ETHIOPIAN FOOD AND DRUG AUTHORITY

Medicine Evaluation and Marketing Authorization Lead Executive office

Guideline for Good Review Practices (GRevPs)

Document No.:	**EFDA/GDL/024**	Version No:	002
Date of approval:	10/10/2023	Date of First issue:	30/10/2023

Document History

Version No.	Reason for Amendment	Effective Date
001	New	30/10/2023
002	To align with WHO Good Review practice Guideline	05/11/2023

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I. Forward

Pre-market evaluation of medicinal products which is conducted to ensure that these products meet standards of quality, safety and effectiveness before they are allowed to enter into the market is one of the key regulatory functions undertaken to meet this goal. Medicines Evaluation and marketing authorization is the fundamental requirement for marketing of medicinal products in Ethiopia. The assessment of registration dossier submitted for medicines marketing authorization should be carried out by competent staff and with a well established standardized procedure that ensures consistent assessments of the applications. This guideline describes the internal process conducted during evaluation of medicine marketing authorization applications. Therefore, adherence to the guidelines will ensure achievement of high quality and timely outputs in a predictable and consistent manner. It will also instil transparency, clarity and efficiency of the review process. Hence, all dossier assessors should adhere to this guideline and further enrich its contents based on gaps identified during day to day dossier assessment practices and by incorporating feed backs or opportunities for improvements suggested by both internal and external stakeholders.

II. Abbreviations and Acronyms

eRIS: electronic Regulatory Information System

GMP: Good manufacturing Practice

GrevPs: Good Review Practices

EFDA: Ethiopian Food and Drug Authority

IGAD: Inter Governmental Agency for Development

MA: Marketing Authorization

ME and MA: Medicine Evaluation and Marketing Authorization

MOU: Memorandum of Understanding

QMS: Quality Management System

RRA: Reference Regulatory Authority

SOP: Standard Operating Procedure

WHO: World Health Organization

1. Introduction

The Ethiopian Food and Drug Authority (EFDA) is striving and exerting efforts to become a strong and resilient regulatory authority so as to safeguard the health of the Ethiopian population from health risks associated with food and medical products marketed in the country. Regulatory system thinking and optimization; and wise implementation of quality management system aligned with the regulatory policies, legal frameworks and standard procedures are important for establishing and maintaining reliable regulatory systems. Cognizant of this, improving the medicine marketing authorization review systems, practices and procedures is one of the main areas that EFDA needs to transform.

Bearing in mind that the complex and multidisciplinary assessment approach of medical products; the authority endeavour to meet the scientific and evidentiary standards for safety, efficacy and quality reviews. Good review practices (GRevPs) are considered as ways to improve the Authority performance and ensure the quality of the regulatory systems. Good review Practices are an integral part of overall good regulatory practices and forms the scientific foundation for regulatory decisions. To continuously improve practice, systems and procedures of medical product assessments, all aspects of GRevPs should be continuously evaluated and updated.

Reaffirming the need for well functioning regulatory authority that reach maturity level three in all its functions in the near future and anticipating to attain maturity level 4, it necessitates implementation and improving of good review practices (GRevP) as the basis for improved regulatory quality decision making. This will help achieve high quality, timeliness, predictability, consistency, transparency, clarity and efficiency of the scientific process, content and management of reviews of medical products.

Therefore, this good review practice (GRevP) guideline was developed based on international regulatory best practices and contextualized to the authority`s purpose. The guidance set out in each section of this guideline is general in nature. Assessors should follow other technical guidelines and standard operating procedures for detail instructions on how to conduct in depth technical evaluations.

2. Objective

The objective of this guideline is to provide high-level guidance on good review (GRevP) principles and processes related with medical products dossier review including submission of application and evaluation of products. It is not intended to provide detailed instruction on how to conduct in depth technical evaluation.

3. Scope

This Guideline is applicable to the review practices of safety, effectiveness and quality data of medical products marketing authorization applications, throughout all the evaluation key steps.

4. Definitions

1. **Applicant**: The person or company who submits an application for marketing authorization of a new medical product or a variation to an existing marketing authorization.
2. **Application**. The information provided by the applicant to the Authority for evidence-based review and marketing authorization decision.
3. **Authority**: Ethiopia Food and Drug Authority
4. **Good Review Practices (GRevPs)**: The documented best practices for any aspect related to the process, format, content and management of a medical product review.
5. **Marketing authorization (also called product licence or registration certificate)**: A legal document issued by the Authority that authorizes the marketing or free distribution of a medical product in the Ethiopian territory after evaluation of safety, efficacy and quality.
6. **Principles (of a good review)**: The important GRevP elements for the Authority to implement in order to achieve successful review outcomes.
7. **Project management (for the review process)**: The planning, organization and resources to achieve a complete and high-quality review of an application within a specified time frame.
8. **Quality Management (QM)**: The coordinated activities that direct and control an organization with regard to quality.
9. **Quality Management (QM) System**: An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources and systematic actions

necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

10. **Review (also called assessment)**: A highly complex, multidisciplinary assessment of medical product applications to assess whether the medical products meet scientific and evidentiary standards for safety, effectiveness and quality.
11. **Review Strategy**: The approach or plan of action that a reviewer or review team uses to review a medical product application.
12. **Standard Operating Procedure (SOP).** An authorized written procedure giving instructions for performing operations (both general and specific).
13. **Transparency**: Defining policies and procedures in writing and publishing the written documentation and giving reasons for decisions to the public.
14. **Medical products:** includes drug, biological products, and product that is a combination of medical devices and drugs or biological products

5. Principles of a good review

The authority has adopted the below listed ten key principles of WHO GRevP as a general guide during GRevP (see table 1).

Table 1: Ten key principles of good review practice.

SN	Principle of good review	Description
1	Balanced	A good review is objective and unbiased.
2	Considers context	A good review considers the data and the conclusions of the applicant in the context of the proposed conditions of use and storage, and may include perspectives from patients, health-care professionals and other regulatory authorities' analyses and decisions.
3	Evidence-based	A good review is evidence-based and reflects both the scientific and regulatory state of the art. It integrates legislative, regulatory and policy frameworks with emerging science.
4	Identifies signals	A good review comprehensively highlights potential areas of

		concern identified by the applicant and the reviewers.
5	Investigates and solves problems	A good review provides both the applicant's and the reviewers' in-depth analyses and findings of key scientific data and uses problem-solving, regulatory flexibility, risk-based analyses and synthesis skills to devise and recommend solutions and alternatives where needed.
6	Makes linkages	A good review provides integrated analysis across all aspects of the application: preclinical; nonclinical; clinical; chemistry/biocompatibility; manufacturing; and risk management plan. It includes timely communication and consultation with applicants, internal stakeholders and, as needed, with external stakeholders who have expertise relevant to the various aspects of the application.
7	Thorough	A good review reflects adequate follow-through of all the issues by the reviewers.
8	Utilizes critical analyses	A good review assesses the scientific integrity, relevance and completeness of the data and proposed labelling, as well as the interpretation there of presented in the application.
9	Well-documented	A good review provides a well-written and thorough report of the evidence-based findings and conclusions provided by the applicant in the dossier, and the reviewers'assessment of the conclusions and rationale for reaching a decision. It contains clear, succinct recommendations that can stand up to scrutiny by all the parties involved and could be leveraged by others.
10	Well-managed	A good review applies project and quality management processes, including clearly defined steps with specific activities and targets.

6. Managing the review

Review of medical product application dossiers are managed in a way that maximizes both the potential for a positive public health impact and the effective and efficient use of resources. At EFDA the Medicine Evaluation and Marketing Authorization Lead Executive office manages the process of reviewing medical product marketing authorization applications by the use of electronic registration system (eRIS). Applicants submit their request online through the eRIS and the review process has four clearly defined steps, each with specific activities and targets. These are:

- Application submission
- Screening the application(completeness check)
- Scientific Review
- Approval (Granting MA or rejecting)

6.1. Project management

The Authority has annual plan cascaded from the long term strategic plan objectives and targets. There is a well established practice of planning and monitoring of review activities coupled with timely and informative communications and clearly-defined appropriate work instructions for the reviewers. The planning and monitoring are based on set out key performance indicators which have well defined performance indicator reference sheets developed by the Authority.

Planning, monitoring and management of review process are coordinated by team leader and director of the Medicine Evaluation and Marketing Authorization Lead Executive Office. The progress of applications under review at each mile stone of the review process are monitored by the use of report generated by the electronic regulatory system (eRIS) and higher officials of the authority have access to this information. The system can generate data that can be interpreted and used to to assess the effectiveness of the review strategy including decision-making with respect to balance workload against resources; and outsourcing options could be sought in accordance with the established procedure based on the volume of work.

In addition, there is a quality assurance checks by QMS officers and focal expert responsible for quality assurance of the assessment processes.

6.2. Quality Management

The authority has established and implemented quality management system as stipulated in its quality manual. All review processes are conducted in accordance with the quality management system (QMS) established for marketing authorization function. Quality Management System is an integral part of the medicine marketing authorization application review procedures. The QMS principles include establishment of standardized procedures to ensure that GRevP are in place, regularly monitored and subjected to continuous improvement. As part of continual improvement, the following four components and subsequent main activities are implemented by the Medicine Evaluation and Marketing Authorization Lead Executive office: The four components are:

a) Say what we do

b) Do what we say

c) Prove it

d) Improve it

Say what we do

- EFDA has developed and implemented detailed technical guidelines aligned with the legislative documents and current global best practices
- The application review processes are clearly defined in the way that indicates decision-making processes to create transparency and accountability, such as decision frameworks, time frames for completion and communication modalities of reviews, use of external experts, public meetings and peer-reviews
- Developed and implemented detailed numbered and version controlled Standard Operating Procedure to guide the assessment process.
- Developed and implemented standardized and approved assessment templates and checklists for assessment of different categories of products

Do what we say

- Application screening and the dossier assessment are carried out in accordance with the procedures laid down in the relevant guidelines, and standard operating

procedures (SOPs) to ensure generation of well-written and thorough report of assessment findings that enables the authority to reach at the right conclusions

- Only standardized and approved assessment templates and checklists are used during application screening and dossier application screening and assessment are carried out by authorized competent personnel

Prove it

- The ME and MA Lead Executive Office ensures appropriate implementation of legal frameworks through internal external assessments
- The ME and MA Lead Executive Office ensures implementation of the developed and maintained standardized review templates and checklists through regular internal audit.
- Implementation of the timelines for reviewing applications for each category of application are monitored as defined in the medicines marketing authorization directive
- Records of key documents, such as minutes of meetings and teleconferences, MOU, letters and reports are retained as defined in the records management SOP.
- Consistent interpretation and application of review procedures and templates is ensured through the assessment of various inputs, such as internal and external feedback and periodic evaluation of practices by internal and external experts.

Improve it

- The authority assesses public health impacts of regulatory decisions, such as through a lessons-learned session that could include assessing the impact on disease, the health-care system and any unintended consequences at predefined periods and take appropriate measures
- Internal audit findings are used to improve adherence to and implementation of review processes as defined in relevant SOPs as well as adherence to specified time frames
- Improvements are introducing to the review and decision-making process based on customer feedback, performance review outcomes and global current practices.
- Documentation and decision-making processes are reviewed regularly
- In general, internal assessment of a review; peer-review; internal quality audits; self-assessments; analyses of feedback from stakeholders; post-approval analysis of the

decision in collaboration with other authorities; the public and applicants; and analysis of impact on public health are used as inputs for improvement.

- Professional developments will be offered based on identified gaps or a need to advance the existing services or starting new service, mentoring and regular on-the-job training will be provided to improve personnel capability.

6.3. Standard Operating Procedures (SOPs)

Review of each application is guided by specific SOPs which: -

a) Outline the workflow processes which are also integral part of the eRIS that facilitate project management when there are multiple applications to process;

b) Enables handling and evaluating applications in a consistent manner; and

c) Facilitate staff training.

The ME and MA Lead Executive Office has developed SOPs for managing the marketing authorization process from receiving application, screening, distribution and assigning documents to assessors as well as for consistent technical evaluation and communicating to applicants. The SOPs were developed in alignment with other tools and relevant guidance to support effective implementation of the tasks. Standardized checklists are developed to provide consistency on conducting assessment of a particular type of product. Trainings are provided to experts on the procedures to ensure consistent implementation of the SOPs by all assessors involved in medicinal dossier assessment.

6.4. Review Process Stages and Pathways

There are two sets of key stages in the process of reviewing medical products. Those include screening to verify completeness of the submitted application and scientific review. Applicants are made aware on the Authority`s expectations at all stages including the target time frames, guidelines, requirements, templates and checklists. All applications submitted to the ME and MA Lead Executive Office undergoes screening which is done at the point of submission of applications. The review process stage is done in accordance with agreed laws, guidelines, checklists and templates provided for each category of applications and approval pathways.

The Authority implements risk based regulation including categorization and review of medical products marketing authorization applications. Hence, the ME and MA Lead

Executive office is also implementing risk based approach to registration and marketing authorization of medicinal products. This includes:

- Products classification into low risk and high risk products applications and the depth of review corresponds to the level of risk of the medical products
- Conducting full and in depth review for new applications
- Conducting abbreviated review process for applications of medical products that are approved by reference regulatory authorities, WHO prequalified products, applications submitted via low risk products approval pathway, mutual recognition approach and conditional approval pathways.
- Implementing abbreviated /partial review procedure for renewal applications Implementing fast track procedures for evaluation and marketing authorization of applications of products of priority public health interests.

7. Communications

It is the Authority's fundamental belief that its employees and members shall be open to public scrutiny. The authority has developed communication strategy and the ME and MA lead executive office has developed and implemented subsequent standard operating procedure for internal and external communications to ensure that clear, complete and concise information that ensures transparency and clarity during product application review reaches its customers. All relevant policies, laws, guidelines, templates, checklists, review summaries and other non-confidential and relevant information are published on the Authority's websites. All the communications are guided by standard procedures or memoranda or other similar mechanisms.

7.1. Intra-agency

The ME and MA Lead Executive Office will share information to and/or obtain from relevant Lead Executive Offices of the Authority such as method of analysis (MOA), certificate of analysis (CoA) and GMP compliance status, registered medicinal products, and adverse events with relevant Lead Executive Offices of the authority.

Moreover, there is an open, clear, constructive and timely communications regarding the progress of review, review findings, data interpretations and discussion for possible solutions and actions within assessors. There is engagement of experts in application reviews and coordination with different organizational units within the authority, such as pre- and post-

marketing scientific disciplines, pharmacovigilance, inspection and others.There is an internal and external communication SOP to provide clear procedures and guidance to share information within authority.

7.2. Interagency

The Authority may communicate, collaborate and jointly work with other countries regulatory authorities, WHO, IGAD member states and other relevant harmonization schemes regarding medical products application reviews. It will share information, decisions and guiding documents and other relevant data for medical products review as the case may be.

The Authority has established and implemented information-sharing arrangements and procedures, such as signing memoranda of understanding, confidentiality arrangements, filling consent form by the applicant and non-disclosure of specific information, as well as other arrangements and actions to ensure confidentiality of commercial data, trade secrets and personal information.

7.3. Applicants

The authority communicates the applicants through publicly available working legal documents such as proclamation, regulations and directives, and guidelines published on websites, and checklists on the eRIS (http://www.eris.efda.gov.et/). Other notices, regulatory authority review reports, decision summaries, Market Authorizations Certificates and other notification & decision letters will be communicated to applicants through other communication mechanisms. These communications allow applicants to provide better quality applications.

Without negotiating on quality, the Authority will communicate with applicants on specific applications before, during and after the review process.

7.4. External experts

The Authority has created full-fledged system to use external expertise in the form of advisory panel or pool of external experts nominated from academia, industry associations, professional associations, patient organizations and other relevant institutions in scientific assessment of the safety, efficacy and quality of medical products. Experts from universities are also engage in the scientific assessment of the safety, efficacy and quality of medical

products. All experts or members of advisory panel participating in the review process shall sign confidentiality and conflict of interest form prescribed by the Authority.

7.5. The public

The Authority communicates with the public through representatives during planning, evaluation and monitoring of regulatory activities to provide inputs on medical needs, efficacy expectations, risk tolerances and others through public meeting or representative of the public. The Authority has also devised mechanism whereby the public can provide input and comment on content and feasibility of proposed laws and guidelines by publishing draft documents and making publicly available for comment.

8. Review personnel

The Authority shall use a pool of experts or review advisory panel composed of internal staff and external experts. The experts and anyone who participates in the review process of dossiers shall be trained in all section of the dossiers including administrative requirements; technical aspects of the medical product dossier- quality, safety, efficacy; and product information and labelling sections of the dossier including the national laws and guidelines as per the training SOP..

The authority conducts review of actual or perceived conflicts of interests prior to engaging external experts for dossier assessment and it requires the external experts to declare and sign the declaration of conflict of interest form prior to their participation in the dossier assessment.

At the virtue of their working responsibilities, the external experts (reviewers) have access to review proprietary information with respect to the applicant and product related data. It is, therefore, the reviewer's responsibility withholding highest ethical standards to maintain the confidentiality of information that he/she has accessed during delivering of his/her obligations. Hence, EFDA shall also require the external experts to sign confidentiality agreement prior to their participation in the dossier assessment.

8.1. Reviewer expertise and competencies

EFDA shall ensure the expertise and competencies of the experts involved in the review of medical products dossiers. Reviewers are assigned and engaged in the review process based

on their specialization and expertise. Considering the experience and expertise of the assessors, a dossier shall be reviewed by both primary and secondary assessors.

The experts who took basic dossier assessment training shall participate as a primary assessor and shall be mentored by the lead assessors. The primary assessors are responsible for in depth evaluation or assessment of the medicine dossier application, as per relevant directives, guidelines and SOPs as well EFDA recognized official monographs, in a manner that avoids duplication of effort. The primary assessors shall write and communicate the assessment report to the respective quality, clinical or biological lead assessors. Lead assessors are experienced experts who took specialized and advanced dossier assessment trainings and they are not necessarily required to dig in the bulk of the data, unless required. They shall review the dossier review reports submitted by the primary assessors and discuss with the first assessor and may go in to the dossier application, as required, before preparing assessment summary report and sending the assessment report to the desk head. In addition, the lead assessor may return the first assessment report to the primary assessor when observations in the dossier were not discussed in depth by the primary assessor or the assessment was not conducted as per the respective registration guideline, SOPs and/or checklist.

Finally the lead assessor shall submit the commutative and agreed review results to the respective Desk leader of ME and MA Lead Executive Office.

8.2. Review committees/advisory panel

The authority uses review committee composed of experts with background of pharmacology, pharmaceutics, pharmaceutical analysis, law, public health etc from different institutions such as academia.

The committee shall have advisory roles on different areas including providing recommendation on approval of some public priority medical products, providing opinion to proceed to review of medical product with new molecule(s) for Ethiopia, providing opinion for considering medical product with different review pathways and other assignment.

The meeting schedule of the review committee shall be determined on the rules and regulation of the committee and generally shall be on monthly basis. However, when necessary the frequency of meeting deemed shall be called by EFDA based on the applications and issues raised.

9. Conducting the review

EFDA follows risk-based review approach including categorization of products based on risk level and reliance approaches. The Authority has categorized products based on their risk as those which require full assessment, low risk products, skin care and oral care products, antiseptics and disinfectants, as well as different approval pathways were devised based on a well defined strategy to facilitate marketing authorization processes including Reference Regulatory Authority (RRA) procedure, WHO collaborative registration procedure, and approval procedure through regional collaborations (e.g. IGAD) joint assessment of medical product marketing authorization applications. Some of the approval pathways include:

a. Fast track procedure for Public health priority medical product application

EFDA has established fast track registration pathway for public priority medical products. The Authority discloses the medical products category that follows the fast track application pathway to the applicants and public.

b. Reference Regulatory Authority (RRA) procedure

EFDA undertakes an abbreviated review for medicines already approved by a regulatory authority considered by authority as stringent. This pathway applies for products approved by countries recognized as reference regulatory authority by EFDA as well as WHO Prequalified products. EFDA also utilizes the WHO collaborative procedure where experts of EFDA participate in the prequalification process of medicines. EFDA treats products approved by WHO- prequalification the same way as reference regulatory authorities approved products and conduct limited review for such products. The authority has developed and implemented guidelines and SOPs for each approval pathways.

c. Low and high-risk product assessment

EFDA has classified products marketing authorization applications into low risk and high-risk applications: There a specific guideline for reiewing MA application of low risk medicines. The depth of assessment shall correspond with the level of risk of the medical product.

d. Collaborative registration Procedure

EFDA has implemented collaborative procedure with WHO and regional collaborations (IGAD member states) for participating in joint assessments and approval of such products based on the established procedures. Information sharing mechanisms has been established.

e. New product registration and renewal

EFDA conducts a full assessment for all new molecules and any new applications of high risk products; but limited review for renewal applications.

f. Other procedures

EFDA has developed guideline and established procedure for conditional approaches for review of a certain category of medicines.

10. Reference

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