CONTROLLED COPY

بسم الله الرحمن الرحيم

Maldives Food and Drug Authority

Ministry of Health

Male', Maldives

Guideline for Good Review Practice

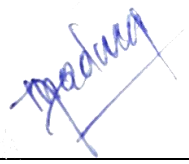
CONTROLLED COPY

Guideline for Good Review Practice is released under the authority of

Ms. Thooma Adam
Deputy Director General
Maldives Food and Drug Authority

It is the property of:
Maldives Food and Drug Authority
Male'
Republic of Maldives

Prepared by:
Director, Pharmaceuticals
Mohamed Fazeen

Approved by: **Ms.Aishath Mohamed** **Deputy Director General, Pharmaceuticals** **Maldives Food and Drug Authority**		13.02.2020
Authorised by: **Ms.Thooma Adam** **Deputy Director General, Laboratory Services** **Maldives Food and Drug Authority**		13.02.2020

CONTENTS

Guideline for Good Review Practice

1 INTRODUCTION

The Medicines and Therapeutic Goods (MTG) Division of the MFDA is constantly endeavoring to improve its performance and ensure the quality of its regulatory systems. Good Review Practices (GRevPs) are an integral part of overall good regulatory practices, that focus on the pharmaceutical product review aspect of regulatory work. Review is a highly complex, multidisciplinary assessment of the medical product applications in meeting scientific and evidentiary standards. It forms the scientific foundation for regulatory decisions.

MTG is cognizant of the fact that the extent to which a regulatory authority can achieve the review goals of timeliness, predictability, consistency, transparency, clarity, efficiency and high quality can have significant impact on public health. It is terms of that recognition that these guidelines have been drawn up – to ensure that the review goals are consistently met. Through this structured approach, MTG ensures monitoring and improvement of the review process.

By definition, GRevPs are documented best practices for any aspect related to the process, format, content and management of a pharmaceutical product review. The goal of GRevPs is to promote the timeliness, predictability, consistency, transparency, clarity, efficiency and high quality of the content and the management of reviews. This is done through the development of review tools such as Standard Operating Procedures (SOPs), and review templates and reviewer learning activities such as training courses, mentoring, discussion sessions.

2 PURPOSE

The purpose of this document is to guide staff at the Maldives Food and Drug Authority (MFDA) on the approved Good Review Practices for MFDA in order to ensure consistent and professional performance. The guide also seeks to make the review process for pharmaceutical products transparent, by ensuring that the various stakeholders understand the internal processes and how they are implemented.

This guide is based on the WHO guide for national regulatory authorities on the basic principles and processes for Good Review Practices.

3 SCOPE

This document provides high level guidance on GRevP principles and processes. It does not provide detailed instructions on how scientific reviews are actually conducted.

This document applies to the review of safety, efficacy/effectiveness and quality data in medical product applications filed with MFDA for marketing authorization. This document applies to pharmaceutical and biological drugs and higher-risk medical devices used in humans. However, the concepts described here may also be applied to other types of medical products.

4 GUIDELINE CONTENT

4.1 Principles

4.1.1 Pharmaceutical product reviews at MTG are based on 10 fundamental principles.

4.1.1.1 Evidence-based: Reviews are evidence-based and reflect both scientific and as far as possible, current regulatory norms and thinking. They integrate legislative, regulatory and policy frameworks with emerging science.

4.1.1.2 Utilize critical analyses: Reviews assess the scientific integrity, relevance and completeness of the data and proposed labelling, as well as the interpretation thereof, presented in the application.

4.1.1.3 Identify signals: Reviews comprehensively highlight potential areas of concern identified by the applicant and the reviewers.

4.1.1.4 Investigate and problem solve: Reviews provide 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.

4.1.1.5 Make linkages: Reviews provide integrated analysis across all aspects of the application: pre-non-clinical, clinical, chemistry/biocompatibility, manufacturing and risk management plan.

4.1.1.6 Consider context: Reviews place the data and the conclusions of both the applicant and the reviewers in the context of the proposed conditions of usage and storage, including perspectives from patients, health-care professionals and other regulatory authorities' analyses and decisions.

4.1.1.7 Involve consultation: Reviews reflect input from colleagues and other internal or external stakeholders with expertise relevant to the various aspects of the application.

4.1.1.8 Balanced: Reviews are objective and unbiased. Every effort is made to ensure that the final decision is reproducible and clearly understood by others.

4.1.1.9 Thorough: Reviews reflect adequate follow-through of all the issues by the reviewers.

4.1.1.10 Well-documented: Reviews provide a well-written and thorough report of the findings and conclusions provided by the applicant, as well as complete and specific accounts of the reviewers' evidence-based findings and conclusions. It contains clear, succinct recommendations that can stand up to scrutiny by all involved parties and can be leveraged by others, such as other regulatory authorities.

4.2 Managing Reviews

4.2.1 Systems and procedures are in place to actively manage the process of reviewing pharmaceutical product applications to ensure best outcomes and the effective and efficient use of review resources. There are clearly defined, separate steps in the process with clearly-defined work instructions, each with specific activities and targets. These combine planning and monitoring of the review activities with timely, informative communications to maximize the efficiency and effectiveness of the review. The main goal is to achieve a completed, high-quality review of an application within a specified time frame. A tracking system is in place to monitor workload and time frames.

4.2.2 The Quality Management System (QMS) described in the organization's Quality Manual is integral to the management of the review process. The QMS ensures standardization of procedures, leading to GRevPs and to continuous improvement. Senior management is committed to the process and is ultimately responsible for the outcomes. Management, through the QMS ensures GRevPs are not just esoteric guidelines but that they have become embedded in the daily practice of MTG.

4.2.3 MTG is committed to continuous improvement. Tracking data is used review practices and evolve where necessary, such as when evolving regulatory science or adoption of new review process and procedures becomes necessary.

4.2.4 To ensure quality of the review process, MTG:

- has developed review tools, workflow processes, SOPs, assessment templates and checklists, and training programs
- has implemented the review tools and learning activities
- constantly evaluates use of the review tools and learning activities and resulting outcomes
- periodically updates and revises the review tools and learning activities
- has defined processes for decision-making,
- uses external experts, public meetings and peer-review.
- offers professional development, mentoring and regular on-the-job training for staff
- ensures 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.

4.2.5 The internal procedures are further complemented by guidelines for applicants, in order to promote transparency and guide applicants on how to submit high-quality marketing authorization applications.

4.3 Review Process Stages

4.3.1 There are two key stages in the process of reviewing pharmaceutical product applications: screening/validation and scientific review.

4.3.2 Screening: The screening/validation stage occurs before the scientific review with the aim of ensuring completeness of the submission, which will subsequently facilitate the scientific review. Screening/validation involves an examination of the application to ensure that it is well-organized and all required forms and relevant documents have been submitted. Identifying application deficiencies prior to scientific review enables MTG to avoid spending time and review resources on an application that does not allow critical analysis, signal identification or regulatory decision-making.

4.3.3 Scientific review: This entails a comprehensive review of all the documents.

4.4 Review Personnel

4.4.1 The quality, timeliness and success of pharmaceutical product application reviews are dependent on adequate review capacity. MTG ensures that reviewers have core competencies required to carry out reviews. There is continued investment into the knowledge, skills, abilities and attitudes of reviewers.

4.4.2 MTG reviews are conducted by competent internal staff, external experts or a combination of both. To ensure the integrity of product reviews and recommendations, MTG has put in place measures to ensure reviewers should be free of actual or perceived conflicts of interests. In this way, MTG seeks to ensure that the review decision or recommendation is not likely to be influenced by personal, family, financial or professional motives, including those of employers when an external expert is also a consultant to the regulated industry. All reviewers have professional qualifications, training and expertise in scientific or medical fields that relate to the assessment of pharmaceutical product safety, efficacy/effectiveness and/or quality. The general skills possessed include scientific writing, presentation of data, data analysis, inferential and deductive reasoning, risk-based analyses and problem-solving. Specific competencies required to conduct review work include:

- knowledge and applicability of statutes, regulations, guidelines and precedents, including international guidelines and precedents;
- knowledge of pharmaceutical product development from early development phases to post-marketing surveillance and risk management;

- scientific communication skills including written evaluations, public presentations and negotiation/consensus building with applicants and stakeholders.

4.4.3 Reviewers are encouraged to remain up to date in their scientific expertise. Opportunities are made available for reviewers to attend relevant conferences, courses, and international meetings. Reviewers are also encouraged to read scientific journals and maintain memberships in professional societies or relevant organizations. In addition, experienced reviewers mentor and train junior reviewers, through established, structured training programs within the Authority.

4.5 The Review Process

4.5.1 Product applications are considered on a first-come, first served basis. However, public health priority of the pharmaceutical product is also taken into consideration as each product application poses unique and varied scientific questions, challenges and opportunities.

4.5.2 MTG makes use of reviews and decisions from other regulatory authorities and SOPs for this are in place. The goal is to gain efficiencies and improve the quality of the review through leveraging other regulatory authorities' reviews and/or decisions in appropriate situations.

4.5.3 During the review process, the Authority makes use of both publicly available information (for example, decisions, review reports and summaries from WHO Prequalification and Stringent Regulatory Authorities; and information obtained directly from applicants or other regulatory authorities (for example, review packages which include responses to questions posed by regulatory authorities). MTG may also seek information from other regulatory authorities where the same product application has been lodged. In such cases, MTG will seek prior approval from the applicant for this information to be divulged by the other regulatory authorities directly to MTG. The applicant reserves the right to refuse to grant such authorization, with the full understanding that this may limit the availability of information for an appropriate decision.

4.5.4 A multidisciplinary team will provide broader expertise, but in some cases a single reviewer may be required to cover several or all aspects of a review.

4.5.5 The review is evidence-based, taking into account national, regional and international guidelines, monographs and standards If problems are identified during the review, reviewers can first review data of greatest relevant to the application, or seek external advice if desirable. A summary of scientific questions can also be posed to the applicant in order to obtain information to supplement or clarify information supplied. The list of questions is returned to the applicant, with a specified time for response and one further round of assessment of the responses prior to a decision being made, until the reviewer is satisfied that enough information has been provided to form a conclusion.

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

- periodic meetings to allow consideration of views from 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.

4.5.7 The overall benefits and types of risks are described in the review report. Benefits and risks are often quantified or qualitatively characterized, including the levels of certainty surrounding the benefits and risks. The acceptability of benefits and risks depends 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.

4.5.8 The findings and conclusions of the review are well-documented in the review report.

4.5.9 Once the final decision is made it is communicated in writing to the applicant. If a decision not to grant authorization is reached, a statement of reasons is provided which details the documents, information and applicable regulatory requirements taken into account in reaching the decision.

4.5.10 An appeal mechanism is in place to ensure that applicants have an opportunity to present their case to an independent arbiter.

4.5.11 MTG staff offer meeting opportunities to discuss with applicants to help mitigate future application deficiencies.

4.5.12 A register of approved products is maintained and this is available to the public online.

4.6 Communication

4.6.1 Communication within the organization and with applicants is pivotal to the review process.

4.6.2 Intra-agency: Product reviews are conducted in a collaborative environment. They often require expertise from and coordination with different units within the Authority, providing a platform for open, clear and constructive communications regarding the progress of the review, review findings, differing data interpretations and discussion of possible solutions and actions.

4.6.3 Inter-agency: As has already been explained, reviewers consider information and decisions made by other regulatory authorities during the review process. As a means of peer collaboration and cooperation, inter-agency communication facilitate greater regulatory convergence such that the decisions made by MTG are not at glaring variance from other regulators in the region and internationally. Reviewers typically access information on other regulatory authority websites, such as guidelines, application decisions, product recalls for safety; use information from other regulatory authorities, such as assessment reports, regulatory decisions; actively share information with other regulatory authorities, such as during an application review; actively work with other regulatory authorities, conducting joint reviews of applications, developing new guidelines. At all times, information-sharing arrangements safeguard the rights of applicants and prior consent from the applicant is always sought where needed such as when sharing of confidential commercial, trade secret or personal privacy information is involved.

With applicants: MTG employs the public availability of guidelines, notices, circulars, frequently asked questions and answers and presentations, to provide insight into the Authority's current thinking and expectations. These communications allow applicants to provide better quality applications. MTG also communicates applicants on specific applications before, during and after the review process, acknowledging receipt of applications, availing product-specific queries and product review decisions. This is designed to increase applicants' understanding of evolving regulatory expectations in a changing pharmaceutical and scientific environment; whilst also giving industry the opportunity to express and make known to the Authority the challenges being faced and proposals from applicants on alternative approaches that address the same requirements, such that credible solutions are reached in the interest of public health. Communication with applicants is also for the purpose of providing applicants with the progress and status of the review of their applications.

4.6.4 With external experts: Whenever MTG calls upon external expertise in the scientific assessment of the safety, efficacy/effectiveness and quality of pharmaceutical products from academic institutions, industry associations, patient organizations and medical and scientific organizations, MTG ensures both confidentiality and lack of conflict of interest through transparent processes for the management of confidential information and screening of potential conflicts.

4.6.5 With the public: MFDA exists primarily to safeguard public health. As one of our biggest and most important stakeholders, communication with the public about our mission and accomplishments helps us to foster greater public awareness, understanding and confidence in our systems and operations. Our transparency initiatives include availing information on our website about how MFDA is organized and operates, its decision-making processes and criteria and its actions for things like product application approvals and product recalls for safety. From time to time, we avail opportunities for the public to provide input on pharmaceutical product needs, efficacy expectations and risk tolerances, often through public meetings and advisory boards. We can further make public consultations on specific applications under review by the Authority through surveys, focus groups, public meetings, workshops and appointment to advisory boards.

5 REFERENCES

- Good Review Practice for Regulatory Authorities, WHO. 2014 Draft for comments