BADAN POM

Pedoman Cara Evaluasi Obat yang Baik
Good Review Practices (GRevP) Guideline

BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA
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Kata Pengantar

Dengan memanjatkan puji syukur kepada Allah SWT, Pedoman Cara Evaluasi Obat yang Baik (CEOB) telah selesai disusun. Registrasi obat merupakan pengawasan pre-market yang dilakukan dengan cara evaluasi mutu, khasiat, keamanan, dan informasi produk serta pemenuhan persyaratan Cara Pembuatan Obat yang Baik (CPOB). Hal ini bertujuan untuk memastikan obat yang akan diedarkan telah memenuhi persyaratan mutu, khasiat dan keamanan. Dalam rangka mewujudkan hal ini, diperlukan adanya pedoman cara evaluasi obat yang baik untuk evaluator registrasi obat. Pedoman ini mencakup prinsip evaluasi obat yang baik, pengelolaan evaluasi, komunikasi dengan para pemangku kepentingan, kompetensi evaluator, dan cara evaluasi obat yang baik.

Secara umum, pedoman ini mengacu pada prinsip-prinsip yang tercantum pada pedoman WHO. Hal-hal teknis lebih lanjut didetailkan dalam petunjuk kerja yang terkait. Kami menyadari bahwa pedoman ini adalah suatu *live-document* yang sewaktu-waktu dapat diperbaharui mengikuti dinamika perkembangan ilmu dan teknologi. Untuk itu, kami terbuka terhadap masukan dan saran dari berbagai pihak terkait untuk penyempurnaan pedoman ini ke depannya.

Akhir kata, kami menyampaikan terima kasih kepada semua pihak yang telah memberikan kontribusi dalam penyusunan pedoman ini.

Jakarta, 22 November 2021

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Pedoman Cara Evaluasi Obat yang Baik

Good Review Practices (GRevP) Guideline

A. Latar Belakang

Berdasarkan Peraturan Menteri Kesehatan Republik Indonesia No. 1010 Tahun 2008 tentang Registrasi Obat, obat yang akan dipasarkan di wilayah Indonesia harus memiliki izin edar. Sesuai dengan Peraturan Presiden Republik Indonesia No. 80 Tahun 2017, Badan POM diberikan amanat untuk melakukan pengawasan meliputi pre- dan post-market untuk produk obat dan makanan.

Salah satu pengawasan pre-market untuk obat antara lain melakukan evaluasi terhadap dokumen registrasi untuk memastikan efikasi, keamanan dan mutu obat sebelum diedarkan. Izin edar akan diterbitkan apabila setelah hasil evaluasi dapat dipastikan dan berdasarkan *risk-benefit analysis*, manfaat melebihi risiko.

B. Ruang Lingkup

– Ruang lingkup produk: obat

Obat adalah obat jadi termasuk Produk Biologi, yang merupakan bahan atau paduan bahan digunakan untuk mempengaruhi atau menyelidiki sistem fisiologi atau keadaan patologi dalam rangka penetapan diagnosis, pencegahan, penyembuhan, pemulihan dan peningkatan kesehatan, dan kontrasepsi untuk manusia.

– Ruang lingkup proses: evaluasi pre-market

Pedoman ini mencakup pedoman untuk mengevaluasi obat sebelum beredar.

C. Tujuan Pedoman

Untuk menjaga mutu evaluasi supaya konsisten dan reprodusibel, maka Badan Pengawas Obat dan Makanan (BPOM) mempertimbangkan perlunya pedoman untuk mengevaluasi dokumen registrasi obat yang dituangkan dalam bentuk buku pedoman Cara Evaluasi Obat Yang Baik (CEOB) untuk evaluator di lingkungan Badan POM. Pedoman CEOB Indonesia sepenuhnya mengadopsi panduan yang ditetapkan dalam Pedoman WHO dengan judul *Good Review Practices: Guidelines For*

National And Regional Regulatory Authorities yang tercantum dalam *WHO Technical Report Series No. 992, 2015, Annex 9*.

Dengan adanya pedoman ini bertujuan sebagai panduan bagi evaluator dalam memahami prinsip-prinsip dasar evaluasi meliputi:

1. Menjelaskan konsep dan prinsip evaluasi obat yang baik.
2. Memberikan panduan kepada evaluator terkait cara evaluasi obat.
3. Membantu mencapai ketepatan waktu evaluasi, prediktabilitas, konsistensi, transparansi, kejelasan, efisiensi, dan kualitas yang baik dalam isi hasil evaluasi.

Pedoman ini bukan merupakan instruksi rinci terkait tahapan teknis evaluasi obat. Untuk itu, teknis evaluasi obat dapat mengacu pada SOP dan Petunjuk Teknis (Juknis) terkait.

Annex 9

Good review practices: guidelines for national and regional regulatory authorities[1]

Background

The good review practices (GRevP) guidelines for regulatory authorities emanate from a partnership between the Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC) and the World Health Organization (WHO). This 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). Although the RHSC does not directly produce guidelines, contributing to WHO guidelines is in line with the RHSC's principle of working with appropriate partners to achieve common objectives.

In June 2013 the RHSC convened an expert working group with WHO representation to develop a draft GRevP document, intended to cover both medicines and medical devices, for submission to WHO in early 2014. The draft document subsequently underwent the required WHO consultation process with a view to its further development into WHO guidelines for adoption by the Expert Committee on Specifications for Pharmaceutical Preparations and the Expert Committee on Biological Standardization. This led to these new GRevP guidelines for regulatory authorities adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its forty-ninth meeting.

[1] 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).

1. Introduction

1.1 Document objective

The objective of this document is to provide high-level guidance on the principles and processes of good review practice (GRevP) 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 to ensure that they meet the scientific and evidentiary standards for safety, efficacy[2] and quality. It forms the scientific foundation for regulatory decisions.

The extent to which an RA can achieve timeliness of the review (i.e. completion within a specified time frame), as well as predictability, consistency, transparency, clarity, efficiency and high quality, can have a significant impact on public health (for example, in relation to patients' access to important medical products, and costs to both government and applicants). Implementation of GRevPs helps to achieve these outcomes by ensuring that 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 exchange of review reports and the enhancement of mutual understanding among RAs.

Several RAs have introduced ways of monitoring and improving their review process through structured approaches or by 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 needs for improvement of a diverse range of RAs.

[2] Although effectiveness is the term often used for medical devices, efficacy is used throughout this document.

1.3 Definition of 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 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.

1.4 Scope

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

Although this 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.

2. Glossary

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

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

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

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

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

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

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

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

project management (for the review process). The planning, organization and resources to achieve a complete and high quality review of an application within a specified time frame.

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

quality management (QM) system. An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

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

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

review. A highly complex, multidisciplinary assessment of medical product applications to assess whether they meet scientific and evidentiary standards for safety, efficacy and quality. It forms the scientific foundation for regulatory decisions. The first stage of the review process, validation (sometimes referred to as screening), occurs before the scientific review with the aim of ensuring completeness of the application in order to subsequently facilitate the scientific review.

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

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

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

3. Principles of a good review

As noted in the definition of GRevP, the objective of GRevPs is to help achieve successful review outcomes. The principles of a good review describe the GRevP elements that are important for RAs to implement in order to achieve successful review outcomes. Listed in alphabetical order in Box A9.1, the 10 key principles of a good review are provided as a general guide for RAs. Although not prescriptive in nature, they can serve as a solid GRevP foundation upon which RAs can continue to build.

Box A9.1

10 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.

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 labelling, 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, 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.

4. 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 the 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 within the RA and clearly-defined work instructions for the reviewers, can maximize the efficiency and effectiveness of the review.

4.1 Project management

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

Techniques to monitor the progress of applications under review will be specific 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 one time. Data should be periodically collected and interpreted to assess the effectiveness of the review strategy (see section 7) 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 that of many applications under review at any one time;
- interpretation of the data to help in decision-making with respect to balancing workload against resources;
- monitoring that can be performed and/or interpreted by the relevant people.

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

4.2 Quality management

Quality management (QM) is defined as the coordinated activities that direct and control an organization with regard to quality. A QM system refers to the appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

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 that provide consistency and predictability, QM has the ultimate goal of supporting robust regulatory decisions and actions.

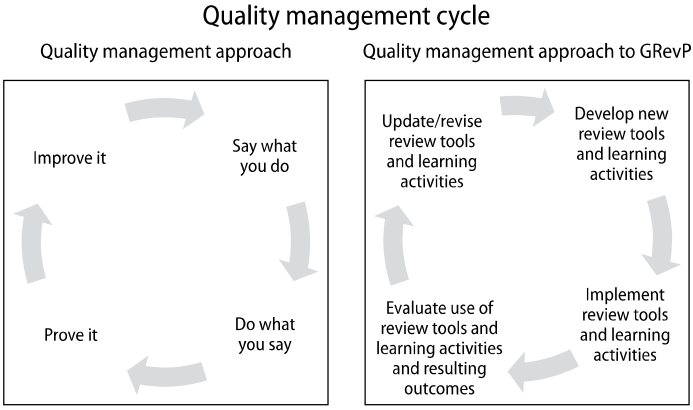
An RA's QM system will be influenced by a number of factors including size and resources of the RA, competencies, its particular objectives, the processes it employs, and its organizational structure. However, even RAs with limited resources can institute the key elements of QM. Successful QM implementation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

The quality cycle is made up of four key components:

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

This cycle ensures that GRevPs are not just esoteric guidelines (say what you do) but become embedded in the daily practice of an agency (do what you say). Quality management is also important as it can help an agency review its practice (prove it) and evolve where necessary, either in response to evolving regulatory science or through the adoption of a new review process and procedures (improve it) (Figure A9.1).

Figure A9.1
Quality management cycle



Source: Based on United States of America Food and Drug Administration figure.

4.2.1 Say what you do

- Provide key documents, such as SOPs and assessment templates.
- Define processes for decision-making, such as decision frameworks, time frames for completion and communication of reviews, use of external experts, public meetings and peer-review.

4.2.2 Do what you say

- Implement processes defined in key documents and adhere to specified time frames.
- Offer professional development, mentoring and regular on-the-job training.
- Record and collect key documents, such as minutes of meetings and teleconferences, memoranda, letters and reports.

4.2.3 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 any unintended consequences.

4.2.4 Improve it

- Review documentation and decision-making processes regularly.
- Consider introducing improvements to the review and decision-making process, 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 in collaboration with other authorities; the public and applicants; and analysis of impact on public health.
- Implement new and improved work practices, the latest evaluation techniques, and scientific and technological advancements.

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

4.3 Standard operating procedures

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

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

SOPs are authorized written procedures giving instructions for performing operations (both general and specific). They describe procedures (or processes) in a step-by-step manner. They may be detailed or brief, but should describe the overall procedure from start to finish. SOPs should be written clearly to provide both instruction and consistency related to the work being performed.

SOPs may be structured to contain additional tools that will assist in performing the procedure. Alternatively, companion documents can be created to give more detailed instruction and structure in support of an SOP. These companion documents (for example, guidelines for reviewers, templates and checklists) can describe in detail how a particular procedure is performed or give advice on handling a specific situation when performing the procedure.

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

While SOPs have often been kept internal within an RA, making templates and checklists available to applicants can be beneficial in 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. Guidelines for applicants can be made available using a step-wise approach, usually involving informing applicants of the guidelines before making them publicly accessible.

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

4.4 Review process stages

Two key stages in the process of reviewing medical product applications are validation[3] and scientific review. The validation stage occurs first, with the aim of ensuring completeness of the application in order to facilitate the subsequent scientific review.

Validation involves an examination of the application to ensure that it is well-organized and that all the required forms and relevant documents have been submitted. Identifying missing information in the application prior to scientific review enables the 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 7.

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

5. 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 process, allowing patients faster access to important medical products. It can also improve the quality of the review by providing access to additional expertise.

Communications can take many active forms, 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 used to the advantage of others, including other RAs.

5.1 Intra-agency

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

Therefore, good communication will improve efficiency. Open, clear, constructive and timely communications regarding the progress of the review, review findings, differing data interpretations and discussion of possible solutions and actions within the RA are desirable. In addition to establishing

[3] Although screening is a term that is also sometimes used, validation is used throughout this document.

meetings, forums and other vehicles for exchange of ideas among reviewers, a checklist of personnel or departments involved on specific issues or actions may be helpful. Information management systems should be process-centric rather than organizational structure-centric to ensure appropriate and efficient information flow.

5.2 Interagency

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

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

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

Information-sharing arrangements and procedures, such as memoranda of understanding, confidentiality arrangements, consent from the applicant, redaction and non-disclosure of specific information, as well as other arrangements and actions, have been used to ensure confidentiality of commercial data, trade secrets and personal information.

5.3 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.

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

- foster efficient medical product development through the provision of scientific advice;
- increase applicants' understanding of evolving regulatory expectations in a changing medical and scientific environment;
- increase the RA's 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 for alternative approaches that address the same requirements);
- inform applicants about the progress and status of the review of their applications.

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

5.4 With external experts

Expertise in the scientific assessment of the safety, efficacy 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 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. RAs have used advisory panels, both in public and closed sessions, to ensure that expertise and health-care contexts are addressed. RAs may also use a system whereby external experts conduct the review of all or part(s) of the application. Ensuring both confidentiality and absence of conflict of interest is important and can be achieved through transparent processes for management of confidential information and screening for potential conflicts.

5.5 With the public

Communication with the public about the mission and accomplishments of the RA can foster greater public awareness, understanding of and confidence in the RA. Transparency refers to defining policies and procedures in writing, publishing the written documentation, and giving reasons for decisions to the public. For the RA, transparency initiatives usually involve web-based information about how it is organized and operates, its decision-making processes and criteria,

and its actions, such as application approvals and product recalls. Additionally, there may be mechanisms whereby the public can provide input on medical needs, efficacy expectations and risk tolerances, such as through public meetings and RA advisory boards. Providing the public with the opportunity to comment permits enhanced content and feasibility of proposed guidelines and regulations. Use of plain language will ensure RA communications are properly 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.

6. 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 number of reviewers, capacity relates to many personnel factors including the knowledge, skills, abilities and attitudes of reviewers. Together, these considerations define the core competencies for personnel involved in the various aspects of managing and conducting reviews.

Reviewers may be RA staff, external experts or both. To ensure the integrity of product reviews and recommendations, reviewers should be free of actual or perceived conflicts of interests. To be free of any conflict of interest means the review decision or recommendation is not likely to be influenced by personal, family, financial or professional motives, including those of employers when an external expert is also a consultant to the regulated industry.

6.1 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 who 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 and/or quality. Both practical and theoretical knowledge is desirable in order to achieve a good understanding of the issues likely to be associated with the product under review.

Reviewer competencies depend on the duties and scope of review work. Scientific writing, presentation of data, data analysis, inferential and deductive reasoning, risk-based analyses and problem-solving are important skills for reviewing a medical product application. Review staff should also follow sound ethical practices.

General competencies required to conduct review work include:

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

Reviewers should keep their scientific expertise up to date. Increasingly, regulatory science curricula from universities and international regulatory initiatives and organizations are available. Reviewers should have the opportunity to attend relevant conferences, courses and international meetings. Reviewers should also be encouraged to read scientific journals and to be members of professional societies or relevant organizations.

For on-the-job training, a site visit programme that allows reviewers to visit sites such as laboratories, manufacturing facilities and clinical settings may be considered. In addition, experienced reviewers should be encouraged to mentor and train junior reviewers. The establishment of structured training programmes within RAs to facilitate the professional development of review staff should also be considered, whenever feasible.

6.2 Critical thinking

Critical thinking requires an objective and systematic approach to analysing information and to problem-solving. It relies on the collection of data and evidence-based decision-making instead of generalizing from one's own experience, intuition or trial and error. Decisions should be reproducible and clearly understood by others.

Nevertheless, every regulatory decision involves judgement. Therefore, core competence in public health and bioethics, and the ability to integrate up-to-date scientific knowledge with an understanding of the evidentiary standards for regulatory action (including the flexibility inherent in those standards and regulations), can guide decisions.

Beyond their professional qualifications, reviewers should have the ability to critically appraise the information presented in an application and not just accept it as presented. This skill may often be developed or strengthened during the training process, for instance, by evaluating the responses to questions raised by a senior reviewer so that the questioning process becomes a learning tool.

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

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

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

7. Conducting the review

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

7.1 Key elements in defining a review strategy

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

7.1.1 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 needs may be helpful in setting and communicating review time frames, the extent of involvement of management and other RAs, resources assigned to the review team (which helps determine who may review what portions of the application), need for public input and other plans.

7.1.2 Understanding other RAs' action on the application

The use of reviews and decisions reached by other RAs is expected to become increasingly important in making the review process more efficient in the face of pressures on resources. To implement optimal and consistent use of other RAs' reviews and decisions, development of a policy framework and review strategy is critical. Such strategies should consider both the use of publicly available information (for example, decisions, review reports and summaries) and of confidential 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 achieve efficiencies and improve the quality of the review through use of other RAs' reviews and/or decisions in appropriate situations. When considering another RA's action, it is important to understand whether there are differences in the product reviewed (for example, formulation or final container presentation) and any differences in the proposed indications or conditions of use in the local population.

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

- encouraging greater transparency and public availability of non-confidential regulatory information (for example, decisions, review reports and/or summaries and review processes);
- promoting confidence and trust in the regulatory system that produced the review report and the 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.

7.1.3 Understanding specific intrinsic and extrinsic factors

Whether or not a medical product is authorized by another RA, the review should focus on available information that may be clinically relevant to the population of the country where the product is being authorized. Such information could include: identification of potential differences in genotypes and phenotypes; disease manifestation; and comparison of available alternatives and medical practice in both the study population relevant to the application and the population of another RA that has already rendered a decision on the application under review.

7.1.4 Identification of major scientific questions and their possible resolution

Early identification of complex, precedence-setting or high uncertainty issues in the application is important and can lead to faster and more efficient resolution. Major scientific application-specific questions would be likely to relate to product safety, efficacy or quality. Examples may include:

- 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;
- use of conditions for stability testing that are not appropriate for the RA's regional climate.

If problems are identified early on, reviewers can formulate a plan to first review the data in the application that are of greatest relevance to these problems, 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 postmarketing period, is an important aspect of regulatory decision-making.

7.2 Applying the review strategy

The way a review is conducted will depend on the resources available. While a multidisciplinary team will provide broader expertise, in some cases an application may be assigned to a single reviewer. In this case, input from external experts and/or the information and decisions of other RAs may be necessary to ensure that scientific and evidentiary standards for safety, efficacy and quality are adequately met.

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

The model adopted for review may allow for questions to be asked during the review to supplement or clarify information supplied, until the reviewer is satisfied that enough information has been provided to allow a conclusion to be reached. In other models, the review is completed on the basis of the information submitted, and a list of questions is then sent to the applicant setting a specified time-limit for response, and one further round of assessment of the responses takes place before a decision is 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 the views of different reviewers;
- peer review, in the context of a co-rapporteur, or a team meeting;
- an internal panel review;
- an external panel review;
- the involvement of senior management.

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

Various methodologies can be used to quantify benefits and risks. The choice depends on circumstances such as complexity of issues and 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 conducting responder analyses to identify a population more likely to experience benefits). 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, judgement may vary from within and among RAs. Evidence-based and public health-focused decision-making principles may serve to mitigate some of the variation.

The findings and conclusions of the review must be described in a well-documented review report (see section 3). 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 to hold a post-action discussion with the applicant to help improve the quality of future applications. 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.

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