出國報告（出國類別：國際會議）

參加「2014 年醫療法規及管理會議 (2014 RAPS REGULATORY CONVERGENCE)」出國報告

服務機關：衛生福利部食品藥物管理署
姓名職稱：劉麗玲組長
派赴國家：美國德州
出國期間：103 年 9 月 27 日至 10 月 3 日
報告日期：103 年 12 月 30 日

摘 要

美國醫療法規學會(Regulatory Affairs Professionals Society，簡稱 RAPS)是一個國際性的非營利組織，主要積極推動法規專業人員的能力認證，是一個專門於醫療產品法規的國際專業會員組織。該學會於 2014 年 9 月 27 日至 10 月 1 日在德州奧斯汀舉辦 2014 年年會，本次大會主題是法規調和(THE REGULATORY CONVERGENCE)，議程共包括五天的研討會，範圍涵蓋藥品、生物製劑、醫療器材及體外診斷試劑及健康食品等領域。

本署所申請計畫書「以優良審查規範及優良送審規範提升查驗登記效率」獲大會接受且部分支助出國經費，並於此次會議進行一場歷時 90 分鐘的專題演講及討論，本人受邀於會中就我國在亞太經濟合作(APEC)推動的優良審查規範工作成果提出報告，此外加拿大官方代表、美國官方代表及日本製藥協會代表亦受邀擔任講員，就加拿大官方推動優良審查規範的經驗、APEC 提交世界衛生組織的優良審查規範指引草案及日本製藥協會規劃中的優良送審規範提出報告。該會議引發與會官方代表及業界學員的熱烈討論，充分達到促進各國主管機關及業界重視優良審查規範及優良送審規範的目的。

關鍵字：美國醫療法規學會、法規調和、優良審查規範、優良送審規範

目 次

壹、目的

RAPS 是全球大規模的法規專業人員組織，自 1976 年創立以來，積極推動法規專業人員的訓練及能力認證，是一個專門於醫療產品法規的國際專業會員組織，已於我國成立 RAPS 台灣分會。法規調和是現今本署參與國際交流合作的重要目標，也是 2014 RAPS 年會的主題。本署所申請的計畫書「以優良審查規範及優良送審規範提升查驗登記效率」(附件一)獲大會接受，並於本次會議召開一場歷時 90 分鐘的專題演講及討論，本人受邀於會中就我國在亞太經濟合作(APEC)推動的優良審查規範工作成果提出報告。本次參加會議的主要目的係為使各國主管機關及業界重視優良審查規範及優良送審規範。

貳、行程與工作紀要：

日期	行程
9 月 27-28 日	啟程（臺北→美國德州）
9 月 29 日- 10 月 1 日	參與研討會並受邀演講
10 月 2-3 日	回程(美國德州→臺北)

參、過程

一、出席研討會

本人參加 RAPS 年會在藥品、生技產品領域之研討會。其中，本署規劃的「以優良審查規範及優良送審規範提升查驗登記效率」(Enhancing Regulatory Efficiency through Good Review Practices (GRevPs) and Good Submission Practices (GSP))獲大會接受，於本次會議召開一場歷時 90 分鐘的專題演講及討論，會議主持人、講員及講題如下：

主持人：Mike Ward (Health Canada)

講員/講題：Marilena Bassi (Health Canada) / Implementation of good review practices in Health Canada

講員/講題：Deborah Jansen (US FDA) / Overview of WHO Good Review Practice Guidelines

講員/講題： Li-Ling Liu (FDA, Ministry of Health and Welfare, Taiwan) / Update of APEC Good Review Practice Roadmap

講員/講題：Toshihiko Tsunenari (Japan Pharmaceutical Manufacturers Association) / APAC Good Submission Practice

本人受邀於會中就我國在亞太經濟合作(APEC)推動的優良審查規範工作成果提出報告，此外加拿大官方代表、美國官方代表及日本製藥協會代表亦受邀擔任講員，就加拿大官方推動優良審查規範的經驗、APEC 提交世界衛生組織的優良審查規範指

引草案及日本製藥協會規劃中的優良送審規範提出報告。

肆、成果

本人受邀就 APEC 優良審查規範計畫推動成果發表演說，講題是 APEC Good Review Practices Roadmap Update，簡報資料如附錄。內容概述 APEC 法規調和指導委員會(Regulatory Harmonization Steering Committee, RHSC)推動優良審查規範的目標、挑戰、時程及工作項目、評估指標、成果及未來展望。

RHSC 推動優良審查規範的目標有兩點：(一)於參加的 APEC 會員體以逐步推動方式，在 2020 年之前提升主管機關的行政效能、可預期性及透明度；(二)增進會員體間的信任，以促進法規調和。現今 APEC 會員體主管機關落實優良審查規範的程度並未一致，持續有創新醫療產品提出上市申請，各國應加強落實優良審查規範，以確保各國病患皆能夠儘早使用創新性醫療產品。發展路徑圖的四個推動步驟如下：

步驟一(2011-2012 年)：差異分析

步驟二(2011-2014 年)：辦理相關活動以因應差異

步驟三(2012-2015 年)：評估優良審查規範訓練及管理資訊交換的影響

步驟四(2015-2020 年)：以法規合作促進優良審查規範最終目標的落實

在 APEC 經費及 10 個會員體的支持下，該計畫已完成發展路徑圖的步驟一及步驟二，重要成果包括：(1) 2011-2012 年間在台灣辦理兩場大型 APEC 優良審查規範國際研討會及 APEC 會員體落實優良審查規範的差異分析；(2) 2013 年接受世界衛生組織(WHO)的邀請，與該組織合作研擬優良審查規範指引文件，經 RHSC GRevP 工作小組一年的努力，該指引文件已於 2014 年 WHO 專家委員會建議採納，成為第一個全球性的優良審查規範指引文件。未來將以 2011-2014 年間所建立的成果，進一步推動建立優良審查規範卓越中心、年度課程或線上學習資料，以提升 APEC 會員體主管機關的審查效能，並促進區域法規調和。

伍、心得及建議

一、RAPS 為國際性生技醫療法規專業協會，本人已連續二年擔任其年會之 program committee member，並每年主持由 Taiwan 提出之「Taiwan Forum」及「GRevP / GSP」計畫構想書均獲大會接受，並由大會資助演講者大部分差旅費用。日後，應鼓勵同仁多申請計畫以提升國際競爭力。

二、我國在 APEC 倡議之 Good Review Practice Project 獲 Canada, China, Korea, Peru, Thailand, United States, Philippine, Indonesia, Malaysia and Mexico 等十國支持，2020 GRevP Roadmap 亦獲 APEC RHSC 通過，並負責 Good Review Practice Guideline 之跨國合作撰寫，亦於今(2014)年 10 月獲 WHO 認可，成為全球首創規範(附件)，建議未來本署亦須組成 GRevP 推動小組，積極推動，使生技醫療產品審查達到 Efficiency、Transparency、Clarity、Consistency 及 Quality 五大目的。

三、我國亦開始在 APEC 促產業端推動優良送審規範(Good Submission Practice)，其與政府法規人員遵循之 GRevP 相輔相成，據以提升查驗登記效率，使好的產品能及早上市嘉惠民眾，日本製藥公會(JPMA)已認定其重要性，並積極引導產業界推動，建議未來積極鼓勵我國產業界推動 GSP。

APEC Good Review Practices Roadmap Update

Li-Ling Liu, MS, RPh
Director, Division of Medicinal Products
Food and Drug Administration
Ministry of Health and Welfare
Taipei, Taiwan
2014/9/29

2014 RAPS THE REGULATORY CONVERGENCE

RAPS

Outline

- Goal
- Background and Challenges
- Specific Activities and Time Frames
- Performance Indicators for Implementation of Good Review Practices
- Accomplishments
- Future Perspectives

Title and Goal of the Roadmap

- Title: 2020 Roadmap for Good Review Practices (GRevP) on Medical Products
- Goal:
  - To strengthen performance, predictability, and transparency of regulatory agencies through the implementation or enhancement of Good Review Practices (GRevP) stepwise in each interested APEC economy by 2020
  - To enhance mutual trust for regulatory convergence among economies

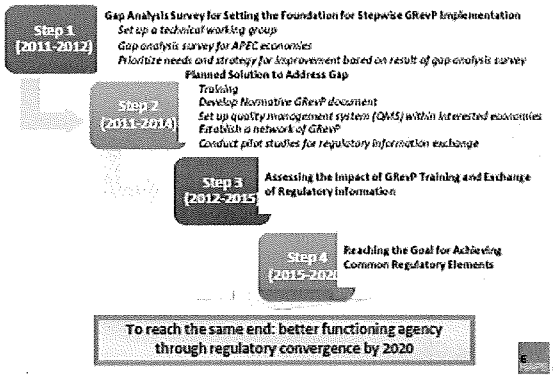
Background and Challenges (1)

- There is no single definition of Good Review Practices (GRevP). A GRevP definition in the draft guideline:
  - GRevPs are documented best practices for any aspect related to the process, format, content and management of a medical product review.
- Challenges:
  - Various economies have different levels of sophistication and approach of GRevP.
  - The rapid development of innovative medical products poses uncertainties in risk and benefit consideration.

Background and Challenges (2)

- Implementation of GRevP is important in enhancing domestic regulatory performance and regulatory convergence among different economies.
- In order to allow early access of innovative medical products by patients across borders, it is imperative to set up GRevP via this roadmap.

Specific Activities and Timeframe



To reach the same end: better functioning agency through regulatory convergence by 2020

Step 1 (2011-2012)

Gap Analysis Survey for Setting the Foundation for Stepwise GRevP Implementation

- Set up a technical working group
- Gap analysis survey for APEC economies
- Prioritize needs and strategies for improvement based on the result of the gap analysis survey

Step 2 (2011-2014)

Planned Solution to Address Gap

- Training
  - kick-off, basic and advanced training workshop
  - annual curriculum or e-learning
- **Develop Normative GRevP document**
  - working definition, essential elements, suggested strategies and approaches for implementation or enhancements in various resource setting, metrics, competency-based training and assessment for the effect of implementation

Step 2 (2011-2014)

Planned Solution to Address Gap *(continued)*

- Set up quality management system (QMS) within interested economies
- Establish a network of GRevP
- Conduct pilot studies for regulatory information exchange

Step 3 (2012-2015)

Assessing the Impact of GRevP Training and Exchange of Regulatory Information

- The effect of the trainings should be evaluated for the status of implementing relevant guidelines.
  - Repeat similar gap analysis survey of 2011
  - Develop qualitative/quantitative indicators in a self-assessment
  - Present results and invite comments

Step 4 (2015-2020)

Reaching the Goal for Achieving Common Regulatory Elements

- Update and revise training program based on the results of assessment in Step 3.
- Recommendations for further alignment of regulatory activities
- Reach the goal of GRevP via regulatory partnership

Performance Indicators (1)

Roadmap Outputs:

- Basic and advanced training workshops and a formal annual curriculum or e-learning targeting on training of regulators
- Related documents based on each step of the roadmap, including gap analysis survey reports, final assessment survey report, progress reports and normative GRevP document
- Final assessment report on the impact of this roadmap in promoting GRevP and exchange of regulatory information

Measurable Outcomes:

Reviewer Competency and Training

- Implementation of technical training programs and soft skills training

Performance Indicators (2)

Use of Templates and Procedures

- Number of SOPs and templates available
- Degree of adherence required for following SOP

Transparency, Consistency, Predictability and Timeliness

- Number/Type of information accessible by public online
- Involvement of stakeholders
- Establish checkpoints and set target timelines for review, and determine how many reviews have met these targets
- Adoption of peer review
- Establishment of a quality system

Accomplishments

- **Gap analysis survey (2011-2012)**
  - Complete a survey of APEC member economies on the implementation of GRevP in collaboration with Centre for Innovation in Regulatory Science (CIRS).
- **Workshops (2011-2012)**
  - Basic and Advanced Good Review Practices Workshops were held in Taiwan in 2011 and 2012.
- **WHO GRevP Guidelines (2013-2014)**
  - A draft Good Review Practices Guidelines for Regulatory Authorities was completed by the APEC RHSC GRevP Working Group and submitted to WHO for comments and discussion in the WHO Expert Committees in October 2014.

Observations from the Survey

- Most NRAs would improve their GRevP through natural evolution and training/embedding
- All 14 NRAs felt the need for GRevP training by APEC especially on:
  - Using Assessment Frameworks
  - Good Review Practices
- 10 NRAs willing to share their NDA assessment templates with CIRS.
- Most NRAs consider it beneficial for better quality and efficiency in review.
- Some minor concerns need to be solved before exchange like confidentiality issues.

Basic GRevP Workshop (2011) Overview

Session A. The Basic
- Common understanding of the scope and key elements in GRevPs / Tools

Session B. The Details
- Knowledge and Skills
- Regulations and Procedures; Templates

Session C. Metrics
- Measurement, Stakeholder Feedback

Session D. Information Resources
- Peer review and external experts

Session E. Transparency & Information Sharing

Advanced GRevP Workshop (2012) Overview

Session A. Review of Findings from Basic GRevP Workshop

Session B. Quality System for Reviewers

Session C. Key Elements & Strategies of a Good Review

Session D. Critical Thinking & Decision Making

Session E/F. Transparency and Interactions

2012 APEC Advanced Workshop of Good Review Practice on Medical Products (Nov 6th-8th), New Taipei City, Taiwan: TFDA, 2012. Available at http://www.fda.gov.tw/EN/site.aspx?sid=3330

Draft Agenda for 8th Asia Regulatory Conference

– Advancing Best Practices for Regulatory Review and Submission in Asia

- Date: February 4-5, 2015
- Co-organizers: IFPMA, DIA, and TFDA
- **Day 1 Theme: Good Review Practices**
  - Session 1: Principles of Good Review Practice
  - Session 2: Co-operation, Convergence, Competencies & Capacity, and Communication in Managing the review
  - Session 3: Innovation in regulatory review practices
- **Day 2 Theme: Good Submission Practices**
  - Session 4: Industry perspective: Challenges and opportunities – multi-region simultaneous submission
  - Session 5: Evolving and establishing regulatory framework for multi-regional clinical trials
  - Session 6: Challenges & Opportunities: Regulatory convergence – path to minimize divergence of submissions in Asia

Future Perspectives

- To establish a network of GRevP
- To plan for an annual curriculum or e-learning courses for GRevP on medical products
- To evaluate the progress of the roadmap using performance indicators and update the training courses

Thank You for Your Attention.

RAPS REGULATORY AFFAIRS PROFESSIONALS SOCIETY
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Session Template

Part 1: Session Information

Please complete the following information.

SESSION TITLE: Enhancing Regulatory Efficiency through Good Review Practices (GRevP) and Good Submission Practices (GSP)

STATEMENT OF PURPOSE: GRevP are for regulators to strengthen the performance, predictability, and transparency of regulatory agencies and to enhance mutual trust for regulatory convergence, whereas GSP are the counterpart for industry to improve their submission quality for accelerated regulatory approval. A good submission from industry is indispensable for regulators to conduct a good review. Therefore, GRevP and GSP may complement each other. A common understanding of GRevP and GSP and their best practices are needed for the regulatory professional to improve the performance of regulatory agencies, facilitate early approval of innovative medical products, and reach the goal of regulatory convergence.

LEARNING OBJECTIVES: Upon completion of this session, participants should be able to:

1. Understand high level definitions, principles, and elements of GRevP and GSP, and why they are important,
2. Understand best practices on GRevP and how they may be applied within regulatory agencies, and
3. Understand best practices on GSP and how they may be applied within industry.

LEARNING LEVEL: Basic

PRODUCT COVERAGE: Pharmaceuticals, Medical Devices and/or IVDs, Biologics/Biotechnology, and Regulatory Business

GEOGRAPHIC COVERAGE: Global

FORMAT: Round table (45–60 minutes)
This is a structured discussion on a key learning topic or challenge in a small, focused group of colleagues. This type of session will be led by one or more senior learning executives, who will present a short overview of the key questions and then engage the

audience in an exploratory conversation. These are held in medium to smaller rooms in order to facilitate participation.

Panel discussion (60–90 minutes)
Led by a key industry leader, these sessions bring together several experts and colleagues with diverse experiences around a central theme or challenge.

Case study (60–90 minutes)
Problem-based session, where a situation is presented with specific examples and data, the situation is analyzed to determine what happened, and a well-thought-out solution or recommendation is made.

How-to session (60–90 minutes)
Pragmatic sessions that provide practical advice and suggested actions or steps to successfully implement and/or utilize strategies to execute the intended objective.

Debate (45–60 minutes)
These are sessions surrounding an area of controversy where two sides of an issue are presented.

Short-form conference presentation (15–20 minutes)
These are presentations given in an innovative and engaging way (e.g. careful use of images or illustrations rather than death by PowerPoint). They should be concise, informal and inspiring. These presentations may be grouped around common themes or topics depending on the responses received.

Part 2: Recommended Faculty

Identify appropriate experts to serve as session speakers. Please note that each session should contain a maximum of three faculty (including the session leader and speakers). It is also our goal to provide balance in the sessions (e.g. speakers from different companies, perspectives, etc.). Please note: If you would like to include a speaker from a health authority, official invitations and confirmations will be handled by RAPS.

SESSION LEADER:	Mike Ward, Health Canada, Mike.Ward@hc-sc.gc.ca, +1-613-952-6619
SPEAKER 1:	Li-Ling Liu, Taiwan Food and Drug Administration, LLL@fda.gov.tw, +886-2-2787-7400
SPEAKER 2:	Deborah L. Jansen, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, cberspeakerliaison@fda.hhs.gov (Deborah.Jansen@fda.hhs.gov), +1-240-402-8080
SPEAKER 3:	Caroline Vanneste, Health Canada, Caroline.Vanneste@hc-sc.gc.ca, +1-613- 957-6448
SPEAKER 4:	Toshihiko Tsunenari, Japan Pharmaceutical Manufacturers Association, tsunenari@jpma.or.jp, +81-(0)3-3241-0326

Working document QAS/14.576 Rev.1
August 2014
Document for comment

World Health Organization

Good review practices

guidelines for regulatory authorities

(August 2014)

DRAFT FOR COMMENT

Should you have any comments on the attached text, please send these to:
Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies, Standards and Norms, World Health Organization, 1211 Geneva 27, Switzerland; email: kopps@who.int; fax: (+41 22) 791 4730 (kopps@who.int) and to Ms Marie Gaspard (gaspardm@who.int), by 30 September 2014.

Working documents are sent out electronically and they will also be placed on the Medicines website for comment. If you do not already receive directly our draft guidelines please let us have your email address (to bonnyw@who.int) and we will add it to our electronic mailing

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Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies, Standards and Norms, Department of Essential Medicines and Health Products, World Health Organization, CH-1211 Geneva 27, Switzerland. Fax: (41-22) 791 4730; email: kopps@who.int.

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38 **SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/14.576**

39 **Good review practices guidelines for regulatory authorities**

40

	Date
Draft document endorsed by APEC Regulatory Harmonization Steering Committee (RHSC) for submission to WHO	21 February 2014
Accepted internally for parallel consultative processes for both the WHO Expert Committee on Specifications for Pharmaceutical Preparations and the WHO Expert Committee on Biological Standardization	21 February 2014
Draft mailed for comments	March 2014
Collation of comments	April-May 2014
Reviewed/revised in consultation with APEC	May-August 2014
Circulation for comments	August 2014
Collation of additional comments, if any	September 2014
Presentation to forty-ninth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations	13-17 October 2014
Further follow-up action as required	…

41

42

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

44

45 NMRAs from:

46 Australia, Canada, Japan, Korea, Saudi Arabia, Singapore, Chinese Taipei, USA;

47

48 and the pharmaceutical industry: CIRS, FDAAA and Med Dev

49

Draft for comment

CONTENTS

Draft for comment

79 **Good review practices guidelines for regulatory authorities**
80
81
82 # 1. INTRODUCTION
83
84 ## 1.1 Document objective
85
86 The objective of this document is to provide high level guidance on good review practice (GRevP)
87 principles and processes, for use across a range of regulatory authority (RA) maturities. It is not intended
88 to provide detailed instruction on how to conduct a scientific review.
89
90 This document is envisioned as one building block in a set of tools and is sufficiently expandable to
91 accommodate additional annexes or ancillary documents in the future.
92
93 ## 1.2 Context
94
95 RAs are increasingly seeking ways to improve their performance and ensure the quality of their
96 regulatory systems. GRevPs are an integral part of overall good regulatory practices and focus on the
97 medical product review aspect of regulatory work. Review is a highly complex, multidisciplinary
98 assessment of the medical product applications in meeting scientific and evidentiary standards for safety,
99 efficacy[1] and quality. It forms the scientific foundation for regulatory decisions.
100
101 The extent to which an RA can achieve review timeliness (i.e. completion within specified time frames),
102 predictability, consistency, transparency, clarity, efficiency and high quality, can have significant impact
103 on public health (for example, in relation to patient access to important medical products, and costs to
104 both government and applicants). Implementation of GRevPs helps to achieve these outcomes by
105 ensuring that those involved in the review process have the critical thinking skills and tools needed to
106 optimize scientifically sound, evidence-based decisions. It also facilitates progress towards regulatory
107 convergence through the exchange of review reports and the enhancement of mutual understanding
108 among RAs.

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

Draft for comment

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 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), 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 and quality data in medical product applications filed with RAs for marketing authorization.

Although this document was written for pharmaceutical and biological drugs 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 lifecycle from investigational testing to new product applications, updates or variations to existing marketing authorizations and maintenance of the product.

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2. PRINCIPLES OF A GOOD REVIEW

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

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 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.

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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. It includes timely communication and consultation with applicants, internal stakeholders, and as needed, external stakeholders with 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 involved parties 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.

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

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within the RA and clearly-defined work instructions for the reviewers, 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 complete and 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

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.

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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).

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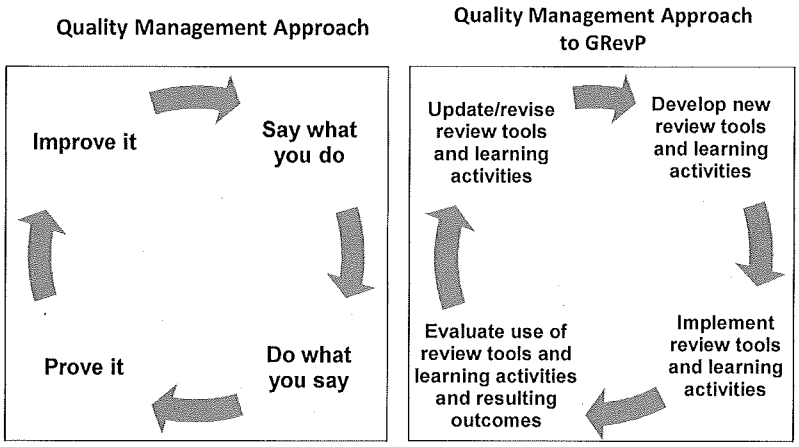
Quality Management Cycle



Say what you do

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

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 from meetings and teleconferences, memoranda, letters and reports.

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.

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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 with other authorities, the public and applicants and impact analysis on public health.
- Implement new and improved work practices, latest evaluation techniques, and scientific and technological advancements.

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 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, checklists) can describe in detail how a particular procedure is performed or give advice in handling a specific situation when performing the procedure.

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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. 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 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, available resources, increased application volumes, collaborative work-sharing, national laws and regulations, etc.

3.4 Review process stages

Two key stages in the process of reviewing medical product applications are validation[2] and scientific review. The validation stage occurs before the scientific review with the aim of ensuring completeness of the application, in order to subsequently facilitate the scientific review.

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 missing information in the application prior to scientific review enables the RA to avoid spending time and review resources on an application

[2] Although screening is also a term sometimes used, validation is used throughout the document.

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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 target time frames, guidelines, requirements 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, 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 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 organizational units within the RA, such as pre- and post-marketing scientific disciplines, pharmacovigilance, inspection and others.

Therefore, good communication will improve efficiency. Promoting 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, is desirable. Beyond establishing meetings, fora and other vehicles for idea exchange 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.

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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 communications 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 from other RAs' public websites, such as guidelines, application decisions and product recalls for safety;
- Using information from other RAs, such as review reports and certificates of pharmaceutical product;
- Actively sharing information between RAs, such as non-clinical, clinical, and inspection findings, during an application review;
- Actively working with other RAs, such as 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 leverage 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.

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.

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RA communication with 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 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.

Procedures for 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 post-market.

4.4 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 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. 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 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.

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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 refers to defining policies and procedures in writing and 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 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. Providing the public with the opportunity to comment on guidelines and proposed regulations and requirements, permits enhanced content and feasibility. 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.

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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 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.

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For on the job training, a site visit programme which 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.

5.2 Critical thinking

Critical thinking requires an objective and systematic approach to analysing 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.

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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 setting and communicating review time frames, 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

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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 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 gain efficiencies and improve the quality of the review through leveraging other RAs' reviews and/or decisions in appropriate situations. When considering another RA's action, it is important to understand differences in the product (for example, formulation or final container presentation) and any differences in 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, 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 focus on available information that may be clinically relevant to the RA's population now being considered. Such information could include: identification of potential differences in genotypes and phenotypes, disease manifestation, and comparison of available alternatives and medical practice to both the application's study population and the population of another RA that has already rendered a decision about the application.

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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 issues would likely relate to product safety, efficacy or quality. Respective 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 endpoint 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. If problems are identified early, reviewers can formulate an in-depth plan to first review data of greatest relevance 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. While a multidisciplinary team will provide broader expertise, in some cases an application may be assigned to a single reviewer. In the latter case, use of 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 form a conclusion. In other models, the review is completed on the information submitted and a list of

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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 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, judgment may vary from within and among RAs. Evidence-based and 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

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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. GLOSSARY

Application: The information provided by the applicant to the RA for evidence-based review and marketing authorization decision. (Different from WHO definition).

Applicant (WHO definition (3) modified to 'medical' product): 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.

Good Regulatory Practices (GRP): Reference definition in WHO GRP Guideline (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. 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), 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 on an ongoing basis.

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Marketing Authorization (WHO definition (6) modified to 'medical' products. Also referred to as product licence or registration certificate): A legal document issued by the competent medicines regulatory authority 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): Describe the important GRevP elements for RAs to implement in order to achieve successful review outcomes.

Project Management (for the review process): The planning, organizing and resourcing to achieve a complete and high quality review of an application within a specified time frame.

Quality Management (QM) (WHO definition): The coordinated activities that direct and control an organization with regard to quality.

Quality Management (QM) System (WHO definition (1)): 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. (Based on WHO definition (1) for 'drug regulatory authority' with 'national' removed and 'medical' used instead of 'pharmaceutical' products).

Regulatory Convergence (APEC Regulatory Harmonization Steering Committee (RHSC) definition): Represents 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 guidances, standards and best practices.

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Review: A highly complex, multidisciplinary assessment of medical product applications in meeting 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 Personnel Capacity: In addition to having a sufficient amount of scientifically trained review personnel (RA staff and/or external experts free of conflicts of interest), capacity also considers the core competencies for personnel involved in the various aspects of managing and conducting reviews. These core competencies encompass the knowledge, skills, abilities and attitudes of review personnel.

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) (WHO definition (4)): An authorized written procedure giving instructions for performing operations (both general and specific).

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

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