the following vaccines into Bangladesh. The application has been evaluated/screened by the Registration and Marketing Authorization Department of Vaccines and Biologics and the application has been rejected due to incompleteness of the required documents. To continue further process of EUA application following documents are required to be submitted"

Name of the vaccine:
Vaccine details
Vaccine composition:
Vaccine presentation:
Packaging:
Name and full address of the manufacturer:
Manufacturer email and telephone number:
Vaccine marketing authorization holder
Indication
Name and address of the legal organization in the country:
Shelf life & Storage conditions:
The reasons of rejection of Emergency Use Authorization of [Vaccine Name]/ The List of the required documents-

1.

……

2.

……

3.

……

Signature

Annex 4: Format of the Summary Report

Government of the People's Republic of Bangladesh
Directorate General of Drug Administration
Ministry of Health and Family Welfare
Mohakhali, Dhaka-1212

Memo no: ……. Date: ……

Summary Report of the EUA Application of [vaccine name]

Date of the application	
Name of the vaccine	
Vaccine details	
Vaccine composition	
Vaccine presentation	
Packaging	
Name and full address of the manufacturer	
Manufacturer email and telephone number	
Vaccine marketing authorization holder	
Indication	
Name and address of the legal organization in the country:	
Shelf life and storage conditions:	

Application Fees

Proof of deposit of applicable fees as per DGDA requirements	Yes	No

Category of applied vaccine for EUA application-

- ★ Imported Covid-19 finished vaccine (for reliance and recognition)
- ★ Imported Covid-19 finished vaccine (for critical review)
- ★ Indigenous or locally developed Covid-19 vaccine
- ★ locally manufactured Covid-19 vaccine through bulk
- ★ Locally manufactured Covid-19 vaccine through technology transfer
- ★ Locally produced Covid-19 vaccine from Master Cell Bank (MCB) which is approved in other countrie

The documentation received during the application-

Imported Covid-19 finished vaccine (for reliance and recognition)

Documents	Yes	No
Evidence of EUA by the NRA in the country of origin		
Evidence of EUA/EUL/CMA any of the 7 countries (USA, UK, Switzerland,		
Germany, France, Australia, and Japan, and/ or EMA or WHO EUL		
The review report of the referring regulatory authority for reliance		
The CTD dossier to be submitted to DGDA (if it is required by DGDA).		
RMP for applied Covid-19 vaccine to be submitted by local agent/ manufacturer.		
Proper labeling and Product Information Leaflet		
Summary of product characteristics should be submitted		

Imported Covid-19 finished vaccine (for critical review)

Documents	Yes	No
Preclinical study report		
Phase-I phase-II & phase-III full study report		
Dossier in CTD format with complete CMC data		
Evidence of EUA by the NRA in the country of origin.		
RMP for applied Covid-19 vaccine to be submitted by local agent/ manufacturer.		
Proper labeling and Product Information Leaflet		
Summary of product characteristics should be submitted		

Indigenous or locally developed Covid-19 vaccine

Documents	Yes	No
Permission documents for importing master seed/ cell line for target vaccine.		
Research license of the manufacturer from DGDA. (form 17 of Bengal Drug Rule 1946)		
Preclinical study report.		
Clinical trial protocol to be approved by DGDA, having prior ethical clearance from BMRC.		
Phase-I phase-II & phase-III satisfactory full study report.		
Complete Dossier in CTD format with full CMC data		
RMP for applied Covid-19 vaccine to be submitted by the manufacturer.		
Proper labeling and Product Information Leaflet		

Local Manufacturing through bulk

Documents	Yes	No
Source validation certificate		
Evidence of EUA by the NRA in the country of origin		
Lot release certificate from NRA/ NCL of country of origin.		
Preclinical study report		
Phase-I phase-II & phase-III full study report		
Dossier in CTD format with complete CMC data.		
RMP for applied Covid-19 vaccine to be submitted by the manufacturer.		
Proper labeling and Product Information Leaflet		
Summary of product characteristics should be submitted		

Locally manufactured Covid-19 vaccine through technology transfer

Documents	Yes	No
Agreement copies of technology transfer between sending & receiving company		
Transfer of starting materials including cell bank and seeds, manufacturing process, analytical methods.		
Evidence of demonstration of analytical comparability at commercial scale – "process performance qualification" batches		
Evidence of comparability of commercial scale batches with clinical batches to demonstrate safety and efficacy (A comparability study between the vaccine of tech-transfer plant and vaccine of sending unit with a reasonable number of subjects).		
Product performance qualification from two different sites of sending unit and receiving unit.		
TRS 961 annex-7, can also be referred.		
Research license (Form 17 of Bengal Drug Rules 1946)		
Audit report of Sending Unit		
Evidence of EUA by the NRA in the country of origin.		
EUA/ registration from any of the 7 countries (USA, UK, Switzerland, Germany, France, Australia, Japan, and/or EMA or WHO EUL (if any).		
Preclinical study report		
Phase-I phase-II & phase-III full study report		
Complete Dossier in CTD format		
RMP for applied Covid-19 vaccine to be submitted by the manufacturer.		
Proper labeling and Product Information Leaflet		
Summary of product characteristics should be submitted		

Locally manufactured vaccine produced from Master Cell Bank (MCB) which is approved in other countries

Documents	Yes	No
Agreement copies of Master Cell Bank (MCB) transfer between innovator & receiving manufacturer		
Permission documents (NOC) for importing master seed/ cell line for target vaccine.		
Evidence of EUA of the vaccine (Reference Vaccine) by the NRA which contains same Cell Line		
Preclinical study report of the MCB provider / Innovator		
Clinical trial protocol to be approved by DGDA, having prior ethical clearance from BMRC.		
Comparative Immunogenicity Clinical Trial between Reference vaccine vs Locally produced vaccine (Non-inferiority study design)		
Complete Dossier in CTD format with full CMC data		
Risk Management Plan (RMP) for applied Covid-19 vaccine to be submitted by the manufacturer.		
Proper Labelling and Product Information Leaflet (PIL).		
Summary of product characteristics (SmPC) should be submitted.		

Summary: ----------

……..……..

Head

Registration and Marketing Authorization

Department for Vaccines and biologics

Directorate General of Drug Administration

Annex 5: Decision on Outcomes of EUA Procedures for Registration of COVID-19 Vaccine by the DGDA

Government of the People's Republic of Bangladesh

Directorate General of Drug Administration
Ministry of Health and Family Welfare
Mohakhali, Dhaka-1212

Memo no: ……. Date: ……

To

Name of the applicant & address

……

Subject: Emergency Use Authorization of COVID-19 vaccine – [Vaccine Name]

In response to your letter number- …….. dated…….. as per directive section- 4.2 (Kha) of The Drug Policy-2016 and notification published in the additional number of the Bangladesh Gazette dated on 17 May 2020 in page no: 3825-3826 which bears notification number- 45.00.0000.182.99.017.08-110 dated 13 May 2020 of Health Service Division of MOHFW, Director General of Drug Administration issues Emergency Use Authorization (EUA) for manufacturing/ importing the following vaccines into the Bangladesh-

Name of the Vaccine:

Vaccine details

Vaccine Composition:

Vaccine Presentation:

Packaging:

Name & full address of the Manufacturer:

Manufacturer email & telephone number:

Vaccine Marketing Authorization Holder

Indication

Name and address of the legal organization in the country:

Shelf life & Storage conditions:

Conditions of Emergency Use Authorization of [Vaccine Name]

1. ……

2. ……

3. ……

Signature
Director General
Directorate General of Drug Administration
Date

Government of the People's Republic of Bangladesh

Directorate General of Drug Administration

Ministry of Health and Family Welfare

Mohakhali, Dhaka-1212

Memo no: ……. Date: ……

To

Name of the applicant & address

……

Subject: Rejection of Emergency Use Authorization of COVID-19 vaccine – [Vaccine Name]

In response to your letter number- …….. dated…….. for Emergency Use Authorization (EUA) for manufacturing/ importing the following vaccines into Bangladesh. The Registration and Marketing Authorization Department for Vaccines and Biologics and Public Health Emergency Committee have evaluated the application and the application has been rejected for the below mentioned reason:

Name of the Vaccine:

Vaccine details

Vaccine Composition:

Vaccine Presentation:

Packaging:

Name & full address of the Manufacturer:

Manufacturer email & telephone number:

Vaccine Marketing Authorization Holder

Indication

Name and address of the legal organization in the country:

Shelf life & Storage conditions:

The reasons of rejection of Emergency Use Authorization of [Vaccine Name]

4. …….

5. …….

6. …….

Signature

Director General

Directorate General of Drug Administration

Date

Annex 6: Required Documents for Source Validation for Covid-19 Vaccines

1. Principal company profile.
2. Copy of valid manufacturing license.
3. GMP certificate issued by the licensing authority of country of origin. If local GMP certificate is not available, then DGDA may perform onsite audit.
4. List of countries where they export the same bulk.
5. Certificate of Analysis (COA) with specification of each API.
6. Comparability study report (physicochemical and biological with reference product)
7. Form-9 signed by authorized person of Principal Company.
8. Full Clinical Trial Report (CTD format) with complete CMC data along with master cell/cell line information from bulk manufacturer or satisfactory clinical trial report conducted in Bangladesh or other country with reference product.
9. Lot release certificate

Annex 7: Format for Evaluation Report

Government of the People's Republic of Bangladesh
Directorate General of Drug Administration
Ministry of Health and Family Welfare
Mohakhali, Dhaka-1212

Memo no: ……. Date: ……

Vaccine Name:

Vaccine Details:

Manufacturer/Importer:

Site:

The required documents have been submitted by the manufacturer/importer as per published guidance documents. The submitted documents ensure the following:

1. The product is manufactured and licensed in

☐ WHO EUL ☐ 7 countries (Please specify the country name) ..... ☐ Other countries ☐ Nowhere	Comments: (If any)

2. The Vaccine has already been registered and used in country of origin. The vaccine has been additionally licensed and used in _____other countries.
3. _____Number of Vaccine doses have been used so far in_____Countries.
4. The consistency of production, safety and potency has been verified from certificate of analysis provided by manufacturer/importer and National Control Laboratory of origin country.
5. The CTD dossier provided by manufacturer was screened by group and relevant sections on safety and efficacy we ere evaluated.
6. The documents submitted by applicant were verified from NRA of origin country and/WHO-EUL listing as published on NRA and WHO website.

Thus, based on the review of the available data on quality, safety and efficacy, this Committee considers that for dealing with and public health, the risk-benefit balance of this vaccine is:

	YES	NO
POSITIVE	□	□
NEGATIVE	□	□

The major objections are related to the following deficiencies (indicate all that apply if the outcome is negative):

	Yes	No
a) Quality	☐	☐
b) Safety	☐	☐
c) Efficacy/Immunogenicity	☐	☐
d) GMP, GLP, GCP compliance	☐	☐
e) Other	☐	☐

We have additionally consulted guidelines from WHO and regulatory bodies, WHO recommendations, international guidance documents, scientific reports, and publications.

Proposed post-authorization measures: (if any): (Yes □ /No □)

4. Final Recommendations and Remarks:

Signature
Chairman
Public Health Emergency Committee (PHEC)

Date

Annex 8: Specific Data Should Be Submitted to Answer the Following Questions

The applicant should consider whether, and how, their submission to EUA addresses the following questions The questions may not apply to all vaccine types.

Clinical efficacy

i. What is the evidence of an effect of vaccination on efficacy against COVID-19 (regardless of severity); mild symptomatic, moderate, and severe disease; hospitalizations and death. How does efficacy vary by age-group (children, younger adults, older adults), by sex, in pregnant and lactating women, and in specific co-morbidity risk groups?

- Measured as % vaccine efficacy and 95% confidence intervals, What is the evidence of an effect of vaccination on efficacy against SARS-CoV-2 infection?
- Measured as percentage vaccine efficacy and 95% confidence intervals
- Measured difference in viral load (PCR Ct values) in upper respiratory tract samples
- Measured as seroconversion to viral antigens not contained in the vaccine

iii. What is the evidence of the efficacy of post-infection immunization?

The WHO Target Product Profile should serve as a guide.

Immunogenicity

i. What is the evidence of induction and levels of neutralizing antibodies and of immunoassay-measured antibodies after partial or full primary vaccination in the different groups listed above (under clinical efficacy)?

- Measured as concentrations/titres of antibodies or seroconversion rates versus pre-vaccination values or, if a correlate is established, seroprotection rates.

ii. What is the evidence that immunobridging can be used to estimate vaccine efficacy in specific groups for which clinical efficacy is not available from clinical trials? This is important as, based on the inclusion/exclusion criteria of the currently ongoing large phase III trials, certain population and age groups have in some instances been excluded from participation (e.g. infants, those with co-morbidities, pregnant and lactating women, etc.).

iii. What is the evidence of persistence of protective / neutralizing / immunoassay-measured antibodies over time (over an interval lasting as long as feasible after completion of partial or full primary vaccination in the different groups listed above?)

iv. For vaccines with regimens of two or more doses, what is the evidence for interchangeability of vaccines?

Effectiveness

i.What is the evidence from observational post-implementation studies on vaccine effectiveness (in different populations)?

ii. What is the evidence of effectiveness of the intervention in specific subpopulations?

iii. What is the evidence of vaccine effectiveness after a single dose of vaccination or after using an incomplete schedule?

Duration of protection

What is the evidence of continued efficacy/ effectiveness of vaccination (in different populations) after completion of 1 or 2 dose course of immunization in the different at-risk populations (e.g. elderly)? This can be measured as decay in antibody titers over time.

Questions on indirect effects and biomarkers

Transmission

i. What is the evidence of the relation of viral shedding post-vaccination and SARS-CoV-2 transmissibility?

Measured as viral load among those infected

Other measures of infectiousness (e.g., subgenomic viral RNA)

ii. What is the evidence of an effect of immunization on the duration of shedding of SARS-CoV-2?

Measured as viral shedding through active surveillance of respiratory tract sampling in vaccinated and control i ndividuals

iii. What is the evidence of reduction in new SARS-CoV-2 infections in contacts of vaccinated as compared to

unvaccinated study subjects who become infected?

(For example: this could be answered by adjunctive protocols to large randomized controlled trials (RCTs), comparing infection rates among contacts of vaccinated and control study subjects)

iv. What is the evidence of reduced rates of infection in unvaccinated individuals in vaccinated populations?

(For example: this could be answered by cluster randomized studies focusing on infection rates in un-vaccinated members of vaccinated clusters – if logistical and ethical challenges of undertaking such trials could be overcome)

Biomarkers and correlates of protection

i. What is the evidence from functional antibody assays /neutralizing antibody assays? What is the evidence of their standardization and use in phase 1-3 clinical trials? What is the evidence that one or more of the described assays have been correlated to clinical protection?

ii. What is the evidence from immunoassays used to assess responses to vaccines? What is the evidence that these assays have been correlated to functional/neutralization assays or to clinical protection?

iii. What is the evidence concerning characterization of T cell responses, both to naturally acquired infection and to v accination that are (expected to be) protective?

iv. What is the evidence that certain aspects of immune responses to vaccination (e.g. predominant development of certain types of CD4+ T cells, such as T helper cells (Th) type 1,overTh type 2 or Th type 17 and their distinct cytokine production patterns, elicited by the specific vaccine) are predictive of effective protection and/or absence of vaccine enhanced disease when exposed to SARS-CoV-2 following immunization?

Target populations

i. How to extrapolate to potential target populations (age, ethnicities, co-morbidities) for whom there may be insufficient data (effectiveness, safety). It is acknowledged that data for all target groups may not be available when vaccines is considered for EUL/PQ in the early stages of the response to COVID-19.

Vaccine safety

i. What is the evidence on rates of local and systemic reactogenicity signs and symptoms (e.g., pain at injection site, fever, headaches, malaise, etc.) using standardized definitions and ascertainment methods in the different target-populations and what is the impact on tolerability of the vaccine?

ii. What is the evidence of disease enhancement in either vaccine recipients subsequently exposed to the virus, in vaccine

recipients with prior infection/pre-existing antibodies or those with incomplete immunization schedule?

iii. What is the evidence of any suspected unexpected serious adverse reactions (SUSARs), including but not limited to cases of (or absence of cases of) inflammatory disease or other manifestations following vaccination (e.g., mimicking pediatric multisystem inflammatory syndrome and toxic-shock - PIMS-TS)?

iv. What is the evidence of adverse events of special interest, related or possibly related serious adverse events and medically attended adverse events (MAAE) after vaccination (in all vaccinees with a minimum of 3 months,

preferably up to 12 months, of follow-up after completion of administration of all doses in the vaccination schedule; in line with regulatory requirements and the points to consider for manufacturers of COVID-19 v accines3)?

v. What is the evidence of adverse maternal and neonatal outcomes after vaccination of pregnant women?

vi. What is the evidence on co-administration of COVID-19 vaccines with other vaccines included in routine immunization schedule leading to decreased immune response to either vaccine?

vii. What is the evidence that vaccinated persons are less likely to adopt other measures to reduce the risk of infection?

Manufacturers should provide safety data as indicated in the list of adverse events of special interest proposed by WHO GACVS.27 The Brighton Collaboration standardized case definitions, whenever available, should be applied to assess level of diagnostic certainty.

Benefit Risk Assessment Report

A detailed review of available data and objective Benefit and Risk assessment of the vaccine [e.g., via the appropriate Brighton Collaboration standardized templates for benefit–risk assessment of vaccines (by technology platforms)] should be provided at the time of submission.