Norms and standards

Good review practices:
guidelines for national and regional regulatory authorities *

This is a summary of a guideline on good regulatory review practices developed through an inter-organizational collaboration. It is the first set of guidelines of its kind globally and addresses an important gap identified at the 2012 International Conference of Drug Regulatory Authorities (ICDRA).

The full text as adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2014 will be published as an annex to the Expert Committee's report; the draft published for comment prior to the Committee's meeting is available on the WHO web site (1).

The benefits of good review practices
Regulatory authorities (RAs) are increasingly seeking ways to improve their performance and ensure the quality of their regulatory systems. Medical product review is that part of regulatory work that forms the scientific foundation for regulatory decisions on marketing authorizations. It requires a highly complex, multidisciplinary assessment of product data to ensure that products submitted for regulatory approval meet adequate scientific and evidentiary standards for safety, efficacy and quality.

Implementation of good review practices helps RAs to achieve timely reviews with high quality outcomes, with a significant impact on public health, for example in terms of patients' access to important medical products, and costs to both government and applicants.

Good review practice also facilitates progress towards regulatory convergence through the exchange of review reports and better mutual understanding among RAs. This is a significant benefit as the use of reviews and decisions reached by other RAs is expected to become increasingly important in achieving review efficiencies in the face of pressures on resources.

Guideline development
In June 2013 the Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC) convened an expert working group with WHO representation to develop a draft good review practices document, intended to cover both medicines and medical devices, for submission to WHO in early 2014. WHO risk management principles (2) and the results of an APEC survey (3) were among the key references used in developing this text.

The draft document was accepted for parallel public consultation processes

* Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC) good review practices (GRevP) with the participation of Working Group Members representing the regulatory authorities (RAs) from the economies of Australia, Canada, Taipei (China), Japan, Republic of Korea, Saudi Arabia, Singapore, United States of America; and representatives of the Centre for Innovation in Regulatory Science (CIRS); and the Food and Drug Administration Alumni Association International (FDAAA).
for both the WHO Expert Committee on Specifications for Pharmaceutical Preparations and the WHO Expert Committee on Biological Standardization. This led to a guidance text on good review practices for regulatory authorities being adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its forty-ninth meeting, held on 13–17 October 2014 in Geneva.

Objective and scope
The objective of the document is to provide high-level guidance on the principles and processes of good review practice for use across a range of RA maturities. It is not intended to provide detailed instruction on how to conduct a scientific review. Rather, it 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. The principles and elements described in this document can be adapted to meet the continuous needs for improvement of a diverse range of RAs.

Although the document was written to provide guidance on pharmaceutical products and biologicals and higher-risk medical devices used in humans, the concepts may be applied to other types of medical products. Similarly, the concepts could also be applied to the entire product life cycle from investigational testing to new product applications, updates or variations to existing marketing authorizations and maintenance of the product.

What is good review practice?
The guidelines define good review practices (GRevPs) as “documented best practices for any aspect related to the process, format, content and management of a medical product review. The objective of GRevPs is to help achieve timeliness, predictability, consistency, transparency, clarity, efficiency and high quality in both the content and management of reviews. This is done through the development of review tools (for example, standard operating procedures (SOPs) and templates) and reviewer learning activities (for example, training courses, mentoring, orientation packages and discussion sessions). To promote continuous improvement, all aspects of GRevPs should be continuously evaluated and updated.”

The document proposes ten key principles of a good review as a general guide for RAs (see Box 1).

Managing the review
The principles of project management and quality management are critical to achieve efficient and effective review processes.

Project management refers to the planning, organizing and resourcing necessary to achieve a complete and high-quality review of an application within a specified time frame. RAs should identify the most suitable techniques enabling them to monitor the progress of one or many applications under review at any one time, to help in decision-making on how to balance workload against resources, and to enable monitoring and/or its interpretation by the relevant people.

Quality management – the coordinated activities that direct and control an organization with regard to quality – ensures that GRevPs are in place, regularly monitored and subject to continuous improvement. The quality cycle is made up of four key components:
• say what you do,
• do what you say,
• prove it, and
• improve it.
**Box 1: Ten key principles of a good review**

**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.

**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.

**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.

**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 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.

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

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

**Standard operating procedures (SOPs)** enable RAs to outline workflow processes, handle and review product applications in a consistent manner, and facilitate staff training. SOPs can be complemented by companion documents such as guidelines, templates and checklists, and can be designed both for internal use and to guide applicants seeking marketing authorization.

SOPs will require updating in line with evolving 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.
Review process stages
The review process has two key stages: firstly a validation stage (also called screening) to identify missing information in the application, ensuring that time and review resources are only spent on applications that have enough data to allow critical analysis, signal identification and regulatory decision-making, and secondly the actual scientific review, discussed in more detail below. Applicants should be made clearly aware of the RA’s expectations at both stages.

Communications
Good communication is critical and has many advantages for RAs, applicants and the public. It can improve the efficiency of the development and review processes and thus ultimately speed up patient access to good quality medical products.

Communications can take many active forms, from providing information on RAs’ websites to engaging with the international community on RA projects. The guidelines outline best practices for communication and their benefits at various levels:
- within RAs, for effective coordination of organizational units carrying out different pre- and postmarketing functions (for example pharmacovigilance, inspection and others);
- between RAs, enabling peer collaboration and cooperation, whereby interagency communications can also facilitate greater regulatory convergence;
- with applicants, to provide insight into the RA’s current thinking and expectations, enabling a mutual better understanding and therefore better quality applications;
- with external experts (for example from academic institutions, industry associations, patient organizations and medical or scientific organizations) to make use of valuable expertise while ensuring confidentiality and absence of conflict of interest; and
- with the public, to foster awareness, understanding of and confidence in the RA, and to obtain input on proposed regulations and/or specific applications.

Review personnel
The quality, timeliness and success of medical product reviews are dependent on a sufficient number of competent reviewers. The guideline outlines the expertise, competencies and training required to deal with the various aspects of managing and conducting reviews.

Reviewers may be RA staff, external experts or both. Reviewers should be free of actual or perceived conflicts of interests, meaning 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. Review staff should follow sound ethical practices.

Reviewers should keep their scientific expertise up to date. The guidelines propose various approaches for professional development of review staff, making use of opportunities both within and outside the RA.

Critical thinking and good judgement
Critical thinking is important for reviewers to make decisions that are reproducible and clearly understood by others. Reviewers should have the ability to critically appraise the information presented in an application and not just accept it as presented. This skill can be strengthened by learning from
senior reviewers and through discussion among reviewers and external experts on application-specific issues.

Good judgement is required for reviewers to come to balanced decisions. This involves focusing on the important issues in the application and adopting those regulatory approaches that will maximize public health benefits while minimizing adverse, unintended consequences.

Regulatory decision-making should be based on the best current science, in the context of each country’s public health needs and its medical care system. The scientific rationale for decision-making, including all information used and any dissenting, evidence-based views, should be documented to ensure the integrity of the review process. Decision-making by an RA should be independent of influences beyond public health.

Review strategy
For each specific application, a review strategy – i.e. an approach or plan of action – should be defined and followed by the reviewer or review team to ensure a sound review process. The strategy employed may be shaped by:
• the public health priority of the medical product submitted for review;
• other RAs’ action on the product, taking into account any product differences (for example formulation or final container presentation) and any differences in the proposed indications or conditions of use in the local population;
• specific intrinsic and extrinsic factors that are clinically relevant to the population served by the RA; and
• major scientific questions on product safety, efficacy or quality (examples: identification of possible cases of organ toxicity in a patient population with a high background incidence of the same organ disease, use of a new end point for regulatory approval that may not be a direct measure of clinical benefit, or use of conditions for stability testing that are not appropriate for the RA’s regional climate). Early identification of complex or precedent-setting issues or areas of high uncertainty in the application can lead to faster and more efficient resolution, based on an early review of the most relevant available data.

Conducting the review
The way in which a review is conducted will depend on available resources. While a multidisciplinary team will provide broader expertise, in some cases an application may be assigned to a single reviewer, seeking input from external experts and/or considering the information and decisions of other RAs as needed.

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, and consider what further studies (if any) can be left for the post-approval stage without compromising safety.

The model adopted for review may allow for questions to be asked during the review to supplement or clarify the information supplied, until the reviewer is satisfied that enough data have been provided for a conclusion to be reached. In other models, the review is completed on the basis of the information submitted, a list of questions is then sent to the applicant with a time-limit for response, and one further round of assessment of the responses takes place before a decision is made.
The following internal processes may help ensure an efficient, consistent and effective review process:

• 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; and
• the involvement of senior management.

**Quantifying risks and benefits**

The review strategy should enable the reviewer or review team to understand and describe the benefit–risk profile of the medical product, given its indication and context of use. 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 the findings and what (if any) additional information may be needed to clarify benefits and risks.

The acceptability of benefits and risks will depend on public health priorities, available alternative therapies, the size and certainty of the treatment effect versus that of the adverse reactions, and possible risk mitigation or benefit enhancement measures (for example responder analyses to identify a population more likely to experience benefits). The benefit–risk profile may vary depending on intrinsic and extrinsic factors that may differ among countries and regions. Moreover, judgement may vary within and among RAs. Evidence-based and public health-focused decision-making principles may serve to mitigate some of the variation.

**Review report**

The findings and conclusions of the review must be described in a well-documented review report, and the final decision 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 regulatory requirements taken into account in reaching the decision. An appeal mechanism should be provided giving applicants an opportunity to present their case to an independent arbiter.

Some RAs may offer to hold a post-action discussion with the applicant to help improve the quality of future applications. Lastly the RA may also implement mechanisms for public communication of review outcomes and related information, increasing the transparency of its regulatory actions.

**References**

