Good review practices

guidelines for regulatory authorities

(February 2014)

DRAFT FOR COMMENT

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addressed to the World Health Organization, 1211 Geneva 27, Switzerland,
attention: Department of Essential Medicines and Health Products (EMP).
Comments may also be submitted electronically to the Responsible Officer: Dr
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**Good review practices guidelines for regulatory authorities**

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**APEC RHSC good review practices (GRevP) – participation of Working Group Members**

NMRAs from:
- Australia, Canada, Japan, Korea, Saudi Arabia, Singapore, Chinese Taipei, USA;
- and the pharmaceutical industry: CIRS, FDAAA and Med Dev
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1. INTRODUCTION

1.1 Document objective

The objective of this document is to provide high level guidance on good review practice (GRevP) principles and processes, for use across a range of regulatory authority (RA) maturities. It is not intended to provide detailed instruction on how to conduct a scientific review.

This document 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.

1.2 Context

RAs are increasingly seeking ways to improve their performance and ensure the quality of their regulatory systems. GRevPs are an integral part of overall good regulatory practices and focus on the medical 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.

The extent to which an RA can achieve the review goals of timeliness, predictability, consistency, transparency, clarity, efficiency and high quality can have significant impact on public health (for example, delays in patient access to important medical products, added costs to government and applicants). Implementation of GRevPs help to achieve these review goals by ensuring those involved in the review process have the critical thinking skills and tools needed to optimize scientifically sound, evidence-based decisions. It also facilitates progress towards regulatory convergence through the development of common platforms for exchanging review reports and the enhancement of mutual trust among RAs.
Several RAs have introduced ways of monitoring and improving their review process through structured approaches or moving towards stepwise implementation of GRevPs. RAs should consider review models and best practices within the context of available resources and legal requirements. The GRevP principles and elements described in this document can be adapted to meet the continuous improvement needs of a diverse range of RAs.

1.3 Definition

Good review practices

GRevPs are documented best practices for any aspect related to the process, format, content and management of a medical 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 (for example, standard operating procedures (SOPs), templates) and reviewer learning activities (for example, training courses, mentoring, orientation packages, discussion sessions). To promote continuous improvement all aspects of GRevPs should be evaluated and updated on an ongoing basis.

1.4 Scope

This document applies to the review of safety, efficacy/effectiveness and quality data in medical product applications filed with RAs for marketing authorization.

This document was written for 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, as well as to applications for investigational testing.

2. PRINCIPLES OF A GOOD REVIEW

Evidence-based

A good review is evidence-based and reflects both scientific and regulatory state-of-the-art. It integrates legislative, regulatory and policy frameworks with emerging science.
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.

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

Investigates and problem solves
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: pre-(non-)clinical, clinical, chemistry/biocompatibility, manufacturing and risk management plan.

Considers context
A good review places the data and the conclusions of both the applicant and the reviewers in the context of the proposed conditions of use and storage, including perspectives from patients, health-care professionals and other RAs’ analyses and decisions.

Involves consultation
A good review reflects input from colleagues and other internal or external stakeholders with expertise relevant to the various aspects of the application.

Balanced
A good review is objective and unbiased.
Thorough
A good review reflects adequate follow-through of all the issues by the reviewers.

Well-documented
A good review provides 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 could be leveraged by others.

3. MANAGING THE REVIEW
RAs actively manage the process of reviewing medical product applications in order to maximize both the potential for a positive public health impact and the effective and efficient use of review resources. RAs should clearly define separate steps in the process, each with specific activities and targets.

The principles of project management and quality management are critical to well-functioning RAs. The practices of planning and monitoring review activities coupled with timely, informative communications and clearly-defined work instructions can maximize the efficiency and effectiveness of the review.

3.1 Project management
Project management for the review process is the planning, organizing and resourcing to achieve a completed, high-quality review of an application within a specified time frame.

Techniques to monitor the progress of applications under review will be individual to each RA. For example, an individual reviewer can use a simple table or spreadsheet, or a project manager may use computer software to monitor many applications at a time. Data should be periodically collected and interpreted to assess the effectiveness of the review strategy (see section 6) for completing reviews within the specified time frame.

The technique most suitable for the RA will be one that enables:
Interpretation of the data to show the progress of one application as well as many applications under review at 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.

### 3.2 Quality management

The World Health Organization (WHO) defines quality management (QM) as “the coordinated activities that direct and control an organization with regard to quality” and a QM system as “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.”

In an RA, QM includes standardized procedures to ensure that GRevPs are in place, regularly monitored and subject to continuous improvement. Beyond standardized processes and procedures for consistency and predictability, QM has the ultimate goal of supporting a robust regulatory decision and action.

An RA’s QM system will be influenced by a number of factors including size, resources, competencies, its particular objectives, the processes it employs and its organizational structure. However, even RAs with limited resources can institute the key elements of QM. Successful QM implementation requires senior management commitment but is ultimately the responsibility of everyone in the organization.

The quality cycle is made up of four key components:

1. Say what you do.
2. Do what you say.
3. Prove it.
4. 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 due to evolving regulatory science or adoption of new review process and procedures (Improve it).

### Quality Management Cycle

**Say what you do**
- Provide key documents, such as SOPs and assessment templates.
- Define processes for decision-making, such as decision frameworks, use of external experts, public meetings and peer-review.

**Do what you say**
- Implement processes defined in key documents.
- Offer professional development, mentoring and regular on-the-job training.
- Implement new and improved work practices, latest evaluation techniques and scientific and technological advancements.
Prove it

- 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 unintended consequences.

Improve it

- Review documentation and decision-making processes regularly.
- Introduce improvements to the review process and decision-making, such as internal assessment of a review, peer review, internal quality audits, self-assessments, analyses of feedback from stakeholders, post-approval analysis of the decision with other authorities, the public and applicants and impact analysis on public health.

Implementing QM is an iterative process that incorporates lessons learned for improved processes and decision-making.

3.3 Standard operating procedures

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

- outline the workflow processes which 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 describe processes in a step-by-step manner. They may be detailed or brief, but should describe the overall process (or 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, checklists) can describe in detail how a particular procedure is performed or give advice in handling a specific situation when performing the procedure.

Templates and checklists serve to 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 that either information has been provided or 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.

While SOPs have often been kept internal within an RA, making templates and checklists available to applicants can be beneficial by ensuring mutual understanding of the information to be submitted for review. 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.

SOPs, guidelines, templates and checklists will require revision over time (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, new reviewers, increased application volumes, collaborative work-sharing, etc.

### 3.4 Review process stages

Two key stages in the process of reviewing medical product applications are screening/validation and scientific review. 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 the RA to avoid spending time and review resources on an application that does
not allow critical analysis, signal identification or regulatory decision-making. Scientific review will be
discussed further in section 6.

It is essential that applicants are aware of the RA’s expectations at both stages, including targets,
guidelines and templates/checklists. This results in a more predictable and clear process for applicants. In
turn the RA benefits when applicants submit complete applications at the outset.

4. COMMUNICATIONS

Communication is critical as it has many advantages for RAs, applicants and the public. It can improve
efficiencies in the development and review process, resulting in earlier patient 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 from providing information on RAs’ websites to engaging
with the international community on RA projects. In turn these active forms of RA communications can
be leveraged by others, including other RAs.

4.1 Intra-agency

Product reviews are conducted in a collaborative environment. They often require expertise from and
coordination with different units within the RA. Therefore good communication will improve efficiency.
Promoting open, clear and constructive communications regarding the progress of the review, review
findings, differing data interpretations and discussion of possible solutions and actions within the RA is
desirable. Beyond establishing meetings, fora and other vehicles for idea exchange among reviewers, a
checklist of personnel or departments to involve 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.
4.2 Interagency

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

- accessing information on other RA websites, such as guidelines, application decisions, product recalls for safety;
- using information from other RAs, such as assessment reports, regulatory decisions;
- actively sharing information between RAs, such as during an application review;
- actively working with other RAs, such as joint reviews of applications, development of new guidelines.

Interagency communication may evolve from awareness, to consideration of findings from one RA by another in its decision-making, to use of reliance on those findings to leverage resources.

Information-sharing arrangements or prior consent from the applicant may be needed for some types of communications, including sharing of confidential commercial, trade secret or personal privacy information.

4.3 With applicants

Public availability of RA guidelines, notices, questions and answers and presentations, as well as finalized RA review reports and decision summaries (redacted as needed), provide insight into the RA’s current thinking and expectations. These communications allow applicants to provide better quality applications. RA communication with 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 RA understanding of challenges and trade-offs with various requirements;
• foster applicants’ compliance with requirements (although it is also important for RAs to be open to proposals from applicants on alternative approaches that address the same requirements);
• provide applicants with the progress and status of the review of their applications.

Having procedures for applicants to engage the RA, both on product development requirements and on issues identified during the application review, can facilitate the development, review and availability of medical products.

4.4 With external experts

Expertise in the scientific assessment of the safety, efficacy/effectiveness and quality of medical products 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 leveraged.

Obtaining external expert input into RA decision-making improves public confidence, provides additional perspectives for the RA to consider and provides needed expertise that otherwise may be lacking. Some RAs use advisory panels, both in public and closed sessions, to ensure expertise and health care contexts are addressed. Other RAs may use a system of external experts to conduct the review of parts or all of the application. Ensuring both confidentiality and lack of conflict of interest is important and can be achieved through transparent processes for management of confidential information and screening of potential conflicts.

4.5 With the public

Communication with the public about the mission and accomplishments of the RA can foster greater public awareness, understanding and confidence about the RA. Transparency initiatives usually involve web-based information about how the RA is organized and operates, its decision-making processes and
criteria and its actions such as application approvals and product recalls for safety. 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 RA advisory boards. Use of plain language will ensure RA communications are clearly understood.

The public may also be consulted on specific applications under review by the RA. There are various mechanisms by which this can be achieved, such as surveys, focus groups, public meetings, workshops and appointment to advisory boards.

5. REVIEW PERSONNEL

The quality, timeliness and success of medical product application reviews are dependent on adequate RA review capacity. In addition to having a sufficient amount of reviewers, capacity relates to many personnel factors. Among the important considerations are 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 RA staff, external experts or a combination of 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, including those of employers when an external expert is also a consultant to the regulated industry.

5.1 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.

Core competency starts with reviewers that are scientifically trained. Reviewers should have professional qualifications, training and expertise in scientific or medical fields that relate to the assessment of medical product safety, efficacy/effectiveness 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 as part of public service.

General competencies required to conduct review work include:

- knowledge and applicability of statutes, regulations, guidelines and precedents, including international guidelines and precedents;
- knowledge of medical 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.

Reviewers should remain up to date in their scientific expertise. Increasingly, regulatory science curricula from universities and international regulatory initiatives and organizations are available. Opportunities should be made available for reviewers to attend relevant conferences, courses, international meetings, etc. Reviewers should also be encouraged to read scientific journals and maintain memberships in professional societies or relevant organizations.

For on the job training, a site visit programme which allows reviewers to visit product manufacturing facilities and clinical settings where products are used can be considered. In addition, experienced reviewers should be encouraged to mentor and train junior reviewers. The establishment of structured training programmes within RAs to facilitate the professional development of review staff should also be considered, whenever feasible.
5.2 Critical thinking

Critical thinking requires an objective and systematic approach to analyzing information and 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. The decision should be reproducible and clearly understood by others.

Nevertheless, every regulatory decision involves judgment. Therefore core competence in public health, 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 judgment skills are required to come to a balanced decision. This involves focusing on the important issues in the application, rather than on data that provides more information, but will not ultimately affect the outcome of an application. Good judgment 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 medical-care system provide context to this decision-making. In decisions to grant authorization the benefits must on balance outweigh risks, based on sound scientific evidence. Documentation of scientific rationale for decision-making, taking into account regulatory requirements, allows 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.

6. CONDUCTING THE REVIEW

Defining and then following an application-specific review strategy, amending 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.

6.1 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:

Public health priority of the medical product application

Each medical product application poses unique and varied scientific questions, challenges and opportunities for the public health of a nation and these, in turn, determine the public health priorities of the application. Given the limitations of resources within RAs, prioritization based on public health may be helpful in determining review timelines, extent of management and other RAs’ involvement, resources assigned to the review team (which helps determine who may review what portions of the application), need for public input and other plans.

Understanding other RAs’ action on the application

The use of reviews and decisions from other RAs is expected to become increasingly important to achieving review efficiencies in the face of resource pressures. To implement optimal and consistent use of other RAs’ reviews and decisions, development of a policy framework and review strategy is critical. Strategies should consider both the use of publicly-available information (for example, decisions, review reports and summaries) and information obtained directly from applicants or other RAs (for example, review packages which include responses to questions posed by RAs). Clear direction and support from senior management on the use of regulatory outputs from other RAs is also essential. The goal is to consider how to gain efficiencies and improve the quality of the review through leveraging other RAs’
reviews and/or decisions in appropriate situations. In all such cases it is important to understand similarities and differences in the product and proposed indications/conditions of use.

GRevPs are important in promoting the use of information from other RAs, by:

- encouraging greater transparency and public availability of regulatory information (for example, decisions, review reports and/or summaries, review processes);
- promoting confidence and trust in the regulatory system that produced the review report and regulatory decision;
- applying the same GRevP principles to the consistent integration of the scientific reviews and decisions of other RAs into the domestic review process.

As previously noted the implementation of GRevPs also facilitates opportunities for work-sharing between RAs.

Understanding specific intrinsic and extrinsic factors

Whether or not a medical product is authorized by another RA, the review should target what is clinically relevant to the RA’s population now being considered. Identification of potential differences in genotypes and phenotypes, disease manifestation, available alternatives and medical practice compared to both the application’s study population, as well as to the population of another RA that has already rendered a decision about the application, may help focus the review.

Identification of major scientific questions and their possible resolution

Early identification of complex, precedence-setting or high uncertainty issues is important and can lead to faster and more efficient resolution. If problems are identified early reviewers can formulate an in-depth plan to first review data of greatest relevant in the application, the RA can develop a plan to seek external advice if desirable, or if the application does not permit a conclusion about benefits and risks, the RA can avoid spending time and resources altogether.
Understanding what information is needed to reach an acceptable level of certainty to resolve scientific questions and meet regulatory standards for marketing authorization, versus what information can be collected in the post-marketing period, is an important aspect of regulatory decision-making.

6.2 Applying the review strategy

The way a review is conducted will depend on the resources available. 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.

The review should be evidence-based, taking into account national, regional and international guidelines, 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 form a conclusion. In other models the review is completed on the information submitted and a list of questions 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.

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 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.
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, including the levels of certainty surrounding the benefits and risks. 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 exist that quantify benefits and risks. These could be used depending on circumstances such as complexity of issues and utility to the RA. 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 identifying non-responders early and terminating use of the medical product or identifying responders and ensuring appropriate use). It is important to note that the benefit-risk profile may vary depending on intrinsic and extrinsic factors that may differ among countries and regions. Moreover, judgment may vary from within and among RAs. Evidence-based, public health-focused decision-making principles may serve to mitigate some variation.

The findings and conclusions of the review must be described in a well-documented review report (see section 2). Once the final decision is made it should be conveyed to the applicant. If an RA 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.

Some RAs may offer post-action discussion with the applicant to help mitigate future application deficiencies. The RA may also 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.
7. REFERENCES

