Ethiopian Food and Drug Authority (EFDA)

Good Review Practices (GRevPs) Guideline

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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. Recognizing this, improving the medicine review systems, practices and procedures is one of the main areas that EFDA needs to renovate.

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 four in all its functions in the near future, 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 our purpose. The guidance set out in each section of the guideline is general in nature. Comments and suggestions are welcome and can be sent to the Ethiopian Food and Drug Authority, P.O. Box 5681, Addis Ababa, Ethiopia.

1.1. 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. It is not intended to provide detailed instruction on how to conduct a scientific review.

1.2. Scope

This Guideline will be applicable to the review practices of safety, effectiveness and quality data of medical products.

1.3. 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 medicines, vaccines, diagnostics and medical devices

2. Principles of a good review

The authority will follow the below ten key principles 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.

3. Managing the review

Review of medical product application dossiers shall be managed in a way to maximize both the potential for a positive public health impact and the effective and efficient use of review resources. The Authority shall actively manage the process of reviewing medical product applications and clearly define steps in the process, each with specific activities and targets.

3.1. Project management

The Authority shall strengthen the practices of planning and monitoring of review activities coupled with timely and informative communications and shall clearly-define appropriate work instructions for the reviewers. The planning and monitoring shall be based on set out key performance indicators developed by the Authority.

Planning, monitoring and management of review/assessment shall be coordinated by team leader, director of the registration department and higher officials of the authority as appropriate. In addition, there shall be quality assurance manager or expert responsible for the organization, monitoring and quality assurance of the assessment processes.

3.2. Quality Management

All review processes shall be done in line with the quality management system (QMS) of the Authority. Dossier assessment shall be done in accordance with laid down procedures to ensure well-written and thorough report of assessment findings and conclusions.

As part of the quality manual and quality management principles of the authority, the following main activities has to be implemented to improve the good review practice of applications submitted to the authority.

- Develop and implement appropriate legal frameworks and detailed technical guidelines aligned with international practices.
- Develop and implement detailed, numbered and version controlled Standard Operating Procedure to guide the assessment process.
- Only standardized and approved assessment templates and checklists shall be used. The registration directorate shall develop, maintain and implement numbered, version controlled and approved review templates and checklists for all review processes.
- There shall be timelines for reviewing applications for each category of application
- Define processes that clearly indicate decision-making processes which 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.
- Adhere and implement review processes defined and adhere to specified time frames.
- Offer professional development, mentoring and regular on-the-job training.
- Record and collect key documents, such as minutes of meetings and teleconferences, MOU, letters and reports.
- Ensure that review procedures and templates are being consistently interpreted and applied through the assessment of various inputs, such as internal and external feedback and periodic evaluation of practices by internal and external experts.

- Assess 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.
- Review documentation and decision-making processes regularly.
- Consider introducing improvements to the review and decision-making process. Conduct 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.

3.3. Review process stages and pathways

The EFDA sets key stages in the process of reviewing medical products. Those includes application submission, screening, verifying and scientific review. The Authority will aware applicants on its expectations at all stages including the target time frames, guidelines, requirements, templates and checklists. All applications shall undergo screening and shall be done at the point of submission of applications. All the review process stage shall be done according to agreed laws, guidelines, checklists and templates provided for each category of applications.

The Authority shall implement risk based categorization and review of applications. This shall include:

- Classification of product into low risk and high risk applications and the depth of review will correspond the level of risk of the medical products
- Full review shall be conducted for new applications. However, applications for medical products that are approved by SRA, WHO prequalified, low risk products approval pathway, mutual recognition approach and conditional approval pathways follow the partial review process.
- Limited/partial review shall be done on renewal applications.
- The registration Departments will be expected to implement risk based approach to registration of medicinal products

4. Communications

It is the Authority's fundamental belief that its employees and members of the Authority shall be open to public scrutiny. Clear, complete and concise that ensures transparency and clarity

during product application review shall be followed. The Authority will publish its policies, laws, guidelines, templates, checklists, review summaries and other non-confidential and relevant information on the Authority's websites. All the communications shall be guided by standard procedures or memoranda or other similar mechanisms.

4.1. Intra-agency

The Medicine Registration and Licensing Directorate will share information to and obtain from relevant directorates 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 directorates of the authority.

Moreover, there shall be 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 will be clear procedures and guidance to share information within authority.

4.2. Interagency

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

The Authority shall fulfil the information-sharing arrangements and procedures, such as memoranda of understanding, confidentiality arrangements, consent from 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.

4.3. Applicants

The communication between EFDA and the applicants will be based on quality assurances. Publicly available working legal frameworks and guiding documents such as guidelines, notices, finalized regulatory authority review reports, decision summaries, Market Authorizations Certificates and other notification & decision letters will be communicated to applicants through websites, eRIS (http://www.eris.efda.gov.et/) and other communication mechanisms.

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

4.4. External experts

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

4.5. The public

The Authority shall communicate with the public 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 shall also devise mechanism whereby the public can provide input and comment on content and feasibility of proposed laws and guidelines.

5. 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 of assessors.

EFDA shall conduct review of actual or perceived conflicts of interests when the Authority use external experts for dossier review and shall require the external experts to declare and sign the 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.

5.1. Reviewer expertise and competencies

EFDA shall ensure the expertise and competencies of the experts involved in the review of medical products dossiers. Reviewers shall be 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 secondary assessors. Secondary assessors who are experienced and took specialized and advanced dossier assessment trainings shall review the dossier reviewed by primary assessor and submit the commutative and agreed review results to the team leader of Medicine Registration and Licensing Directorate.

5.2. Review committees/advisory panel

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

The committees shall have advisory roles on different areas including providing recommendation on approval of some public priority medical products, providing opinion to proceed 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 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.

6. Conducting the review

EFDA shall follow risk-based review approach including categorization based on risk level and reliance approaches. The Authority shall develop well defined strategy to facilitate marketing authorization processes including Stringent Regulatory Authority (SRA) procedure, mutual recognition approach, WHO collaborative registration, and regional collaborations (e.g. IGAD) such as joint assessment of medical product applications.

a. Public health priority of the medical product application

EFDA shall provide and establish fast track registration pathway for public priority medical products. The Authority shall disclose the medical products category that follows the fast track application pathway to the applicants and public.

a. Stringent Regulatory Authority (SRA) procedure

EFDA shall conduct a limited review for medicines already approved by a regulatory authority considered by authority as stringent. This shall include products approved by countries recognized as stringent regulatory authority by EFDA including registration of WHO Prequalified products. EFDA shall have a close collaboration with WHO. Experts of EFDA participated in the prequalification process of medicines. EFDA shall recognized WHO- prequalification as stringent and conduct limited review for WHO Prequalified products. To facilitate this, EFDA shall have separate registration guidance for WHO prequalified products.

b. Low and high-risk product assessment

EFDA shall classify the product into low risk and high-risk applications: The depth of assessment shall correspond with the level of risk of the medical product

c. Collaborative registration with WHO, and regional collaborations (e.g. IGAD) review works.

EFDA shall implemented conduct collaborative procedure with WHO and regional collaborations such as IGAD. Information sharing among the authority shall be established.

d. New product registration and renewal

EFDA shall conduct a full review on new applications; and limited review for renewal applications.

e. Other procedures

EFDA shall implement mutual recognition and conditional approaches for review of a certain category of medicines.

Reference

1. Good review practices: guidelines for national and regional regulatory authorities, World Health Organization, Technical Report Series No. 992, 2015, Annex 9.

2. Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications Guidance for Industry and Review Staff, Good Review Practice, Draft Guidance, U.S. FDA, Sept 2018.
3. Expediting Medicine Market Authorization Strategy, Ethiopian Food and Drug Authority (EFDA), Addis Ababa, Oct 2017.
4. Good Abbreviated New Drug Application Assessment Practices. Office of Generic Drugs and Office of Pharmaceutical Quality. Policy and Procedures (MAPP 5241.3), Effective date 1/3/18. Manual of Policy and Procedures, Center for Drug Evaluation and Research, U.S FDA.
5. Good Review Practices Policy. Food and Drug Authority of Ghana (Ghana FDA), Office of, Effective date 1/3/19.
6. Good Reliance Practices in Regulatory Decision-Making: 6 high-level principles and recommendations: Draft Working Document, World Health Organization, 2020.