Food and Drug Authority of Ethiopia (EFDA)

Guidance for managing Dossier applications of the Medicinal products proposed for public Health Emergency situation

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Contents

Abbreviation

cGMP	Current Good Manufacturing Practice
CTD	Common Technical documentations
EFDA	Ethiopian Food and Drug Authority
EPSA	Ethiopian Pharmaceutical Supply Agency
EPHI	Ethiopian Public Health Institute
EUA	Emergency Use Authorization
EUL	Emergency Use list
MoH	Ministry of Health
NRA	National Medicine regulatory Agencies
PHE	Public Health Emergency
SRA	Stringent regulatory Agency
WHO	World Health Organization
WLA	WHO listed Authority

1. Introduction

Public health emergency (PHE) is a true test for the medical products supply chain, and it is urgent that all players including national health regulatory authorities take appropriate steps to improve access to quality assured medical products and protect the safety of patients and the public. Otherwise, various actors might take the opportunity of gaps in product availability and repeated shortages to proliferate illegal practices that could endanger public safety.

According to article 20(1) of Food and Medicine Administration proclamation number 1112/2019, any medicine shall not be manufactured, imported, exported, and distributed for use with out registration and marketing authorization. However, sub-article 5 of this article indicated that Ethiopian Food and Drug Authority (EFDA) may in compelling circumstances; grant a permit for the importation or use of unregistered medicine.

COVID-19 pandemic is one of such compelling circumstance that presents an extraordinary challenge to the country. It re-emphasise the importance for the necessary preparation of the system, process and procedure to be in place to address future such PHE.

To address this challenge, EFDA has developed and implemented guidance on how to manage Marketing Authorization (MA) applications using a non-routine MA application procedure during PHE. This guideline provide guidance on the critical administrative and technical requirements that need to be submitted and reviewed by the EFDA (e.g. administrative information, product information (summary of product characteristics, patient information leaflet and labelling information), chemistry, manufacturing and controls (including current Good Manufacturing Practice (cGMP) certifications and reports) and information on safety and effectiveness.

However, this guideline for the Emergency Use Authorization of COVID-19 Vaccine is specific to this particular health threat. Therefore, it is based on the experience obtained from dealing with the marketing authorization applications for the COVID-19 products and global reference guidance that this general guideline is developed to provide information for the applicant on how to compile and submit their application and guide the regulator on how to manage Marketing Authorization applications intended for the declared PHE. Therefore, this guideline is applicable to the medicines, Vaccines and IVDs.

2. DEFINITIONS

The following definitions are provided to facilitate interpretation of the Guideline; they apply only to the words and phrases used in this Guideline. Although every effort has been made to use standard definitions, the words and phrases used here may have different meanings in other contexts and other documents.

Active pharmaceutical ingredient (API)

Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings. Drug Substance" and "Active Substance" are synonymous to "Active Ingredient.

Applicant

The person or entity who submits a registration application of product to the Authority and responsible for the product information

Authority

The Ethiopian Food and Drug Authority (EFDA)

Authorized local agent (Representative)

Any company or legal person established within a country or jurisdiction who has received a mandate from the manufacturer and/or license holder to act on his behalf for specified tasks with regard to the manufacturer's and/or license holder's obligations under legislation of the medicine and other regulatory guidance's issued by the Authority.

Excipient

Any component of a finished dosage forms other than the claimed therapeutic ingredient or active ingredients.

Finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling

Labelling

All labels and other written, printed, or graphic material that is affixed to a medicine or any of its container or wrapper and includes any legend, word, or mark attached to, inserted in, belonging to, or accompanying any medicine including: 1) the immediate container label; 2) cartons, wrappers, and similar items; 3) information materials, such as instructional brochures and package inserts.

Manufacturer

A company that carries out operations such as production, packaging, repackaging, labelling, and relabeling of products

Marketing authorization

An official document issued for the purpose of marketing or free distribution of a product after evaluation of safety, efficacy, and quality of the product

Public Health Emergency of International Concern (PHEIC)

Extraordinary event determined to constitute a public health risk to other States through the international spread of disease and potentially requires a coordinated international response. This implies a situation that: is serious, unusual or unexpected; carries implications for public health beyond the affected State's national border; and may require immediate international action

Specification

A document describing in detail the requirements with which the products or materials used or obtained during manufacture have to conform. Specifications serve as a basis for quality evaluation.

Stability

The ability of an active ingredient or a drug product to retain its properties within specified limits throughout its shelf-life; the chemical, physical, microbiological, and biopharmaceutical aspects of stability must be considered

Reference Authority:

A national regulatory authority included in the WHO listed authorities or other national regulatory authority recognized as reference authority by EFDA. Although not a regulatory authority, EFDA consider WHO as reference authority for the purposes of reliance on prequalified products and/or WHO EUL products.

Regulatory reliance:

The act, whereby, the NRA in one jurisdiction may consider and give significant weight to a total or partial rely upon—evaluations performed by another NRA or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken even when it relies on the decisions and information of other.

Validation

The demonstration, with documentary evidence, that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

3. The General regulatory preparations and considerations in public health emergency situations

For the registration or marketing authorization applications to be considered for Emergency approvals (EA) or emergency use authorization (EUA): the PHE should be believed and announced to be an emergency threat for the country which means a hazard of biological, chemical, environmental or unknown origin is likely to spread across the nation and may cause a potential severe risk to public health necessitating a coordinated action at national level. It should be under the leadership of Ministry of Health (MoH) that the Ethiopian Public Health Institute (EPHI) will take the responsibility for the overall management and coordination of public health emergencies.

Up on declaration of PHE,EFDA will establish the emergency steering committee which leads regulatory services including

- Identifying and listing of the eligible medicinal products based the eligibility criteria.
- deciding whether the declared PHE could be addressed by the EFDA registered medicinal products or require the submission for the new dossier application including the application for the generic and/or innovator products which are not yet registered for Ethiopian market
- interacting with and inviting the potential applicant to submit their pre-import permits and/or the dossier application as applicable
  - ***Note:*** *EFDA may grant a permit for the importation or use of unregistered medicine depending on the compelling circumstances of the declared PHE as per the article 20 (5) of the percolation 1112/2019.(e.g. extraordinary nature of the emergency situation as in COVID-19 or other public health emergency of national concern)*
- Organising the necessary expert groups, advisor groups and ethics committees required. Such pool of expertise should cover all technical/scientific areas to be considered during the pre-emergency, emergency and post-emergency phases, so that the required task can be rapidly established when required for assessment and other activities related to declared PHE.
  - **Note:** The selected experts will be requested for any potential conflicts of interest and be required to enter into a confidentiality undertaking.
- Collaborating with WHO, relevant WHO listed authority(the NRA which licensed the product, if any), relevant external experts, to facilitate speedy access to medicinal products
- Signing of agreements with WHO and Relevant NRA for information sharing including the outcome of the assessment of quality, preclinical and clinical information, inspection reports of facilities and authorization for emergency use of the product under application
- Coordination of scientific regulatory matters and expediting approval of products, research and innovation related to product development, clinical trials,

manufacturing and marketing authorization of medical products claimed to be used for the declared PHE

- Review of assessment outcomes and other applicable reports from the established task forces
- Ensuring safety of patients and protecting public health from falsified and substandard medical products.
- Creating proper channel for information exchange during PHE situations
- Mitigating the challenges of shortage of medical products by setting and/or monitoring a system that enables the availability of the products.
- Monitoring of the post emergency approval or authorization reports

4. The supply of registered medicinal products in emergency situations

The supply of the medical products is a crucial issue in resource limited setting and it is particularly important when an outbreak (a sudden increase in occurrences of a disease in excess of normal expectancy for the location or season) occur in such settings. Such outbreaks may affect a small and localized group at start but could also be PHE which have impact upon thousands of people across an entire country when not properly managed.

From the past experience, it is also noted that some of the already registered products are found to be supportive in PHE situations, example use of Dexamethasone in Covid-19 pandemic. For such registered medicinal products, it will be sufficient for the local agent or the government procurement agency or the donor (if any) to apply directly for the purchase order and/or the pre-import permit, as applicable. EFDA is responsible for accelerated approval of pre import permit and port clearance of these products to accelerate their supply.

This means, there is no need for the submission of the product dossier application for marketing authorization provided that the manufacturing site has a valid GMP certificate or waiver letter issued by the EFDA and there is not major variation that impacted the quality of the product has been declared.

Table 1: list of activities in pre import approval process in emergency situation

Activity	**Responsibility**	**Timeline**
Organizing emergency steering committee	EFDA	1day
Verification of eligibility of the candidate product	Steering Committee	1days
Interacting with EPSA, MOH and other importers including donors	Steering Committee	1day
GMP status verification and Approvals of pre-import permits for the candidate product	Responsible directorate Of EFDA	3days
GMP waiver or audit		
Post approval monitoring	EFDA and Applicant	

5. Regulatory reliance in emergency situations

EFDA may use reliance and recognition on WHO listed authorities for the marketing authorization or emergency use authorization (EUA). Therefore, EFDA shall conduct an expedited review of the quality, nonclinical and clinical information and apply reliance, and recognition approaches to support approval.

EFDA adopts published guidelines/recommendations that may be applicable where there is evidence of scientific consensus that make recommendation on the risk/benefit assessment regarding the use of the product or published as standard treatment guidelines.

However, it is the responsibility of the applicant to provide that the product recommended for emergence situation has been granted a marketing authorization (MA) or EUA in the country of the reference NRA. EFDA may consider the issued MA or EUA of the indicated NRA or may decide to wait until multiple WHO listed authorities issue MA or EUA as part of its risk-benefit assessment. As an assurance of the sameness, the applicant is expected to submit at least the following in addition to filling of available supporting documentation which include product-specific characteristics, manufacturing and labelling, nonclinical, clinical and quality information.

- A formal declaration (as indicated in cover letter in Annex 1) confirming the product offered to the EFDA correspond in all respects (e.g. qualitative/quantitative formula, manufacturing of finished pharmaceutical product (FPP) and active pharmaceutical ingredient (API) facilities, stability, summary product characteristics and labelling, etc.) to the product approved by the reference authority or WHO Prequalification.
- The product EUA or marketing authorization certificate issued by the reference authority.
- The corresponding web-link to the registration database.

6. Requirements for submission of the dossier application

The requirements for the data or information to be provided in the dossier vary depending on whether the medicinal product recommended for the declared public health emergency is available or new to global market. For the medicinal product available on the global market complete information as per the national registration or marketing authorization requirements should be submitted and EFDA may conduct abridged or full review based on the reference NRA that has issued marketing authorization or WHO prequalification records, where applicable. For the new medicinal product (including investigational product), available information are expected to be provided as indicated in this guideline.

6.1.For Special pre import permits in Emergency situations

This is applicable, when medicinal products proposed for the PHE are available in global markets but not yet registered in Ethiopia. For such products, it is assumed that adequate information is available regarding the quality, safety and efficacy of the products. Therefore,

the dossier application shall be compiled in modular presentation in CTD format as required in the most current medicine registration guideline of the authority and submitted via the https://www.eris.efda.gov.et/login. The applicant shall consult the EFDA or request for pre submission meeting for any alternative compilation of the information to be provided in the product dossier application, when deemed necessary.

The applicant shall submit the application for the GMP inspection and the dossier application at the same time. It is also required to include the regulatory status (registered, rejected, and withdrawn) of the product by the WHO and the WHO listed Authorities including applicable documentations for regulatory reliance as indicated under section 5 of this guideline.

For the products prequalified by the WHO and/or licensed by WHO listed authority, an immediate request for pre import permit could be made provided that complete application is submitted and necessary service fees are made including the fee for the GMP inspection.

Applications will be assigned immediately to the group of assessors which will be specifically organized as emergency taskforce as per the EFDA Regulatory-Preparedness-and-Mitigation-Strategy-for-Emergency-Health-Threats during the PHE situation.

The expedited dossier assessment will be conducted as per the applicable guideline for the registration of the medicines, vaccines and IVDs and the GMP could be waived or inspection will be organized by the emergency taskforce.

Appropriate preliminary decisions shall be made within not more than15working days from the date of submission unless justified as in case which may require the involvement of the national drug advisory committee. The preliminary decision shall include the decision to

- Issue MA or request for additional data based on the outcome of the dossier assessment
  - ***Note:*** *If the applicant has provided a timeline for additional results according to the product development plan, this will be indicated in the consolidated report*
- Issue waiver of the manufacturing site inspection based on the documentation evidence provided.
  - ***Note:*** *EFDA task force for inspection will conduct a desk review of available inspection reports. As appropriate, the inspection team may also undertake on-site inspection of manufacturing and clinical sites, within not more than 30days depending on the outcome of the desk review or if the task force for dossier assessments recommends.*
- Issue emergency pre-import approval (for Not More Than 6months)provided that the applicant committed to address any outstanding issues within agreed time period or time specified by EFDA.
  - ***Note:*** This is for the product which was not WHO prequalified or licensed by the WHO listed authority, *as these products can get pre-import approvals based on submission of application for dossier assessment and GMP inspection along with necessary service fee as discussed above.*

- ***Submission of updates:*** *as this emergency pre import permit is not equivalent or an alternative for the EFDA marketing authorization, applicant shall submit the additional information requested as per the commitment within agreed time period or time specified by EFDA.*

Table 2: List of activities in special pre-import permit process in emergency situation

Activity	**Responsibility**	**Timeline**
Declaration of PHE	MOH and EPHI	1days
Organizing emergency steering committee	EFDA	1day
Interacting with applicable stakeholders: WHO, WHO listed Authority and others: signing agreement when required	Steering Committee	2days
Verification of eligibility of the candidate product	Steering Committee	2days
Establish task force for dossier assessment and GMP(when required)	Steering Committee	1day
Assessment of dossier and GMP documentation verification and reporting	Task force	5days
review of reports from task force and recommendation to issue or not to issue special pre import permit	Steering committee	2days
Issue GMP waiver, special pre import permit	Applicable directorate of EFDA	1day
Submission of updates by manufacturer	Applicant	
Post approval monitoring	EFDA and Applicant	

6.2.For Emergency use authorization (EUA)

This is applicable, when the declared PHE is an epidemic or pandemic for which no licensed product is available (as in case for COVID-19). In such PHE situations, there will be less evidence of efficacy and safety when the procedure is initiated than that required in a non-emergency situation. The EFDA emergency steering committee will decide on how to issue emergency use authorization (EUA) for the candidate products including investigation products and any other related products which are supposed to address the declared public health threat.

For the products listed by the WHO-EUL procedure or authorized for the emergency use by the WHO listed authorities, EFDA may rely on these decisions to issue EUA.

However it is very important to note that the EUA is also not equivalent or an alternative to EFDA marketing authorization, and should not be thought of as such. The EUA is a special procedure for unlicensed vaccines, medicines and in vitro diagnostics in the event of a Public health emergency when EFDA is willing to tolerate less certainty about the efficacy and

safety of products, given the morbidity and/or mortality of the disease and the lack or paucity of treatment, diagnosis/detection or prevention options. It is intended to provide a time-limited authorization for unlicensed products in an emergency context when limited data are available and the products are not yet ready for application for marketing authorization.

Eligibility of candidate products

Though the three product streams (vaccines, therapeutics and IVDs) each have specific requirements the following criteria must be met in order to qualify for assessment under EUA,

- The disease for which the product is intended is serious or immediately life threatening, has the potential of causing an outbreak, epidemic or pandemic and it is reasonable to consider the product for an EUA assessment, e.g., there are no licensed products for the indication or for a critical subpopulation (e.g., children);
- Existing products have not been successful in eradicating the disease or preventing outbreaks (in the case of vaccines and medicines);
- The product is manufactured in compliance with current Good Manufacturing Practice (GMP) in the case of medicines and vaccines and under a functional Quality Management System (QMS) in the case of IVDs, and;
- The applicant undertakes commitment to complete the development of the product (validation and verification of the product in the case of IVDs) and apply for approval once the complete quality, safety and efficacy information is available. For that purpose, the remaining clinical trials and other testing needed to complete the development of the product must already be underway at the time of the application for EUA.

EFDA may consider reviewing a candidate product for EUA that does not meet all of the requirements. In such situations, the application letter and documentation provided to EFDA should justify the application of the product although it does not meet all eligibility requirements.
When EFDA carries out its assessment under these circumstances, it considers all available scientific data, including non-clinical and clinical information. Therefore, the compilation of the dossier application to follow the modular presentation in CTD format is encouraged.

Since the expectation is that the manufacturing/quality control and clinical development of the product submitted for EUL will continue to product licensure, the submission for EUL of medicines and vaccines should follow the ICH CTD format. In the CTD dossier, sections for which no information is available at the time of the initial submission should be indicated as “data or information not available”, “study on-going” or “not applicable” as the case may be. The Authority may request for the written commitment where applicable.

For IVDs, the dossier structure to be used for the submissions as per the format developed by the authority. Applicants should follow the dossier structure requirements laid down in medical device registration guideline. For IVDs, the dossier content requirements may differ

depending on the analyte being detected and clarification of specific data requirements will require discussion between the applicant and EFDA in advance of submission.

The applicant shall consult the EFDA or request for pre submission meeting for any alternative compilation of the information to be provided in the product dossier application, when deemed necessary. These pre-submission exchanges may be done via a chosen method of communication, including face-to-face meetings. Pre-submission meetings should be scheduled as early as possible, with a predefined agenda addressing questions sent to EFDA in advance by the applicant. Such meetings are important for discussing the availability of essential data required for specific products, expected timelines for submission and updates, monitoring of safety and effectiveness after deployment, and other relevant information. Additional meetings may be held during the assessment process, as required.

Table 3: List of activities in emergency Use authorization procedure

Activity	Responsibility	Timeline
Organizing emergency steering committee	EFDA	1day
Interacting with applicable stakeholders: WHO, WHO listed Authority and others: signing agreement when required	Steering Committee	2days
Verification of eligibility of the candidate product	Steering Committee	2days
Establish task force for dossier assessment and GMP	Steering Committee	1day
Assessment of dossier and GMP documentation verification and reporting	Task force	5days
Assessment of reports by task force and decision for GMP waiver, EUA and/or pre import permit	Steering committee	3days
GMP waiver, EUA and pre import permit	Applicable directorate of EFDA	1day
Submission of updates by manufacturer	Applicant	
Post approval monitoring	EFDA and Applicant	

6.2.1. Documentation requirements in the Dossier for EUA

The following are considered the minimum technical requirements for the medicines dossier applications for emergence use authorization

1) Covering letter

The manufacturer must submit an application/covering letter using the template set forth in Annex 1 of this guideline, duly completed, signed and dated by the applicant/manufacturer with the product, to EFDA's Director General, with a copy to the Directorates responsible for the regulatory oversight and Marketing Authorization. The application letter should include details of the product (name, strength, and dosage form), country and sites of manufacture the product and information on whether or not the candidate product has an authorization for emergency use or equivalent. This evidence may include the copies of the emergence use

authorization or valid marketing authorization certificates issued by the reference NRA or the WHO prequalification of the product for use for the declared emergence situation, as appropriate.

When the product proposed for the emergence health situation was not approved by reference NRA or not WHO prequalified, applicant may submit EUA from the NRA of the exporting country and any other supporting document in this regard.

2) The GMP status of the manufacturing facilities

List of all sites involved, including FPP and API, accepted by the WHO, the WHO listed Authorities and the NRA of the exporting country in the manufacturing process, including name, current address and manufacturing responsibilities/activities of each site should be provided.

Copy of valid Good Manufacturing Practice (GMP) certificate of the manufacturing site(s) of the finished pharmaceutical product (FPP) proposed for the declared public health emergency situation and its Active pharmaceutical ingredients (API) manufacturing site. These include copies of the certificates issued by the WHO listed regulatory authority and/or the latest WHO public inspection report provided that the manufacturing site(s) are still available on the list of the WHO inspected FPP and API manufacturers.

EFDA will issue waiver of the manufacturing site inspection based on the documentation evidence provided or the EFDA task force for inspection will conduct a desk review of available inspection reports. As appropriate, the inspection team may also undertake on-site inspection of manufacturing and clinical sites, within not more than 30days depending on the outcome of the desk review or if the task force for dossier assessments recommends.

3) The agency agreement

The import and distribution agreement between the actual manufacturer/product license holder or the legal supplier and the local representative and such agreement should fulfil the requirement outlined in the current medicine registration guideline.

The registration agreement could also be made between the local licensed consulting office or scientific office and actual manufacturer/product license holder or the legal supplier.

This document is not required when the products for emergency use authorization are procured by the government procurement agency and are to be imported by donation

4) ApplicationFee

Each application should be accompanied by a relevant service fee for registration. Applicants are advised to consult the current Rate of Service Fees Regulation of the Authority for the amount to be paid for application and contact the Authority for details of mode of payment. EFDA may exempt the application fee when deemed necessary by the emergency steering committee of the authority

5) Product information and labelling

Product information including the Summary of Product Characteristics (SPC/SMPC), Product monograph, or equivalent, and Package insert/prescribing information approved by the reference authority for pharmaceuticals and biologics (e.g. vaccines)

This information should be properly compiled in to relevant sections of the patient information leaflets, product information characteristics and packaging labels to fulfil the requirement set out in EFDA's most current guideline for the registration of medicine. The following will be the minimal requirement for vaccines and medicines

1. Summary of product characteristic (information for healthcare provider)
2. Patient information leaflet
3. Container labelling
4. Any other instructional materials provided to the user.
5. A plan to help assure that prospective recipients and healthcare providers are adequately informed about the uncertainties regarding both the potential benefits and risks.

Note:

- When the product is listed, the labelling should clearly indicate that that product is for emergency use only.
- The Applicant must provide a complete set of PDF artworks in English or the national official language Ethiopia including labelling, primary/secondary packaging, and any informational inserts.

6) Essential data requirements for EUA

Clarification of specific data requirements will require discussion between the applicant and EFDA. Applicants are highly encouraged to contact EFDA as early as possible to discuss specifics of the application.

<u>For vaccines</u>

A. Manufacturing and quality control Data:

1. Full characterization of cell banks according to WHO Technical Report Series (TRS) 978, and any subsequent updates.
2. Full characterization of master and working seed organism(s), based on reference to the most appropriate WHO TRS.
3. Process validation (based on quality risk assessment for the development stage) and demonstration of consistency of production at the production scale used for the lots to be distributed. If deemed appropriate by WHO data on clinical batches with a commitment to complete validation on production batches and to submit the data as part of lot release review may be considered.

   N.B., if full characterization is not possible at the time of submission, adequate justification must be submitted as to why not, and a plan must be presented to address the data gaps. Validation of potency tests and other critical assays. If novel test methods have been developed, full description of the test development and qualification must be presented.

4. Justified specifications for starting material, intermediates, and final products.
5. Stability data for the vaccine produced at the scale produced for the lots to be supplied. If available, accelerated stability data must be included. For vaccines being assessed for emergency use, EFDA steering Committee for Emergency, when convened, will consider programmatic suitability
   a) Vaccines requiring storage at less than -20°C,the steering committee responsible for emergency response will evaluate and consider whether responsible agency (example: Ethiopian airline, EPSA or local agents)have available infrastructure for vaccine storage and distribution at required temperatures.
   b) Routinely, if a vaccine presented for registration requires storage below +2°Cduring its shelf-life period, it should have a minimum period of storage between+2°C and +8°C of 6 months. Under this emergency procedure, vaccines with a shelf-life at +2 to +8°C of less than 6 months may be considered. The application should include stability data at +2 to +8°C to determine the minimum acceptable storage period at +2 to +8°C. Upon receipt of such an application, the steering committee responsible for emergency response will evaluate and consider whether responsible agency (example: Ethiopian airline, EPSA or local agents) have available infrastructure for vaccine storage and distribution at required temperatures. Routinely, multi-dose vaccines for registration should contain adequate preservative, unless they are live attenuated vaccines (where the preservative may have an adverse effect on the viability of the microbe). However, if a multi-dose vaccine submitted under this emergency procedure does not contain a preservative, information/plans on how such a vaccine could be safely managed in the field should be submitted.
6. Inspection report(s) from the responsible NRA or from the WHO inspection team showing compliance with GMP requirements – if available, and;
7. Process changes: by the time of submission, it is likely that the manufacturing process is not finalized and that numerous changes will have to be applied after the first listing. These changes should be submitted as updates.

B. Non-clinical and Clinical Data:

Non-clinical data demonstrating acceptable safety, immunogenicity, and efficacy – if available- in the most appropriate animal model should be submitted. The applicant must justify the choice of animal model. If the non-clinical package is not complete at the time of submission, the applicant must submit adequate justification for the lack of complete data and a plan and timeline for submitting those data.

Clinical data demonstrating the appropriate dose to be used and initial acceptable safety and immunogenicity in the population in which the vaccine will be used in the context of the public health emergency.

Preliminary data showing some efficacy, if available, should be provided. If preliminary human data showing some efficacy are not available for the vaccine under consideration and if not imminently available for other vaccines being concurrently developed, EFDA will consider whether the preponderance of evidence from the non-clinical, and early human

studies justifies considering the immunogenicity data as a potential surrogate that is thought to be reasonably predictive of clinical efficacy. In such cases, the emergency use listing can proceed, provided there are trials underway that will ultimately provide confirmation that immunogenicity is a surrogate. Safety and immunogenicity data from other vaccines made by the manufacturer using the same product platform may be considered as supportive data for review if applicable.

Note: products developed under the animal rule will also be considered for review.

Medicine

A. Manufacturing and Quality Data:

1. Inspection report(s) from an SRA/WLA or from a WHO prequalification inspection showing compliance with GMP requirements for other, but similar products. Based on the acceptability of the SRA/WLA report, EFDA may or may not need to perform its own assessment of GMP compliance.
2. Information on the active ingredient(s) and finished product, including characterization (including known and potential impurities), composition, preparation, controls (specifications, analytical methods and their validation).
3. A list of intended changes for scale up, if any, along with a discussion on impact of these changes on the quality and safety/efficacy profile of the product.
4. Stability data.

B. Non-clinical and Clinical Data:

1. All relevant in vitro and in vivo pharmacodynamic (PD) data, e.g., on microbiologic/virologic activity (including any modelling performed).
2. Data on efficacy and safety in in-vitro tests and in animal model(s) under well controlled and documented conditions. The preferred model depends on the disease and may vary according to the medicine's mechanism of action. The applicant must justify the choice of animal model.
   a) Evidence of efficacy should include improved survival and/or reduced morbidity of animals in the preferred model under relevant conditions. Surrogate markers, validated or reasonably expected to predict efficacy, would be supportive.
   b) All available evidence of the medicine's activity in vitro and in other animals, together with pharmacokinetics and efficacy in humans, also against other diseases should be submitted
3. A rationale should be provided for the proposed dosing in humans, with reference to drug exposures shown to be safe and effective in suitable models. Ideally, human pharmacokinetic data should be available, demonstrating similar levels of the drug following administration at the proposed dose, compared to blood levels found to be safe and efficacious in the relevant animal model.
4. If human pharmacokinetic trials or studies in other indications at the exposure level proposed for treatment of the PHE disease have been conducted, assessment of safety using standard parameters (e.g., adverse events, clinical laboratory monitoring, etc.) will

be done. This safety evaluation may be supplemented by any other non clinical and clinical data at different exposure levels.

5. If available, clinical data demonstrating safety and efficacy at the proposed dose for PHE field use should be submitted.

<u>In vitro diagnostics</u>

A. Quality management system (QMS)

A manufacturer's quality management system (QMS) documentation and specific manufacturing documents should be provided. There should be sufficient evidence that:- the applicant is the manufacturer ; an adequate QMS in place; and that the requisite manufacturing capability exists. Therefore, the applicant should provide

- Evidence of implementation of a manufacturing quality management system (e.g., ISO13485 certificate and most recent regulatory (or certification body) audit report, quality manual, exclusions or non-applications, list of valid quality management documentation, management review report);
- Details of the production workflow including QC points (in process and final release activities);
- Critical supplier list including supplied products (components/raw materials) and services;
- If the product was approved for Research Use Only (RUO), details on the experience with the product;
- Details on the manufacturing capacity (existing inventory, minimum time to provide finished product, maximum batch/lot size).
- Procedure/s relevant to control of non-conforming goods, including but not limited to procedures for corrective and preventative actions, recalls, field safety notices etc.

B. Safety and performance

The available documentary evidence of safety and performance should be provided. It is acknowledged that many of the required studies to meet full regulatory requirements may not have been performed for IVDs undergoing EUA assessment. An initial evidence that includes studies using banked specimens from previous studies, relevant studies in the literature, and studies using contrived specimens to supplement testing of clinical specimens including representative analyte may be acceptable in the absence of complete analytical and/or clinical performance studies, if this evidence provides a reasonable assurance of safety and performance. It is based on the submitted documentation that a risk- based judgment will be made on whether there is a favourable benefit/risk profile. Therefore, below information should be submitted by the applicant

1) Product Information

a) Regulatory versions of this product
b) Product description including variants (configurations) and accessories
c) Essential principles checklist
d) Risk analysis and control summary

Note: *the regulatory version of the product is defined by all of the documentation related to development, manufacture and intended use, labelling and post-market surveillance of the product and all the documented evidence supporting the safety and performance claims associated with that submission. If any aspect of this documentation differs in any way between the submissions to different regulatory authorities or assessment bodies (United States Food and Drug Administration, Health Canada, a Notified Body for CE marking, etc.) it is considered to be a different regulatory version.*

2) **Design and Manufacturing Information**
   a) **Product design:** design overview, formulation and composition, biological safety and documentation of design changes
   b) **Manufacturing processes:** overview of manufacture and sites of manufacture
   c) **Key suppliers**

3) **Product Performance Specification, and Associated Validation and Verification Studies**
   a) **Analytical performance**: this should include stability of specimens, validation of specimens, metrological traceability of calibrators and control material values, accuracy of measurement (Trueness and Precision (repeatability & reproducibility)), analytical sensitivity (LOD & LOQ), analytical specificity, high dose hook effect, measuring range of the assay, validation of assay cut-off, validation of assay procedure, usability/human factors, stability of the IVD (Claimed shelf-life, In-use stability (open pack or open vial stability) and Shipping stability
   b) **Clinical evidence:** Clinical/diagnostic sensitivity and Clinical/diagnostic specificity

7. Assessment of dossier Applications for the PHE situations

EFDA may conduct an abridged review and full review of product dossier applications based on reliance on the NRA that has previously assessed the product and /or the WHO prequalification record.

7.1.Screening of applications

The customer service office in the emergence task force will perform the screening of the submission to ensure that sufficient information is available to initiate the assessment by the emergence task force dedicated for assessment of safety, quality and efficacy under emergency situation based on the essential data requirements discussed under section 6 above. If the screening indicates that the assessment cannot start due to lack of information, this will be communicated to the applicant. This should be made within a day or two from the date of submission. A complete dossier may be submitted any time afterwards.

7.2.Assessment of Applications

The Assessment taskforce will conduct assessment of submitted information and additional data from applicant as a response to the list of queries (if any) and provide the emergency steering committee with a documented outcome of the evaluation of the quality, safety, efficacy/immunogenicity/performance of the product based on currently available data. This

should be made within a week from the date of submission by format included as Annex 3 and 4. The emergency steering committee should made decisions within not more than 3days from the date of receiving the assessment outcome unless justified. Thismay include the decision to

- accept or request for additional data based on the outcome of the dossier assessment
    - *Note: If the applicant has provided a timeline for additional results according to the product development plan, this will be indicated in the consolidated report. This means the report will also indicate when the next set of data is expected (for example, full report of phase II trials).*
- Issue emergency use authorization provided that the applicant committed to address any outstanding issues required for the dossier application to be accepted within agreed time period or time specified by EFDA.
- Publish and /or communicate information about the product in a public report available on a dedicated portal of the EFDA website. This may include negative assessment outcomes. However, this will be to the protection of any commercially sensitive confidential information of the manufacturer.

For the IVDs: A review of the manufacturer's quality management system (QMS) documentation and specific manufacturing documents is the first step in the process. At the conclusion of this step, EFDA may either decide to proceed or to request further documentation, or to terminate the application. The decision to proceed with the assessment process will be made if there is sufficient evidence that the applicant is the manufacturer, that there is evidence of an adequate QMS in place, and that the requisite manufacturing capability exists. The second step is the assessment of the documentary evidence of safety and performance. It is acknowledged that many of the required studies to meet full regulatory requirements may not have been performed for IVDs undergoing EUA assessment. The outcome of this step will determine if the application will proceed to step 3, whether further documentation should be requested, or whether the application should be terminated.

7.3.Assessment Approaches

For Vaccines

For vaccines, the initial EUA assessment will use similar principles as those used for registration and take into account the following, if any:

- Agreements with NRAs to share reports,
- Past inspections of the manufacturer's facilities,
- The assessment of the manufacturer's quality systems and any record of performance of the manufacturer and its product (s).

Table 4: Assignment of assessment category for vaccines

	Manufacturer with registered vaccines	Manufacturer with registered vaccines
Vaccine approved for emergency use by a WHO/WLA for the target disease and agreement in place between WHO and EFDA or between WLA and EFDA for the exchange of information	**A**	**C**
Vaccine not approved for emergency use by a WHO/WLA for the target disease or no agreement in place between WHO and EFDA or between WLA and EFDA for the exchange of information	**B**	**C**

Table 5: Vaccines assessment approach for each category

Category	Assessment approach
A	Abridged assessment, consisting of initial assessment of: - Report(s) from the responsible SRA/WLA (Summary basis for the emergency use approval or equivalent) - Programmatic aspects *
B**	Abridged assessment, consisting of initial assessment of: - Application (see content above) - Programmatic aspects
C	WHO will conduct a full initial review of: - Application (see content above) - Inspection report (conducted by WHO) - Programmatic aspects
* Programmatic aspects include: indication, dosage, conservative, storage temperature, autodisable syringe, etc. ** Company has prequalified products, therefore, they have been inspected by WHO	

For medicines

1) For medicines authorized for emergency use by a WHO/WLA for the target disease, abridged assessment will be conducted based on the WHO/WLA report and GMP could be waived based on the desk review of available WHO/WLA inspection reports. Inspection by EFDA will be conducted only if required.

2) For medicines not authorized for emergency use by a WHO/WLA for the target disease, full assessment by EFDA of the submitted dossier information and GMP inspection will be conducted. EFDA may consider available assessment reports written by other NRAs and desk review of available WHO/WLA or PIC/s member inspection reports covering other but similar products, when available.
3) When the manufacturer has been previously inspected by EFDA and accepted for different product, inspection of the site is not required for the sole purpose of the product under application for EMA, even if the EFDA-GMP certification is not valid.

For in vitro diagnostics

1) For product assessed through another emergency mechanism of an acceptable standard, abridged initial assessment of reports and Desk review of the QMS could be considered to issue EUA
2) For product not assessed through another emergency mechanism of an acceptable standard, full initial assessment by EFDA of the submitted documentary evidence and Desk review of the QMS will be conducted.

7.4.Submission of Updates

After the initial submission of the application with all the required information for initial assessment, applicants should promptly submit any additional information on the development of the product to EFDA, particularly if it may affect the product's benefit/risk assessment.
The applicant should – as much as possible- provide tentative timelines for the submission of additional/supplementary information based on the expected dates of completion/planned interim analyses of studies currently on-going/or being initiated soon.

8. Post emergency use authorization

8.1.Post emergency use authorization changes/Variations

Once a product has been issued an EUA, the development of the product must -whenever possible- continue to completion for marketing authorization and be submitted to EFDA for registration. The applicant must promptly inform EFDA of all changes regarding formulation, manufacturing process, testing methods, specifications, facilities and any other aspects that might (a) result in a change of the safety and/or efficacy and/or performance of the product or

(b) change the basis for the listing recommendation. Such changes to the product must follow the procedure for submission of updates described above.

8.2.Post Market Surveillance

Since the products proposed for the EUA have not been licensed for use in routine utilization settings, post marketing data would not be available at the time of application, Therefore, the manufacturer should have a system to ensure the collection and analysis of information on the safety and effectiveness of the product during the period when the EUA would be in effect and for a reasonable time following such period. EFDA may request applicants to provide risk management plan for active data collection and follow-up mechanisms to capture information on adverse event/incidents/non-conforming goods and processes under the EUA once the EUA is granted.

For any risk related to the products authorized for emergency use, the supplier must provide a copy of the Risk Management Plan and commit to submit Vigilance Report approved by the reference authority (e.g. Periodic Safety Update Report and Periodic Benefit Risk Evaluation Report) when they become available. The plan must be in alignment with the EFDA guidance on post- market surveillance and a post market surveillance system that includes a reporting system for adverse events and substandard/falsified medicines so that health system stakeholders (patients, providers, industry, etc. can report if there are issues with the EUA product).

In collaboration with the appropriate bodies including the MoH, EPSA/EPSS, the manufacturer or product license holder, the local agents and any other concerned stakeholder, EFDA shall keep records of the product's lot deployment, implement the national post-marketing surveillance plan, continue to update the EUA as additional information is received from manufacturers concerning the full-product life-cycle (e.g. product safety update reports /PSUR, variations, etc.) which approved by the reference authority, and continue to monitor the status of the EUA from the WHO and the reference authority.

Based on the reports on safety surveillance, efficacy/effectiveness/performance monitoring, quality complaints and other relevant data that may impact the validity of the authorization status, EFDA reserves the right to restrict or revoke the emergency use Authorization.

8.3.Environmental Risk Assessment (ERA)

If the product contains a Genetically Modified Organism (particularly applicable for vaccines), the applicant must submit a completed Environmental Risk Assessment report.

Annex 1: sample cover letter to be submitted along with the application EUA

[COMPANY LETTERHEAD – Name, address, phone number, email]

DATE:

TO: Ethiopian Food and drug Authority (EFDA)

Address: Addis Ababa Ethiopia

SUBJECT: Application for Emergency Use Authorization (EUA) (Insert Trade Name) (Insert International Non-proprietary Name of the Active Pharmaceutical Ingredient(s) (API), strength, dosage form or In Vitro Diagnostic device name)

(Insert NAME OF APPLICANT) of (Insert ADDRESS OF APPLICANT) has submitted this application for EUA of the aforementioned product. The details of the product are included in the submitted application.

(Insert Trade Name) has an EUA or marketing authorization in (Insert REFERENCE AUTHORITY COUNTRY NAME). The current EUA/marketing authorization was issued by (REFERENCE AUTHORITY) on (insert date of issuance) and will expire on (insert date of expiry, if applicable)

We confirm that the product, including but not limited to composition/formulation, strength, manufacturing of finished product and active pharmaceutical ingredients, specifications, packaging, product information, etc.- will, at the time of submission and after EUA, be the same in all respects as the product given EUA or marketing authorization with the (insert reference Authority Name) . Note, there is an exception for different languages on labeling and packaging, if applicable.

We confirm that all the information in the accompanying documentation concerning this application is true and correct.

We confirm that we have read and understood the EFDA guidance document on applications for EUA.

We therefore kindly request that The EFDA consider the submitted application for this product in order to grant an EUA.

Yours faithfully, _[Insert signature]

[Insert Full Name of Signee]

[Insert Company Position]

[Insert Signee's Email and Phone number (if different from that stated otherwise)]

Annex 2: The Format for the preparation of application dossier for product available in global market but not registered in Ethiopia

It is the responsibility of the applicant for marketing authorization Application or an Emergency Use Authorization (EUA) to provide a well-organized summary of the available scientific evidence regarding the product's quality, safety, effectiveness, risks (including an adverse event profile) and benefits.

The general format and guidance for the preparation of the dossier application included in the EFDA guideline for the registration of medicine is applicable with some exception when the emergency situation and the proposed product is new for the market in which case alternative approach for compilation of the available data could be considered. In this case, applicant shall consult EFDA before submitting the dossier application for the emergence use authorization.

Scientific literature may be appropriate to fulfil the requirements for some of the information or parameters outlined in this Guideline. Furthermore, the requirements outlined in certain sections may not be applicable for the product proposed the declared public health emergency. In these situations, a summary and the full reference to the scientific literature should be provided, or the non-applicability of the requested information should be clearly indicated as such with an accompanying explanatory note.

It is also important to note that the Authority may request information or material, or define conditions not specifically described in this guidance, in order to adequately assess the safety, efficacy, and quality of the medicines prior to and after approval.

The following Modular format of PDs in the CTD content should always be considered during dossier preparation for registration submission to the Authority:

Table 6: content of the dossier in CTD format

Module 1- Administrative and product information
1.1. Cover letter
1.2. The table Contents of the Application, including Module 1 (Modules 1-5)
1.3. Application Form
1.4. Agency Agreement
1.5. Good Manufacturing Practice Certificate and Certificate of Pharmaceutical Product
1.6. Certificate of Suitability (CEP), if any
1.7. Product Information
1.7.1. Summary of Product Characteristics
1.7.2. Labelling Information (immediate and outer label)
1.7.3. Patient Information Leaflet (PIL)
1.8. Evidence for an Application Fee
Module 2 – Dossier Overall Summary of Product Dossier (DOS-PD)
2.1. PD Table of Contents (Modules 2-5)
2.2. PD Introduction

2.3. Quality Overall Summary of Product Dossier (QOS-PD)
2.4. Nonclinical Overview – generally not applicable for multisource products (some exceptions may apply)
2.5. Clinical Overview
2.6. Nonclinical Written and Tabulated Summaries – generally not applicable for multisource products (some exceptions may apply)
2.7. Clinical Summary – generally not applicable for multisource products
Module 3- Quality
3.1. Table of Contents of Module 3
3.2. Body of Data
3.3. Literature References
Module 4 – Nonclinical Study Reports – generally not applicable for multisource products (some exceptions may apply)
4.1. Table of Contents of Module 4
4.2. Study Reports
4.3. Literature References
Module 5 – Clinical Study Reports
5.1. Table of Contents of Module 5
5.2. Tabular Listing of all Clinical Studies
5.3. Clinical Study Reports
5.3.1. Reports of Biopharmaceutical Studies (mainly BE study reports for generic products)
5.3.2. Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials
5.3.3. Reports of Human Pharmacokinetic (PK) Studies
5.3.4. Reports of Human Pharmacodynamic(PhD) Studies
5.3.5. Reports of Efficacy and Safety Studies
5.3.6. Reports of Post-Marketing Experience
5.3.7. Case Report Forms and Individual Patient Listings – generally not applicable for multisource products (some exceptions may apply)
5.4. Literature References

Annex 3: Assessment taskforce reporting format for Vaccines and Medicines

Assessment Report for the Product (insert Name)submitted for EUA

Assessment taskforce chair	
Name and signature of Members	1.
	2.
	3.
	4.
Date of this report	

1. **Executive summary**

1.1.The product

Description of the product, location of production, stage of clinical development

1.2.Authorizations granted by the NRA responsible for the regulatory oversight of the product

Details of any kind of authorization for use granted for the unlicensed product for emergency use, or exceptional circumstances, etc

1.3.Recommendation

Based on the review of information and documentation from initial submission, additional information from the applicant as a response to the list of queries and based on the deliberations among the members of the taskforce, we considers that since a PHE has been declared justifying the need for the product for emergency use before additional data on (quality), (safety) (performance) is provided as the development of the product advances, the risk-benefit balance of this product is: □ Positive □ Negative

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

a) Quality
b) safety
c) efficacy/immunogenicity
d) GMP, GLP, GCP compliance
e) Other

2. **Guidelines used for the assessment**

List of guidelines from WHO and regulatory bodies, WHO recommendations, international guidance documents, scientific reports and publications and any other relevant documents that the assessment task force has agreed to use as a set of parameters to assess the information submitted for the product.

3. **Scientific review of the submission**

3.1. Quality assessment

a) Summary of reviewed information
b) Rounds of questions and answers from the applicant
c) Conclusion

3.2. Non-Clinical assessment

a) Summary of reviewed information
b) Rounds of questions and answers from the applicant
c) Conclusion

3.3. Clinical assessment

a) Summary of reviewed information
b) Rounds of questions and answers from the applicant
c) Conclusion

3.4. GMP/GLP/GCP compliance

a) Summary of reviewed information
b) Rounds of questions and answers from the applicant
c) Conclusion

3.5. Proposed labelling

a) Summary of reviewed information
b) Rounds of questions and answers from the applicant
c) Conclusion

3.6. Benefit-risk assessment

3.7. Proposed post listing measures

4. Final remark

Annex 4: Assessment taskforce reporting format for IVDs

Assessment Report for the Product (insert Name) submitted for EUA

Assessment taskforce chair	
Name and signature of Members	1.
	2.
	3.
	4.
Date of this report	

1. Executive summary

1.1.The product

Description of the product, location of production, stage of clinical development

1.2.Authorizations granted by the NRA responsible for the regulatory oversight of the product

Details of any kind of authorization for use granted for the unlicensed product for emergency use, or exceptional circumstances, etc

1.3.Recommendation

Based on the review of information and documentation from initial submission, additional information from the applicant as a response to the list of queries and based on the deliberations among the members of the taskforce, we considers that since a PHE has been declared justifying the need for the product for emergency use before additional data on (quality), (safety) (performance) is provided as the development of the product advances, the risk-benefit balance of this product is: □ Positive □ Negative

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

a) Labelling
   - Labels
   - Instructions for use
b) Product Performance Specifications, and Associated Validation and Verification Studies
   - Non-clinical evidence (analytical performance)
   - Clinical evidence
c) Quality management systems (QMS) requirements

2. Guidelines used for the assessment

List of guidelines from WHO and regulatory bodies, WHO recommendations, international guidance documents, scientific reports and publications and any other relevant documents that the assessment task force has agreed to use as a set of parameters to assess the information submitted for the product.

3. Scientific review of the submission

3.1.Labelling

3.2.Product information

3.3.Product Performance Specifications, and Associated Validation and Verification Studies

- Specimen type
- Analytical performance characteristics/non-clinical evidence
- Clinical evidence (clinical or diagnostic sensitivity and specificity)
- Intended testing population

3.4.Quality management system (QMS) requirements

3.5.Benefit-risk assessment

3.6.Proposed post listing measures

4. Final remarks

Annex 5: Format for final decision from emergency steering committee

Emergency steering the Product (insert Name) submitted for EUA

Assessment taskforce chair	
Name and signature of Members	1.
	2.
	3.
	4.
Date of this report	

1. The product

Description of the product, location of production, stage of clinical development

2. **Authorizations granted by the NRA responsible for the regulatory oversight of the product**

Details of any kind of authorization for use granted for the unlicensed product for emergency use, or exceptional circumstances, etc.

3. Information assessed by the taskforce

4. Recommendation

Based on information and documentation submitted to the EFDA emergency steering committed (which includes [the report prepared by the Assessment task force and GMP inspection task force], [additional information from the applicant] and ……), and based on the deliberations among the members of this Committee, the Committee considers that since a PHE has been declared justifying the need for the product for emergency use, the risk-benefit balance of this product is: □ Positive □ Negative

Rationale for the decision: ……..

Therefore, the recommendation from this taskforce to EFDA emergency steering committee is to: issue EUA/not to issue EUA.

9. References

1. EFDA Guideline for Emergency Use Authorization of COVID-19 Vaccine, 2021
2. EFDA Guideline for registration of Medicines, 2020
3. Pan American Health organization, Reliance for Emergency Use Authorization of Medicines and Other Health Technologies in a Pandemic (e.g. COVID-19), 2020
4. Regulatory-Preparedness-and-Mitigation-Strategy-for-Emergency-Health-Threats
5. WHO emergency use List procedure, version 9 August 2022