# GUIDELINE OF GOOD REVIEW PRACTICES

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**Drug Regulatory Authority of Pakistan**
Islamabad-Pakistan

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## 1. HISTORY

This is the first edition of this document.

## 2. APPLICATION - Guideline for assessors / evaluators

This document is meant to provide guidelines for the assessors / evaluators on the principles and processes of good review practice (GRevP) for use within the Authority across evaluation of pharmaceutical and biological drug products market authorization applications. It is not intended to provide detailed instruction on how to conduct a scientific review?

## 3. PURPOSE

The purpose of GRevPs is to promote timeliness, predictability, consistency, transparency, clarity, efficiency, and high-quality standards in both the content and management of reviews.

## 4. INTRODUCTION

The objective of this document is to provide high-level guidance on the principles and processes of good review practice (GRevP) for use within the Authority. It is not intended to provide detailed instruction on how to conduct a scientific review. This document is an adaptation of the WHO Good review practices: guidelines for national and regional regulatory authorities (Technical Report Series 992, Annex 9) (1) and is envisioned as one building block in a set of tools and is sufficiently expandable to accommodate additional annexes or ancillary documents in the future.

GRevPs play a crucial role in upholding comprehensive regulatory practices, concentrating on the regulatory tasks associated with reviewing medical products. This review process involves a sophisticated, multidisciplinary evaluation of applications for medical products to guarantee their compliance with scientific and evidentiary criteria regarding safety, efficacy, and quality. The review process serves as the scientific basis for making regulatory decisions.

## 5. LEGAL REQUIREMENTS

i. Section 7 (c) (ix) of DRAP Act 2012, mandated the systematic implementation of internationally recognized standards of World Health Organization, International Conference on Harmonization (ICH), and Food and Drug Administration guidelines etc.

ii. These guidelines conform to DRAP Act 2012, Drugs Act 1976 and rules framed there under and some parts such as classification, definitions, and description etc., have been adopted from WHO guidelines on registration / market authorization procedures.

## 6. ACRONYMS & DEFINITIONS

The definitions given below apply to the terms used in this document. They may have different meanings in other contexts.

**applicant.** The person or company who submits an application for marketing authorization of a new medical product, an update to an existing marketing authorization or a variation to an existing marketing authorization.

**application.** The information provided by the applicant to the RA for evidence-based review and marketing authorization decision.

**authority.** Drug Regulatory Authority of Pakistan

**good regulatory practices (GRP).** Reference definition in WHO GRP guidelines (currently under development)

**good review practices (GRevP).** Documented best practices for any aspect related to the process, format, content and management of a medical product review.

**marketing authorization.** Also referred to as product licence or registration certificate. A legal document issued by the competent medicines RA that authorizes the marketing or free distribution of a medical product in the respective country after evaluation of safety, efficacy and quality. In terms of quality it establishes inter alia the detailed composition and formulation of the medical product and the quality requirements for the product and its ingredients.

It also includes details of the packaging, labelling, storage conditions, shelf-life and approved conditions of use.

**principles (of a good review).** The important GRevP elements for RAs to implement in order to achieve successful review outcomes.

**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.

**quality management (QM).** The coordinated activities that direct and control an organization with regard to quality.

**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.

**regulatory authority (RA).** The agency responsible for the registration of and other regulatory activities concerning medical products.

**regulatory convergence.** The process whereby regulatory requirements, approaches and systems become more similar or aligned over time as a result of the adoption of internationally recognized technical guidance, standards and best practices.

**review.** A highly complex, multidisciplinary assessment of medical product applications to assess whether they meet scientific and evidentiary standards for safety, efficacy and quality. It forms the

scientific foundation for regulatory decisions. The first stage of the review process, validation (sometimes referred to as screening), occurs before the scientific review with the aim of ensuring completeness of the application in order to subsequently facilitate the scientific review.

**review strategy.** The approach or plan of action that a reviewer or review team uses to review a medical product application.

**standard operating procedure (SOP).** An authorized written procedure giving instructions for performing operations (both general and specific).

**transparency.** Defining policies and procedures in writing and publishing the written documentation, and giving reasons for decisions to the public.

## 7. Principles of a good review

The following are the principles of good review:

**i. Balanced**

A good review is objective and unbiased.

**ii. 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 RAs' analyses and decisions.

**iii. 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.

**iv. Identifies signals**

A good review comprehensively highlights potential areas of concern identified by the applicant and the reviewers.

**v. 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.

**vi. 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.

**vii. Thorough**

A good review reflects adequate follow-through of all the issues by the reviewers.

**viii. Utilizes critical analyses**

A good review assesses the scientific integrity, relevance and completeness of the data and proposed labelling, as well as the interpretation thereof, presented in the application.

**ix. 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.

**x. Well-managed**

A good review applies project and quality management processes, including clearly defined steps with specific activities and targets.

## 8. Managing the review

The process of reviewing drug product applications shall be managed to harness the potential for a positive public health impact and the effective and efficient use of review resources.

The separate steps in the process, each with specific activities and targets shall be identified. The principles of project management and quality management are very critical to well-functioning of the Authority. The practices of planning and monitoring review activities coupled with timely, informative communications within the Authority and clearly-defined work instructions for the reviewers, can maximize the efficiency and effectiveness of the review.

## 9. Project management

Project management for the review process refers to the planning, organizing and resourcing necessary to achieve a complete and high-quality review of an application within a specified time frame.
Techniques should be developed to monitor the progress of applications under review. Data should be periodically collected and interpreted to assess the effectiveness of the review strategy for completing reviews within the specified time frame.

The technique most suitable for the will be one that enables:

- interpretation of the data to show the progress of one application as well as that of many applications under review at any one time;
- interpretation of the data to help in decision-making with respect to balancing workload against resources;
- monitoring that can be performed and/or interpreted by the relevant people.

As the conditions, resources and workload for the RA evolve, the techniques and complexity of project management should also be adapted.

## 10. Quality management

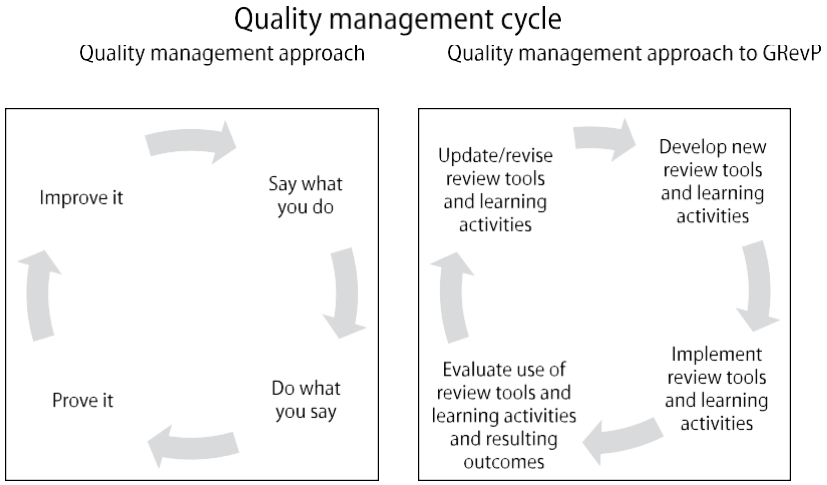
Quality management (QM) is defined as the coordinated activities that direct and control an organization with regard to quality. A QM system refers to the appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality. QM shall include standardized procedures to ensure that GRevPs are in place, regularly monitored and subject to continuous improvement. Beyond standardized processes and procedures that provide consistency and predictability, QM has the ultimate goal of supporting robust regulatory decisions and actions.

The quality cycle is made up of four key components:

- say what you do
- do what you say
- prove it
- improve it.

This cycle ensures that GRevPs are not just esoteric guidelines (say what you do) but become embedded in the daily practice of an agency (do what you say). Quality management is also important as it can help an agency review its practice (prove it) and evolve where necessary, either in response to evolving regulatory science or through the adoption of a new review process and procedures (improve it).

**Quality management cycle**




## 11. Standard operating procedures

Creating and adopting a set of SOPs enables the Authority to:

- outline the workflow processes that facilitate project management when multiple reviewers assess different parts of the same application and when there are multiple applications to review;
- handle and review product applications in a consistent manner;
- facilitate staff training.

SOPs shall describe procedures (or processes) in a step-by-step manner. They should describe the overall procedure from start to finish. SOPs should be written clearly to provide both instruction and consistency related to the work being performed. SOPs may be structured to contain additional tools that will assist in performing the procedure. Alternatively, companion documents can be created to give more detailed instruction and structure in support of an SOP. These companion documents (for example, guidelines for reviewers, templates and checklists) can describe in detail how a particular procedure is performed or give advice on handling a specific situation when performing the procedure.

Templates and checklists present information in a structured manner to facilitate understanding of the information submitted for review. Templates prompt the user to provide specific information, while checklists prompt the user to ensure either that information has been provided or that a particular task has been completed. Templates and checklists have the added benefit of training reviewers and review teams on how to provide information in a structured, consistent manner.

SOPs can be further complemented by guidelines for applicants, in order to promote transparency and guide applicants on how to submit high-quality marketing authorization applications. Guidelines for applicants can be made available using a step-wise approach, usually involving informing applicants of the guidelines before making them publicly accessible.

SOPs, guidelines, templates and checklists will require updating (or in some cases even cancellation) as technological advances occur or scientific and regulatory thinking evolves. This evolution could be related to influences including scientific progress, international harmonization of guidelines, changes in review strategy, available resources, increased volume of applications, collaborative work-sharing and national laws and regulations, among others.

## 12. Review process stages

Two key stages in the process of reviewing drug product applications are validation and scientific

review. The validation stage occurs first, with the aim of ensuring completeness of the application in order to facilitate the subsequent scientific review.

Validation involves an examination of the application to ensure that it is well-organized and that all the required forms and relevant documents have been submitted. Identifying missing information in the application prior to scientific review enables the Authority to avoid spending time and review resources on an application that does not allow critical analysis, signal identification or regulatory decision-making.

It is essential that applicants are made aware of the Authority's expectations at both stages, including the target time frames, guidelines, requirements, templates and checklists. This results in a more predictable and clear process for applicants. In turn the Authority benefits when applicants submit complete applications at the outset.

## 13. Communications

Good communication is critical and has many advantages for Authority, applicants and the public. It can improve the efficiency of the development and review process, allowing patients faster access to important medical products. It can also improve the quality of the review by providing access to additional expertise.

Communications can take many active forms, such as providing information on Authority's website, sending e-mails, sending letters via post etc. In turn, these active forms of Authority's communications can be used to the advantage of others, including other Authorities.

### 13.1 Intra-Authority

Product reviews are conducted in a collaborative environment. They often require expertise from and coordination with different organizational units within the Authority, such as pre- and post-marketing scientific disciplines, pharmacovigilance, inspection and others.

Therefore, good communication will improve efficiency. Open, clear, constructive, and timely communications regarding the progress of the review, review findings, differing data interpretations and discussion of possible solutions and actions within the Authority are desirable. In addition to establishing meetings, forums and other vehicles for exchange of ideas among reviewers, a checklist of personnel or departments involved on specific issues or actions may be helpful. Information management systems should be process-centric rather than organizational structure-centric to ensure appropriate and efficient information flow.

### 13.2 Interauthority

Authority to Authority communications have become more frequent and in many cases normative. As a means of peer collaboration and cooperation, interauthority communications can facilitate greater regulatory convergence. This, in turn, can increase the efficiency and quality of medical product development and Authority review processes and improve patient access. Types of interauthority communication include:

- accessing information from other RAs' public websites, such as guidelines, application decisions and product recalls;
- using information from other RAs, such as review reports and certificates of pharmaceutical product;
- actively sharing information between RAs, such as nonclinical, clinical and inspection findings during an application review;
- actively working with other RAs, for example, on joint reviews of applications and development of new guidelines.

Interauthority communication may evolve from sharing and awareness of information, to consideration of findings from one Regulatory Authority (RA) by another in its decision- making, to using and relying on those findings to make the best use of resources.

Information-sharing arrangements and procedures, such as memoranda of understanding, confidentiality arrangement, consent from the applicant, redaction and non-disclosure of specific

information, as well as other arrangements and actions, have been used to ensure confidentiality of commercial data, trade secrets and personal information.

### 13.3 With applicants

Public availability of guidelines, notices, questions and answers and presentations, as well as finalized review reports and decision summaries (redacted as needed), provide insight into the Authority's current thinking and expectations. These communications allow applicants to provide better quality applications.

Communication between the Authority and individual applicants on specific applications before, during and after the review process is also important as it can:

- foster efficient medical product development through the provision of scientific advice;
- increase applicants' understanding of evolving regulatory expectations in a changing medical and scientific environment;
- increase the Authority's understanding of challenges and trade-offs with various requirements;
- foster applicants' compliance with requirements
- inform applicants about the progress and status of the review of their applications.

Procedures allowing applicants and the Authority to engage with each other can facilitate the development, review and availability of medical products. Topics for dialogue can relate to product development requirements (including feedback on guideline development and implementation), as well as issues identified during the application review or post marketing.

### 13.4 With external experts

Expertise in the scientific assessment of the safety, efficacy and quality of medical products is not limited to applicants and Authority. Academic institutions, industry associations, patient organizations and medical and scientific organizations all have extensive expertise that may be useful to the review.

Input of external experts into Authority decision-making improves public confidence, provides additional perspectives for the Authority to consider and provides expertise that otherwise may be lacking. Ensuring both confidentiality and absence of conflict of interest is important and can be achieved through transparent processes for management of confidential information and screening for potential conflicts.

### 13.5 With the public

Communication with the public about the mission and accomplishments of the Authority can foster greater public awareness, understanding of and confidence in the RA. Transparency refers to defining policies and procedures in writing and publishing the written documentation. Transparency initiatives usually involve web-based information about how it is organized and operates, its decision-making processes and criteria and its actions, such as application approvals and product recalls. Additionally, there may be mechanisms whereby the public can provide input on medical needs, efficacy expectations and risk tolerances, such as through public meetings and e-mails. Providing the public with the opportunity to comment permits enhanced content and feasibility of proposed guidelines and regulations. Use of plain language will ensure communications are properly understood.

## 14. Review personnel

The quality, timeliness and success of medical product application reviews are dependent on adequate review capacity. In addition to having a sufficient number of reviewers, capacity relates to

many personnel factors including the knowledge, skills, abilities and attitudes of reviewers. Together, these considerations define the core competencies for personnel involved in the various aspects of managing and conducting reviews.
Reviewers may be staff, external experts or both. To ensure the integrity of product reviews and recommendations, reviewers should be free of actual or perceived conflicts of interests. To be free of any conflict of interest means the review decision or recommendation is not likely to be influenced by personal, family, financial or professional motives.

### 14.1 Reviewer expertise, competencies and training

The use of core competencies can contribute to improved application review by encouraging evidence-based, population-focused, ethical decision-making.
Reviewers should have professional qualifications, training and expertise in scientific or medical fields that relate to the assessment of medical product safety, efficacy and/or quality. Both practical and theoretical knowledge is desirable in order to achieve a good understanding of the issues likely to be associated with the product under review.
Reviewer competencies depend on the duties and scope of review work. Scientific writing, presentation of data, data analysis, inferential and deductive reasoning, risk-based analyses and problem-solving are important skills for reviewing a medical product application. Review staff should also follow sound ethical practices.

General competencies required to conduct review work include:

- knowledge of statutes, regulations, guidelines and precedents, including international guidelines and precedents, and their applicability;
- knowledge of the process of medical product development from early development phases to post marketing surveillance andrisk management;
- scientific communication skills for written evaluations, public presentations and negotiation and consensus building with applicants and stakeholders.

Reviewers should keep their scientific expertise up to date. Increasingly, regulatory science curricula from universities and international regulatory initiatives and organizations are available. Reviewers should have the opportunity to attend relevant conferences, courses and international meetings. Reviewers should also be encouraged to read scientific journals and to be members of professional societies or relevant organizations.
For on-the-job training, a site visit programme that allows reviewers to visit sites such as laboratories, manufacturing facilities and clinical settings may be considered. In addition, experienced reviewers should be encouraged to mentor and train junior reviewers. The establishment of structured training programmes within Authority to facilitate the professional development of review staff should also be considered, whenever feasible.

### 14.2 Critical thinking

Critical thinking requires an objective and systematic approach to analysing information and to problem-solving. It relies on the collection of data and evidence-based decision-making instead of generalizing from one's own experience, intuition or trial and error. Decisions should be reproducible and clearly understood by others.
Nevertheless, every regulatory decision involves judgement. Therefore, core competence in public health and bioethics, and the ability to integrate up- to-date scientific knowledge with an understanding of the evidentiary standards for regulatory action (including the flexibility inherent in those standards and regulations), can guide decisions.

Beyond their professional qualifications, reviewers should have the ability to critically appraise the information presented in an application and not just accept it as presented. This skill may often be

developed or strengthened during the training process, for instance, by evaluating the responses to questions raised by a senior reviewer so that the questioning process becomes a learning tool.

Discussion among reviewers and external experts on application-specific issues can promote critical regulatory thinking and problem-solving.

Good judgement is required to come to a balanced decision. This involves focusing on the important issues in the application, rather than on data that provide more information, but will not ultimately affect the outcome of an application. Good judgement includes, where applicable, using international harmonized regulatory requirements and adopting regulatory approaches that show flexibility to maximize public health benefits while minimizing adverse, unintended consequences.

Regulatory decision-making or recommendations from reviewers should be based on the best current science. The public health needs of the country and its health-care system provide context for this decision-making. In decisions to grant authorization the benefits must, on balance, outweigh the risks, based on sound scientific evidence. Documentation of scientific rationale for decision- making, taking into account regulatory requirements, provides a record to ensure the integrity of the review process. The decision-making document should address dissenting, evidence-based views and clearly identify the information that was considered. Decision-making by an RA should be independent of influences beyond public health.

## 15. Conducting the review

Defining and then following an application-specific review strategy that is amended only as needed when new information comes to light, ensures soundness of the review process, the quality of the report and the efficient use of resources.

### 15.1 Key elements in defining a review strategy

A review strategy is the approach or plan of action that a reviewer or review team uses to review a medical product application. The strategy employed may be shaped by the following.

- Public health priority of the medical product application.
- Understanding other RAs' action on the application, especially SRAs.
- Understanding specific intrinsic and extrinsic factors that are clinically relevant to the Nigerian population.
- Identification of major scientific questions and their possible resolution.

### 15.2 Applying the review strategy

The way a review is conducted will depend on the resources available. Input from external experts and/or the information and decisions of other RAs may be necessary to ensure that scientific and evidentiary standards for safety, efficacy and quality are adequately met.

The review should be evidence-based, taking into account national laws and regulations, regional and international guidelines, and, where applicable, monographs and standards. The reviewer should determine the information necessary to approve the product application and consider whether further information can be obtained in post-approval studies without compromising safety.

The model adopted for review may allow for questions to be asked during the review to supplement or clarify information supplied, until the reviewer is satisfied that enough information has been provided to allow a conclusion to be reached.

There are a number of internal processes that may be implemented to help ensure an efficient, consistent and effective review process. These include:

- periodic meetings to allow consideration of the views of different reviewers;
- peer review, in the context of a co-rapporteur, or a team meeting;

- an internal panel review;
- an external panel review;
- the involvement of senior management.

The review strategy should ultimately enable the reviewer or review team to understand the benefit–risk profile of the medical product, given the indication and context of use. The nature of the benefits and types of risks should be described as part of the review. Benefits and risks can be quantified or qualitatively characterized, and the levels of certainty surrounding the benefits and risks should be stated. The review should address generalizability of the data, the clinical significance of findings and what (if any) additional information may be needed to clarify benefits and risks.

Various methodologies can be used to quantify benefits and risks. The choice depends on circumstances such as complexity of issues and relevance. The acceptability of benefits and risks will depend on public health priorities, presence of available alternative therapies, size and certainty of the treatment effect versus that of the adverse reactions and possible risk mitigation or benefit enhancement that can be implemented (such as conducting responder analyses to identify a population more likely to experience benefits).

The findings and conclusions of the review must be described in a well- documented review report. Once the final decision is made it should be conveyed to the applicant. If the Authority decides not to grant authorization, a statement of reasons should be provided, which details the documents, information and applicable regulatory requirements taken into account in reaching the decision. An appeal mechanism should be provided to ensure that applicants have an opportunity to present their case to an independent arbiter.

A post-action discussion with the applicant may be done to help improve the quality of future applications. The Authority should have mechanisms for communication with the public on the approval of the product and/or action taken in relation to the application. Publication of information on the approval of products increases transparency of regulatory actions.

## Reference

1. Good review practices: guidelines for national and regional regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2013: Annex 9 (WHO Technical Report Series, No. 992).

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