Guidelines on Good Review Practices (GRevP)

REGISTRATION AND MARKETING AUTHORIZATION (MA)

Directorate General of Drug Administration (DGDA)
Health Service Division
Ministry of Health & Family Welfare (MOH&FW)
Government of the People's Republic of Bangladesh

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Document History

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This Guideline is harmonized with

Good review practices: guidelines for national and regional regulatory authorities (WHO Technical Report Series 992, Annex 9), Drug and Cosmetics Act-2023 and current regulatory practices of DGDA.

Acknowledgments

List of Abbreviations

CoP	Chief of Party
CTD	Common Technical Document
DGDA	Directorate General of Drug Administration
EMA	European Medicines Agency
GRevP	good review practice
MA	Registration and marketing authorization
PMDA	Pharmaceuticals and Medical Devices Agency
QMS	quality management system
RA	Regulatory Authority
SOP	standard operating procedure
TGA	Therapeutic Goods Administration
UKMHRA	UK medicines and healthcare products regulatory agency
USFDA	U.S. Food and Drug Administration
USP	United States Pharmacopeial Convention
WHO	World Health Organization

1.0 Introduction

The Directorate General of Drug Administration (DGDA) is creating a robust and resilient regulatory authority to protect public health from health risks linked with medical products marketed in the country. It is critical to think about and optimize the regulatory system and develop a quality management system (QMS) that aligns with regulatory policies, legal frameworks, and standard processes. Recognizing this, one of the primary areas that the registration and marketing DGDA has established the medicine review systems, methods, and procedures.

Good review practices (GRevPs) are an essential component of overall sound regulatory practice and provide the scientific foundation for regulatory decisions. All components of GRevP should be assessed and updated regularly to continually enhance medical product evaluation practices, systems, and procedures.

Emphasizing the importance of a well-functioning regulatory authority DGDA that will achieve maturity level 3 in all of its responsibilities requires introducing and improving GRevP as the foundation for better regulatory quality decision-making. This will contribute to high quality, timeliness, predictability, consistency, transparency, clarity, and efficiency in the scientific method, content, and management of medical product reviews.

1.1 Objectives

The main objective of this guideline is to guide regarding the principles and processes of GRevP for use within the DGDA to aid high quality in review content and management. This is accomplished by creating review tools following relevant standard operating procedures (SOPs) and reviewer learning exercises, for example, training courses, mentoring, orientation packages, and best practice sharing. To achieve ongoing progress, all components of GRevPs should be continually assessed and updated.

2.0 Scope

This guideline will apply to the review of safety, efficacy, and quality data in medical product applications (pharmaceutical products, biologicals, and medical devices) filed with DGDA's Registration and Marketing Authorization (MA) for registration and marketing authorization.

3.0 Glossary

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

Applicant: The person or company who submits an application for MA of a new medical product (Introduced or Unintroduced Products), an update to an existing MA, or a variation of an existing MA.

Application: The information provided by the applicant to the DGDA for evidence-based review and MA decision.

DGDA: The national regulatory authority of Bangladesh responsible the registration of and other regulatory activities concerning medical products.

Good review practices: 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 license or registration certificate. A legal document issued by the competent medicines Regular Authority (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, labeling, storage conditions, shelf-life, and approved conditions of use.

Principles (of a good review): The important GRevP elements for DGDA 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: The coordinated activities that direct and control an organization with regard to quality.

Quality management system: Quality management includes the determination of a quality policy, creating and implementing quality planning and assurance, and quality control and quality improvement.

Regulatory Authority: 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: An authorized written procedure giving instructions for performing operations (both general and specific).

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

4.0 General Considerations

This is a national guideline for GRevPs in Bangladesh. It explains comprehensive procedures of GRevPs.

Responsibility for the quality, safety, and efficacy of pharmaceutical (procedure for the registration of pharmaceuticals products; procedure for the registration of vaccines and biological products; procedure for the registration of active pharmaceutical ingredient), and medical devices lies first and foremost with the manufacturer/MA holder. The DGDA in Bangladesh establishes procedures to ensure that the products and manufacturers meet the established regulatory criteria.

Vaccines are products of biological origin that exhibit some intrinsic variability. They are characterized by complex manufacturing processes and are administered to large numbers of healthy children, adolescents, and adults. Their quality cannot be assessed solely by testing the finished product alone. It is recommended that the DGDA establish a specific regulatory system for this type of product.

A basic function of DGDA is to evaluate the quality, safety, and efficacy of biologicals, including vaccines and blood products, and pharmaceutical and medical devices as well. This involves authorizing their use, distribution, and sale, which implies granting an MA.

In order to license a vaccine, the DGDA has set requirements for applicants to comply with. These requirements include the information needed in the application dossier and evidence that the vaccine has passed the stages of research, development, production, quality control, and clinical testing and that the quality, safety, and efficacy required of the vaccine to be used in humans has been established.

4.1 Legal and Related Documents

The Drug and Cosmetics Act 2023[1] clearly defines that no drug can be manufactured in or imported into Bangladesh unless it obtains an MA from DGDA, Bangladesh.

The whole application dossier consisting of quality, non-clinical, and clinical information according to the Common Technical Documents as per ICH guideline M4 (R4).[2]

For moderate and major variation of any pharmaceutical or biopharmaceutical products, manufacturer should be informed prior approval from DGDA to handle the application for MA and the application for variation.

5.0 Principles of Good Review Practices

DGDA will follow the 10 World Health Organization (WHO) listed principles[3] while applying GRevP in order to achieve the following desired objectives:

Balanced	A good review is objective and unbiased.
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.

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[1] https://www.dgdagov.info/index.php/laws-and-policies/3674-drug-and-cosmetics-act-2023

[2] ICH guideline M4 (R4) on common technical document (CTD) for the registration of pharmaceuticals for human use - organization of CTD

[3] *Technical Report Series 992 – Annex 9: Good review practices: guidelines for national and regional regulatory authorities*. (2024, August 19). Accessed September 2024. Available at: https://www.who.int/publications/m/item/annex-9-trs-992

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.
Identifies signals	A good review comprehensively highlights potential areas of concern identified by the applicant and the reviewers.
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.
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.
Thorough	A good review reflects adequate follow-through of all the issues by the reviewers.
Utilizes critical analyses	A good review assesses the scientific integrity, relevance, and completeness of the data and proposed labeling, as well as the interpretation thereof, presented in the application.
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, as well as the reviewers' assessments 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.
Well-managed	A good review applies project and quality management processes, including clearly defined steps with specific activities and targets.

6.0 Managing the review

The review process should be handled through project management principles. The practices of planning and monitoring review activities, coupled with timely, informative communications and clearly defined work instructions for the reviewers, can maximize the efficiency and effectiveness of the review.

6.1 Project Management Principles

Project management for the review process refers to the planning, organization, and resource allocation required to conduct a thorough and high-quality assessment of an application within a given time frame.

Progress monitoring should be done using established methods that are properly documented. Data should be collected and analyzed periodically to determine the effectiveness of the review strategy for completing reviews within the specified time frame.

The ideal technique should allow for the following:

- Data interpretation to track the status of multiple applications under evaluation at once
- Data interpretation for workload and resource balance decisions
- Monitoring accessible to key personnel

The team leader of the registration department, and higher-level officials of the authority will coordinate the planning, monitoring, and management of the review/assessment as needed. In addition, a quality assurance manager or expert will be in charge of organizing, monitoring, and ensuring the quality of the assessment processes.

Project management approaches and complexity should change in tandem with changing conditions, resources, and workloads.

6.2 Quality Management System

The QMS provides a systematic and risk-based approach to consistently and efficiently achieve the desired state of quality. The review process should follow the principles of the requirements for the QMS at DGDA, including Internal Communication, Risk Assessment, Quality Monitoring and Management Review. DGDA is committed to improving the overall outcomes of performance by delivering products and services that meet the needs and expectations of our customers, regulatory authorities, employees and ultimately of our patients as per "Procedure of Management Review''.

Processes are implemented and monitored with nine functions of DGDA in a productive way to ensure continuous improvement within the frame of the quality cycle as follows:
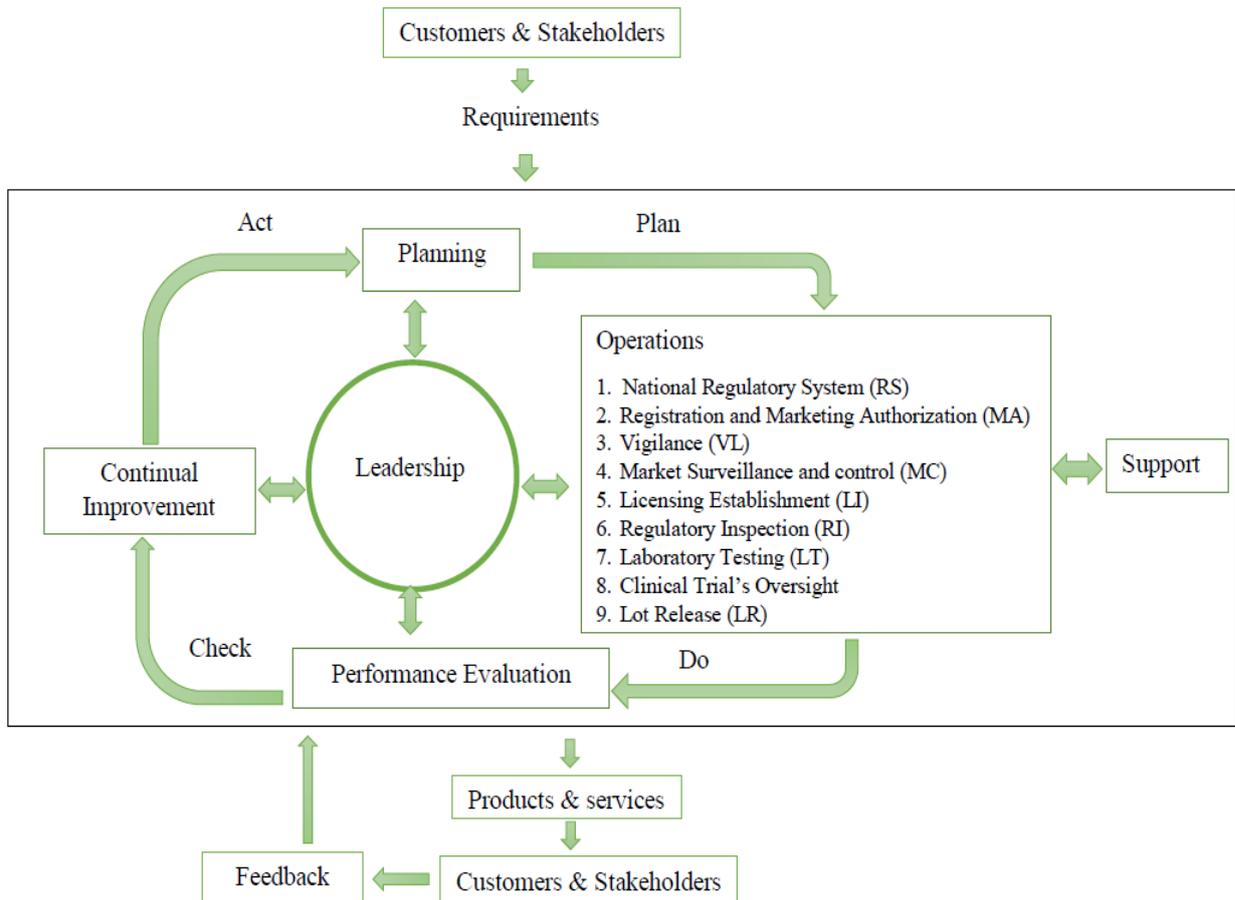
Figure: Flow Diagram of processes of QMS and their interactions.

A QMS for regulatory system function ensures good documentation practice, and GRevP is ensured by a quality manual, quality objectives, continual improvement plan, and following SOPs-

- Procedure for Competency Assessment, performance Evaluation & Staff Appraisal,

- Procedure for Management Review.

- Procedure for Record Control and Monitoring,

- Procedure for Document Code Numbering,

- Procedure for Controlling Documents,

- Procedure for CAPA and its effectiveness,

- Procedure for Root Cause Analysis,

- Procedure for Quality Risk Management,

- Procedure for Selection, Evaluation, and Re-evaluation of outsourcing services,

- Procedure for change control, and

- Procedure for employee training etc.

6.3 Review Process Stages

MA set key stages in the process of reviewing medical products. Those include application submission, screening, scientific review and approval or rejection. For example, in case of vaccines and biologics "Procedure for registrations of vaccines and biologicals" and for API "Procedure for Locally manufactured Active Pharmaceutical Ingredient" are being used for registration. Applicants should be aware of the expectations at all stages, including the target time frames, guidelines, requirements, templates, and checklists. All applications undergo validation first to ensure that it is well organized and that all the required forms and relevant documents have been in a more predictable and clear process. All the review process stages shall be done according to agreed laws, guidelines, checklists, and templates provided for each category of applications through DGDA's website.[4] For example, in case of regulatory submission of vaccines and biologics in "Open RIMS'' software as per user manual.[5]

7.0 Communication

One of the primary goals of enhancing the efficiency of the development and review process is to provide good communication among the RA, applicants, and the general public, allowing patients' faster access to crucial medical products. It can also improve the review's quality by granting access to additional expertise.

DGDA updates all information on its website (https://dgda.gov.bd/sites/), which is one of the active forms of communication that aids in connecting with the international audience about DGDA programs.

7.1 Intra-agency

Product reviews are carried out in a collaborative atmosphere. As a result, during the reviewing process, experts from various DGDA organizational units cooperate and coordinate. Meetings, forms for exchanging ideas among reviewers, and a checklist of

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[4] https://dgda.gov.bd/sites/,
[5] https://dgda.gov.bd/site/notices/6e376b63-0945-4b73-a117-54ee98671cfa/DGDA-RIMS

persons or departments involved in a certain issue or activity that may be beneficial are all examples of intra-agent communication.

For example, in case of Vaccines and Biologics, the MA department will evaluate as per "Procedure for the Registration of Vaccine and Biological products."

- Module 1 (Administrative and Prescribing Information)
- Module 2 (Quality Overall Summary)
- Module 3 (Quality) of submitted dossier along with sample testing by NDCL.

The Clinical Trial and Oversight department of DGDA will evaluate as per "Procedure for the Registration of Vaccine and Biological products."

- Module 4 (Preclinical study report)
- Module 5 (Clinical study report)

As a result, effective communication aids in accomplishing the GRevP goal. Open, clear, productive, and timely communication about the review's progress, review results, conflicting data interpretations, and discussion of potential solutions and actions within the DGDA is desirable.

7.2 Interagency

The Authority can interact with other regulatory agencies to assess medical products. Interagency communication can lead to greater regulatory convergence. This can, in turn, improve the efficiency and quality of medical product development and review processes, as well as patient access. Interagency communication can take several forms, including the following:

- Accessing information from other RAs' public websites, including guidelines, application decisions, and product recalls
- Using information from other RAs, such as review reports and certificates of pharmaceutical products
- Actively sharing information among RAs
- Collaborating with other RAs

7.3 With Applicants

DGDA communicates with applicants through the public availability of DGDA rules, notices, questions and answers, and presentations, as well as checklists used to screen submitted applications, which aid in offering insight into our current thinking and expectations. These messages enable candidates to submit higher quality applications.

The DGDA establishes communication with individual applicants on specific applications before, during, and after the review process through "Open RIMS'' software as per user manual[6] and DGDA website[7].

7.4 With external experts

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

Asking for the input of external experts into RA decision-making improves public confidence, provides additional perspectives for the RA to consider, and provides expertise that otherwise may be lacking.

7.5 With public

Communication with the public on the DGDA's mission and accomplishments can help raise public awareness, understanding, and trust in the RA.

Transparency initiatives include web-based information regarding the organization's structure and operations, decision-making procedures and criteria, and actions, such as application approvals and products.[8]

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[6] https://dgda.gov.bd/site/notices/6e376b63-0945-4b73-a117-54ee98671cfa/DGDA-RIMS
[7] https://dgda.gov.bd/sites/
[8] http://dgdagov.info/index.php/information-center/guidance-documents/

8.0 Review Personnel

8.1 Reviewer expertise, competency, and training

Reviewers should have professional qualifications, training, and experience in scientific or medical fields relevant to the evaluation of medical product safety, efficacy, and/or quality. Practical and theoretical knowledge are both desirable to gain a thorough understanding of the challenges that are likely to arise with the product under assessment.The competencies of reviewers are determined by their performance, skill, and qualification. Scientific writing, data presentation, data analysis, inferential and deductive reasoning, risk-based evaluations, and problem-solving abilities are essential for analyzing all review applications. When the Authority uses external experts for dossier review, the DGDA must conduct a review of real or apparent conflicts of interest and compel the external experts to disclose and sign a conflict-of-interest form before their participation. External experts should also be competent and knowledgeable with the regulations and procedure of assessment.

Staff members who conduct reviews should also adhere to ethical standards. To conduct review work, general competencies include the following:

- Knowledge of statutes, regulations, guidelines, and precedents, including their applicability.
- Understanding of medical product development from early stage to finished product stage, PMS and risk management.
- Scientific communication skills for written evaluations, public presentations, negotiating, and consensus building with applicable parties.

8.2 Critical thinking

Critical thinking necessitates an impartial and methodical approach to information analysis and issue solving. Instead of forming assumptions based on personal experience, intuition, or trial and error, critical thinking depends on data collecting and evidence-based decision-making. Decisions should be replicable and understandable to others.

Beyond their professional credentials, assessors should be able to critically evaluate the information supplied in an application rather than simply accepting it as is. This talent is

frequently taught or reinforced during the training process, for example, by analyzing responses to questions posed by a senior reviewer, thereby transforming the questioning process into a learning tool.

9.0 Conducting the review

Defining and adhering to an application-specific review strategy, which can be adjusted based on new information, assures a sound review process, high-quality reports, and efficient resource use.

9.1 Key components in developing a review approach

A review strategy is the approach or plan of action that a reviewer or review team employs when reviewing a medical product application. The following factors can influence the strategy chosen.

  a. Prioritizing public health for medical product applications,
  b. Understanding the impact of various regulatory authorities, particularly stringent regulatory authorities,
  c. Identifying unique intrinsic and extrinsic aspects, and
  d. Identification of key scientific questions and their potential solutions.

9.2 Applying the review strategy

DGDA shall use a systemic review method and reliance approaches while taking into account national laws and regulations, regional and international guidelines, and, where relevant, monographs and standards. The reviewer should ask to the manufacturer for more value-added information if required to approve the product application.

The review approach may allow for questions to be asked during the review to supplement or clarify the information provided until the reviewer is satisfied that enough information has been provided to conclude.

The Authority may adopt a well-defined strategy to facilitate MA processes, including stringent regulatory authority procedures like USFDA, UKMHRA, PMDA, TGA, EMA, Swiss medic, and France NRA, WHO cooperation, and regional collaborations.

These include periodic meetings to consider different reviewers' perspectives.

  ▪ Periodic meetings to allow consideration of the views of different reviewers

- Peer review, in the context of a co-rapporteur, or a team meeting,
- Internal panel review,
- External panel review, and
- The involvement of senior management.

Various approaches can be used to calculate benefits and risks. The decision is based on factors such as the intricacy of the challenges and the benefit of the patient. The acceptability of benefits and risks will rely on public health priorities, the presence of available alternative therapies, the size, and certainty of the treatment impact versus that of the adverse reactions, and any risk reduction or benefit enhancement that can be implemented.

10.0 References

10.1 *Technical Report Series 992 – Annex 9: Good review practices: guidelines for national and regional regulatory authorities.* (2024, August 19). Accessed September 2024. Available at: https://www.who.int/publications/m/item/annex-9-trs-992

10.2 Drug and Cosmetics Act-2023. (2023, September 23). Accessed September 2024. Available at: http://www.dgdagov.info/index.php/laws-and-policies/3674-drug-and-cosmetics-act-2023

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CONTACT INFORMTAION

REGISTRATION AND MARKETING AUTHORIZATION (MA)
DIRECTORATE OF GENERAL DRUG ADMINISTARTION (DGDA)

AUSHAD BHAVAN, MOHAKHALI, DHAKA-1212

TEL   : 8802 9880803, 9880864, 9880897, 9880924
FAX   : 880 9880854
E-mail : dgda.gov@gmail.com

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