ETHIOPIAN FOOD AND DRUG AUTHORITY

Medicine Evaluation and Marketing Authorization Led Executive office

Guideline for Non-Routine Registration

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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
MoH	Ministry of Health
NRA	National Medicine regulatory Agencies
PHE	Public Health Emergency
WHO	World Health Organization
WLA	WHO listed Authority

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.

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.

Legal supplier

A pharmaceutical trading firm located in the exporting country or a third country but a legal agreement with the actual manufacturer/the license holder of the product and its local representative for the distribution of the products in Ethiopian market

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

Extraordinary event determined to constitute a hazard of biological, chemical, environmental or unknown origin which is likely to spread across the nation and may cause a potential severe risk to public health necessitating a coordinated national and/or 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

Reference authority

Is a national, regional or international body whose decision or public information are considered by EFDA for its decision-making process with respect to the marketing authorization of medicinal products. WHO, WHO listed authorities and other national and regional bodies could be listed as reference authority as may be updated from time to time.

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.

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

Unmet medical needs

Are conditions for which there exist no adequate method of diagnosis, prevention and treatment and an alternative means will be therapeutics advantage to those affected in the country as declared by the ministry of Health and EFDA. This may include medicinal products for priority health issues of the country or shortage of medicines listed by the Authority where fast-track registration procedure will be followed.

Validation

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

1. Introduction

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 grant a permit for the importation or use of unregistered medicine in compelling circumstances.

The legal provisions are further detailed in article 23 and 24 of the medicine marketing authorization directive No.963/2023. Such compelling circumstances include emergency situation and other unmet medical needs, for example orphan drugs and Medicines indicated for seriously debilitating or life-threatening conditions (such as cancer and multi-drug resistant tuberculosis). For such medicinal products, it would be inappropriate from the public health perspective to use a routine approval procedure which may delay the approval of the medicinal product due to longer queue of applications. Therefore, alternative non-routine procedure should be devised to provide access to the above indicated medicinal products where routine Marketing Authorization procedure may not be followed.

Unlike the routine procedure, where submission of complete application dossier containing comprehensive data is required and a full review of applications is performed in a first-in -first-out principles (FIFO), the Authority may accept a less compressive data than normally required by exempting or considering rolling submission and may exempt the FIFO principle. Based on the situation at hand, available data and therapeutic benefits of the candidate product etc EFDA may issue emergency use authorization or conditional approval or marketing authorization for these products. However,

- The preliminary assessment available data/information of such Finished Pharmaceutical Product (FPP) should indicate that the benefit of the product outweighs its inherent risk. This means, though comprehensive data are not available, submitted information should show promising therapeutic effect. For vaccines, the benefit risk balance should be based on data from at least one well designed phase III clinical trial that demonstrates tha vaccine' safety and efficacy in a clear and compelling manner
- Immediate availability of the product on the market will fulfil the unmet medical needs,
- The risk due to missing data/information is tolerable and it is likely that the applicant will provide the compressive data within agreed up on commitment period.

Therefore, the purpose of these guidelines is to provide technical guidance for both the assessors of the medicinal products and the applicant for the registration of medicines through non routine procedure; to facilitate expedited review and implementation of risk-based approach without compromising the overall quality, safety and efficacy of the medicinal products.

2. Scope

A medicinal product category to be processed under non routine application pathway should be limited to

a) the medicinal products to be used in emergency situations
b) medicines for treatment of unmet medical needs (as justified by the ministry of health and/or pharmaceutical supply agency and verified by EFDA)
c) orphan medicines listed for Ethiopia, as may be updated from time to time or
d) investigational medicines (under clinical trial phase III) with promising therapeutic effect for seriously debilitating or life-threatening disease which have no other alternative

For these categories of medicinal products, there may be less evidence of efficacy and safety when the procedure is initiated. Therefore, EFDA will consider all available scientific data, including non-clinical and clinical information to decide for approval, import and distribution of the product under non routine procedure. In other word, a waiver /exemption may be granted for submission of some information/data depending on the specific situations for each category of medicines. A risk –based approach will be followed without compromising the overall safety, quality and efficacy of the product under consideration.

However, it is very important to note that the EUA or conditional approval is not equivalent or an alternative to EFDA marketing authorization and should not be thought of as such. These are special procedures for unlicensed vaccines and medicines in the event of a public health emergency (PHE) or under certain defined conditions 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 of treatment for unmet medical need, or better prevention or curative options.

It is the EFDA's expectation that, following submission of an application under non routine procedure, applicant would continue to collect placebo-controlled data in any on-going trials for as long as feasible and would also work towards submission of application for normal medicine registration as soon as possible.

3. The submission of the application

It is the responsibility of the applicant to provide a well-organized documentation of the available scientific evidence regarding the product's quality, safety, effectiveness, risks (including an adverse event profile) and benefits and any adequate, approved, available alternatives to the product.

However, the requirements for the data or information to be provided in the dossier vary depending on products nature (medicine, vaccine), emergency of the health condition (novel product or repurposed product recommended) and whether the medicinal product under non-routine application procedure has been accepted by the reference authority. For the medicinal product accepted by the reference authority and available on the global market; EFDA may rely on information or decision of reference authority to conduct abridged assessment.

In general the submitted application should fulfil the following administrative and specific technical documentation requirements described in section 3.1 and 3.2 of this guidelines unless specific exemption is granted by EFDA for certain information or data requirements.

3.1. General and administrative requirements

3.1.1. Covering letter

The applicant must submit a 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 unit responsible for the regulatory oversight and Marketing Authorization. The covering letter should include details of the product (name, strength, and dosage form), country and sites of manufacture the product

When the product under non-routine application has been approved by the reference authority for public health emergency use, under specific condition or as orphan drug, a covering letter should include declaration confirming that the product offered to the EFDA correspond to the product approved by the reference authority 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.).

When the product under non-routine procedure was not approved by reference authority, applicant may submit approval (EUA and conditional approval) from the National Regulatory Authority of the exporting country and any other supporting document in this regard.

3.1.2. Application form

Application for approval of the medicinal products under non-routine procedure may be requested by the applicant or proposed by EFDA depending on the situations. In both case, each application should be accompanied by the dully filled application form (Annex 2 of this guideline). During public health emergency, EFDA steering committee for emergency may identify the candidate product and invite applicant to submit their application.

3.1.3. Regulatory status of the product under application

Applicant should declare the regulatory status of the product in other countries including where the application is rejected, suspended, denied marketing authorization revoked, etc withdrawn along with the justification for such decisions.

For the products that have a valid approval from the reference authorities, copies of such evidence documents (emergence use authorization, conditional approval or marketing authorization certificates or equivalent) should be provided. The information provided should cover the intended purpose of approval and information on the use of the product.

The corresponding web-link to the registration or information database of the reference authority should also be indicated in the submission to access to these documents

When the copy of the issued EUA or marketing authorization certificate or equivalent is provided, EFDA may consider the decision of the reference authority or decide to wait until multiple reference authority to pass the decision as part of its risk-benefit assessment.

3.1.4. Commitment letter

Where certain information/data is not available at the time of submission, a signed commitment describing the missing data and information and the proposed time line for the submission of the missing data or information should be provided as per annex 3 of this guideline.

The letter should include the commitment to submit periodic safety update report every six months for less serious issues and immediately for more serious safety concerns following granting and/or renewal of emergency use authorization or conditional approval

EFDA will review the time line and may require revision to include the agreed up on commitment period for submission of information/data.

3.1.5. The GMP status of the manufacturing facilities

Copy of valid Good Manufacturing Practice (GMP) certificate of the manufacturing site(s) of the finished pharmaceutical product (FPP) and its Active pharmaceutical ingredients (API) manufacturing site should be provided. These include copies of the certificates issued by the reference authority for all sites involved in the manufacture. For the sites whose compliance with the cGMP is inspected and accepted by WHO, the same should be accessed in the latest WHO public inspection report. EFDA may issue waiver of the manufacturing site inspection based on the documentation evidence provided or may conduct a desk review of available inspection reports.

In an emergence situation, EFDA may also exempt or undertake on-site inspection of manufacturing and clinical sites, depending on the outcome of the desk review on case by case when decided to do so by the emergency steering committee.. The authority may also consider GMP compliance for similar product produced at the site if the product under application is a medicine, but not vaccine

3.1.6. The agency agreement

The registration, import and distribution agreement between the actual manufacturer/product license holder and/or the legal supplier and the local representative should be provided and such agreement should fulfil the requirement outlined in the current medicine registration guideline available on the web site of the authority. This 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 requirement may be exempted under emergence situation

3.1.7. Product information and labelling

Product information including the Summary of Product Characteristics (SPC/SmPC), Package labelling information and patient information leaflet should be provided. Applicants are advised to consult the current medicine registration guideline available on the web site of the authority for detail requirements regarding the product information.

Where applicable, product information approved by the reference authority for pharmaceuticals or vaccines under non routine procedure should be submitted.

As the product information should facilitate the proper use of the product, necessary instructions should be included to assure that potential recipients and healthcare providers are adequately

informed about the uncertainties regarding the potential benefits and risks associated with the use of the product. However, any information appearing in the product information should be based on scientific justification and should not vary significantly from the claims made for the same product in any other jurisdiction.

Where available product information is not yet comprehensive during the initiation of application, the provided information should at least cover

- the intended use, proposed dosing regimens and method of administration for use (for adults, paediatric and other specific populations such as geriatric, pregnant, lactating, immune-deficient individuals)
- safety and efficacy information including identification of the serious or life threatening disease or condition
- discussion of risk and benefit for the proposed use including information concerning the threat posed by the product and how that threat would be addressed including any steps taken to mitigate risk or optimize benefit, any recommended restrictions to ensure safety use, any situation under which the product should not be used (i.e contradictions) and important information that should be considered prior to use of the product
- The need for the product, including identification of any approved alternative product(s), if any and their availability and adequacy for the proposed use
- Product information including proposed package insert; Fact Sheets to be furnished to health care professionals or authorized vaccine administrators, as well as those to be furnished to recipients of the product.

When the product is intended for emergence use or approved under certain condition, the labelling should clearly indicate that that product is for emergency use only or mention that conditional marketing authorization has been granted subject to certain specific obligation to be reviewed annually, as applicable.

3.1.8. Evidence for payment of Service fees

The applicant shall pay all the required application fees for the registration, laboratory testing & GMP inspection as per the rate of service fees unless exempted. The application fee shall be made per application and the payment receipt shall mention the application number issued by the electronic registration information system (eRIS). If the payments are made for more than one application and

gross payments are made, a tabular listing of the application number and payment for each application shall be prepared and submitted along with the attachment for the total payment.

With respect to the amount to be paid per application, applicants are advised to consult the current Rate of Service Fees Regulation of the Authority and//or may contact the Authority for details of mode of payment.

An exemption for the application fee payment may be granted under public health emergency situation based on the decision of the emergency steering committee of the authority or when deemed necessary by the EFDA in other situations.

3.2. Technical and Specific requirements

Where available comprehensive data should be provided, which refers to a complete application with all quality, safety and efficacy information. Comprehensive data may only be available for some applications; such as for products which are used for other indications and have been repurposed for use particularly in the PHE; orphan drugs which are not novel products. For such products data requirements will be the same as new registration applications, as the product have relatively known safety profile. Since the safety profile is known, non-clinical data does not have to be submitted; however clinical data to support the new indication must be included. For example, for products that are repurposed, literature data on the safety of the product may be provided, However if dosage differs for the PHE disease, safety data for this dose should be provided. Therefore, these will be determined on a case-by-case basis. In this case, the ICH CTD format and guidance for the preparation of the dossier application for routine procedure included in the EFDA guideline for the registration of medicine is still applicable with non-applicability of certain sections, as appropriate.

On the other hands, for new/ novel products, only limited information may be available at early stages of submission and comprehensive data will be available at a later stage and should be submitted once available. Data that are not available at time of application and authorization should be discussed by the applicant and the Authority in pre-submission meetings. Since the expectation is that the chemistry, manufacturing/quality control and clinical development of the product submitted under non routine procedure will continue to product licensure, the use of the same ICH-CTD format is still encouraged, where possible. 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. But the non-applicability of the requested information should be

clearly indicated as such with an accompanying explanatory note. The Authority may request for additional written commitment where applicable.

The applicant shall consult the EFDA for any alternative compilation of the information to be provided in the product dossier application, when deemed necessary. This pre-submission consultation may be done via a chosen method of communication, including face-to-face meetings. Pre-submission consultation should be scheduled as early as possible, with a predefined agenda addressing questions sent to EFDA in advance by the applicant. Such consultations 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 for clarification on specific data requirements that require discussion between the applicant and EFDA. Therefore, applicants are highly encouraged to contact EFDA as early as possible to discuss specifics of the application.

EFDA may also rely on the decision of the reference regulatory authorities where the product under non routine registration procedure has been approved by one or more of the listed reference authorities. In this case reliance will be applicable whether the comprehensive data has been submitted to the specified authority or not provided that the data and/or information required by EFDA are accessible and fulfil the requirements for the decision making with respect to the authorization of that product for Ethiopian market. Applicants are advised to refer to the EFDA reliance guideline for the compilation and submission of application for the products approved by the reference authority.

Scientific literature may be appropriate to fulfil the requirements for some of the information or parameters outlined in this Guideline. In this case, a summary and the full reference to the scientific literature should be provided.

3.2.1. Documentation requirements for application under non routine procedure

The following are considered the minimum available evidence for the submission applications under non routine procedure when comprehensive data is not available during the initiation of the procedure.

a) Non-clinical and early clinical phase data that demonstrate promising evidence of safety and efficacy.

For a conditional approval, comprehensive non-clinical and pharmaceutical data should be available and only the clinical data could be less comprehensive than is normally the case. However, for products to be used in emergency situations, higher risks related to the absence of some data may be acceptable. In such cases an emergency use authorization can be granted also if preclinical or pharmaceutical data are not comprehensive. But such applications will be assessed on a case-by-case basis, taking into account the respective health threats and effects of the medicinal product.

b) written confirmation that phase 2/3 trials have started and that sufficient participants are expected to be enrolled to determine evidence of safety and efficacy within an appropriate and reasonable amount of time; and

c) a plan stipulating the proposed timelines for submitting the various components of the application. If not available at the time of submission the applicant should make a commitment to provide the plan as soon as possible.

3.2.1.1. Chemistry, manufacturing and control data:

Manufacturer

Name, address, and responsibilities of each site involved production and quality control with their specific unit block should be provided. If more than one manufacturing facility is used to produce Drug Substances and Drug Products, data should be provided to support the consistency of product quality between manufacturing sites. Particularly, for manufacturers of API intermediates (and FPP intermediate, where applicable), the basis for establishing that these sites are operating under GMP should also be provided.

For medicine

1) 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). Applicant should consult EFDA registration guideline, in this regard

2) 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.

3) Stability data for a minimum of 1 month accelerated and 3 months long term stability studies under emergency situation whereas a minimum of 6months accelerated and 6months long term data is expected for applications intended for the conditional approval

For vaccine

1) Full characterization of cell banks, master and working seed organism(s), according to the most appropriate WHO TRS and any subsequent updates.
2) 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 the EFDA, data on clinical trial batches with a commitment to complete validation on production batches and to submit the data as part of lot release review may be considered.

   Note: *if full characterization is not possible at the time of submission, adequate justification must be submitted and a plan must be presented to address the data gaps.*
3) Justified specifications for starting material, intermediates, and final products. If novel methods for validation of potency tests and other critical assays have been developed, full description of the test development and qualification must be presented.
4) Submission of updates: at the time of submission, it is likely that the manufacturing process will not have been finalised and that numerous changes will have to be made after the first emergency authorisation. These changes should be submitted as updates.
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

3.2.1.2. Non-clinical and Clinical Data

Data on the non-clinical and clinical studies on the candidate product should be provided. For a conditional approval, comprehensive non-clinical and pharmaceutical data should be available and only the clinical data could be less comprehensive than is normally the case.

However, for products to be used in emergency situations, higher risks related to the absence of some data may be acceptable. In such cases a emergency use authorization can be granted also if preclinical or pharmaceutical data are not comprehensive. But such applications will be assessed on a case-by-case basis, taking into account the respective health threats and effects of the medicinal product.

3.2.1.2.1. Non clinical data

For medicine

1) All relevant *in vitro* and *in vivo* pharmacodynamic (PD) data (e.g. on microbiologic/virology activity, including any modeling performed; the relevance of the applied cell types/line(s) for the target disease) should be justified.
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) will be done. This safety evaluation may be supplemented by any other non-clinical and clinical data at different exposure levels.

For vaccine

1) Non-clinical data demonstrating acceptable safety, immunogenicity, and efficacy – if available- in the most appropriate animal model. The applicant must justify the choice of animal model.
2) 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.

3.2.1.2.2. Clinical data

For medicine

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

For vaccine

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 should be provided.

Preliminary human data showing some efficacy should be submitted, if available. 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, the Authority 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 authorisation can proceed, provided there are trials that immunogenicity is a reliable surrogate endpoint.

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.

4. Review of Application

Applications under non routine procedure are always done on priority base. Thus, EFDA will assign task force composed of appropriate experts, immediately up on receipt of such application. In an emergency situation, the director general will assign the task force; whereas, this will be the responsibility of the medicine registration and marketing authorization lead executive office in other cases.

4.1.Screening process:

Where comprehensive data is not available and data are be submitted on a rolling submission schedule, applications will not undergo standard screening.

For applications containing comprehensive data, the expert from application screening team included in the assigned task force for assessment of application under non routine procedure will perform the screening of the submission to ensure that sufficient information is available to initiate the assessment by the task force assigned for assessment of safety, quality and efficacy based on the essential data requirements discussed relevant guideline. If the screening outcome indicates that the

assessment cannot be started due to lack of mandatory information, this will be communicated to the applicant within a day or two from the date of submission. However, when the missing data/information could not hinder the application from moving forward to the assessment, the applicant will be asked for submission of the missing information and submitted information will be forwarded for detail assessment.

4.2.Assessment process

EFDA may rely on the information and decisions of reference authorities for approval under non routine procedure depending on the submission and accessibility of required information from the reference authority. The decision of the EFDA based on the abridged assessment outcome could be marketing authorization, the emergency use authorization (EUA) or conditional approvals of the product based on the decision of the reference authority, situation for which the product is proposed and the availability and accessibility of the required specific data. In this case applicants are advised to consult the guideline for the regulatory reliance of Authority and compile their application dossier accordingly.

When the product under the non-routine application is intended for the declared public health emergency situation:-

- The director general of the authority will assign an emergency task force for the assessment application and select chairperson for each task force.
- The task force assigned for assessment of dossier will perform assessment and provide the emergency steering committee with a documented outcome of the evaluation of the quality, safety and efficacy or immunogenicity (for vaccine) of the product based on currently available data within a week from the day of recommendation for assessment after positive outcome of the screening. If the applicant has provided a timeline for additional data according to the product development plan, this should be indicated in the consolidated report so that the report will also indicate when the next set of data is expected (for example, full report of phase II trials).The summary report to the emergency steering committee should be compiled as per annex 4 of this guideline.
- The emergency steering committee should made decisions within not more than 3days from the date of receiving the assessment outcome unless justified. This may include the decision to accept the report or propose for request for additional data based on the outcome of the

dossier assessment. The decision of the steering committee should be compiled as per the annex 5 of this guideline.

- When the report is accepted, the medicine registration and marketing authorization of the authority will 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.

For the product intended for other medical purpose covered under scope of this guideline; the chief executive officer in consultation with each head of the desks responsible of application within the registration and marketing authorization shall appoint the team of expert for review. The team should include an expert for screening, quality data review, non-clinical and clinical data review and product information review. The chair person will be selected to the assigned task force. The assessment report should be submitted to the chief executive office within a week from the data of assignment to the task.

In general, the assessment approach will be as follows;

a) When the manufacturer have registered other product, the current product under non routine application has been accepted by the reference authority, exchange of information with the reference authority is possible, EFDA may conduct abridged assessment of reports from the reference authority and rely on the decision based on the summary basis of approval or equivalent.
b) When the manufacturer have registered other product, the current product under non routine application has not been accepted by the reference authority, but exchange of information with the reference authority is not possible, EFDA will conduct abridged assessment of application as per this guideline.
c) When the product under non-routine application does not fulfil the above condition under (a) and (b), EFDA will conduct a full initial review of application.

When the manufacturer has registered product as in case (1) and (2) above, the site has been previously inspected by EFDA and accepted or waived for different product, inspection of the site is not required for the sole purpose of the current product under non routine application procedure, even if the EFDA-GMP certification is not valid.

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.

4.3.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.

5. Validity period for emergency use authorization or conditional approval

5.1. The emergency use authorization will remain valid as long as declared public health emergency is not lifted or the marketing authorization is granted for product under EUA based on submission and review of full dossier.

5.2. The maximum time period for provisional marketing authorization of medicines under conditional approval is limited to a maximum of one year unless cancelled prior to this time due to serious safety and quality concern on the product

5.3. The conditional marketing authorization will automatically be discontinued at the end of a specified period unless the applicants are able to submit all relevant data required by the EFDA for full registration.

5.4. Extension of provisional registration could be accepted that requires additional clinical data for transition to full registration. Such application should be submitted one month before the expiry. Based on the full dossier reports; full marketing authorization may be granted

6. Post EFDA decision

6.1.Changes/Variations

Once a product has been issued approval for emergence use or conditional approval or as an orphan drug while the development is not yet completed, the development of the product must 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 of the product or (b) change the basis for the temporary approval. Such changes to the product must follow the procedure for submission of updates described above.

6.2.Post Market Surveillance

When the products under non routine procedure 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 or conditional approval 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 products. In this case, properly documented plan should be submitted to the responsible unit of the EFDA.

For any risk related to the products that have received conditional approval or 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 product).

In collaboration with the appropriate bodies including the MoH, EPSA, 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 decision 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 decision from 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 previous decision made as EFDA reserves the right to restrict or revoke the granted Authorization.

6.3.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.

7. Annexes

Annex 1: Template for cover letter

DATE:

[COMPANY LETTER HEAD – Name, address, phone number, email]

TO: Ethiopian Food and drug Authority (EFDA)

Address: Addis Ababa Ethiopia

SUBJECT: Application for (Insert Trade Name) (Insert International Non-proprietary Name of the Active Pharmaceutical Ingredient(s) (API), strength, dosage form) under non routine procedure

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

(Insert Trade Name) has (insert the decision of reference authority e.g EMERGENCE USE AUTHORIZATION or CONDITIONAL APPROVAL or MARKETING AUTHORIZATION) in (Insert COUNTRY NAME) The current 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 EFDA approval, be the same in all respects as the product given authorization with the (insert reference Authority Name) .

We confirm that all the information in the accompanying documentation concerning this application is true and correct. We also confirm that we have read and understood the EFDA guidance document on applications under non routine procedure.

We therefore kindly request that The EFDA consider the submitted application for this product in order to grant an appropriate authorization to access the market of Ethiopia

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: APPLICATION FORM FOR REGISTRATION (Form-MRMA-001.001)

Food and Drug Authority of Ethiopia, P.O. Box 5681, Addis Ababa, Ethiopia

A. Type of application (check the box applicable)

New Application			
A. Details on the product			
Proprietary name (trade name)			
Approved generic name (s) (use INN if any)			
Standard claimed (BP, Ph.In, Ph. Eur.,USP, IH, etc.)			
Strength(s) per dosage unit			
Dosage form			
Route of administration			
Shelf life (months)			
Storage condition			
Visual description			
Description of container closure			
Packaging and pack size			
Complete qualitative and quantitative composition (indicate per unit dosage form, e.g., per tablet, per 5ml, etc.) ** ** Add/delete as many rows and columns as needed.	Composition	Strength	Function
Complete qualitative and quantitative composition (indicate per batch in Kg, L, etc.). Type of batches should be described.	Composition	Strength	Function
Statement of similarity and difference of clinical, bio-batch, stability, validation, and commercial batch sizes			
Regulatory situation in other country (Provide a list of countries in which this product has been granted a marketing authorization and the restrictions on sale or distribution, e.g., withdrawn from the market, etc.)			

B. Details on the applicant

Name	
Business address	
Street number and postal address	
Telephone number	
Fax number	
E-mail and website address	
Contact person in a company	Name:
	Position:
	Postal address:
	Telephone number:
	Fax number:
	E-mail:
Details of Manufacturer, if different from above	<<Insert the required information as indicated above>>>

C. Details on active pharmaceutical(s) ingredient(s) manufacturer

Name of manufacturer	
Street and postal address	
Telephone/Fax number	
E-mail	
Retest period/Shelf life	

D. Details on local agent (representative) in Ethiopia

Name of local agent	
Sub-city and postal address	
Telephone/Fax number	
E-mail	
Contact person in company and address of company	

E. Details on dossiers submitted with the application

Section of dossier	**Annex, page number, etc.**
Module 1	
Module 2	
Module 3	
Module 4	
Module 5	

CERTIFICATION BY A RESPONSIBLE PERSON IN THE APPLICANT COMPANY

I, the undersigned, certify that all the information in the accompanying documentation concerning an application for a marketing authorization for:

Proprietary name (trade name)	
Approved generic name(s) (INN)	
Strength(s) per dosage unit	
Dosage form	
Applicant	

Manufacturer	

… is correct and true and reflects the total information available. I further certify that I have examined the following statements and I attest to their accuracy.

1.The current edition of the WHO Guideline, "Good manufacturing practices for pharmaceutical products," is applied in full in all premises involved in the manufacture of this product.

2.The formulation per dosage form correlates with the master formula and with the batch manufacturing record forms.

3.The manufacturing procedure is exactly as specified in the master formula and batch manufacturing record forms.

*4.*Each batch of all starting materials is either tested or certified against the full specifications in the accompanying documentation and comply fully with those specifications *before it is released for manufacturing purposes.*

5.All batches of active pharmaceutical ingredient(s) are obtained from the source(s) specified in the accompanying documentation.

6.No batch of active pharmaceutical ingredient will be used unless a copy of the batch certificate established by the active ingredient manufacturer is available.

*7.*Each batch of the container/closure system is tested or certified against the full specifications in the accompanying documentation and complies fully with those specifications *before it is released for manufacturing purposes.*

*8.*Each batch of the finished product is either tested or certified against the full specifications in the accompanying documentation and complies fully with the release specifications *before it isreleased for sale.*

9.The person releasing the product for sale is an authorized person as defined by the WHO guideline "Good manufacturing practices: Authorized person - the role, functions and training."

10. The procedures for control of the finished product have been validated for this formulation.

11. The market authorization holder has a standard operating procedure for handling adverse reaction reports on its products.

12. The market authorization holder has a standard operating procedure for handling batch recalls of its products

All the documentation referred to in this Certificate is available for review during a GMPinspection.

13. Any clinical trials including bioequivalence study were conducted according to WHO's"Guidelines for good clinical practice (GCP) for trials on pharmaceutical products."

Signature:_____

Name:_____

Position in company (print or type):_____

Date:_____

Annex 3: Commitment letter

[COMPANY LETTER HEAD – Name, address, phone number, email]

DATE:

TO: Ethiopian Food and drug Authority (EFDA)

Address: Addis Ababa Ethiopia

SUBJECT: Commitment for submitting information/data not available during the initiation of application

(Insert NAME OF APPLICANT) of (Insert ADDRESS OF APPLICANT) has submitted this application product whose details of the product are included in the submitted dossier.

We commit to submit the data/information indicated in the table below as missing in the estimated date of submission.

We also commit to submit periodic safety update report every six months for less serious issues and immediately for more serious safety concerns following granting and/or renewal of emergency use authorization or conditional approval

Section of CTD format missing	Missing information/data	Estimated date of submission
3.2.S.1.3	Polymorphic nature of the API was not studied and no literature available	A batch of the will be characterized and data will be submitted with 3months from the data of submission
3.2.P.3.5	Process was not validated in pilot batches	Validation report for exhibit batches will be submitted within 1month
3.2.P.8	Available stability report covers only 3months	Study will be continued and data of the batch under stability will be submitted progressively

Annex 4: Assessment task force reporting format

Assessment Report for the Product (insert Name) submitted under non routine procedure for EUA/conditional approval/ product listed as orphan drug/product proposed for conditions

Assessment team chair	
Name and signature of Members	✓
	✓
	✓
	✓
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 reference authority

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, efficacy and safety 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 EFDA, reference authorities and their 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 5: Format for final decision from emergency steering committee

Emergency steering the Product (insert Name) submitted for EUA

Steering committee chair	
Name and signature of Members	1.
	2.
	3.
	4.
Date of this report	

1. The product

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

2. **Authorizations granted by the reference authority**

Insert: 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 team

Insert: information assessed by the taskforce to generate the submitted report

4. Recommendation

Based on information and documentation submitted to the EFDA emergency steering committee (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.

8. References

1. EFDA Guideline for Emergency Use Authorization of COVID-19 Vaccine, Jan 2021
2. EFDA Guideline for registration of Medicines, Jan 2021
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. EFDA,Regulatory-Preparedness-and-Mitigation-Strategy-for-Emergency-Health-Threats, 2020
5. WHO emergency use List procedure, version 9 August 2022
6. TFDA, Guidelines on processing of applications for registration of medicinal products through non-routine procedure, April, 2023
7. SAHPRA, availability of medicines for use in a public health emergency (phe), 2022
8. EMA, Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorization for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004