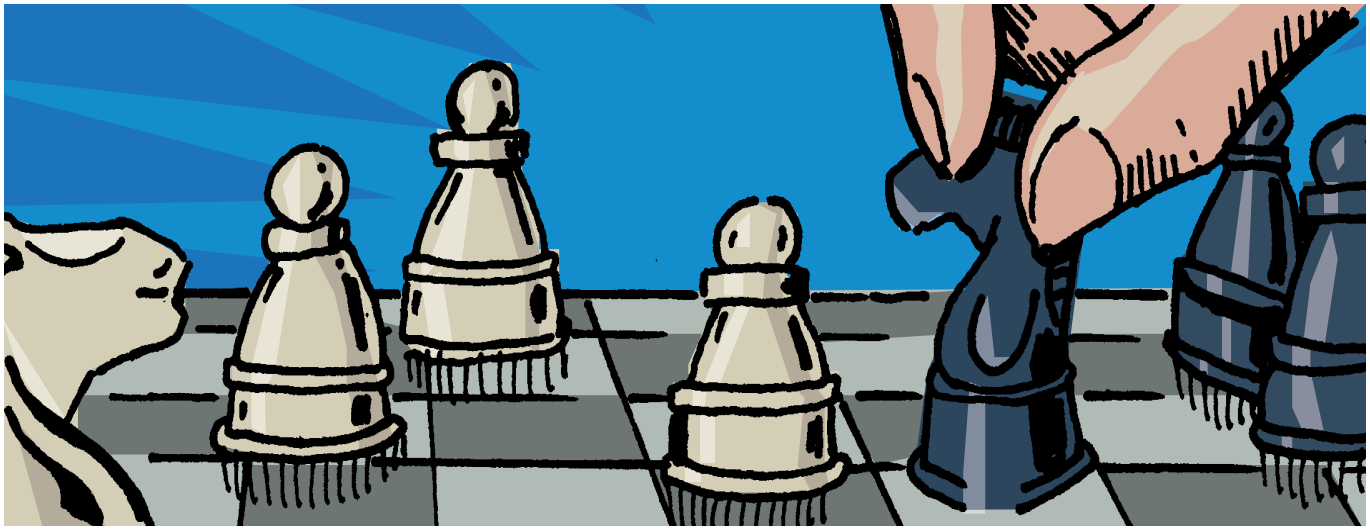


REGULATORY REVIEW – HOW DO AGENCIES ENSURE THE QUALITY OF THE DECISION?

The role of decision frameworks in the review of new medicines: What are the challenges and solutions that can facilitate agencies to make quality decisions?

24-25 JANUARY 2013
BEIJING, CHINA

WORKSHOP REPORT

CIRS Centre for Innovation in Regulatory Science

Workshop report authors

Lawrence Liberti, MSc, RPh, RAC

Neil McAuslane, PhD

Prisha Patel, MSc

Patricia Connelly, BA, ELS

CIRS - The Centre for Innovation in Regulatory Science - is a neutral, independent UK-based subsidiary company, forming part of the Intellectual Property and Science business of Thomson Reuters. The mission of CIRS is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. It is governed and operated for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards and its funding is derived from membership dues, related activities and grants.

Centre for Innovation in Regulatory Science (CIRS)
The Johnson Building, 77 Hatton Garden, London, EC1N8JS, UK

Email: cirs@cirsci.org

Website: www.cirsci.org

Report date: August 2013

Section 1: Executive Summary

Background to the Workshop

It is well established that the elements of a good-quality review are clarity, transparency, predictability and timeliness and that it is important that the process that an agency undertakes, whether to review a new medicine or carry out its daily activities, is both efficient and effective. This viewpoint has been embedded in most agencies with the adoption of Good Review and Good Review Management Practices. However, whilst it is possible to identify the processes that agencies have set up to enable them to ensure that a science-driven review is undertaken, these processes need to be built around good decision frameworks. Although decision frameworks may be less well articulated in evolving regulatory agencies, they are equally important to ensure good-quality decision making.

It should also be recognised that decision-making processes within agencies are guided by the legislative or regulatory frameworks in force in their jurisdiction. Moreover, it has been suggested that the quality of the review and quality of decision making are two distinct aspects, although the former should facilitate the latter.[1] Indeed, one of the questions being asked by agencies is how to ensure that they are not only undertaking a good-quality review process but that they are also making a good-quality regulatory decision.

It may be considered that one way to gauge the quality of regulatory decisions is to plot the outcome and consequences of those decisions. However, it is often impractical to measure these consequences, they may be subject to varied interpretation among stakeholders and in fact, a good decision may have poor consequences and a bad decision may result in good outcomes. Therefore, there is a need to ensure that the decision frameworks within an agency are structured so as to enable consistent, good-quality decisions.

The science of decision making is well established and a number of common features have been identified that characterise good-quality decisions such as a good decision framework; creative doable options; meaningful, reliable information; clear values and tradeoffs; logically correct reasoning; and a commitment to action.[2] However, methods for building these qualities into the regulatory decision process remain to be elucidated. Moreover, although international work is being undertaken to ensure that there is an acceptable and established framework for the benefit-risk component of decision processes, the challenges within agencies to ensure that quality decisions are being made across all aspects of the dossier review remain to be addressed. It is, therefore, important that the decision processes within an agency — from the processes used by the individual reviewer through to the final decision maker — are well understood and characterised.

Workshop Objectives

- **Identify the different decision-making frameworks** used by sponsors and agencies
- **Understand the challenges** for organisations in making quality decisions
- **Discuss and make recommendations** for activities and processes that sponsors and agencies can consider to enable quality decision making

Opening remarks

As the country with the largest population in the world and the third largest pharmaceutical market, China plays a critical role in the global supply chain for drug products, producing not only active pharmaceutical ingredients but also finished products for the world market. In addition, Chinese scientists and researchers actively participate in global R&D activities for many diseases with unmet medical needs and make important contributions to global health. In his Opening Remarks for the Workshop, **Dr. YIN Li**, *Commissioner, State Food and Drug Administration (SFDA), P.R. China* said that China has made a rapid progress in the past decades; it has already benefited and will continue to gain more from economic growth and healthcare reform and the current goal of the SFDA (now known as the China Food and Drug Administration; CFDA) is clear: to make science-based decisions to provide safe and effective drugs for the public. He concluded his keynote speech with a call to action, quoting an old

saying: "Knowing is not enough, we must apply. Willing is not enough, we must do."

Introduction

Day 1 Co-Chair, Prof Robert Peterson, *Executive Director, Drug Safety and Effectiveness Network, Canadian Institutes of Health Research* welcomed global regulatory representatives from 11 countries, the European Medicines Agency (EMA) and the World Health Organization (WHO) and representatives from 18 multinational pharmaceutical companies to the annual CIRS Emerging Markets Workshop to explore the enablers of quality decision making.

CIRS Executive Director, **Lawrence Liberti** informed participants that this international forum was the result of a recommendation made during the 2012 CIRS Emerging Markets Workshop in Kuala Lumpur, Malaysia and culminated a year of close collaboration with colleagues at the Chinese Center for Drug Evaluation (CDE) to provide this opportunity to explore the diverse elements that enable quality decision making by both regulatory authorities and developers of medicine.

Key points from presentations

SESSION: GOOD REVIEW PRACTICES: PROCESSES THAT UNDERPIN GOOD DECISION MAKING

The CDE has undergone significant changes in the past several decades and by 2011 had developed Review Principles and Procedures, adopted Good Review Practices (GRevP) and set up review processes for investigational new drugs, new drugs and abbreviated new drug applications. **FENG Yi**, *Associate Center Director, CDE, SFDA, Beijing, China*, detailed other recent CDE achievements relevant to good review practice including enhanced communication with sponsors as well as the provision of publicly available regulatory review reports, the assignment of priority review status to new drug applications, the development of a clinical trial registration system, enhancements to the CDE website, the opening of advisory committee meetings to the public and an effort to reduce review times.

Advantages to having a good review practices system in place include acceptance and a basis for understanding outcomes by the review community, enabling consistent approach to reviews that enhances both predictability and timeliness. **Barbara Sabourin**, *Director General Therapeutic Products Directorate, Health Canada* also cited the ability of GRevPs to aid in dispute resolution because of the consistent approach to analysis that they provide as well as their function as a mechanism to institute continuous process improvement. However, a dedicated, experienced, enthusiastic champion is needed to oversee the development and implementation of GRevPs and ongoing management support and the realisation of its importance as a key activity in the regulation of medicine are also required.

In a presentation of the industry perspective on good review practices, **Dr Joseph Scheeren**, *Head of Global Regulatory Affairs, Head of Global Development Asia, Bayer Healthcare Pharmaceuticals, China* indicated that in addition to timeliness, consistency, transparency and communication, benefit-risk decision making was a critical component of GRevP and in order to optimise benefit-risk decision making, industry needs for regulators to provide structure and transparency for sponsor-regulator alignment throughout the review process. Regulators should establish a clear set of processes and tools to guide decision making and develop metrics to assess benefit-risk profiles and identify the tools needed to facilitate the communication of decisions. In addition, clarity is required regarding the establishment of the relative importance or the weighting of different factors in the benefit-risk assessment and flexibility should be built into the assessment methodology to allow situational adaptation. Finally, a rational method to integrate qualitative and quantitative elements of benefit-risk assessment must be developed, which is then reflected in the product label.

Dr Churn-Shiouh Gau, *Executive Director, Center for Drug Evaluation, Chinese Taipei* provided an overview of the Asia Pacific Economic Cooperation project "Best Regulatory Practice for Medical Products: A Strategic Approach for Good Review Practice", initiated in 2010. As a first step in the project, CIRS conducted a gap analysis of GRevP among APEC economies in 2011. Results of the study indicated that a consistently defined GRevP code has been implemented either formally or informally by most of the surveyed APEC regulatory agencies. In addition, basic (2011) and advanced (2012) regulatory training workshops were also conducted as part of this programme. The future goals of the APEC GRevP project are to continue to refine GRevP scope, definitions, key elements, implementation approaches and methods and metrics for assessment.

Prof Stuart Walker, *Founder, Centre for Innovation in Regulatory Science* outlined the advantages to using a structured framework for decision making in the development and regulation of new medicines, including enhancement of the objectivity and transparency of the decision-making process and a "paper trail" for tracking the process thereby providing greater accountability for the decision. It allows industry to evaluate the benefit-risk data for new products before submitting an application in order to identify areas where data may need to be strengthened or clarified and permits an assessment of the consistency of regulatory decisions on marketing authorisation applications in order to learn from past experience.

The framework specific for benefit-risk assessment, which is a potential tool to aid in fulfilling the evolving expectations from stakeholders on regulatory decisions has been a recognised area for enhancement. Accordingly, Singapore, Canada, Australia and Switzerland sought the assistance of CIRS for the development of a standardised systematic approach to benefit-risk evaluation that would facilitate an understanding of respective decision processes. **James Leong**, *Senior Regulatory Specialist, Health Sciences Authority, Singapore* explained that this group, known as the Consortium on Benefit-Risk Assessment (COBRA) recently piloted the use of a benefit-risk template, which is a tool for documenting contributing factors, showing the progressive logic and basis of benefit-risk decisions. The template correlates to and is supported by the Unified Methodologies for Benefit Risk Assessment (UMBRA) eight-step framework, which provides the fundamentals and the principals for making benefit-risk decisions.

Multiple rounds of regulatory review can be avoided through an alignment of internal sponsor assumptions with those of regulators. **Dr Mark Goldberger**, *Divisional Vice President, Regulatory Policy and Intelligence, AbbVie, USA* outlined the issues that the alignments should cover such as expected efficacy and safety profiles, a development programme that supports desired labelling, the incremental value of additional studies and the suitability of proposed risk management strategies to address the likely and potential benefit-risk profiles and whether better "targeting" of a proposed patient population might improve the benefit-risk profile.

SESSION: REGULATORY REVIEW – WHAT ARE THE KEY ACTIVITIES THAT CAN INFLUENCE DECISIONS AND WHAT FRAMEWORKS ARE BEING USED TO ENSURE GOOD-QUALITY DECISIONS ARE MADE?

Day 1 Co-Chair Prof Hans-Georg Eichler, *Senior Medical Officer, EMA* introduced the session by hypothesising that although overregulation or poor decision making can have a deleterious effect on the value of medicine, good regulation, with its foundation in evidentiary standards increases the public health and economic value of new medicines.

Regulatory administration, evaluation and approval in Korea are conducted in accordance with the Korean Pharmaceutical Affairs Act (PAA). **Dr Won Shin**, *Division of Gastroenterology and Metabolism Products, Korea Food and Drug Administration* explained that the KDFA (now known as the Ministry of Food and Drug Safety (MFDS) also uses various review templates and follows standard operating procedures and approximately 100 guidelines for good review practices, which provide for the standardisation and documentation of process, format, content and the management of product reviews. In addition, because good-quality decisions are based on good-quality reviews, the KDFA has a rich educational programme for its reviewers, which consists of more than 100 hours of training per year on key aspects of a good review.

Dra Lucky S. Slamet, *Head of National Agency of Drug and Food Control (NADFC), Republic of Indonesia* described the decision-making pathways with the NADFC and presented two examples of the use of scientific information as the basis of regulatory decisions in Indonesia. In the first case, although an HPV vaccine was approved in Australia for patients from 10 to 45 years of age and the EMA approval was granted with no upward limit on age, the NAFDC limited approval for use of the vaccine to patients 10 to 25 years of age, based on the clinical data that showed the best efficacy profile in this age group. In a second example, although the US FDA and the EMA granted approval to a tablet for emergency contraception within 120 hours of unprotected sexual intercourse or contraceptive failure, the NADFC approval limited the indication for use within 72 hours based on the clinical study data that the agency believed demonstrated that the product significantly lowered the observed pregnancy rate when administered within 72 hours after unprotected intercourse but efficacy within 72-

120 hours had not been confirmed.

A comprehensive review procedure that includes the use of templates and instructions for their use and a clear benefit-risk assessment tool are essential requirements for good regulatory decision making. Standard operating procedures and guidelines support a well-defined decision structure; however, there are additional requirements as outlined by **Prof Tomas Salmonson**, *Chair, Committee for Medical Products for Human Use (CHMP) Director, Medical Products Agency, Sweden*. It is also important that regulators, particularly novice assessors, should have a clear and common understanding of their role. That is, it is important to recognise that the primary function of regulators is not to prevent marketing through labelling restrictions or to consider the financial aspects of new medicines but to function as true patient representatives, determining the most appropriate use of new medicines for a population. For this reason it may be necessary to obtain more patient input to develop that perspective. Finally, it is vital that regulatory agencies foster the scientific environment that will encourage the open professional dialogue essential to quality decision making.

At GSK, the day-to-day progression of a product under development is undertaken by a multi-disciplinary project team that draws experts from different functional groups within the pharmaceutical company. **Dr Paul Huckle**, *Chief Regulatory Officer, GlaxoSmithKline* detailed the complete governance process for new medicines at GSK, in which multiple senior-level reviews that include the Chief Medical Officer, Chief Product Quality Officer and Chief Regulatory Officer, ensure that the quality, safety and efficacy of new products are evaluated thoroughly and objectively and that the correct decisions are being made from a company and societal perspective throughout a product's life cycle.

Regulatory dossier review and the subsequent decision making is a highly complex process involving many people who care deeply about what they are doing and who feel intensely the responsibilities they have undertaken and the potential consequences of their opinions and decisions. Reviewers may see issues through their own lenses of knowledge, experience and feelings, making differences of opinion in regulatory agencies inevitable and ultimately, a positive thing. **Dr Murray M. Lumpkin**, *Commissioner's Senior Advisor and Representative for Global Issues, US Food and Drug Administration (FDA)* explained that dispute resolution, if required within the FDA, is typically informal and in most cases, alignment or agreement is achieved through discussions as reviews proceed. However, formal and informal processes are in place that provide a mechanism for appeal for individuals with dissenting opinions regarding regulatory decisions that they feel will have a serious impact on public health.

Regulators, who are expected to maintain the highest level of knowledge and expertise in their field, often require expert assistance as the complexity of science and medicine continues to grow. **Prof Bruno Flamion**, *Past Chair, Scientific Advice Working Party of the CHMP and Committee for Reimbursement of Medicines, Belgium; Professor of Physiology & Pharmacology, University of Namur, Belgium* discussed EMA and US FDA use of expert advisors in this regard, cautioning that this advice requires that potential conflicts of interest be dealt with in a consistent way. The EMA's mix of internal and external expertise at various stages of the procedures is an interesting model for consideration but like all models, the cost-effectiveness of obtaining external advice must be seriously evaluated.

In her discussion of the use of external experts in the regulatory review process in Malaysia, **Noorizam Ibrahim**, *Deputy Director, National Pharmaceutical Control Bureau* explained that external reviews of safety and efficacy are performed by clinical experts in relevant disciplines appointed by an Advisory Committee in the Ministry of Health, with feedback from relevant associations. These assessments and recommendations to approve, not approve or approve with limitations along with the recommendations of the National Pharmaceutical Control Bureaus (NPCB) Product Evaluation Committee, are an integral part of the evaluation and final decision rendered by the Malaysia Drug Control Authority (DCA).

Although there is a need for transparency and a better understanding of scope regarding how regulatory agencies might share information, companies could benefit from an appropriate process, including the promotion of mutual understanding of data through scientific discussions and data interpretations. In addition, differences based on legal frameworks and issues of geographic relevance versus those of judgement could be clarified and savings in time and resources realised through the elimination of duplicative or non-productive efforts across jurisdictions. **Dr Florence Houn**, *VP, Regulatory*

Policy and Strategy, Celgene Corporation also cited the capacity-building potential for regulatory agencies that may be associated with activities such as shared inspections.

SESSION: HOW SHOULD AGENCIES ENSURE THE QUALITY OF THEIR DECISIONS?

Day 2 Chair, Prof Sir Alasdair Breckenridge, *Former Chairman, Medicines and Healthcare products Regulatory Agency, UK*, introduced the Workshop Syndicate Rapporteurs who presented summaries of the discussions in their groups on three topics: *What are the key elements of the review for which decision frameworks are required - both from an agency and company perspective*; *Communication between companies and agencies: How can this aid both quality of the submission and quality of the final approval decision?* and *What role does external stakeholder input have to enable high-quality decision making?*

Dr Peng Wang, *Chief Scientific Officer, Simcere*, provided an industry perspective on regulatory review in China, saying that the Chinese CDE follows principles of scientific review and openness and former gaps in filing requirements and review capability are being closed. Among recent enhancements, the agency has begun to publish review summaries and has established a standard operating procedure for managing meetings with sponsors. The review process, however, remains lengthy and some administrative steps such as certificate preparation should be simplified or expedited and there remains opportunity for better and more effective communication among stakeholders.

Because health systems increasingly depend on the availability of safe, quality health products such as medicines, vaccines and medical devices, the WHO actively promotes good governance and transparency in the pharmaceutical sector and promotes and facilitates building up national regulatory systems as part of overall strengthening of health systems toward the goal of universal health coverage. **Lembit Rägo**, *Coordinator, Quality Assurance and Safety: Medicines, Essential Medicines and Health Products Health Systems and Innovation, World Health Organization, Switzerland* explained that WHO has performed 61 assessments of 55 national regulatory systems and facilitates information exchange and work sharing and various training courses and capacity building among regulatory agencies through such organisations as the Pan American Network for Drug Regulatory Harmonization and the International Conference of Drug Regulatory Authorities .

Transparency of process and decisions that are made is an important element of information exchange and according to **Prof Steffen Thirstrup**, *Director of Licensing Division, Danish Health and Medicines Authority*, transparency to sponsors is provided by the CHMP of the EMA by the sharing of assessment reports at each step of the evaluation, the provision of the final list of questions and possible clarification meetings with the Rapporteurs. Regulatory transparency to other stakeholders is ensured by the publication of the European Product Assessment Report (EPAR), which contains the final Assessment Report provided to sponsors without the confidential information and which communicates the decision-making process for that product. However, the volume of information contained in the documents can present a challenge for both the regulator and applicant and transparency regarding potential conflicts of interest for CHMP reviewers and the accessibility of clinical data to all users have been identified as potential areas for improvement.

The Workshop concluded with a presentation by **ZHANG Peipei**, *Center Director, CDE , SFDA, PR China* who described the ongoing evolution of the Chinese CDE of the State Food and Drug Administration, a young and growing agency currently facing many challenges and opportunities. Dr Zhang detailed planned and ongoing strategies to implement regulatory science throughout the assessment process, workforce development, partnerships and international cooperation that will assist the agency in their efforts to fulfil their vision to become an agency of international standards based on the values of openness, innovation, trust, evidence and impartiality.

References

1. McAuslane N, Patel P, Liberti, L, Connelly P. *Evolving the regulatory review process: What are the features that enable a transparent, timely, predictable and good-quality review?* Workshop report, 6-7 December, Kuala Lumpur, Malaysia. Available at http://cirsci.org/sites/default/files/CIRS_December_2011_WS_Report.pdf. Accessed July 2013.
2. McAuslane N, Liberti L, Connelly P. *Regional alignment in Asia Pacific: What needs to be in the regulatory science "toolkit" to enable good regulatory decision making?* Workshop report, 26-27 January 2011, Tokyo, Japan. Available at http://cirsci.org/sites/default/files/January_%202011%20Workshop_070711_lowres.pdf. Accessed July 2013

Recommendations from across the Syndicates

- A *decision framework* should be defined as a structured, flexible, systematic and scientific approach to organising, evaluating, quality assuring, summarising and re-assessing over time both the known and the unknown information and the subjective values and judgements that form the basis of the decision. This leads to high-quality transparent life cycle decisions being made, documented and communicated irrespective of the legal or regulatory framework applicable to the product under consideration.
- Key attributes for trusted decisions should include: structure, clarity and consistency; clear roles and responsibilities; efficiency and effectiveness; acknowledgement of constraints, biases and context; transparency; considers impact; helps range of stakeholders.
- Decision frameworks should be used at the common time points of a standard regulatory review; that is, at the time of the acceptance of the file, the outcome of primary scientific assessment and the review of the scientific assessment by managers and external committees, when needed for conflict resolution, when scientific questions or answers are received from sponsors, patients or healthcare providers, when the benefit-risk decision is rendered and at the time a decision is made to approve or reject the application. In addition, decision frameworks could and should be applied across agencies and through all phases of product development, during which time data that are available for decision making and consequently, the decisions themselves will vary.
- For pre-submission meetings or discussions between regulatory agencies and industry, industry should
  - Be better prepared for these meeting, including having a clear objective
  - Ensure the quality, clarity and transparency of communication
  - Consider inviting a topic expert since affiliate representatives sometimes do not have adequate expertise
  - And working with agencies where needed, develop a guideline for the format of these meetings that defines their scope.
- For meetings or discussions between regulatory agencies and industry during the review process, agencies should
  - Consider adopting the concept of Project Manager.
- For labelling meetings or discussions between regulatory agencies and industry
  - Agencies should work within a timeframe to perform a quality label review and provide appropriate time for sponsors to prepare complete responses to information requests regarding labelling issues.
  - Industry should submit reference-annotated labelling to facilitate the review.
- For post-decision meetings between regulatory agencies and industry, agencies should
  - Create an opportunity for discussion in which reviewing teams can provide feedback to a company on the quality of the application.
  - Make their decision documents available on the web in an appropriate form for public use.
- Inform physicians, patients and other external experts of the way in which their advice and opinions were utilised as well their impact on the final regulatory decision.
- Obtain individual patient input and the collective disease experience though systematic data collection using various methods such as public fora and proactive patient questions on a health authority website.
- Peer Health Authorities should develop an exchange programme to understand and learn from each other's standards and decision processes; work toward mutual recognition of selected dossier sections such as *Nonclinical, CMC* and *Statistical,* as well as mutual recognition of multinational generic regulatory reviews.

Workshop Programme

Day 1: 24 January 2013	
SESSION 1: GOOD REVIEW PRACTICES: PROCESSES THAT UNDERPIN GOOD DECISION MAKING	
Chairman's welcome and introduction	**Prof Robert Peterson**, *Executive Director, Drug Safety and Effectiveness Network, Canadian Institutes of Health Research*
Opening remarks	**Commissioner YIN Li**, *State Food and Drug Administration, P.R. China*
Framing the workshop: CIRS introduction	**Lawrence Liberti**, *Executive Director, Centre for Innovation in Regulatory Science*
Keynote: The Center for Drug Evaluation and the role of Good Review Practice in underpinning a quality review process within CDE	**FENG Yi**, *Associate Center Director, Center for Drug Evaluation, SFDA, P.R. China*
How does Good Review Practice become embedded within an agency's philosophy and culture and what are the advantages both internally and externally?	**Barbara Sabourin**, *Director General, Therapeutic Products Directorate, Health Canada*
Good Review Practices: What does this mean to companies, how important is it and what assurances does it give about the decision making?	**Dr Joseph Scheeren**, *Head of Global Regulatory Affairs, Head of Global Development Asia, Bayer Healthcare Pharmaceuticals, China*
APEC Best Practice Project: What are the ambitions of this project and how will this increase the competency for Good Review Practices across APEC?	**Dr Churn-Shiouh Gau**, *Executive Director, Center for Drug Evaluation, Chinese Taipei*
Good Decision-Making Practice: What role do frameworks have in ensuring a good decision and what aspects need to be considered?	**Prof Stuart Walker**, *Founder, Centre for Innovation in Regulatory Science, UK*
Benefit-Risk decision making: An example of how the use of a decision framework can improve regulatory decision making	
Regulatory Viewpoint	**James Leong**, *Senior Regulatory Specialist, Health Sciences Authority Singapore*
Industry Viewpoint	**Dr Mark Goldberger**, *Divisional Vice President, Regulatory Policy and Intelligence, AbbVie, USA*
SESSION 2: REGULATORY REVIEW: WHAT ARE THE KEY ACTIVITIES THAT CAN INFLUENCE DECISIONS AND WHAT FRAMEWORKS ARE BEING USED TO ENSURE GOOD-QUALITY DECISIONS ARE MADE?	
Chairman's introduction	**Prof Hans-Georg Eichler**, *Senior Medical Officer, European Medicines Agency*
Panel: Decision making within agencies - What are the key frameworks and process? Internal approaches	**Dr Won Shin**, *Division Director, Division of Gastroenterology and Metabolism Products, Department of Drug Evaluation, Korea Food and Drug Administration* **Dra Lucky Slamet**, *Head, National Agency of Drug and Food Control, Indonesia* **Prof Tomas Salmonson**, *Chair, CHMP, Director, Medical Products Agency, Sweden*

How are the decisions made to submit a new medicine within companies - What are the key frameworks and decision-making processes? Company viewpoint	**Dr Paul Huckle**, *Chief Regulatory Officer, GlaxoSmithKline, USA*
Dispute resolution – How are differences in opinion regarding data interpretation dealt within agencies and within companies? An agency approach	**Dr Murray Lumpkin**, *Commissioner's Senior Advisor and Representative for Global Issues, Food and Drug Administration, USA*
Use of advisory committees and external experts **Improving regulatory decision-making: What role do Scientific Advisory Committees play?**	**Prof Bruno Flamion**, *ast Chair, Scientific Advice Working Party of the CHMP and Committee for Reimbursement of Medicines, Belgium; Professor of Physiology & Pharmacology, University of Namur, Belgium*
Use of external experts as part of the review	**Noorizam Ibrahim**, *Deputy Director, National Pharmaceutical Control Bureau, Malaysia*
What do companies see as the benefits and the issues for agencies sharing information/work to help inform their own decision-making process? Company viewpoint	**Dr Florence Houn**, *Vice President Regulatory Policy and Strategy, Celgene, USA*

Day 2: 25 January 2013	
SESSION 3: HOW SHOULD AGENCIES ENSURE THE QUALITY OF THEIR DECISIONS?	
Chairman's introduction	**Prof Sir Alasdair Breckenridge**, *Chairman, Medicines and Healthcare products Regulatory Agency (MHRA), UK*
Introduction to the Syndicate Session	
Syndicate A topic: What are the key elements of the review for which decision frameworks are required - both from an agency and company perspective	
Chair	**Dr Murray Lumpkin**, *Commissioner's Senior Advisor and Representative for Global Issues, Food and Drug Administration, USA*
Rapporteur	**Chris Walker**, *Executive Director, Regulatory Affairs, Amgen, UK*
Syndicate B topic: Communication between companies and agencies: How can this aid both quality of the submission and quality of the final approval decision?	
Chair	**Dr Paul Huckle**, *Chief Regulatory Officer, GlaxoSmithKline, USA*
Rapporteur	**Leyla Lister-Mora**, *Head of Emerging and Regional Affiliates, F. Hoffmann-La Roche Ltd, Switzerland*
Syndicate C topic: What role does external stakeholder input have in enabling high-quality decision making?	
Chair	**Prof Hans-Georg Eichler**, *Senior Medical Officer, European Medicines Agency*
Rapporteur	**Sharon Olmstead**, *Global Head, Development and Regulatory Policy, Novartis, USA*

Panel viewpoint following syndicate discussion	
Company Representative: Local	**Dr Peng Wang**, *Chief Scientific Officer, Simcere Pharmaceutical Group, China*
Company Representative: MNC	**Dr Zili Li**, *Executive Director and Head of Emerging Market Regulatory Strategy Merck & Co, USA*
Agency 1	**Prof Thomas Salmonson**, *Chair, CHMP, Director, Medical Products Agency, Sweden*
Agency 2	**Dra Lucky Slamet**, *Head, National Agency of Drug and Food Control, Indonesia*
How the evolution of regulatory science supports training, alignment and regulatory convergence which can underpin GRevPs (quality, transparency, clarity, consistency, timeliness) and good decision-making practices?	**Dr Lembit Rägo**, *Coordinator, Quality Assurance and Safety: Medicines, Essential Medicines and Health Products Health Systems and Innovation, World Health Organization, Switzerland*
Transparency of decisions a key component of good decision-making practices – how good are agencies in communicating their decision to their stakeholders?	**Prof Steffen Thirstrup,** *Director of Licensing Division, Danish Health and Medicines Authority*
The Center for Drug Evaluation – what are the future challenges, opportunities and strategies to evolving the core competency and capacity of the CDE?	**ZHANG Peipei**, *Center Director, Center for Drug Evaluation, SFDA, P.R. China*

Section 2: Syndicate Discussions

Syndicate Discussion A

What are the key elements of the review for which decision frameworks are required from both an agency and company perspective?	
Chair	**Dr Murray Lumpkin**, *Commissioner's Senior Advisor and Representative for Global Issues, Food and Drug Administration, USA*
Rapporteur	**Chris Walker**, *Executive Director, Regulatory Affairs, Amgen, UK*

Background

A survey undertaken by CIRS in 2011 identified key areas that both agencies and companies believe can enable good-quality review and decision making. These included implementing such processes and procedures as detailed guidelines, target times, transparency around the summary basis of the decision and personnel training. One area that was seen by both companies and agencies as critical to ensuring good-quality decision making as well as enabling consistency and transparency within agencies was having clearly described decision frameworks. Both the submission to a regulatory agency and the review and approval of a new medicine have a number of aspects in which having a clear, well-articulated decision framework could be of value, for example, in communicating the rationale for the final benefit-risk decision.

All agencies have a similar mission; that is, the protection of patients and the improvement of the health of a nation through the use of best practices and processes: the reception of data, validation of the data set, scientific review, committee review, questions to sponsors, benefit-risk decisions for local populations and approval decisions governed by both science and legal mandate of the agency.

CIRS identified a common process for the submission and review of a dossier for this Syndicate group and asked the group to review the process and procedures and identify at which points within this context it would be useful to have decision frameworks and what their key elements would be.

The publication of the identification of situations in which decision frameworks could be of value and the development of their key elements would enable diverse agencies and companies to consider what would be of value for their own jurisdiction. It was also hoped that identifying the areas in the process where decision frameworks could be of value would also facilitate discussions and enable companies and agencies to improve the transparency and clarity of the expectations and decisions undertaken in the review and approval of a new medicine.

The objectives of this Syndicate group were to:

- Agree on a working/common definition of "Decision Framework" in the context of the regulatory review and approval process
- Suggest what should be the key elements of a decision framework
- Identify the key activities/areas of a review for which decision frameworks are required by agencies in the review of new medicines

Questions for consideration

Question 1: In the context of the review and approval process, how would the group define a decision framework? Please recommend a common or working definition.

Syndicate Response

The following definition was decided by this Syndicate for *decision framework*: A decision framework is a structured, flexible, systematic and scientific approach to organising, evaluating, quality assuring and summarising (and re-assessing over time) both the known and the unknown information and the subjective values and judgements that formed the basis of the decision. This leads to high-quality, transparent

life-cycle decisions being made, documented and communicated (irrespective of the legal or regulatory framework applicable to the product under consideration).

Question 2: What are the attributes of a good decision framework and what are the potential perceived benefits for establishing decision frameworks? Can the common elements be identified in what makes a good decision framework that will be accepted by all?

Syndicate Response

Figure 1 identifies the key attributes of a decision framework and the benefits of those attributes as agreed by this Syndicate:

Question 3. Which areas would benefit from the use of a formal decision framework and why?

Syndicate Response

The Syndicate agreed that the use of decision frameworks would be beneficial at the common time points of a standard regulatory review; that is, at the time of the acceptance of the file, the outcome of primary scientific assessment and the review of the scientific assessment by managers and external committees, when needed for conflict resolution, when scientific questions or answers are received from sponsors, patients or healthcare providers, when the benefit-risk decision is rendered and at the time a decision is made to approve or reject the application.

To this list of appropriate standard time points, the Syndicate also indicated that decision frameworks could and should be applied across agencies and indeed through all phases of product development, at which time multiple steps and decisions might be taken. Regulatory decisions occur along a continuum during which time data that are available for decision making and consequently, the decisions themselves will vary. Decisions themselves, however, will continue to be based around probabilities for effectiveness and harm.

Question 4: What are the critical success factors for the development and utilisation of decision frameworks and how could they be measured?

Syndicate Response

Syndicate A agreed that a decision framework must be flexible, that is, it should be applicable to a range of product types and innovative approaches without constraint. Quality assurance is an essential feature of decision making that is enhanced through both the peer-review process and the process of seeking external advice. These processes, which differ among agencies, can strengthen confidence in decision making. Once decisions have been made, it should be recognised that their communication may require a range of formats to accommodate the needs of all stakeholders, including patients, physicians, sponsors, legislators and peer reviewers.

It may not be immediately possible to accurately assess the quality of a decision regarding a product's profile in the post-approval period, since the evaluation should occur on an ongoing basis across the product life cycle as data and experience with a new product develop. A medicine's real-world effectiveness and safety are affected by both physician and patient behaviour, that is, in the appropriateness of prescriptions and patients' compliance with those prescriptions; these factors that are difficult to manage and predict during the initial regulatory review period. Decisions are also affected by global and national context, which can lead to divergent decisions across agencies. Despite these differences in context, the development of a consistency in approach is an important goal for decision making and the role of judgement and subjectivity in decisions should be explicit and transparent to all stakeholders. In addition, the variability in the probability of risks associated with new medicines must be acknowledged and managed.

Finally, innovations in medicine that are developed to fulfil important unmet medical

Figure 1. The attributes and benefits of a good decision framework.

Potential Attributes	Benefits
Structure , Clarity, Consistency	Allows comparison between decision in comparable situations/products and review/challenge of the decision by others
Clear Roles and Responsibilities	Clear decision makers and advisors/contributors, encompasses debate, a range of perspectives
Efficiency and Effectiveness	Timely, provides benefit to those in receipt of decision
Constraints, Biases and Context acknowledged	Identifies uncertainties, biases, limitations, subjectivity/ objectivity context and rationale of the decision or question being asked Human factor in decision making
Transparent	Allowing confidence with the decision and trust of the decision maker
Considers impact	Consider impact to a range of stakeholders, is forward looking and acknowledges the potential need to revisit decisions over the life cycle continuum
Helps range of stakeholders	Other reviewers, other agencies, sponsors, competitors, payers, physicians, patients, public citizens

needs present additional challenges to decision making. A lack of experience and increased unknown factors associated with these new medicines may require information-sharing partnerships between agencies and new development strategies between industry and regulators.

Recommendations

- A *decision framework* should be defined as a structured, flexible, systematic and scientific approach to organising, evaluating, quality assuring, summarising and re-assessing over time both the known and the unknown information and the subjective values and judgements that form the basis of the decision. This leads to high-quality transparent life cycle decisions being made, documented and communicated irrespective of the legal or regulatory framework applicable to the product under consideration.
- Key attributes for trusted decisions should include: structure, clarity and consistency; clear roles and responsibilities; efficiency and effectiveness; acknowledgement of constraints, biases and context; transparency; considers impact; helps range of stakeholders.
- Decision frameworks should be used at the common time points of a standard regulatory review; that is, at the time of the acceptance of the file, the outcome of primary scientific assessment and the review of the scientific assessment by managers and external committees, when needed for conflict resolution, when scientific questions or answers are received from sponsors, patients or healthcare providers, when the benefit-risk decision is rendered and at the time a decision is made to approve or reject the application. In addition, decision frameworks could and should be applied across agencies and through all phases of product development, during which time data that are available for decision making and consequently, the decisions themselves will vary.

Syndicate Discussion B

Communication between companies and agencies: How can this aid both quality of the submission and quality of the final approval decision?	
Chair	**Dr Paul Huckle**, *Chief Regulatory Officer, GlaxoSmithKline, USA*
Rapporteur	**Leyla Lister-Mora**, *Head of Emerging and Regional Affiliates, F. Hoffmann-La Roche Ltd, Switzerland*

Background

The decision to submit a dossier to a regulatory agency is a key decision for a company as it is the culmination of up to 10 to 14 years of work and over a $1 billion investment. The decision for an agency reviewing the dossier on whether to reject or approve the new medicine is also a critical decision not only for the company but also for patients and healthcare providers.

A survey undertaken by CIRS in 2011 identified key areas that both agencies and companies believe can enable a good quality review and decision making. One area that was seen by both companies and agencies as critical to enabling a good-quality review was the ability to have effective communications. However, agencies often note that one of the potential barriers to an effective and efficient review is the limited communication with companies during the review and the quality of the dossier submitted for review. Companies on the other hand note that the inability to get pre-submission advice from the agency or clarification of what the agency is requesting during the review can affect both the submission and provision of the right information to aid the agencies in their decision making.

CIRS asked this Syndicate group to specifically discuss communication between companies and agencies and how this can be utilised to enable good-quality decision making both by companies in the decision to submit a fit-for-purpose dossier and by agencies to undertake a good review. It should be recognised, however, that although agencies have some similarities in the data they receive and the key activities of a review, their organisation, resources and levels of communication with companies during both the development and review can differ vastly.

The Syndicate was asked to identify the critical success factors, inputs and internal factors that both companies and agencies need to consider to enhance communication between these two stakeholders and as such, to enable good-quality decision making.

The objectives of this Syndicate group were to

- Discuss the role and type of communication or interactions between companies and agencies that will be of value to both company and regulatory decision making itself, either directly or indirectly
- Identify which interactions or communications and timing between companies and agencies are of value during the development and review of a new medicine
- Discuss and make recommendations on appropriate routes and methods, critical considerations, and good communication practices for agencies and companies

This Syndicate outlined four different types of meetings or discussions between regulators and industry: pre-submission, review, post-approval and labelling. The group also identified associated issues with discussions during those time points and outlined recommendations to maximise the value of these interactions.

Critical issues for pre-submission meetings or discussions

At least three types of meetings are held between authorities and industry before the submission of a dossier for a new product: portfolio, product and informal. Some authorities mandate pre-submission meetings, while others highly recommend that they be held. Companies feel that pre-submission meetings are a platform where health authorities can share which additional data they may want to see included in applications, allowing industry to be better prepared at time of filing. Agencies meanwhile, regard pre-submission meetings as beneficial as they allow the early screening of applications. Furthermore, difference in EU and US dossiers may generate additional questions from regulatory agencies and these divergences can be addressed at pre-submission meetings.

Procedures for these meetings vary among the agencies and they may be of a formal or informal nature but it was the consensus of the group that informal communication may best suit general and administrative types of questions.

Recommendations for pre-submission meetings or discussions

- Industry should be better prepared for these meeting, including having a clear objective.
- Ensure the quality, clarity and transparency of communication.
- Consider inviting a topic expert since affiliate representatives sometimes do not have adequate expertise.
- Working with agencies where needed, develop a guideline for format of these meetings that defines their scope.

Critical issues for meetings or discussions during review

Industry often sees informal communication as helpful to clarify queries received. Agencies should initiate a formal meeting with a sponsor if an application poses a particular challenge or is deemed not approvable; companies should be able to have a discussion and appeal a negative decision.

Recommendations for meetings or discussions during review

- Agencies should consider adopting the concept of Project Manager.

Critical issues for post-decision meetings or discussions

Although it may be helpful for agencies to organise debrief meetings with an aim to improve performance of the review and interaction with industry, these may be precluded because of resource constraints. Some agencies, however, do have mechanisms in place that ask industry for feedback on a specific review. Likewise, companies could conduct de-brief meetings with agencies with an aim to improve their performance and can request to discuss a decision and appeal a negative outcome.

Recommendations for post-decision meetings or discussions

- Create an opportunity for discussion in which reviewing teams could provide feedback to a company on the quality of application.
- Agencies should make their decision documents available on the web in an appropriate format for public use.

Critical issues for labelling meetings or discussions

The timing for labelling discussions can have an impact on the outcome. Conducting these meetings early in the review is recommended as communicating major differences early during the review process allows sufficient time for discussion and agreement. In addition, many label decisions are made at non-regional headquarters and coordinating the receipt of comments from a particular jurisdiction with the specific response is a labour-intensive activity that can take several months to complete.

Using divergent reference country labels such as those from the EU and US as the basis for reviewing the company-proposed label may generate questions from other jurisdictions, especially where safety differences are of major concern. Sponsors should be prepared to address questions around labelling differences.

Recommendations for labelling meetings or discussions

- Agencies should work within a timeframe to perform a quality label review and provide appropriate time for sponsors to prepare complete responses to information requests regarding labelling issues.
- Industry should submit reference-annotated labelling to facilitate the review.

Syndicate Discussion C

What role does external stakeholder input have to enable high quality decision-making?	
Chair	**Prof Hans-Georg Eichler**, *Senior Medical Officer, European Medicines Agency*
Rapporteur	**Sharon Olmstead**, *Global Head, Development and Regulatory Policy, Novartis, USA*

Background

Communication and input from different stakeholders before and during the review of new medicines is seen as an area that has the potential to be beneficial to a company during development and to an agency in making good-quality decisions. This communication can range from having pre-submission dialogue with sponsors to ensure good-quality dossiers, through the use of experts, either individually or as part of a committee to ensure clarity of critical thinking by the review staff and advice on specific issues to ensure the right regulatory context. Indeed, there is growing interest in increasing patient input to better understand their needs and desires for benefits, as well as the risks they are willing to take so that the decision making within agencies is informed by the key stakeholders.

This Syndicate was tasked with the identification of external stakeholders, groups and individuals with whom agencies should consider interacting during the review, such as external experts, other agencies, patients, caregivers, healthcare professionals and the media. They were also requested to discuss the role of the external expert in aiding agencies to make good-quality decisions.

The objectives of this Syndicate were to discuss:

1. The role external stakeholders have in the review process with the focus on how input from external stakeholders can improve both the quality and regulatory decision making itself, either directly or indirectly
2. Which interactions and with whom are of value and the role external input from experts, patients and other stakeholders can play in aiding the review and decision making process
3. What the appropriate routes and methods for interactions are and what the critical considerations for agencies and external stakeholders should be in aiding agencies to improve the quality of their decision making

Although Syndicate C focussed on three groups of external stakeholders that might provide input for regulatory agencies: physician specialists, patients and peer regulatory authorities, other groups such as healthcare providers, social workers, payers, government and nongovernment agencies were also considered.

Input from physician experts, which can be received through standing advisory committees, one-time panels or from a pooled list of experts is important for agencies as this information provides context for the medicine being evaluated, especially as it applies to currently available therapies. Physicians are also able to provide a point of clinical reference and can summarise the experiences of their patients. Their participation can be mandated by regulatory agencies or used on an ad hoc basis. The group agreed that potential conflicts of interest for physicians providing input should be routinely made transparent.

Patient viewpoints can be obtained through open fora, websites, clinical trials and information collected by companies for weighting the benefits and risks of new medicines; however, information is generally received on an ad hoc basis and agencies would benefit from the development of a structured process for obtaining that input. Patients can inform regulators of the real-life experience of living with the disease to be treated by a new medicine. Although there was some disagreement within the Syndicate regarding the role that patients should play in regulatory decision making and although it was understood that agencies differ in the levels at which they are prepared to engage patients, there was consensus that patient participation in the process may lead to increased understanding and acceptance of regulatory decisions.

Regulatory authorities can turn to peer agencies for mutual recognition of certain dossier sections of identical regulatory packages. These interactions can lead to the ongoing building of

Key elements of quality external inputs into the review process.

	Physician specialist	Patients	Peer Regulators
Why	Provides context for treatment and clinical relevance Provides technical expertise in specialised areas Can summarise diverse patient experiences	Allows regulators to "feel the pain" Patients and other stakeholders can better understand regulatory decision-making by interacting with regulators* Lends legitimacy to decision making	Expands knowledge and/or expertise Learning opportunity Reduces misunderstanding of divergent decisions Resource optimisation
How	Standing advisory committee; ad hoc panel and experts Mandatory; guidance; or as needed	Open public forum Provide guidance as to weighting input Elicit patient views through website Via patients in clinical trials Through formally structured processes	Mutual recognition of reviews Joint or shared reviews Ongoing confidence building interactions (eg, collaborative training)

Figure 2. Methods and rational for external input into regulatory decision making.

* Others: national government agencies; healthcare providers: nurses, pharmacists, social workers; payers; caregivers; NGOs.

confidence in the processes and performance of other regulators; however, recognition and respect must be mutual. In addition to optimising the use of regulatory resources, these interactions can also be an opportunity for learning that can expand knowledge and expertise and reduce the political risk of different decisions by agencies on identical dossier submissions (Figure 2).

Recommendations

- Inform physicians, patients and other external experts of the way in which their advice and opinions were utilised as well their impact on the final regulatory decision.
- Obtain individual patient input and the collective disease experience though systematic data collection using various methods such as public fora and proactive patient questions on a health authority website.
- Peer Health Authorities should develop an exchange programme to understand and learn from each other's standards and decision processes; work toward mutual recognition of selected dossier sections such as *Nonclinical, CMC and Statistical*, as well as mutual recognition of multinational generic regulatory reviews.

Panel Discussion of Syndicate Results: Key points

Discussion Panel

- **Dr Peng Wang**, *Chief Scientific Officer, Simcere Pharmaceutical Group, China*
- **Dr Zili Li**, *Executive Director and Head of Emerging Market Regulatory Strategy Merck & Co, USA*
- **Prof Thomas Salmonson**, *Chair, CHMP, Director, Medical Products Agency, Sweden*
- **Dra Lucky Slamet**, *Head, National Agency of Drug and Food Control, Indonesia*

The Panel and Workshop attendees discussed the results of the Syndicate presentations.

Lexicon

Establishing a lexicon is essential for productive discussion, particularly among international participants. Examples were discussed in which the definitions or interpretations of terms such as peer review and stakeholder varied widely according to individual perspective and experience. As reported at the CIRS 2011 Emerging Markets Workshop, the report known by some as the Summary Basis of Approval is also known among other terms as the Summary Basis of Recorded Reaction, Summary Basis of Decision and the Review Report. In addition, the reports themselves vary widely in the amount and type of content and are mandated in some regions, whereas in other areas they are undertaken at the initiative of the regulatory agency.

Diverse perspective

The consideration of diverse input is not only important as it relates to lexicon development but the individual perspective of all healthcare stakeholders, especially patients should be integral to decision making. In fact, the number and variety of stakeholders, such as patients, patient groups, the media and reimbursement agencies, who want to be active participants in medical decision making have greatly added to its complexity and altered the role of the regulator. In addition, obtaining the viewpoint of patients can be complex when that viewpoint varies so widely. Discussion Panel members were clear, however, that regulators should

continue to use the knowledge that is generated through the assessment process to continually re-evaluate the benefit-risk profile of the new medicine in wider post-approval use.

Life-cycle approach to decisions

The tools for now being considered as novel approaches to medicines development such as adaptive licensing, conditional approvals and accelerated approval include the appropriate use of adaptive clinical trials, scientific advice and risk management plans. All of these elements are important to the life-cycle approach to decision making that was discussed by the Syndicates.

Panellists disagreed with the conclusion of Syndicate A that it was not possible to immediately assess quality decision making because of the need to continually evaluate the decision throughout a product's life cycle. This Syndicate postulated that decisions can be evaluated based on agreement among agencies with similar frameworks and through stakeholder discussion regarding the value judgements used in the decision-making process.

In addition, it should be recognised that the life-cycle management of new medicines will be very resource intensive, which is a particularly important aspect to countries with emerging pharmaceutical markets and limited agency resources.

Industry-regulator meetings

Panellists disagreed as to whether companies were ill prepared for pre-submission meetings with regulators but agreed that discussions can vary according to company objectives and the experience of the industry participants. The question as to whether industry-agency meetings should be based on a specific topic as identified and prioritised by industry or as an open discussion with regulators as to what they perceive to be the potential issues during an application is an interesting topic that might be a relevant focus for a CIRS Workshop. In either case, agency guidance for industry preparation for these discussions would be valuable.

Project management

Panellists agreed on the value of a project manager during the review and the associated "team spirit" that this function can generate.

Decision making and labelling

Regulators may benefit from an industry perspective on the importance of labelling and the implications on the business proposition for a new medicine created by mandates to change that labelling issued by regulators. There was a strong consensus on the high value to regulators of providing well-annotated labelling with references to sections of the dossier that support each statement in the label.

Mutual recognition of dossier assessments

Mutual recognition of assessments of selected sections of dossier by health authorities may be possible where appropriate legal structures are in place.

Patient viewpoint

Health Technology Assessment (HTA) agencies, especially in Europe, are in the political forefront and may be more in touch with patient viewpoints than some regulatory agencies because they need to interpret the economic and societal value of a new medicine and because they stand as the final barrier between patients and access to medicines.

Obtaining the patient perspective in a meaningful and credible rather than emotional way can be challenging but the US FDA has sought public comment at advisory meetings and will also be conducting a number of therapeutic area-focussed patient meetings over the next five years as part of their PDUFA commitment.

Informed patient participation in regulatory decisions may not be yet possible in many Emerging Market countries.

Section 3: Presentations

Dr. YIN Li

Commissioner, State Food and Drug Administration, P.R. China

Respected Colleagues and Experts, Ladies and Gentlemen, good morning. First of all, on behalf of the Chinese SFDA, I would like to welcome all of you in your visit to Beijing. It is my honour and pleasure to make the opening remarks for this Workshop on Regulatory Science, being held in China for the first time. I am glad to see so many international and domestic friends from regulatory agencies, private industries and academic institutions. With the Chinese element being added this year, I am sure that this Workshop will stimulate our thoughts and promote mutual understanding and cooperation in regulatory science.

As the country with the largest population in the world, China has made a rapid progress in the past decades; it has already benefited and will continue to gain more from economic growth and healthcare reform. Today China has become the third largest pharmaceutical market in the world and plays a very important role in the global supply chain for drug products. We produce not only active pharmaceutical ingredients (APIs) but also finished products for the world market. In addition, Chinese scientists and researchers actively participate in global R&D activities for many diseases with unmet medical needs such as rare diseases, diseases of the aged and other life-threatening conditions and have made important contributions to global health. China has been deeply involved in this inevitable globalisation. Drug regulators in China understand our obligations and responsibilities and cooperate well with our colleagues throughout the world.

Ladies and gentlemen, the pharmaceutical industry is a science-based industry and regulatory science is the cornerstone that allows regulators to make the right decisions. In the past one hundred years, we learned from the experience of unfortunate incidents and established the system that ensures the safety and efficacy of drugs. As a relatively young drug regulatory authority in the world, SFDA still has many things to learn. We need to develop our system guided by regulatory science, to meet the needs of the public, to promote innovation and to meet the challenges of globalization. We will continue to move forward and join in the international effort to protect public health and safety.

This Workshop focuses on drug evaluation and on how to use Good Review Practice (GRevP) to ensure the quality of the regulatory decision. We value this great opportunity to learn from our foreign friends and my colleagues in CDE look forward to making contributions to this Workshop with their experiences and ideas as well. I hope that CDE will develop rapidly and become one of the best regulatory agencies in the world. CDE and other parts of the SFDA will guide our activities based on principles of quality, efficiency, clarity, transparency, consistency and predictability. Our goal is very clear, that is to make science-based decisions to provide safe and effective drugs for the public. Here I would like to end my speech with an old saying: "Knowing is not enough, we must apply. Willing is not enough, we must do." Finally, I do hope that this Workshop achieves great success and everyone has a pleasant stay in Beijing. Thank you very much.

The Center for Drug Evaluation and the role of good review practice in underpinning a quality review process within CDE

FENG Yi

Associate Center Director, Center for Drug Evaluation, SFDA, Beijing, China

Changes in CDE structure and review practice

China has the largest population, the second largest economy and the third largest pharmaceutical market in the world. Accordingly, it is the mission of the Center for Drug Evaluation (CDE) to respond to ever-growing public health needs and to ensure the safety of drug use and protect and promote public health by maximising its capacity through innovation and cooperation. Dr FENG described how the CDE reviews small-molecule drugs, biological products and traditional Chinese medicine throughout their life cycle from research and development thorough post-marketing.

The CDE has undergone significant changes since 1985, at which time China relied completely on external reviews and there was no structured process for the review of medicines. In 2000 a single-review process was instituted as the concepts of quality and efficiency were introduced to the agency By 2011, the CDE had developed Review Principles and Procedures, adopted Good Review Principles and set up review processes for investigational new drug, new drug and abbreviated new drug applications. More recently, the Chinese government has developed a national Biomedical Development Plan, Drug Safety Strategy and Science and Innovation Plan that are expected to be fully implemented by 2020.

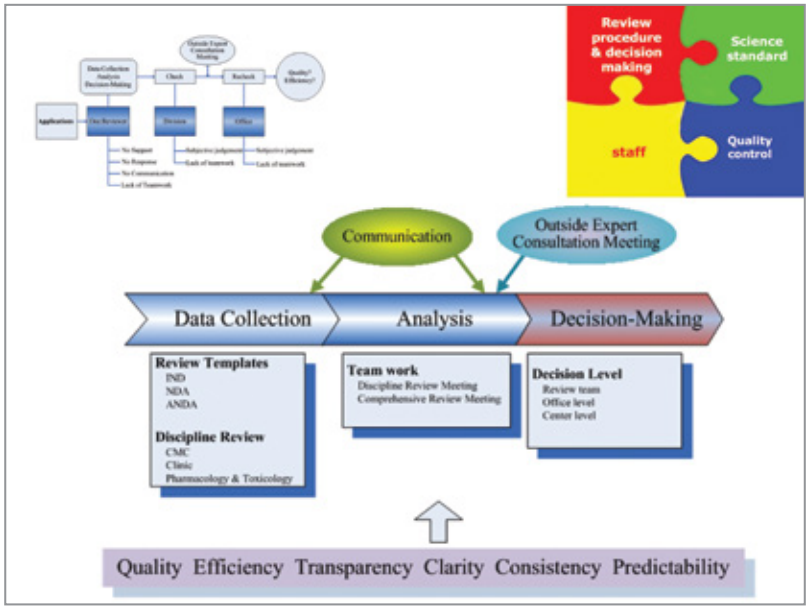


Figure 3. CDE decision-making processes were integrated to maximise team work throughout regulatory review.

As the result of a self-assessment process, the CDE judged that their organisational structure and review processes often were influenced by subjective judgement as well as were complicated by inefficient teamwork, support and communication, which contributed to lengthy review timelines. Consequently, the CDE was restructured and the decision-making path strengthened to proceed simultaneously through informational and organisational channels with enhanced support and teamwork and communication tools throughout the process of data collection, analysis and decision making (Figure 3).

Currently, all CDE processes are enacted in consideration of the GRevP principles of quality, transparency, efficiency, clarity, consistency, predictability and timeliness with the focus on protecting public safety and meeting public demands for timely access to new medicines. In fact, a comparison of current CDE guidelines with those of countries employing guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) reveals a concordance in matters of quality and safety and in many measures of efficacy. The CDE expects that standards for efficacy will continue to be enhanced to develop a greater comparability to those of other countries.

Personal, professional and leadership values are encouraged in CDE staff and managers through development plans and training. In addition, in a move to enhance transparency, a tracking system for product reviews has been made available to sponsors and public information regarding the approval of new substances and documentation relating to the new CDE procedures and requirements will soon be made available on the CDE website, including an English version.

CIRS gap analysis survey

In September 2012, the CDE requested that CIRS perform a survey to identify the baseline

. . . a strong understanding of the value of the value that GRevPs can bring to building quality in to the organisation among CDE senior managers. . .

attitudes toward and knowledge and practice of GRevP among 25 CDE management team members, with the goal of identifying potential gaps in order to lead to a new cycle of enhanced competency and capacity building.

Overall results of the survey among CDE senior management revealed a strong understanding of the value that GRevPs can bring to building quality into the organisation. However, although the managers recognise the importance of elements of GRevP, they are challenged in implementing many of these and specific procedures need to be addressed. Furthermore, when procedures are developed, the respondents asked that all voices within the organisation need to be heard and once developed these procedures should reflect both what is desirable and what is achievable. Following the concepts of "say what you do – do what you say" and "use and improve" can help close these gaps. Finding ways to overcome these challenges in the face of limited resources and growing workload should be the focus of the agency.

In addition to the survey, other CDE achievements in 2012 relevant to GRevP included enhanced communication with sponsors during the review process as well as making regulatory review reports available to sponsors. Priority review has been assigned to abbreviated new drug applications, a clinical trial registration system has been developed for the CDE website and advisory committee meetings were opened to the public. In addition, review times have been reduced on applications including reductions to 5 months for investigative new drug applications, 11 months for new drug applications and 14 months for applications for bridging studies to clinical trials.

Moving forward, the CDE expects to improve internal and external communication and transparent, consistent, high-quality decision making will be supported through a review platform that incorporates the principles of GRevP. Despite challenges, the CDE will continue to protect and promote the public health through the efficient and timely regulation of safe and effective medicines.

Good review practices at Health Canada

Barbara Sabourin

Director General Therapeutic Products Directorate, Health Canada

Good Review Practice

With a population of 35 million people, Canada represents 3% of the world's pharmaceutical market. Ms Sabourin explained that the Therapeutic Products Directorate (TPD) of Health Canada is responsible for the review of clinical trial applications and market authorisation applications for medicines and medical devices as well as some post-market activities for approved medicines. The TPD defines good review practices (GRevP) as encompassing review standards such as standard operating procedures (SOPs) and templates and related initiatives such as reviewer manuals and training programs designed to ensure the timeliness, predictability, consistency and high quality of reviews and review reports, which assist in making high-quality decisions.

The TPD implements and maintains a focus on GRevP through its organisational structure, consisting of a TPD GRevP Project Manager, whose significant experience facilitates her acceptance by reviewers and who is assisted by a small team located in the Review Services Unit. The annual work plan for the GRevP team is approved by the TPD Management Committee. Also part of the organisational structure, the GRevP Steering Committee consists of reviewers from various parts of TPD as well as observers from other areas of Health Canada.

Communication, training and SOPs

There are three main areas of focus for GRevP in the TPD: 1) communications, that is, discussion and information sharing; 2) training and 3) the development and implementation of SOPs

and templates. Communication is facilitated through an intranet site for staff that provides a single location for all scientific and regulatory information with links to external websites and internal intranets, information on training, SOPs and templates, scientific and regulatory presentations and review reports. All reviewers have access to the same, up-to-date information, providing the background and tools for high-quality and consistent reviews. In addition, reviewers can sign up for a weekly newsletter that links to information on other regulatory agency websites and news sites as well as providing information on internal activities. In addition to the intranet, an external internet site facilitates public access to various SOPs that have been developed for Health Canada, providing transparency to external stakeholders that can result in predictable review processes.

In another aspect of GRevP communications, the group conducts interactive meetings called "Bring your own brain," monthly one-hour sessions in which reviewers can discuss a variety of scientific and regulatory topics, such as overviews of work done in other areas of Health Canada, new guidance documents, SOPs and training. Presentations for these sessions are also posted on the GRevP intranet and staff can participate by telephone, eliminating travel time for off-site employees. Examples or case studies provided at these meetings have proved to be very useful methods for group learning and facilitating continuous process improvement, providing easily accessible learning opportunities to busy staff in a timely fashion.

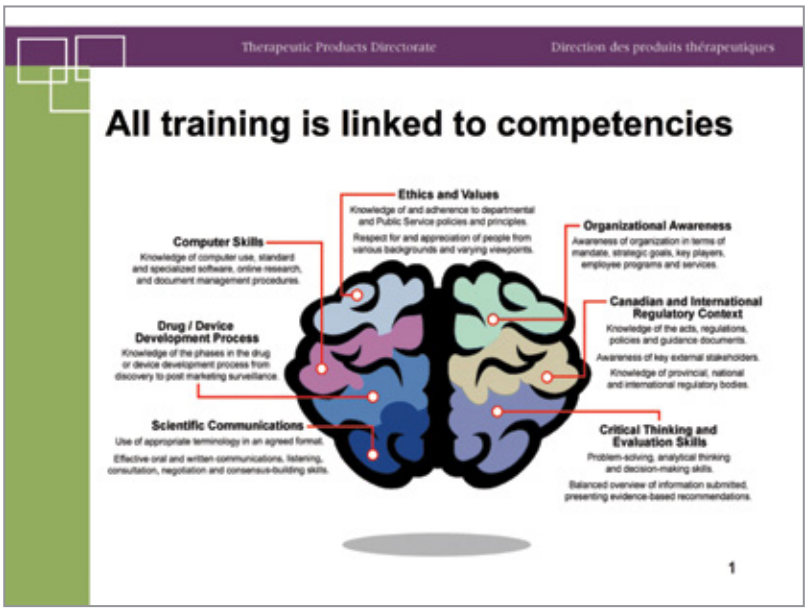


Figure 4. Good review practice training at Health Canada is linked to competency in seven areas.

In terms of training, a competency-based reviewer orientation programme was introduced in 2008 and the SOP on "Orientation of New Drug and Device Reviewers in the Therapeutic Products Directorate" describes the roles and responsibilities of new reviewers, their orientation mentors and supervisors. The GRevP team has also assisted in the development of several new courses for new and experienced reviewers and their oversight in this development has resulted in a comprehensive set of complementary courses. Participation in these programmes is tracked and gaps are addressed.

GRevP training is linked to competencies in seven areas: scientific communication; knowledge of the drug and device development process; computer skills; ethics and values; organisational awareness; international regulatory context and critical thinking and evaluation skills (Figure x). In fact, critical thinking is a key training component for new reviewers and the orientation course on "Applying Critical Thinking Skills to Health Product Regulatory Review" emphasises the difference between academic science and regulatory science and provides information and tools to help reviewers with regulatory decision making. All training has a clear objective: to help staff achieve the competencies that have been identified as necessary to help TPD achieve its regulatory review performance goals.

SOPs provide reviewers with written instructions on a variety of scientific and regulatory topics. SOPs on preparing review reports provide annotated report templates indicating how they should be completed as well as blank templates. Instructions are often written as "items to address", with significant room for flexibility. In addition to publishing the SOPs, the previously mentioned "Bring your own brain" sessions and all staff meetings are used to reinforce procedures and processes that are in place. However, SOPs tell reviewers what to think about, not how to think and complementary critical thinking skills and good judgement are needed. SOPs do provide consistency in the way reviews are conducted just as templates provide consistency in the documentation of decision making.

GRevPs: a component of high-quality review

Advantages to having a GRevP system in place

include increased acceptance of standard processes by the review community and a consistent approach to reviews that enhances both process predictability and timeliness. Because of the consistent approach to analysis provided by the GRevP system it provides an aid in dispute resolution as well as a mechanism to institute improvements. Group meetings and discussions help develop a sense of community among reviewers. However, GRevPs are just one component of a "good regulatory agency". Many other initiatives contribute to the timeliness, predictability, consistency and high quality of reviews and review reports and their resulting good decisions such as adequate resources, clear roles and accountabilities and regulatory project management. The collection and analysis of metrics and the implementation of benchmarking allows for the measurement of performance against similar organisations and the conduct of pipeline meetings with industry permits better resource and budgetary planning. Finally, access to external professionals such as advisory committees provides an important source of expertise and assistance.

. . . a competency-based reviewer orientation programme was introduced in 2008 . . . participation in these programmes is tracked and gaps are addressed.

Conclusions

Good review practices are an essential part but just a part of good regulatory decision making. A dedicated, experienced, enthusiastic resource is needed to oversee the development of GRevPs and ongoing management support and the realisation of its importance as a key activity are also required. Finally, regular communication with the review community is required and patience and a long-term management commitment are essential.

Good review practices: Transparency and consistency through explicit benefit-risk assessment

Dr Joseph Scheeren

Head, Global Regulatory Affairs & Head Global Development Asia, Bayer HealthCare Pharmaceuticals

The importance of good review practice

Industry continues to invest in the research and development of new medicines despite steady increases in cost and development time and decreases in the numbers of new molecular entities approved for marketing. Regulatory review, encompassing the assessment of a product's quality, safety and efficacy, lies at what was considered the end of the development process; however, the assessment of a medicine's benefits and risk are now viewed and managed in the continuum of a product's life cycle. Perhaps a bigger change is resulting from the impact of health technology assessment, which is now regarded by many as the new, additional hurdle to patient access.

To maximise a company's return on investment in light of increasing competition and limited patent life, the need for clarity about the regulatory review timeframe and the reliability and consistency of regulatory decision making is critical for sustainable pharmaceutical development. Although adaptive licensing, in which the safety and efficacy of a new medicine continues to be investigated after an initial conditional approval, may help us understand uncertainty around a product's characteristics and may accelerate patient access, the post-approval financial commitments necessary for this type of approval might only be practical for some products.

Good review practice: Reliability of timelines and more explicit benefit-risk assessment

Industry seek well-defined agency review schedules with timelines for questions and responses that both companies and agencies can commit to in order to allow reliable planning and use of resources. Importantly, this can help in planning simultaneous regulatory submissions to multiple global authorities. Shorter review periods for innovative treatments in areas of unmet medical need are required to improve patient access and incentives, in the form of data and patent protection, should be offered to foster investment in these innovations.

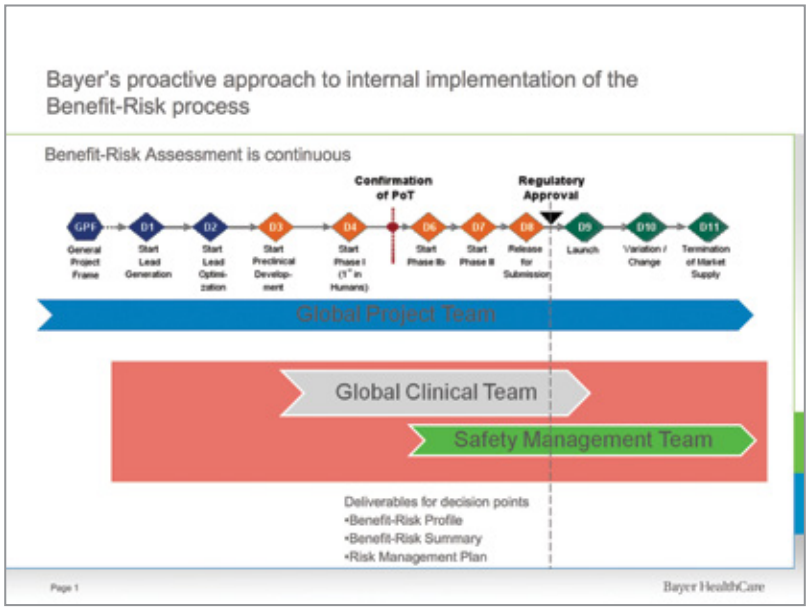
Explicit and aligned benefit-risk assessment practices by regulatory authorities would decrease the risk of late-stage failures after significant industry investments and increase the reliability of predictability of review processes. More consistency in regulatory review practices worldwide and enhanced quality in decision making would provide clarity for the justification of decisions to healthcare stakeholders such as the public, the government and health technology assessment authorities.

There is also added value associated with the introduction of more explicit benefit-risk assessment within companies. These assessments can allow the development of the long-term perspective required to meet regulators' expectations and requirements and to identify the gaps and limitations in data with a focus on medical need, comparator benefits (and the uncertainties of benefits and risks). Potential risk minimisation actions can be enabled that incorporate the preferences and values of patients, physicians and other stakeholders in ranking benefits and risks. Early dialogue can be initiated with regulators to allow more proactive planning of phase 2 and 3 studies.

Clarity in benefit-risk evaluation can also align global project teams on important benefits and risks and support explicit and transparent decision making by internal committees, providing a reference point for internal and external assessments and regulatory documentation. Bayer takes a proactive approach to benefit-risk assessment throughout the life cycle of a product, formulating benefit-risk profiles, summaries and risk management plans (Figure 5). They have found the evaluations to be a useful tool both for guiding internal discussions and for formulating questions to regulatory authorities, thereby obtaining optimal benefit from these interactions.

Clarity in benefit-risk evaluation can also align global project teams on important benefits and risks and support explicit and transparent decision making by internal committees.

Figure 5. Bayer takes a proactive approach to benefit-risk assessment throughout the life cycle of a product.



A common framework

A common, scientifically accepted framework, such as that proposed by the Unified Methodologies for Benefit-Risk Assessment (UMBRA) is needed to frame the decision, identify and assess the benefits and risks and integrate the recommendations. Explicit and aligned assessments can be performed despite differing external confounding factors such as regulatory and medical practice, lifestyles and environment through the use of various methodologies, such as those developed by the US Food and Drug Administration (FDA), the European Medicines Association (EMA) and the Consortium on Benefit-Risk Assessment (COBRA).

The methodology developed by the Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team (PhRMA BRAT, now being managed by CIRS) allows key qualitative criteria associated with a medicine to be organised in a value tree as known or potential benefits or risks for harm. Benefit-risk summary tables summarise key information needed to quantify outcomes in the value tree. Such tools provide an excellent basis for interpretation of how various factors can affect multiple outcomes.

Quantitative models of benefit-risk assessment models such as multi-criteria decision analysis (MCDA), the net clinical benefit model, number needed to treat (NNT) and number needed to harm (NNH) can be difficult to use and explain. In addition, many assumptions are needed for their use and they must be individually established for specific therapeutic areas and indications. In fact, although there are positive and negative attributes for the qualitative, semi-quantitative

and quantitative methodologies being used and tested, ultimately, benefit-risk assessment is dependent on the perspective of the stakeholder. However, those perspectives must now include those of patients, as regulators and industry consider issues such as the need to establish patient-reported outcomes into clinical trials and patients' willingness to accept high levels of risk in return for certain benefits.

The role of Good Review Practices

The key elements of good review practices encompass science-based decision making that is consistent and timely, transparent and based on good communications between the regulator and industry (Figure 6).

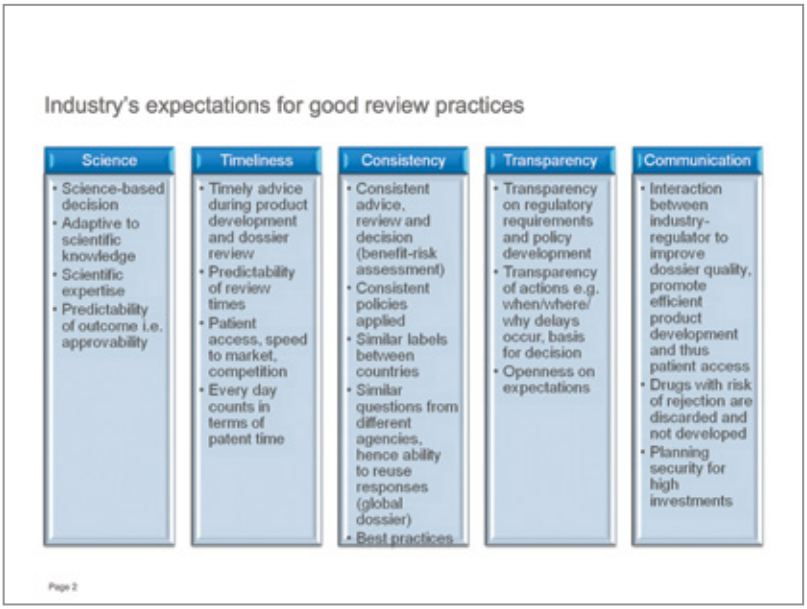


Figure 6. Industry requires that good review practices for regulators, be based in science and reflect optimal standards in timeliness, consistency, transparency and communication.

Good review practices are a crucial element in the product development pathway for pharmaceutical companies and are critical to facilitating patient access to innovative therapies but a suitable framework is necessary for their facilitation.

Conclusions

In order to optimise benefit-risk decision making, industry seeks for regulators to provide structure and transparency for sponsor-regulator alignment throughout the review process. Regulators should establish a clear set of processes and tools to guide decision making and develop methodologies for benefit-risk assessment consistent with internationally acceptable framework approaches. These methodologies can provide transparency around the outcomes and identify the tools needed to facilitate the communication and visualisation of decisions. In addition, clarity is required regarding the establishment of the relative importance or the weighting of different factors in the benefit-risk assessment and flexibility should be built into the assessment methodology to allow situational adaptation. Finally, the outcomes of rational methodologies that integrate qualitative and quantitative elements of benefit-risk assessment should be reflected in the product label.

Overview of APEC Best Practice Project

Dr Churn-Shiouh Gau

Executive Director, Center for Drug Evaluation, Chinese Taipei

In 2010, the Regulation Harmonisation Steering Committee (RHSC) of the Asia Pacific Economic Cooperation Life Sciences Innovation Forum (APEC LSIF) set good review practices (GRevPs) as a priority objective (Figure 7). Accordingly, the Best Regulatory Practice for Medical Products: A Strategic Approach for Good Review Practice project was funded by APEC in 2010 and was co-sponsored by Canada, China, Indonesia, Korea, Malaysia, Mexico, Peru, the Philippines, Thailand and the United States. The goals of this project are:

- to resolve the regulatory challenges in the APEC region and achieve timely market access for medicinal products by promoting and adopting GRevP;
- to reduce regulatory burden by facilitating opportunities for networking and partnership among regulatory authorities within the APEC region by providing a platform for regulatory dialogue and by establishing mutual confidence in assessment reports;
- to build the capacity of regulatory agencies through the development of a training curriculum and the instruction of regulators as agents for change in basic and advanced workshops and
- to develop the Roadmap for GRevP in fulfilment of the APEC goal of regulatory convergence by 2020.

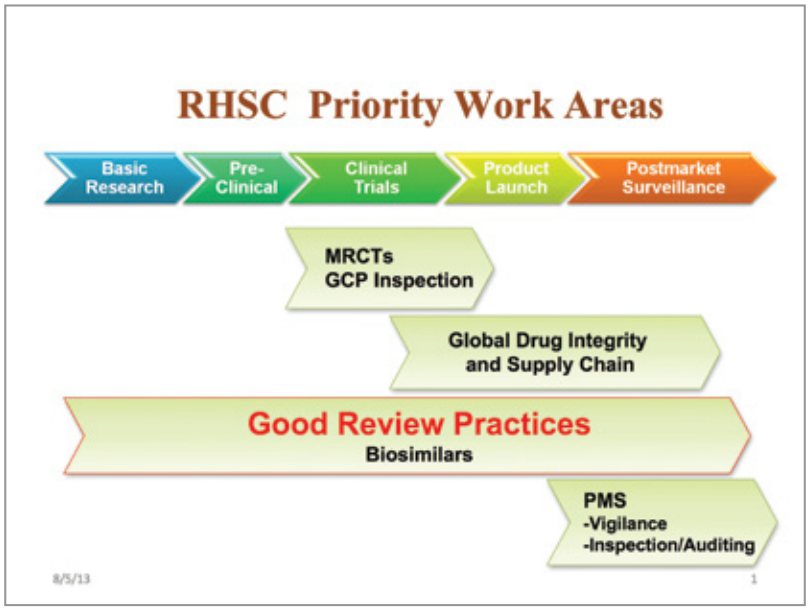


Figure 7. Good review practice is a goal of the APEC Regulation Harmonisation project, which spans the product's life cycle.

GRevP gap analysis survey

As a first step in the GRevP project, CIRS conducted a gap analysis of good review practices among APEC economies in 2011. Results of the study indicated that a consistently defined GRevP code has been implemented either formally or informally by most of the surveyed APEC regulatory agencies. Most of the agencies improve their GRevP through natural evolution and training and quality measures are being implemented to ensure consistency and improve efficiency and transparency. The majority of surveyed agencies have implemented audit or feedback mechanisms to ensure adherence to quality measures and believe that quality measures will increase confidence in their system; however, not all respondents indicated that their agencies use a standard assessment template for the review of new product applications.

Although target timing for reviews are in place at most agencies to help guide review activities, electronic tracking systems are needed to maximise the value of tracking against these target goals. In addition, whilst many authorities have implemented tools such as formal or informal meetings and specified meeting dates to enhance industry interactions, engagement opportunities could be improved. Finally, although the majority of respondents employ several methods to train reviewers, all felt the need for additional GRevP training, especially training on using assessment frameworks, good review practices and good review management practices.

Training workshops

A basic training workshop was conducted among APEC agencies in 2011 to establish a common understanding of GRevPs and their importance and to share best practices from the perspectives of regulatory agencies and industry representatives. The workshop followed the format of lectures and framed discussions in which the experiences and current practices among various agencies were shared and interactive dialogues were conducted among regulatory agencies and stakeholders. A common understanding of the scope and

key elements in GRevPs was promoted and tools provided to enhance the competence of reviewers and standard procedures and templates in use among participants were shared.

Among the conclusions reached by the workshop participants, it was decided that

- GRevPs help to ensure efficiency, predictability, consistency, transparency and the high quality of a science-based assessment of medical products.
- Agencies should provide continuous training programmes to build up knowledge and skills for reviewer competency.
- Whilst standard operating procedures are crucial and templates are also useful, these are used on a limited basis within APEC regulatory agencies.
- Although transparency of the decision-making process is a major concern of healthcare stakeholders in APEC economies and most regulatory agencies are interested in sharing review reports, an appropriate common methodology has not yet been elucidated.
- For each measurement of review quality, targets must be set and progress continually monitored. Timeliness should be measured internally and externally and stakeholder feedback should be regarded as an important component of continuous quality improvement.

Objectives for the advanced GRevP workshop conducted in 2012 were to share the strategies for GRevP and how they may be applied within agencies; to demonstrate the practice of critical thinking and decision making and to explore the various models of GRevP resource sharing among regulatory agencies. This workshop also followed a combined didactic and interactive format and additionally featured the use of case studies.

For this group a quality system was defined as an organisational approach to produce, maintain, ensure and improve the fitness-for-use of a product or service. During the course of the workshop the use of the Plan, Do, Study, Act and the Do What You Say; Say What You Do models for change were validated and the three main components for good decision making were identified as 1) consistent application of 2) clear and well-defined processes by 3) well-trained reviewers..

. . . all felt the need for additional GRevP training, especially training on using assessment frameworks, good review practices and good review management practices.

Workshop attendees listed strategies for regulatory review initiation as 1) screening or validation, 2) early identification of serious deficiencies and 3) kick-off meetings, consultations and pre-submission sponsor meetings; whilst post-initial review strategies to enhance quality and transparency were peer review and team meetings.

Due to limited resources within the region, a systematic approach to the assessment of data and a risk-based approach to decision making were named as key strategies to enhance efficiency. Attendees also agreed that reviewers must judge what is best for public health, evaluate benefit-risk on a population basis and identify questions and define which are critical. Finally, it was agreed that involvement of all stakeholders through review transparency is an important goal and mechanisms must be in place for data protection.

The future goals of the APEC GRevP project are to continue to refine GRevP scope, definitions, key elements, implementation approaches and methods and metrics for assessment. In addition, the APEC GRevP curriculum will be finalised and the GRevP roadmap implemented to achieve the basis of regulatory convergence by 2020.

Good decision-making practice: What role do frameworks have in ensuring a good decision?

Prof Stuart Walker

Founder, Centre for Innovation in Regulatory Science

Structured decision making

Basic decision-making styles have been linked to personality types, that is, they can be subjective, objective, analytical and non-analytical. In addition, some have suggested that there are best practices in decision making that should include such procedures as evaluating the risks associated with the alternatives, using well-defined processes, providing rationales and justifications and evaluating consequences. However, a structured approach such as that discussed in the book Smart choices: A practical guide to making better life decisions and as cited by Prof Larry Philips may be more applicable to decision making within pharmaceutical development and regulation.[1] This approach to decision making is encompassed within an eight-step framework:

1. Define the decision problem
2. Clarify the objectives
3. Decide on the alternatives
4. Describe the consequences
5. Assess the tradeoffs
6. Evaluate the uncertainties
7. Account for individuals risk tolerance
8. Effectively review current and future decisions

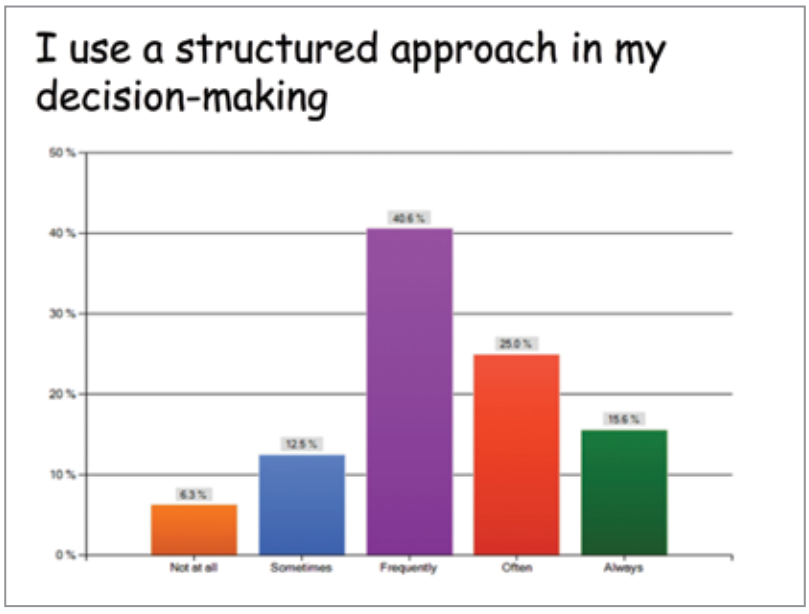


Figure 8. Approximately 66% of respondents use a structured approach to decision making "frequently" or "often."

QoDoS

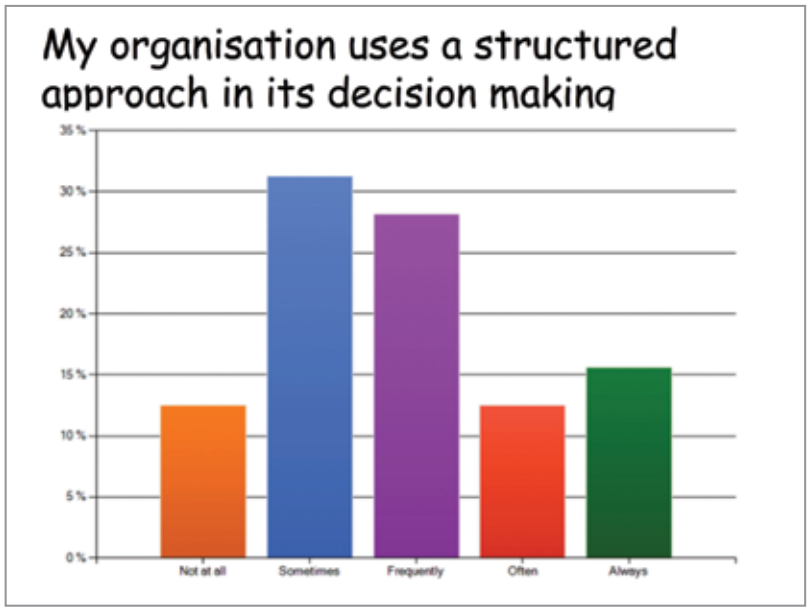
The question remains: is this type of framework necessary for decision making? In recognition of the dearth of understanding regarding quality decision making, Prof Walker along with Prof Salek of the Welsh School of Pharmacy at Cardiff University and doctoral candidate Ronan Donelan designed a programme of research to develop and refine the Quality of Decision-Making Orientation Scheme (QoDoS), an instrument that could facilitate quality decision making.

The research was initiated with the conduct of semi-structured, in-depth interviews with 29 senior-level professionals in regulatory agencies, pharmaceutical companies and contract research organisations. Interview questions, which sought to elicit respondents' opinions regarding the key influences on good decision making and methodologies for improving those decisions, identified 76 themes and considerations that were used to create the original survey instrument. After analysis, refinement and validation by a cohort of 120 participants from the three groups, the final QoDoS tool contained 47 items divided into four sections: organisation decision-making approaches, organisation decision-making cultures, individual decision-making competences and individual decision-making styles.

An analysis of preliminary survey outcomes revealed some unexpected results; for example, whilst 66% of respondents use a structured approach to decision making, "frequently" or "often," only 41% of their organisations employ a structured approach in their decisions (Figures 8 and 9). Additionally, almost a third of organisations do not provide training in the science of decision making and nearly 50% either never evaluate the impact of its discussions or only do so "sometimes."

The results of this research permitted the development of a list of ten hallmarks of good decision making. Good decision makers:

1. Employ scientific rigor and understand the decision context
2. Apply knowledge and experience



3. Examine the integrity of the information for validation and confidence in the decision
4. Use an objective approach and maintain an awareness of your biases and preferences
5. Consider uncertainty and examine alternative solutions
6. Assign values and relative importance to decision criteria
7. Re-evaluate as new information becomes available
8. Evaluate both internal and external influences
9. Apply a structured approach to aid transparency and paper trail
10. Perform impact analysis and effectively communicate the basis of the decision

The need for a benefit-risk decision framework

There has been an acknowledgement that decision making among regulators can be somewhat inconsistent and benefit-risk data and submissions are not always presented by industry in a coherent and well-structured manner that can facilitate decision making.

[the framework can] allow industry to evaluate the benefit-risk data for new products before submitting an application in order to identify areas where data may need to be strengthened or clarified.

Additionally, there has been growing pressure on agencies to increase transparency and accountability and to establish document how decisions are reached.

A decision framework has been defined as a set of principals, guidelines and tools which would guide decision makers in selecting, organising, understanding, summarising and ultimately communicating the evidence relevant to the benefit risk assessment decision.[2] A decision-making framework may assist in better understanding as to why different agencies come to different conclusions when faced with essentially the same submission data. It may also fulfil the need for a system that is sufficiently dynamic and flexible that it can be developed with experience and with the potential that its application could be extended to include the views of a wider range of stakeholders.

Beginning in 2002, the CIRS has had the objective to develop an internationally acceptable, structured systematic, standardised framework for benefit-risk assessment of medicines. It was envisioned that the outcome of such an approach would be a quality, transparent, consistent and predictable decision whose rationale could be effectively communicated to others.

Underneath that overarching framework, a toolbox of different methodologies could be developed and used by industry and regulatory agencies in making decisions for the development and regulation of new medicines. In practice, the five-step framework being piloted by the US FDA, in which after the condition and the unmet medical need to be addressed by a new medicine are described, the clinical benefit and potential risks for harm associated with that medicine are listed and a plan for the management of the risks are specified is an example of one such approach.

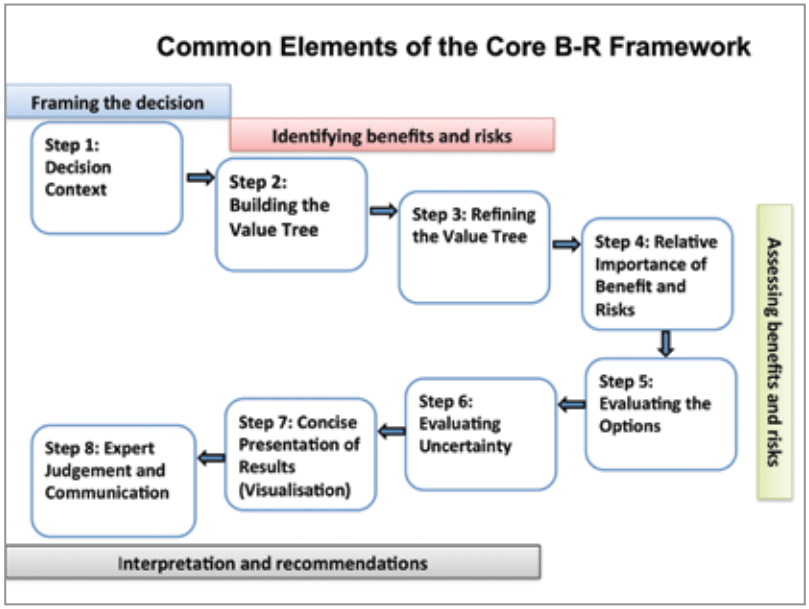
The EMA uses the PROACT URL system in which the nature and context of the PROBLEM to be addressed by a new therapy are determined, the OBJECTIVES or the overall purposes to be achieved are established and the favourable and unfavourable effects identified. Additionally, ALTERNATIVES against which the therapy is to be measured are listed and the CONSEQUENCES of the treatment that is, the incidence, severity and desirability of the effects of a treatment compared with alternatives are named. TRADEOFFS or the balance between favourable and unfavourable effects and the UNCERTAINTY of those effects are assessed. The

relevant importance of the decision makers' risk attitude for the product or their RISK TOLERANCE is judged and LINKED DECISIONS or the consistency of this decision with similar past decisions and its impact on future decisions is considered.

The six-step approach of the Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team (PhRMA BRAT) define the decision context; 2) identify and select benefit and risk outcomes; 3) identify and extract source data; 4) customise the framework; 5) assess outcome importance and 6) display and interpret key benefit-risk measures is now being taken forward by CIRS.

These approaches and the seven-step model previously developed by CIRS and used by Swissmedic, Health Canada, HSA Singapore and Australia's TGA in the Consortium on Benefit-Risk Assessment (COBRA) are encompassed by the overarching Unified Methodologies for Benefit-Risk Assessment (UMBRA) eight-step framework (Figure 10 See discussion of UMBRA on page 32).

Figure 10. The UMBRA Benefit-Risk Framework.



There are advantages to applying the consistent approach embodied by the eight-step UMBRA framework. It can enhance the objectivity and transparency of the decision-making process for benefit-risk assessments by providing a structured and systematic approach and a "paper trail" for tracking the process and providing greater accountability. It allows a review of the consistency of regulatory decisions on marketing authorisation applications in order to learn from past experience. The framework can achieve a better understanding and a more rational explanation of why different agencies reach different conclusions on the basis of the same data. It can provide a training tool for both agency and industry staff involved in the development and assessment of new products and allow industry to evaluate the benefit-risk data for new products before submitting an application in order to identify areas where data may need to be strengthened or clarified. Finally, the framework enables more balanced and objective benefit-risk reassessments in post-authorisation situations for which there was previously a tendency to focus primarily on adverse event reporting. All of these strengths argue in favour of the role that methodologies that can be mapped to this framework play in ensuring good decisions based on a structured systematic approach.

References

1. Hammond JS, Keeney RL, Raifa H. *Smart choices: A practical guide to making better life decisions*. Boston, MA: Harvard Business School Press, 1999.
2. Levitan B. *PhRMA Benefit-Risk Action Team (BRAT) Framework.* Presented at the International Society for Pharmacoeconomics and Outcomes Research 16th Annual Meeting, 24 May 2011.

Regulatory viewpoint: An example of how the use of a decision framework can improve regulatory decision making

James Leong

Senior Regulatory Specialist, Health Sciences Authority, Singapore

Expectations for regulatory authorities are evolving. It is now presumed that regulatory practices will be aligned with rapidly advancing medical science and that timely access to quality, safe and efficacious drugs will be provided that includes accountability to healthcare professionals, patients, industry members and other stakeholders. In addition, there should be a clear and consistent basis for these regulatory decisions, with transparency of the decision-making process and effective communication

to stakeholders. Approved products must be overseen by regulators throughout their life cycle, extending into post-approval. Finally, there should be an overall governance and audit of the processes to ensure confidence in these practices.

Whilst current regulatory decision-making frameworks from submission to evaluation to post-approval are supported by policies, standard operating procedures and training, they are general in nature. The approaches many agencies use specific for benefit-risk assessment, which is a potential tool to aid in fulfilling the evolving expectations of stakeholders for regulatory authorities have remained unchanged for a number of years and is a recognised area for enhancement.

In recognition of this need, four similar-sized regulatory agencies from Singapore, Canada, Australia and Switzerland sought the assistance of CIRS for the development of a standardised systematic approach to benefit-risk evaluation that could ultimately facilitate work-sharing and joint reviews. This group, known as the Consortium for Benefit-Risk Assessment (COBRA) (Figure 11) recently piloted the use of a benefit-risk template, which is a tool for documentation, showing the progressive logic and basis of benefit-risk decisions. The template was based on the 2005 EMA Reflection Paper on benefit-risk assessment methods[1] and correlates to and is supported by the Unified Methodologies for Benefit Risk Assessment (UMBRA) eight-step framework, which provides the fundamentals and the principals for making quality decisions.

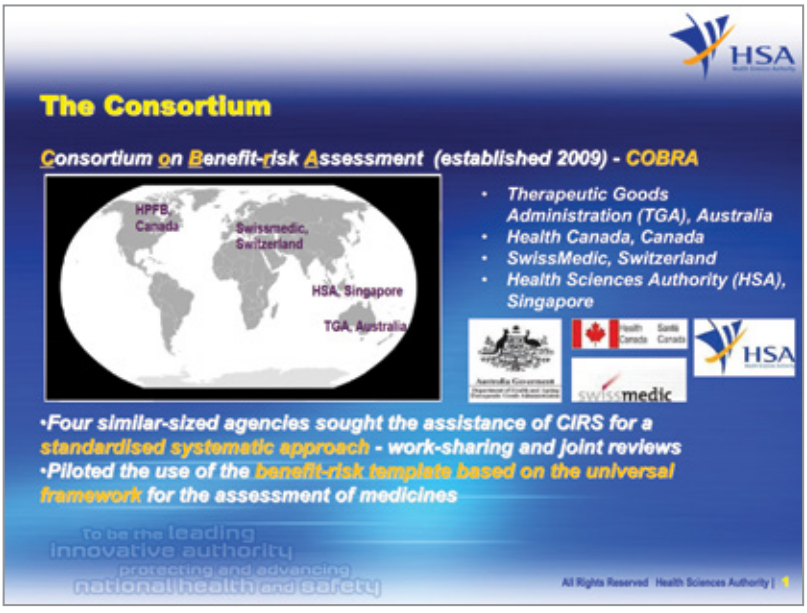


Figure 11. The Consortium for Benefit-Risk Assessment (COBRA) was formed to develop a standardised approach to benefit-risk evaluation.

A user manual has been developed for the template, which includes a glossary and instruction for completion.

Sections of the COBRA template and their correspondence to the UMBRA framework

- Section one of the template assists in the understanding of the context of the request for evaluation and its scope. This section provides a focus on matters that affect the decision and an initial qualification of the medical need for this request. This section corresponds to Step 1 of the UMBRA framework, *Decision Context*.
- Section two incorporates relevant contributions from other aspects of the evaluation besides clinical assessment of benefits and risks.
- Section three clearly articulates the benefits and risks as identified by evaluator and the company. This section corresponds to steps 2 and 3 of the UMBRA framework, *Building the Value Tree and Refining the Value Tree*.
- Section four includes a discussion of the uncertainties surrounding the clinical studies, the appropriateness of the study design, comparators and efficacy endpoints, the validity of the scales and measurements, consistent trending across studies, negative studies, interactions with drugs and food and potential off-label uses and abuse. This section corresponds to step 6 of the UMBRA framework, *Evaluating Uncertainty*.
- Section five entails the clarification of the relative importance and contribution of each benefit and risk to the eventual decision steps. This section corresponds to steps 4, 5 and 6 of the UMBRA framework, *The Relative Importance of Benefit-Risk, Evaluating the Options and Evaluating the Uncertainty* (Figure 12).
- Section six incorporates visualisation as component of effective communication. This section corresponds to step 7 of the UMBRA framework, *Concise Presentation of the Results (Visualisation)*.
- Section seven contains the contribution of risk minimisation plans and other stakeholder perspectives in the form of solicited expert opinions. It also comprises expert judgment and the concluding decision. This section corresponds to step 8 of the UMBRA framework, *Expert Judgement and Communication*.

The COBRA benefit-risk template provides a formal structure to the current process of benefit-risk assessment . . . It also acts as a potential tool for training new evaluators, setting internal standards and consistency for regulatory decision making.

Practical uses and limitations

The COBRA benefit-risk template provides a formal structure to the current process of benefit-risk assessment and reminders and guidance on relevant issues for reviewers to consider. It also acts as a potential tool for training new evaluators, setting internal standards and consistency for regulatory decision making. The four agencies conducted several pilots using this methodology. Although there was some initial resistance from some experienced evaluators who deemed the template as additional work, the clarification of the intent and purpose of template helped the evaluators to be more receptive. In addition, the template's auto-populate function minimised the need to duplicate relevant information for various portions of the template. Nevertheless, some concerns were raised, including those regarding logistics, timelines and the need for re-training on the use of the tool.

Use of the UMBRA framework and associated template aligns to current concept of regulatory processes, does not challenge the scientific rigor of benefit-risk assessment and enhances the clarity of the decision-making process. In addition, it provides proper documentation, improves transparency and effective communication, serves as a reference to enable consistent practices, promotes governance and provides an audit trail and potential use as a tool for regulatory decision-making convergence.

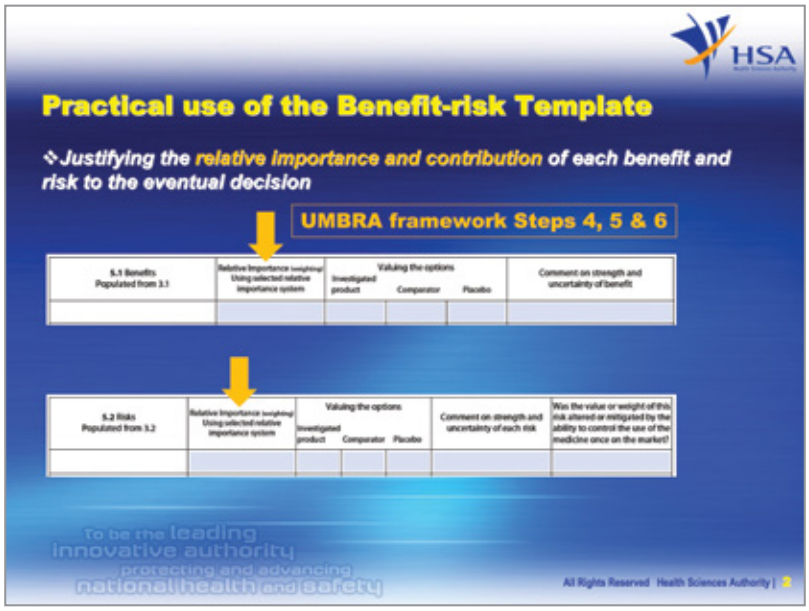


Figure 12. Section 5 of the COBRA benefit-risk template.

Lessons learned

A structured process for decision making allows a shared approach in which the rationale and supporting documentation are clearly defined. The Summary section and more detailed proforma section of the benefit-risk evaluation tool can provide a way to tailor the level of communication regarding agency decisions to different stakeholders. Furthermore, the systematic articulation of each benefit and risk and its relative importance provides consistency and allows comparison with other therapies to support regulatory decision making. A common format enables collaborative work and serves as a platform for peer-review discussion and a vehicle for comparison with members of a therapeutic class and clear communication and visualisation of benefits and risks to various stakeholders.

The role of the template developed by CIRS for the COBRA group, that is, whether it will function to replace or enhance existing documentation and whether the level of required information will increase or decrease has yet to be finalised. In addition, the template must be validated and seen how it can best be incorporated into product life-cycle management. Other issues that require elucidation included the subjective nature of weighting and valuing and the methodologies to be used for optimal visualisation. It is hoped that subsequent experience contributed by other agencies using this approach will help to refine this methodology.

Reference

1. Committee for Medicinal products for Human Use (CHMP). *Reflection paper on benefit-risk assessment method in the context of the evaluation of marketing authorisation applications of medicinal products for human use,2007.* Available at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500069634.pdf Accessed April 2013.

Industry viewpoint: How a benefit-risk framework can improve regulatory decision making

Dr Mark Goldberger

Divisional Vice President, Regulatory Policy and Intelligence, AbbVie, USA

The process and elements of decision making

Despite the fact that regulators and industry members are faced with similar challenges during the development, regulation and reimbursement processes for new medicines, there is a lack of transparency regarding the specific concerns and issues for both of these stakeholder groups. Although it may not be possible for this lack of understanding to be completely resolved, it may be improved through the use of good decision-making practices and a programme of ongoing communication and an alignment of assumptions and goals.

The elements leading to good regulatory decision making include a sound framework, well-trained review staff, a good review model, a robust development programme and good communication between agency and sponsor, including asking the "right questions" and understanding assumptions. A good review involves an efficient process and includes review documentation that demonstrates thoroughness, clarity and insight. In addition, the review document provides clear conclusions and allows third parties to understand the basis for these conclusions. Internal processes to support good reviews require review templates, periodic meetings to allow different disciplines and reviewers to discuss issues, the support and involvement of senior management and agreed-upon and adhered-to timelines to allow adequate assessment by signatory authorities.

A good review process also depends on the quality of the submission and requires complete data, adequate dose finding, a study designed to answer relevant research questions and an appropriate analysis plan. Good internal regulatory processes within a pharmaceutical company will identify deficiencies in these aspects of a submission but if this identification occurs when the dossier is submitted for review it is unlikely that these problems can be fixed in that review cycle.

Internal and external alignment

Multiple rounds of review can be avoided through an alignment of internal sponsor assumptions as well as those of regulators. The alignment should cover issues such as expected efficacy and safety profiles, a development programme that supports desired labelling, the incremental value of additional studies, the suitability of proposed risk management strategies to address the likely and potential benefit-risk profiles and whether better "targeting" of a proposed patient population might improve the benefit-risk ratio.

Alignment should occur through internal discussions within the sponsoring company and through interaction with the agencies during the process of development, the time leading to the submission of the dossier, the review and the post-marketing period. Internal sponsor discussions need to cover the preliminary understanding of the benefit-risk profile of the product and the critical drivers that might improve the profile. They must decide which incremental increase in resources might provide the greatest additive benefit and if that additional spend is reasonable.

Interactions with agencies need to occur at an early phase of development, especially for products intended to treat a serious disease or to address unmet medical need. Potential differences in the definition and acceptance of benefits and tolerance for risk should be defined as explicitly as possible and as early as possible in development and should be open to refinement as assumptions are replaced by data as the program progresses. Certainly, prior to the initiation of a phase 3 programme it must be determined if there is alignment of benefit-risk assumptions between sponsor and agency and if there is not, it must be decided if there are changes to the programme that could produce information to mitigate these differences.

Leading up to the submission of the dossier, stakeholders must evaluate how the benefit-risk profile post-phase 3 compares with the assumptions prior to phase 3. Alignment between sponsor and agency should be re-evaluated at a pre-submission meeting and a determination made if any significant differences can be bridged via additional analyses, alterations in the intended target population or through risk management planning. Opportunities to updates the benefit-risk profile

Potential differences in the definition and acceptance of benefits and tolerance for risk should be defined as explicitly as possible and as early as possible in development and should be open to refinement as assumptions are replaced by data

during the course of the review should be evaluated as well as the feasibility of sharing those updates with the sponsor or using the reassessment in an Advisory Committee setting and determining the anticipated results of such an exchange. Finally, the role of benefit-risk assessment in the post-approval period should be determined.

The use of a benefit-risk model such as that currently being piloted by the FDA, which allows the identification of evidence and uncertainties for the potential benefits and harms associated with a new medicine can help elucidate the benefit-risk decision-making process (Figure 13). Importantly, this model includes the identification of a risk management plan, which continues the process of ongoing benefit-risk assessment as use of a new medicine extends from a clinical trial to a broader "real-world" population. The model does not, however, provide for what many consider the necessary weighting of the relative importance of the benefit and risk parameters.

Figure 13. The US FDA model for benefit-risk assessment of new medicines.

FDA Benefit-Risk Assessment Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Summary of evidence:	Conclusions (implications for decision):
Unmet Medical Need	Summary of evidence:	Conclusions (implications for decision):
Benefit	Summary of evidence:	Conclusions (implications for decision):
Risk	Summary of evidence:	Conclusions (implications for decision):
Risk Management	Summary of evidence:	Conclusions (implications for decision):
Benefit-Risk Summary and Assessment		

Dr Goldberger concluded his presentation with a quote from Dr Bennett Levitan of Johnson and Johnson on the importance of benefit-risk frameworks:

"Because benefit–risk assessment for a drug is rarely straightforward, the framework or similar tools for elucidating the relevant data can help facilitate discussions between sponsors and regulatory agencies, help communicate complex information to other stakeholders, enhance the transparency of assumptions and decisions and provide support for difficult regulatory benefit–risk decisions."[1]

Reference

1. Levitan BL, Andrews EB, Gilsenan A. Application of the BRAT framework to case studies: Observations and insights. *Clin Pharmacol Ther.* 2011;89:217-224.

What are the key activities that can influence decisions and what frameworks are being used to ensure good quality decisions are made

Dr Won Shin

Division of Gastroenterology and Metabolism Products, Korea Food and Drug Administration

Decision making at the KFDA

Between 1999 and 2012, twelve new chemical entities were developed in Korea and many others were imported from other countries. In 2011, 797 drugs were approved by the Korea Food and Drug Administration (KFDA) for manufacturing, import or export and 865 medicines were reported to the regional offices without variation of safety and efficacy (Figure 14). [Editor's Note: At the time of this presentation, the organisation was known as the Korean Food and Drug Administration or KFDA. As of March 2013, the agency was elevated to ministerial level and is now known as the Ministry of Food and Drug Safety or MFDS].

Goals of post-marketing requirements for companion diagnostics

Four key elements ensure quality decisions within the KFDA: regulations, process, communication and capacity building.

Figure 14. In 2011, 797 drugs were approved by the Korea Food and Drug Administration.

Pharmaceutical Development in Korea (drugs)

➢ **Status of Pharmaceutical Industry, 2011**

	No. of manufacturers	No. of products	Production amount (million dollars)
Drug product	267	15,832	13,350
Drug substance	371	10,593	1,407

➢ **Development of New Chemical Entity (NCE) in Korea**

Year	'99	'01	'02	'03	'05	'06	'07	'08	'10	'11	'12	Total
No.	1	3	1	3	2	1	2	1	1	2	2	19

➢ **Number of approved and reported pharmaceutical products, 2011** (cases)

	Manufacturing	Import	Export	Total
Approval	560	136	101	797
Registration	606	76	183	865

Regulation: Regulatory administration, evaluation and approval in Korea are conducted in accordance with the Korean Pharmaceutical Affairs Act (PAA). For situations that fall outside of these regulations, the KFDA adapts international standards such as those of the World Health Organization (WHO) or the International Conferences on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). In addition, the KDFA uses various review templates and follows standard operating procedures and approximately 100 guidelines for good review practices, which provide for the standardisation and documentation of process, format, content and the management of product review.

Process: The KFDA is organised with one headquarters, one affiliated institute and six regional offices. The Pharmaceutical Safety Bureau and the Biopharmaceutical and Herbal Medicine Bureau are responsible for the regulation of drugs and herbal medicines and for clinical trials for these medicines. Investigative New Drug Applications (INDs) and New Drug Applications (NDAs) are evaluated in the Drug Evaluation Department, which consists of six divisions in which five reviewers evaluate a new medicine's safety and efficacy while three reviewers assess the CMC (Figure 15).

The approval time for INDs is 30 working days, 90 days for NDAs for new chemical entities and 60 days for major line extensions. The KFDA can request that sponsors supply supplemental data for their applications, at which time the review clock stops until the sponsor responds to these requests. Sponsors submit application documents and can check the status of their document at any time.

Communication: The KFDA conducts many meetings with sponsors including pre-IND and pre-NDA meetings and product introduction meetings after submission and the Center for Drug Development Assistance was specifically established to coordinate sponsor and manufacturer communications before submission. Other types of agency-sponsor communications include video meetings, telephone contact and e-mails. Internally, Senior Reviewers' Meetings are conducted to discuss issues that require consistency among divisions, Directors' Meetings are held to make final decisions and develop written agreements and Advisory Committee Meetings are convened for circumstances that require additional professional expertise.

Because good-quality decisions are based on good-quality reviews, the KDFA has a rich educational programme for its reviewers that consists of more than 100 hours of training per year . . .

Capacity building: Because good -quality decisions are based on good-quality reviews, the KDFA has a rich educational programme for its reviewers that consists of more than 100 hours of training per year; forms of training include commissioned education, cyber education, international training fellowships of 1 to 2 years, seminars, workshops and symposia.

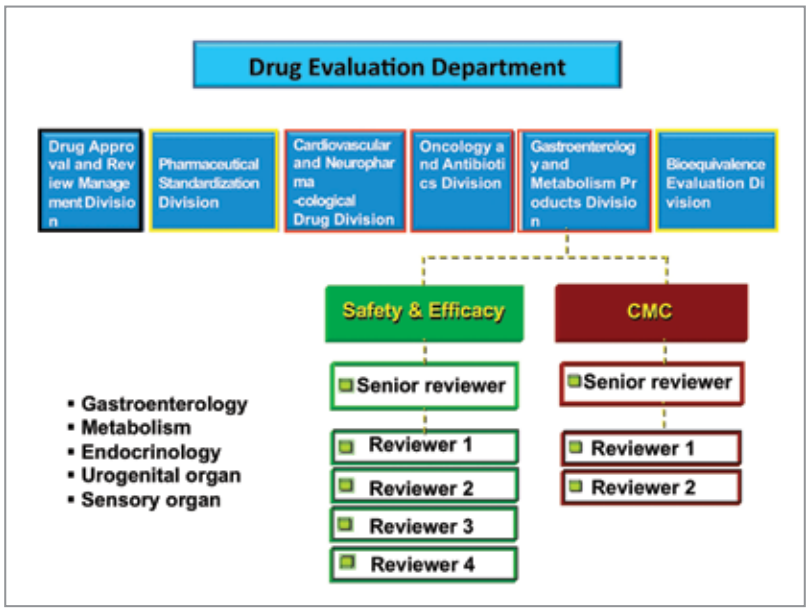


Figure 15. Reviewers in the six departments of the KFDA evaluate the safety, efficacy and CMC aspects of new medicines.

To enhance the consistency and expertise of reviewers, peer review is practiced at regularly scheduled meetings in which reviewers explain the rationale for their decisions to their department. In addition, taskforce teams are formed on an ad hoc basis to manage urgent or temporary reviews such as the reclassification of prescription and over-the-counter drugs.

After approval, labels are updated for new chemical entities through the submission of safety data for six years or 3,000 patients so the KFDA can examine and identify adverse events that had not occurred in the course of development. Labels are then re-evaluated and data exclusivity is guaranteed (if relevant) to sponsors during that additional time of review. For designated classes of drugs there is also a periodic re-evaluation of data, documents and study results. For example, in 2013, all cardiovascular drugs will be re-evaluated and all sponsors must submit the latest scientific information concerning their drug to the KFDA, who will review the data to update or unify the labels. In instances in which additional safety concerns have been raised, the KFDA may request that the sponsors conduct additional clinical trials, after which the label will be updated or the product will be withdrawn depending on the results of the study.

The KFDA is committed to performing quality reviews. Dr Shin concluded by remarking that despite the challenge of confidentiality issues, intensive communication with other agencies who are simultaneously reviewing the same data package may be the best method for meeting the challenge of constrained resources.

Decision making within agencies – What are the key frameworks and processes?

The Indonesian experience

Dra Lucky S. Slamet

Head of National Agency of Drug and Food Control, Republic of Indonesia

Various factors affect marketing approval for a new drug, including the quality of the review process, the quality of the dossier and other factors such as the management of public health expectations for a new medicine, growing concerns regarding safety issues and resource limitations. In addition, marketing authorisation must be based on good-quality decisions that are scientifically sound, finalised within time targets, procedurally predictable and legally and scientifically consistent. This pre-market control of decision making requires the consistent application of good, clear, defined processes by well- trained people employing good management review practices.

The principles of risk-based evaluation of medicines require that regulatory assessments be scientific and evidence based. Preclinical, product development, clinical protocol design and clinical studies data must be carefully evaluated and potential benefits assessed versus risks. Product- or product class-related and clinical and target population safety issues must also be identified and evaluated. To ensure safe and consistent production of new medicines, quality control for the production process must be enforced and CMC, stability study and validation process data evaluated and facility requirements inspected.

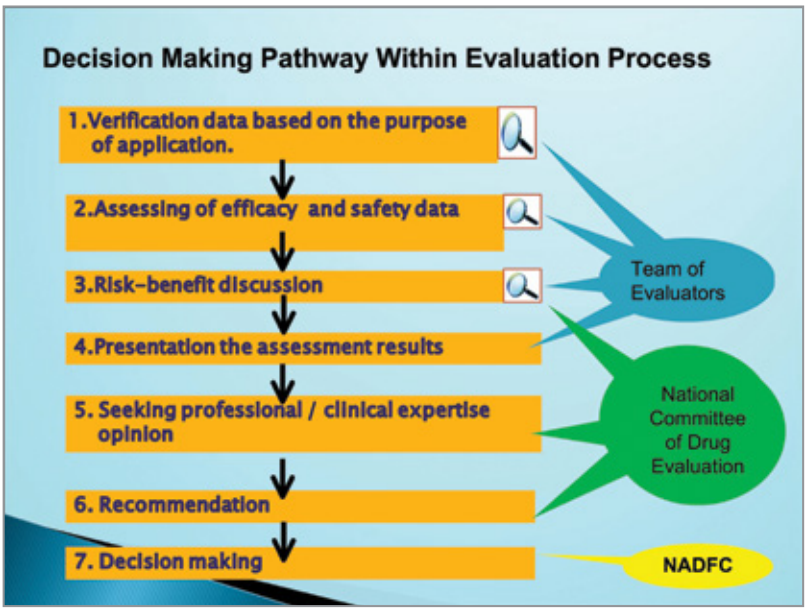


Figure 16. Decision pathway for new medicines as practiced by the Indonesian NADFC.

Decision making within the NADFC

In the Indonesian National Agency for Drug and Food Control (NADFC), the decision-making pathway begins with the assessment of the data in the application by a team of evaluators, who consider both the medical science justification for the product and the public health need. The review team next evaluates both the data for the product's safety and efficacy and its benefits and risks. At the next stage, the assessment results are presented by the team of evaluators to the National Committee of Drug Evaluation. The Committee discusses these results and after seeking additional expert opinions and advice, renders a recommendation (Figure 16).

Case studies

Dra Slamet presented two examples of the use of scientific information as the basis of regulatory decisions in Indonesia. In the first case, a regulatory decision was made for the determination of the age group indicated for treatment in the marketing authorisation for an HPV vaccine. Although the vaccine was approved in Australia for patients from 10 to 45 years of age and the EMA approval was granted with no upward limit on age, the NAFDC limited approval for use of the vaccine to patients 10 to 25 years of age, based on its interpretation of the clinical data that showed superior efficacy in this age group (Figure 17).

In a second example, although the US FDA and the EMA granted approval to ulipristal acetate tablet for emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure, the NADFC review and subsequent approval limited the indication for use within 72 hours (3 days) of unprotected sexual intercourse or contraceptive failure. The rationale for this decision was based on the agency's assessment of clinical study data that demonstrated that the product significantly lowered the observed pregnancy rate when administered within 72 hours after unprotected intercourse. Efficacy within 72-120 hours was not considered to be confirmed because of the limited amount of patients that had used the product within that timeframe; that is, 63

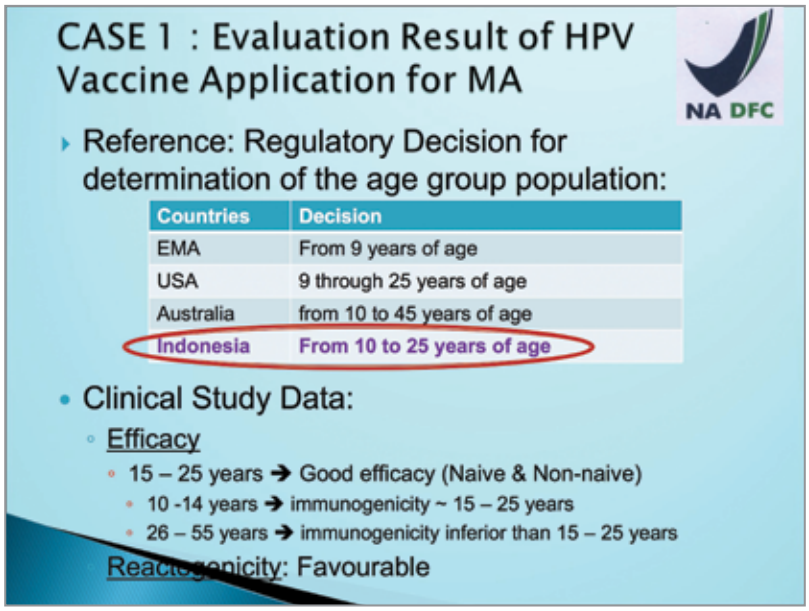


Figure 17. The NAFDC limited the indicated age for the HPV vaccine based on clinical trial efficacy results.

patients had used the product at 72-96 hours, whilst 34 patients used the product within 96-120 hours. In addition, the use of the product 120 hours after unprotected intercourse was not regarded by the NADFC as rescue medication or emergency contraception.

To ensure the safety, efficacy and quality of medicines, the NADFC regulatory framework relies on adherence to good review practice principles of transparency and clarity, responsiveness and flexibility to meet the needs of the Indonesian population. Principles of efficacy and safety are aligned with international standards and the agency's credibility is maintained through the consistent application of practices and procedures. To ensure robust decision making, the NADFC employs a risk-based approach and its decisions are based on scientific evidence, knowledge and experience as well as the needs of the community. Post-approval monitoring of the safety and effectiveness of new medicines is conducted and the agency routinely practices good decision documentation and effective communication.

Challenges remain, however. Moving forward the NADFC will seek to improve consistency by increasing the competency of both internal and external evaluators and by maintaining compliance with current international guidelines as a reference for evaluation. The predictability of decision making will be enhanced by developing quality management systems (QMS) and guidelines and improving communication with applicants and timeliness will also be increased through the development of QMS and a benchmarking strategy.

In conclusion, good regulatory decision making needs to be supported by substantiated clinical data for efficacy and safety and by objective science-based assessment approaches based on knowledge and experience. An effective regulatory framework requires adherence to good review practice. The benefits and risks of new medicines need to be evaluated considering both the target population and medical science. Agencies should develop a benchmarking strategy and consider models of abridged review to meet the challenges of resource constraint. Finally, successful regulatory agencies should establish effective channels of communication with other established National Medicines Regulatory Authorities to understand the rationale of different regulatory decisions.

. . . good regulatory decision making needs to be supported by substantiated clinical data for efficacy and safety and by objective science-based assessment approaches based on knowledge and experiences

Decision making within agencies – a view from MPA, Sweden

Prof Tomas Salmonson

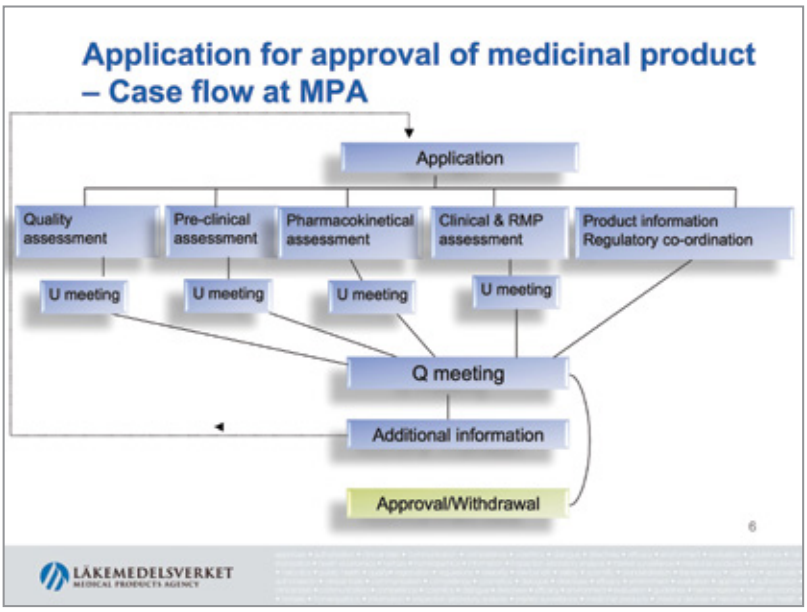
Chair, CHMP, Director, Medical Products Agency, Sweden

Decision making within the MPA

Because decisions rendered at the Medical Products Agency (MPA) in Sweden are regarded as not considered to be reflective of the opinion of an individual assessor but rather the agency as a whole, there is a clear consistency in MPA decision making when compared across therapeutic areas and against past decisions.

Product evaluation at the MPA proceeds through teams that perform quality, preclinical, pharmacokinetic clinical and risk management plan assessments. During the process of review, assessors conduct meetings that are open to all other assessors called U meetings, which in addition to providing the quality assurance measure of peer review, also function as an educational opportunity for new reviewers. After all reviews have been completed, a summary report of product information containing an overview and summary of the benefits and risks of the new product are written by the group and presented at a meeting of the Quality Assurance Group or Q meeting. The Quality Assurance Group focuses on the product overview and the links between the different parts of the assessments to derive the final MPA position and provide recommendations to the Health Outcomes Authority (Figure 18).

Figure 18. The new product review process at the MPA.



Additional requirements

A comprehensive review procedure that includes the use of templates and instructions for their use and a clear benefit-risk section is an essential requirement for good decision making. In addition to a well-defined structure, standing operating procedure and guidelines; however, there are additional requirements for good regulatory decision making. For example, support from other regulators during assessment and training are critical needs, especially for new assessors. Training new reviewers at the MPA mainly focuses on the process of peer review and internal and external collegial discussions.

To strengthen decision-making capabilities, regulators must develop a strong competency in methodology but it is also important that regulators, particularly novice assessors, should have a clear and common understanding of their role. That is, it is important to recognise that the primary function of regulators is not to prevent marketing through labelling restrictions or to consider the financial aspects of new medicines but to function as true patient representatives. For this reason it may be necessary to obtain more patient input to develop that perspective. Finally, it is vital that regulatory agencies foster the scientific environment that will encourage the open professional dialogue essential to quality decision making.

. . . it is vital that regulatory agencies foster the scientific environment that will encourage the open professional dialogue essential to quality decision making.

How is the decision made to submit a new medicine within companies?

Framework and decision-making processes

Dr Paul Huckle

Chief Regulatory Officer, GlaxoSmithKline

When GlaxoSmithKline embarks on the process of new product development, a multifunctional group assesses the clinical need within a therapeutic area that must be addressed and the ideal product profile to meet that need. The team must determine which benefits the proposed product would have to demonstrate for appropriate populations and what an acceptable safety profile would comprise. In addition, the product's commercial viability must be evaluated, that is, whether it can be developed and manufactured at reasonable cost that would permit a commercial return for the shareholders' investment.

Once having identified an opportunity for development, a clinical development programme must be designed that will elicit the data necessary to ultimately produce a regulatory filing. As the data are generated during development they are continually assessed against that ideal product profile that was established at the project's initiation and development programmes may be modified or even terminated as a result of that ongoing assessment.

Meanwhile, a continual assessment of the external landscape is also taking place in which the successes or failures of competitors, the decisions that regulators are making around similar products and any emerging treatment guidelines can all provide valuable information that can impact the direction of development. In addition, by accessing scientific advice within the intended jurisdictions for the product, sponsors ensure that the development programme remains on course to fulfil differing regional data requirements.

The day-to-day progression of a product under development is undertaken by a multi-disciplinary project team. Driven by a team leader, these teams vary in size and draw experts from different functional groups within the pharmaceutical company. Whilst it is the new trend within many companies for the teams to be staffed by more experienced members who are empowered to directly make decisions on a daily basis, the project teams are supported in their decisions by specialty sub-teams. For example, a clinical team may drive the implementation of clinical studies, while a chemistry manufacturing controls team makes decisions regarding the manufacturing process (Figure 19).

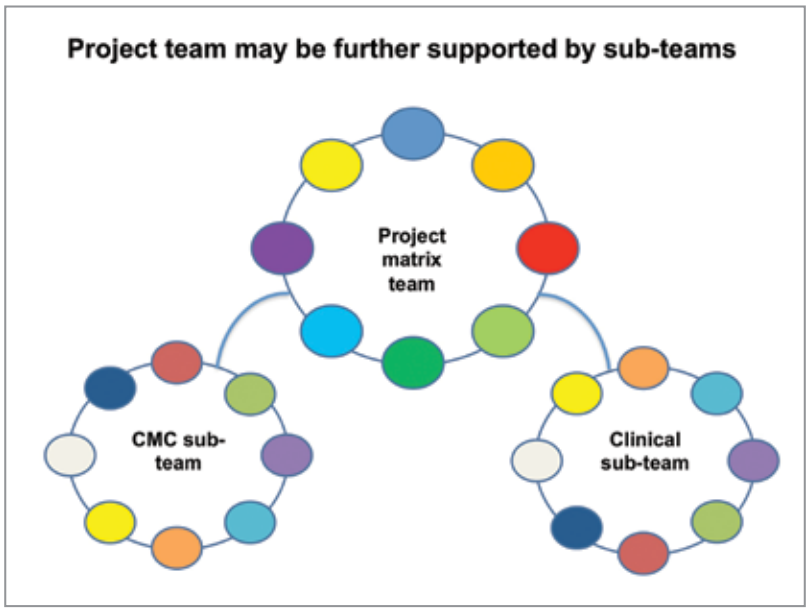


Figure 19. Decision making within product development teams is assisted by experts in specialty sub-teams.

For some medicines, further complexity is added to the control of the decision-making process because of co-development agreements between companies who share development, cost and activities. As previously mentioned, a product profile must be continually assessed throughout its life cycle for alignment with emerging data and decision making. Occasionally, a product development program will generate new data that provides an additional, unforeseen opportunity to expand the product profile but typically, the data are applied for comparison against the target profile benchmark of safety and efficacy, especially at the time of confirmatory studies and commitment to launch (Figure 20). Ongoing checks are performed for CMC readiness and the scientific robustness of data and their potential to satisfy regulatory requirements.

In a scientific review of a product in development at GSK, the underlying science and internal logic of data for the product are evaluated by a panel of experts drawn from different functions from outside the project team who can examine the performance of the drug

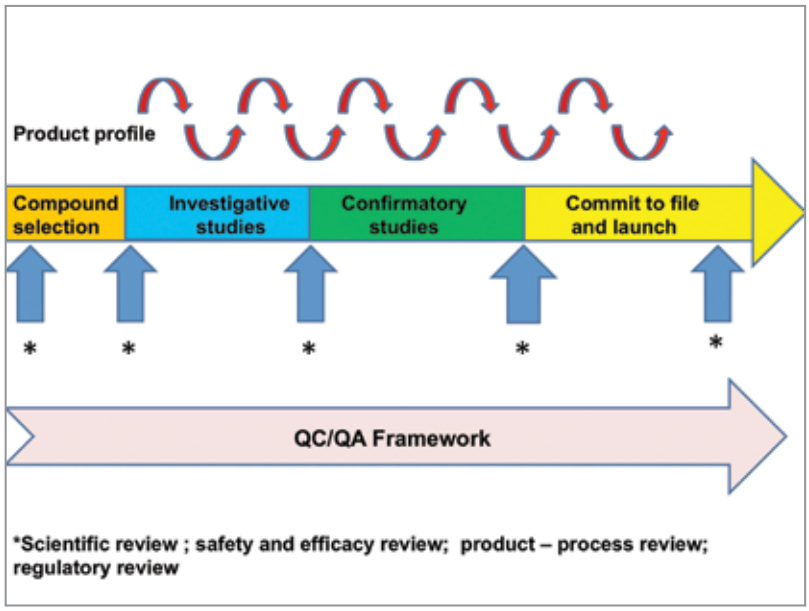


Figure 20. Quality control checks are performed throughout the life cycle of new products.

against a hypothesis for efficacy and safety in a fresh and objective way. As a result of such an evaluation, a product team may be asked to address a perceived evidence gap by additional research.

The next stage of review before submission is a safety review conducted by a multi-disciplinary panel of experts who will make the final determination if a product can be used in a safe way by its intended patient population. This panel examines the benefit-risk assessment for the product that was made by the project and safety teams and the alignment of any proposed risk mitigation strategies with that assessment.

. . . the successes or failures of competitors, the decisions that regulators are making around similar products and any emerging treatment guidelines can all provide valuable information . . .

In parallel with the safety review, another panel evaluates the CMC aspects of the product and its manufacturing process and specifications checking for their consistency with other similar and competitive products as well as with established manufacturing standards. Finally, a regulatory review is conducted by a panel of experts external to the project to evaluate the product's performance against regulatory standards, precedents and requirements and its alignment with received scientific advice.

After a product has undergone these reviews, the recommendations of the review panels are evaluated by the GSK Portfolio Review Board, which spans the research and development, regulatory, safety and commercial divisions of the organisation, to obtain a final commitment to file. The governance process at GSK, in which multiple senior-level reviews that include the Chief Medical Officer, Chief Product Quality Officer and Chief Regulatory Officer, ensure that the quality, safety and efficacy of new products are evaluated thoroughly and objectively and that the correct decisions are being made from a company and societal perspective.

How are differences of opinion regarding proposed regulatory decisions or data interpretation dealt with at the US FDA?

Dr Murray M. Lumpkin

Commissioner's Senior Advisor and Representative for Global Issues, US Food and Drug Administration
Presentation date: 24 January 2013

One of the fundamental issues with which pharmaceutical regulatory agencies are tasked is to decide whether a product may be legally placed on a given market and, if so, under what caveats. Regulatory agencies do not have the luxury of protracted debate but rather must make the best decision possible on the basis of available data and input within a legally imposed time frame, as each decision or lack of decision by the agency produces consequences related to the availability of medicines. These regulatory decisions are ultimately based on what the data reveal about the quality, safety and efficacy of a product in the tested population and what the implications of the data are for the intended population and the larger public health context of the community – all of which are critical factors on which medicines regulators are focused.

The review of marketing applications is conducted by humans practicing both the art and science of medicines regulation for products that continue to grow in complexity. In fact, application review and decision making is a highly complex process involving many people who care deeply about what they are doing and who feel intensely the responsibilities they have undertaken and the potential consequences of their analyses, opinions and decisions. Scientists also see issues through their own lenses of knowledge, experience and feelings – so differences of opinion among staff in regulatory agencies are inevitable – and ultimately, a good thing. Open, free, scientific debate without fear of retribution and in a respectful environment is the healthy foundation on which all science and health issues must be discussed and evaluated whether within a regulatory agency, by healthcare companies, or by the larger community. At the same time, however, regulators must also be respectful of applicable laws governing personal privacy and confidentiality of certain types of information.

Differences of opinion can fall into three categories

1. Scientific, that is, those that relate to an analysis of data;
2. Interpretive, that is, how these data relate to the promotion and protection of public health in the regulator's community. For example, do the benefits outweigh the risks, will the community tolerate the benefit-risk profile, or what is yet unknown about the drug; can the risks be adequately managed and communicated given the current risk management and communication tools available in the specific community? and
3. Regulatory, that is, what is the "best" possible decision based on law, regulation, science, precedents and public health concerns – all of which have equities in the regulatory decision-making process.

When an agency has to make its final decision for the community, there can be challenges associated with resolving lingering differences of opinion and making a decision with which all decision makers ultimately might not agree. These challenges include fostering the necessary recognition and acceptance among colleagues of the fact that that rational people can come to different conclusions. Managers, who are also scientists, must also try to help team members appreciate their expertise and related roles in the decision-making process and to value the scientific perspective that managers, who are scientists, can bring to the discussion and to the decision-making process.

Further complexity is added to the resolution of differences in opinion because although there is "at the table" equality among all disciplines in the review team (including, for example, physicians, chemists, toxicologists, microbiologists, statisticians, epidemiologists, lawyers, pharmacists, project managers and inspectors), there is, nonetheless, a hierarchy of scientific expertise in the FDA review team and management chain of command that must be acknowledged and that might be change, depending on the fundament difference of opinion at issue. Finally, it must be recognised

. . . it is vital that regulatory agencies foster the scientific environment that will encourage the open professional dialogue essential to quality decision making.

that while all team members have the right to be heard, no one person, other than the person to whom decision-authority is down-delegated by regulation, has the right to prevail. Most who are very closely involved with a particular application may only be empowered by regulation to make a recommendation about rather than make the actual regulatory decision in the name of the agency.

The resolution of any differences of opinion must be managed well and all perspectives genuinely heard in order to help fully inform the ultimate regulatory decision. To maintain the trust of internal and external stakeholders, the integrity of the decision-making process must be upheld by activities that are grounded in the principles of transparency, consistency and documentation. The morale of all those involved must be maintained through fairness, openness and genuine mutual respect. It should be recognised that after all appropriate input is obtained, an agency must reach an institutional decision and needs to do so efficiently within legislative, regulatory and practical time limits. The agency cannot regulate either by internal autocracy or by a need for 100% consensus but rather by an understanding of who is designated to be the decision maker with the delegated responsibility and authority to make the decision and document how all viewpoints were taken into consideration. In fact, in many cases, the decision maker is the legal signatory authority to grant an authorisation, such as the Commissioner, Deputy Commissioners, Center Directors, Office Directors or Division Directors.

The goal of "alignment," within the regulatory decision-making context, has been documented by the FDA as "a state of general support for a position to be taken or a decision to be made. Alignment does not necessarily mean full agreement by all disciplines and organisational components involved in a decision. Rather, alignment indicates that all involved individuals agree to support the action to be taken. This alignment should be based on the knowledge that all perspectives (including alternative opinions) and a range of potential options were considered and informed and justified the final action. Therefore, the action to be taken can be considered reasonable, even if the action differs from an individual's recommendation(s)."

Dispute resolution, if required, is typically informal and in most cases, alignment or agreement is achieved through informal discussions as reviews proceed. Such discussions must be undertaken in ways that recognise and respect the independence of each person and with the respect of each party for the need to be consistent with the administrative and scientific policies of their discipline and organisational unit. Discussion and collaboration should be non-coercive and non-retaliatory and appropriate documentation through the administrative record is governed by regulations that specify, among other things, that rather than changing a signed decision document, a cover note documenting dissenting opinions should ideally be included. FDA decision making must include respect for both person and process and alignment achieved if at all possible.

A process has also been developed if a formal appeal is required based on a significant issue of public health. In such cases, the dissenting individual is responsible to raise the issue within his/her management chain:

"If one of the disciplines or organizational components cannot align with a pending interdisciplinary decision because the proposed action is believed to be counter to law, regulation, interpretation of data, or existing precedent without adequate justification for deviation, or will result in a significant adverse impact on public health and safety, the decision should be escalated up the management chain."

Appeals can be made both within each Center and, if needed, to the Agency Scientific Dispute Process Review Board, chaired by the Agency's Chief Scientist, who will make a recommendation to the FDA Commissioner. Based on this recommendation, the Commission will in turn focus on certain basic questions:

- Did the Center follows its processes and provide adequate opportunity for an appellant to express his/her concerns?
- Has all relevant evidence bearing on the scientific question at issue been considered?
- Should the dispute be remanded to the Center Director for corrective action?

These formal and informal processes provide a mechanism for appeal for individuals with dissenting opinions regarding regulatory decisions they feel will have a serious negative impact on public health, although the basic aim is to resolve differences of opinion through the process of trying to reach alignment.

References

1. FDA Administrative Practices Regulations – 21 CFR 10.70 and 10.75. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=10 Accessed May 2013.
2. 21st Century Review Desk Reference Guide for NDA and BLA Reviews (NDA/BLA Review Process), version 12/3/09. Available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf Accessed May 2013.
3. CDER MAPP 4151.8 "Equal Voice": Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions, Effective 9/16/10. Available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm229014.pdf Accessed May 2013.
4. CDER MAPP 4151.1 Revision 1 Scientific/Regulatory Dispute Resolution for Individuals within a Management Chain, Effective 9/16/10. Available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm073557.pdf Accessed May 2013.
5. CDER MAPP 4151.2 Revision 1 Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director Effective 9/16/10 Available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm073558.pdf Accessed May 2013.
6. FDA Staff Manual Guide 9010.1, Scientific Dispute Resolution at FDA, Effective 1/13/09. Available at http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm215422.htm Accessed May 2013.

Improving regulatory decision-making: What role do Scientific Advisory Committees play?

Dr Bruno Flamion

Past Chair, Scientific Advice Working Party of the CHMP and Committee for Reimbursement of Medicines, Belgium; Professor of Physiology & Pharmacology, University of Namur, Belgium

Regulators, who are expected to maintain the highest level of knowledge and expertise in their field, often require expert assistance as the complexity of science and medicine continues to grow. Both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) utilise expert advisors in this regard and both agencies are now also enlisting the assistance and input of patients.

FDA Advisory Committees

At the FDA, special government employees, who may be top-level clinicians with high levels of expertise in clinical trials can work up to 130 days per year after providing confidential financial disclosure reports. If the FDA grants a waiver to a special government employee to participate in an ad hoc advisory committee public disclosure of any potential conflict of interest statements for the employees may also be required. Meetings of these committees are publicly held and this external opinion becomes part of the public record of FDA decision on applications for medicines.

In an analysis of the effect of Advisory Committee recommendations and FDA decision making, Smith and colleagues found a negative and positive predictive value of 86% and 88% respectively. This research also demonstrated the effect of the recommendations on the timing of FDA decisions. When 33% or fewer committee members vote in favour of the approval of a new medicine, the FDA can take as long as 699 days to render a final decision, whilst a positive vote by 33% to 66% of committee members results in a decision within 191 days and positive recommendations by 67% or more of committee members reduces the decision timing to 140 days.[1] However, the general cost effectiveness of FDA Advisory Committees has been called into question. In addition, although it has not often been an issue, potential conflicts of interest for individual Advisory Committee members can be controversial as it was when the *New York Times* revealed that ten of thirty-two experts on a panel reviewing COX-2 inhibitors had strong financial links with the industry involved in developing these drugs.[2]

EMA Advisors

At the EMA, rapporteurs and assessors consult a network of national experts included in a European Experts list, who have all met acceptable levels of conflict of interest. These experts are included in early-stage evaluations and may attend sessions of the Committee for Medicinal products for Human Use (CHMP), thus exposing CHMP members to clinician advice. Meanwhile, key opinion leaders (KOLs) may be recruited by a medicine's sponsor to provide explanations for CHMP members during oral testimonies, which are the subject of critical listening by the CHMP.

If additional clarity is required, the CHMP will convene a Scientific Advisory Group (SAG) meeting. Created by the CHMP as consultative bodies for specific purposes or difficult decisions on new products, SAGs are composed of 12 core members plus additional members as needed.

SAGs can be convened on extremely short notice, provide answers to specific questions and may vote if needed, although the CHMP remains responsible for its final decision.

SAG meetings are not public but the proceedings are usually reflected in the EMA European Public Assessment Reports (EPARs).

SAG meetings are convened in cases of major public health interest for which public controversy might be expected; for example as part of the review of first-in-class new medicines. They may also be held in reviews containing

- substantial disagreement between CHMP members,
- complex technical aspects,
- medicines for rare diseases,
- products with post-marketing issues such as risk minimisation measures affecting clinical practice, major post-authorisation safety issues or the design and feasibility of a clinical trial. [3]

A SAG meeting may also be requested by a sponsor in case of a requested re-examination, as it was for example in the re-examination of a type II variation for panitumumab (Vecatbix) in the treatment of metastatic colorectal cancer in combination with FOLFOX/FOLFIRI. In its initial opinion, the EMA decided that the application to extend the indication to treatment of metastatic colorectal carcinoma in combination with chemotherapy was not approvable because

"The two pivotal studies do not show robust evidence of benefit for the addition of panitumumab to oxaliplatin- or irinotecan-based chemotherapies in the treatment of wild-type KRAS tumours. Furthermore, the harmful effect of the combination with oxaliplatin in patients with mutant KRAS tumours is a major concern"

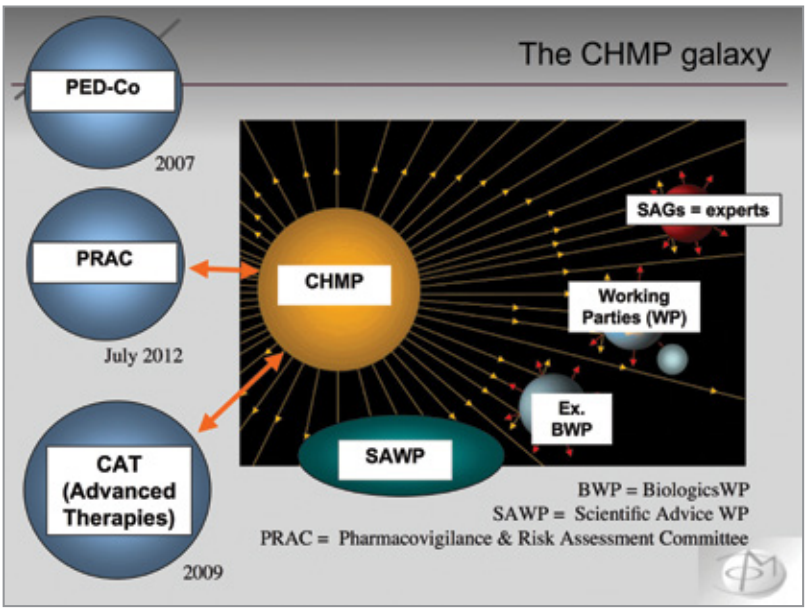
Upon its evaluation, however, the Oncology SAG convened for this re-examination considered that the clinical efficacy of panitumumab in the first-line treatment of wild-type KRAS, metastatic colorectal cancer in combination with FOLFOX was demonstrated and that the toxicity seemed to be manageable. After considering the SAG arguments, other evidence and the proposal for a robust risk management plan, the CHMP subsequently revised its initial opinion and granted the variation for this treatment.[4]

The Oncology SAG may be utilised for the evaluation of therapies for which the benefit-risk profile is considered negative or marginally positive or where there is concern regarding the clinical meaningfulness of benefits or the clinical impact of risks, the need for further studies or the lack of a biologic rationale to support findings or if the use of the therapy would be in disagreement with current treatment guidelines.

Ad hoc SAGs are convened for those products not falling within the remit of the nine established EMA SAGs. Approximately twenty-five SAG meetings are held per year and those present may include core members plus the optional experts, EMA staff and patient, healthcare or scientific society representatives. The sponsoring company may be invited to present their views but cannot be present during the SAG internal discussions.

The EMA policy on handling conflicts of interest states that all interests in the pharmaceutical industry must be declared and are made public in the European Experts list. Direct interests in pharmaceutical industry such as those associated with a consultancy or strategic advisory role, even unpaid, or ownership of a patent are considered as Level 3 conflicts and are acceptable for SAG core members and additional members. Employment or financial interests in companies, however, is not accepted and if a member is involved in current consultancy work they are excluded from meetings on relevant products. Those whose past consultancy work or current status as a principal investigator result in a Level 2 conflict status may attend SAG meetings but are excluded from conclusions or voting on relevant products.

Figure 21. The CHMP interacts with various external groups, each providing a high level of expertise.



. . . all regulatory agencies can benefit from unbiased scientific advice from external experts for optimal decision making.

In addition to SAGs, the CHMP also interacts with groups providing a high level of scientific input based on experience and expertise such as Working Parties, the Pharmacovigilance and Risk Assessment Committee (PRAC), the Scientific Advice Working Party (SAWP) and the Committee for Advanced Therapies (CAT). SAWP, for example, is composed of 27 members, 10 of whom are academic scientists/clinicians who are not full-time members of their National Regulatory Authorities and whose experience with innovative therapies can bring fresh perspective to CHMP evaluations (Figure 21).

The use of patients as external experts in CHMP decision making is considered by some to be controversial. With the agreement of the CHMP, the EMA often consults patient or healthcare professional organisations with no ties to the pharmaceutical industry during marketing authorisation procedures. However, patient organisations are not available for all diseases and patients have limited knowledge and experience with regulatory systems. With this limitation in mind, the European Patients Academy on Therapeutic Innovation (EUPATI) was initiated in Copenhagen in 2012. It is the goal of this initiative to train 100 patient journalists, ambassadors and trainers through a certification programme; to provide educational tools such as slides, webinars and videos for 12,000 patient advocates and an internet library providing information on specific aspects of medicine development for 100,000 individuals with low health literacy.

Prof Flamion concluded his presentation by reiterating that all regulatory agencies can benefit from unbiased scientific advice from external experts for optimal decision making. However, this advice requires that potential conflicts of interest be dealt with in a consistent way. Each agency should set up and assess its own system of scientific advisors. The EMA's subtle mixture of internal and external expertise at various stages of the procedures is an interesting model for consideration but like all models, the cost-effectiveness of obtaining external advice must be seriously evaluated.

References

1. Smith JF, Townsend SA, Singh N, Ma P. FDA advisory committee meeting outcomes. *Nat Rev Drug Discov.* 2012; 11:513-514.
2. Harris G, Berenson A. Ten voters on panel backing pain pills had industry ties. *New York Times;* 25 Feb 2005.
3. Committee for Medicinal Products for Human Use (CHMP). *Procedural Advice for CHMP on the need to convene a SAG or Ad Hoc Expert Meeting.* Found at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/07/WC500109577.pdf Accessed May 2013.
4. European Medicines Agency. *European Public Assessment Report: Vectabix (panitumumab)* 2011. Found at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000741/WC500118765.pdf. Accessed May 2013.

Use of external experts as part of the review

Noorizam Ibrahim

Deputy Director, National Pharmaceutical Control Bureau, Malaysia

Healthcare stakeholders have multiple and varied expectations from the regulators of new medicines. Patients expect treatment using the latest medical innovations, timely access to these innovations and accountability and trustworthiness in regulators. Prescribers expect drugs to be reviewed and approved in a judicious manner and that these medicines will meet the standards for quality, efficacy and safety. They also assume standards for timely access, flexibility, responsiveness and confidence will be met by regulatory agencies. For their part, industry expects that regulators will work toward streamlining bureaucratic procedures, harmonisation of standards and technical requirements and predictability in process and procedures.

Mission, roles and responsibilities

In 1984, the Control of Drugs and Cosmetics Regulations Act empowered the Drug Control Authority (DCA) to implement drug registration in Malaysia. Established in 1985, the objectives of the DCA are to ensure the safety, efficacy and quality of pharmaceutical, traditional, cosmetic and veterinary products marketed in Malaysia. The DCA is led by the Director-General of Health, the Senior Director of Pharmaceutical Services, the Director of the National Pharmaceutical Control Bureau (NPCB) and eight members appointed by the Minister of Health.

The NPCB which was set up in 1978, currently serves as the Secretariat to DCA. The NPCB, which is led by the Director of Regulatory Pharmacy, comprises the Centers for Product Registration, Compliance and Licensing, Post-Registration, Quality Control, Organization and Development and Investigation of New Products. The NPCB is entrusted to carry out regulatory activities through registration and licensing of manufacturers, importers, wholesalers and distributors. Their mission is to ensure the quality and safety of and education about pharmaceutical products through the implementation of relevant legislation working together in strategic alliance toward improving the health of the people. The regulatory missions of the NPCB are registration, pharmacovigilance, surveillance, analysis, licensing and education. The functions of the organisation include the evaluation and registration of products, the issuance of certificates of pharmaceutical product (CPP) and certificates of free sale (CFS), sample analysis, inspection and licensing of manufacturers', importers' and wholesalers' premises; the issuance of licenses for clinical trials; post-registration market surveillance; adverse drug reaction (ADR) monitoring; dissemination of drug information; training and international and regional collaboration.

The registration process

The registration process for new medicines in Malaysia begins with the pre-submission registration application. After the submission, the application and screening process is initiated and data are evaluated by the Product Evaluation Committee and Drug Control Authority. Parallel to these processes, testing of product samples is conducted. Finally the NPCB either approves, licenses and then initiates the post-marketing surveillance for the new product or rejects the application, which the sponsor may appeal (Figure 22).

Along with the recommendations of NPCB Product Evaluation Committee, the assessments of scientific data and recommendations of the external experts are part of the evaluation and final decision rendered by the DCA.

New products are evaluated for quality, safety and efficacy through procedures adopted and adapted from the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). The Drug Registration Guidance Document (DRGD) is employed as the reference guide for both pharmaceutical products for human use and complementary medicines. Separate guidelines are available for biotechnology and biosimilar and veterinary products. Association of Southeast Asian Nation (ASEAN) Working Technical Guidelines are also utilised. DCA decision making is also supported by Technical Working Groups, National Committees, external experts and dialogues with all stakeholders (Figure 23).

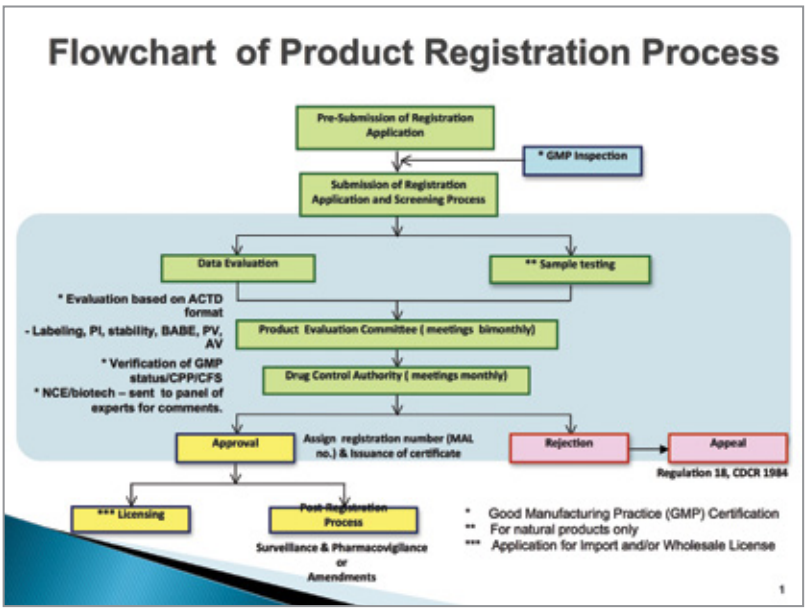
Scientific internal reviews of product quality are conducted by in-house evaluators and an in-house Product Evaluation Committee who make recommendation to the DCA. External reviews of safety and efficacy are performed by clinical experts in relevant disciplines appointed by an Advisory Committee in the Ministry of Health, with feedback from relevant associations.

External experts

External experts are provided with clinical reports and current data and requested to indicate through the use of assessment templates the drug's

- short- and long-term safety issues;
- efficacy and therapeutic advantages against other therapies;
- suitability of proposed indications;

Figure 22. The process for the regulatory review of new medicines in Malaysia.



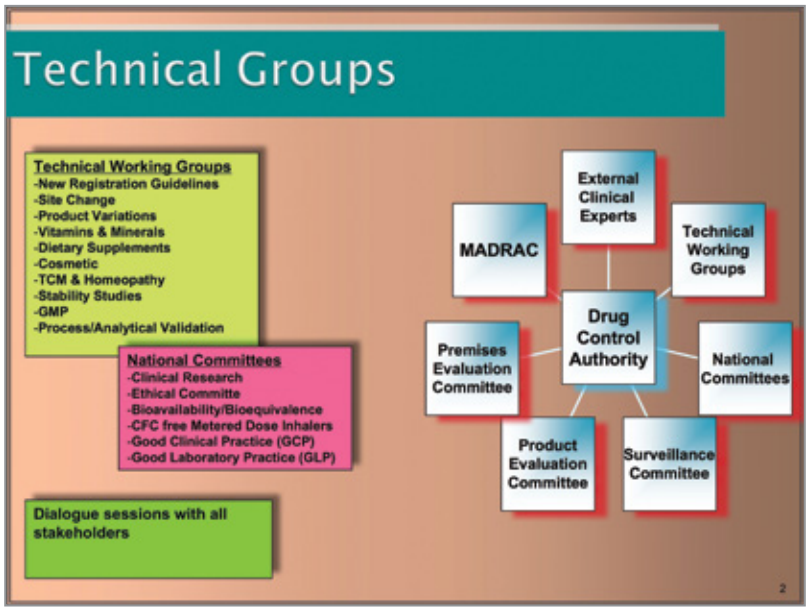


Figure 23. The Malaysian DCA is supported through the efforts of various committees and technical groups.

- limitations that should be included in labelling;
- any comparisons with reference drugs and
- accrued experience of the utilization of the drug culminating with their recommendations to approve, not approve or approve with limitations.

Along with the recommendations of NPCB Product Evaluation Committee, the assessments of scientific data and recommendations of the external experts are part of the evaluation and final decision rendered by the DCA. DCA decisions are transmitted within three days and there is a mechanism for sponsor appeal of negative opinions.

Standardisation, certification and cooperation

The DCA is recognised as a participating World Health Organization Collaborative Center, a member of the Pharmaceutical Inspection Cooperation Scheme and is accredited and certified according to the Malaysian Standard of the International Organisation for Standardisation International Electrotechnical Commission (MS IOS/ IEC).

In addition, through the NPCB, the Ministry of Health of Malaysia signed a Memorandum of Understanding with the Singapore Health Sciences Authority in 2012 to exchange information and strengthen ties with that country.

Data protection or data exclusivity for new chemical entities and additional indications has been in force since 2011. Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S) requirements for all new applications have been required since 2012 in Malaysia and the accreditation of local and international bioequivalence clinical testing facilities was also imposed that year as well.

The way forward

In the near future, Malaysia looks to the implementation of an integrated on-line system known as QUEST 3 plus. They will continue to reinforce good manufacturing processes and process validation and quality control for traditional manufacturers. Surveillance activities for new medicines will be intensified and inspections of clinical testing facilities and the use good clinical practices, bioavailability and bioequivalence studies and good laboratory practices will be strengthened. Greater emphasis will be placed on research and development regulations and the enforcement of international manufacturing, clinical and laboratory standards and practices and the control of Advanced Therapy Products (ATPs). Finally, Malaysia will work to extend the scope of its MS ISO/IEC surveillance activities.

The progressive continuous quality improvement initiatives of the Malaysia DCA reflect its serious commitment to ensure the timely delivery of safe, high-quality and efficacious products to the public while employing the use of strategic partnerships, international standards and benchmarking and best practice approaches.

What do companies see as the benefits and issues for agencies sharing assessment reports?

Dr Florence Houn

VP, Regulatory Policy and Strategy, Celgene Corporation

Although almost all information today can be rapidly disseminated and sharing of data among healthcare stakeholders is already occurring, there is recognition of sensitivities around communicating confidential commercial information, trade secrets and personal privacy. With those sensitivities in mind, transparency around the boundaries, definitions and procedures of sharing and disclosures would be helpful for all those concerned. Moreover, it must be recognised that because regulatory authorities share information it does not mean that those authorities will arrive at the same regulatory decisions.

Agencies typically share information through their websites, press releases that are issued relative to agency actions, communications regarding threats to public health represented by counterfeit medicine or supply chain issues and through decision-making documents and letters to sponsors. Additionally, agencies can direct companies to share information with other companies and to other external groups such as journals, or officials conducting trials or hearings.

Considerable benefits can be accrued to companies through these communications including the promotion of mutual understanding of data through the discussion of science, data and interpretations. Differences based on legal frameworks and issues of geographic relevance versus those of judgement and scientific interpretation can be clarified and savings in time and resources realised through the elimination of duplicative efforts. Finally, sharing can foster convergence on national standards and approaches.

There are important caveats to sharing. Information that is commercially sensitive, trade secrets, personal information or internal agency pre-decisional information must be handled properly. It is critical that the ground rules for information sharing be understood, such as when sponsor permission is needed and when sponsors should be informed. Because concerns may persist that trade secret information might be divulged without the consent of the owner, the sharing of non-public information should be conducted under confidentiality commitments and other legal structures. There should be a legal basis for sharing information government-to-governmental with the public disclosure of confidentiality agreements, memoranda of understanding and cooperative agreements.

. . . it is critical that stakeholders understand how shared assessment reports are used and what procedures, accountabilities and programmes for evaluation and improvement of the information sharing are in place.

The future of sharing and cooperation can be guided by international guidelines and recommendations. Movements towards international regulatory convergence are already taking place through the efforts of organisations such as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Asia Pacific Economic Cooperation (APEC) and the Pan-American Network for Drug Regulatory Harmonization (PANDRH). Partnerships with non-profits, the World Health Organisation, industry and academia can also foster these efforts.

Endeavours in this regard may also act to facilitate multi-regional clinical trials and capacity can be built within regulatory agencies through activities such as shared inspections and developing systems through which the shared data are able to be housed or analysed. Dr Houn concluded by citing the recent recommendation from the Institute of Medicine which underlined the value of agency-shared information and which called for countries with stringent regulatory agency systems to convene a working group to foster the sharing of inspection reports to avoid duplication of efforts and to establish mutual recognition of reports among international agencies.[1]

Reference

1. Institute of Medicine of the National Academies. *Strengthening core elements of regulatory systems in developing countries.* Found at http://www.iom.edu/Activities/Global/RegulatoryCoreElements.aspx
Accessed May 2013.

Simcere's recent experiences in IND/NDA review and approval in China

Dr Peng Wang

Chief Scientific Officer, Simcere

Established in 1995, Simcere Pharmaceutical Group employs approximately 4,400 employees and has two research and development centres in China, with capabilities ranging from early-stage discovery to clinical operations. In addition, seven facilities support small-molecule and biologics manufacturing, employing the highest standards of transparency and compliance with good manufacturing processes.

More than 8% of Simcere revenues are invested in research and development and the company specialises in first-in-market generics and innovative products through internal discovery and international collaborations. Because the number of investigational new drugs in China is low compared with Western economies, at the present time these international collaborations remain an important focus for Simcere (Figure 24).

Simcere has a robust pipeline, with eight regulatory filings for innovative products, over the last three years. Dr Wang presented case studies of review by the Chinese Center for Drug Evaluation (CDE) for three of those products.

Figure 24. International collaborations are an important focus for Simcere.

The CDE follows principles of scientific review and openness and former gaps in filing requirements and review capability are being closed.

The first example was an NDA application for Iremod (iguratimod) for the treatment of rheumatoid arthritis, which was submitted by Simcere to the CDE shortly after a submission by another company in a western country. The CDE conducted an independent and science-based review of the product with a focus on risk mitigation strategies and Iremod received the first-in-world approval in China as a Category 1.1 new drug.

In the second example, which represents a model for future collaboration between companies in emerging markets and companies from the West, Simcere and BMS created a novel co-development model in China for the oncology development candidate BMS-817378. The submitted data package consisted primarily of BMS data, supplemented by Simcere, which also performed all the chemistry, manufacturing and control development according to Chinese regulations. The open and science-based CDE review supported the Simcere international collaboration strategy and the review and approval process was one of the fastest in recent years.

The final example of CDE review of a Simcere application was for Edaravone Injection (edaravone-borneol) for the treatment of stroke. Edaravone is a free radical scavenger, approved for stroke in Japan and China. Borneol is a key ingredient in several traditional Chinese medicines with anti-inflammatory activities but had not yet been approved as a pure chemical entity. This novel, unique combination is a first-in-class drug candidate from Simcere research and development, with strong scientific rationale and a preclinical development data package generated by three laboratories using different animal models and pharmacology parameters. These data demonstrated better efficacy than with edaravone monotherapy and an extended therapeutic time window, achieved with lower doses, potentially fulfilling unmet medical need with decreased safety risks (Figure 25). The application was approved in a relatively short time period and Simcere has completed phase 1 development in China and is preparing for R&D filing in the United States.

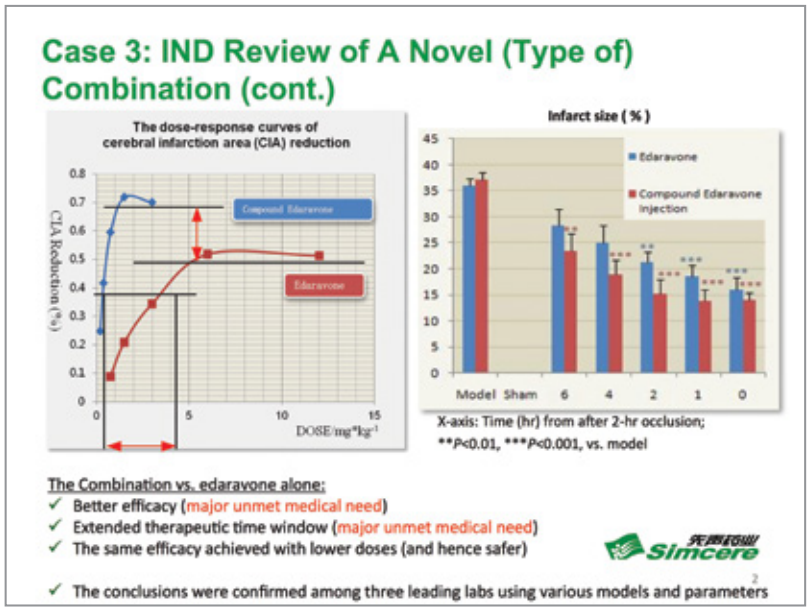


Figure 25. The investigative new drug application for the Simcere novel combination product Edaravone Injection (edaravone-borneol) was supported by a well-developed preclinical data package.

The CDE follows principles of scientific review and openness and former gaps in filing requirements and review capability are being closed. Among recent enhancements, the agency has begun to publish review summaries and has established a standard operating procedure for managing meetings with sponsors. The review process, however, remains lengthy and some administrative steps such as certificate preparation should be simplified or expedited. For their part, Chinese pharmaceutical companies play a critical role in research and development in China and are gradually becoming a primary force in innovation. These companies, however, must adjust their thinking and strategies in order to adapt to ongoing regulatory changes and there remains significant room for better and more effective communication among stakeholders.

How the evolution of regulatory science supports training, alignment and regulatory convergence, which can underpin good review practices and good decision-making practices

Lembit Rägo

Coordinator, Quality Assurance and Safety: Medicines, Essential Medicines and Health Products Health Systems and Innovation, World Health Organization, Geneva, Switzerland

The evolution of regulatory science

As regulatory science continues to evolve, quality testing has progressed to understanding how quality is built into products, including new concepts for quality control such as designs that assess and diminish quality risks. Simple efficacy and safety assessment has advanced to become benefit-risk assessment and continues to develop into more complex decision making about benefits and risks. In fact, the entire basis of regulatory decision making has moved forward in terms of the number of specific scientific and more general guidances available -- to the extent that no single evaluator can absorb them.

Despite this evolution in regulatory science, huge gaps in regulatory capacity exist in different countries in terms of human and financial resources, with for example, the number of regulators in individual jurisdictions ranging from less than one to 10,000. Significant differences also persist in regulatory expertise and the level to which regulatory functions are effectively performed, the availability of proper systematic training for regulators and the application of quality management principles. In addition, adherence to general good governance principles varies widely as does the set up of regulatory systems on both macro and micro levels. Unfortunately, no clear vision or policy exists to set up regulatory systems and

Figure 26. Factors required for quality, transparency, clarity, consistency and timeliness in the regulation of medicines.

there are no harmonised views on what exact competencies are needed for regulators, nor any core curricula for training.

In addition to these disparities, new products are likely to be more complex and sophisticated, demanding advanced health systems and "quality use," giving rise to questions as to their suitability for use in economies with less than optimal health systems or health providers. It may need to be determined if regulatory benefit-risk assessment should consider the health systems in which products are to be used or if this issue should be addressed by health technology assessors, provided of course, that health technology assessment exists in the economy in question.

Industry sees regulations as a means to create a more predictable environment for assessing the quality, safety and efficacy of innovative products. Naturally, when the same scientific guidelines and data sets are employed by different regulatory and health technology agencies, disparate decisions often result, leading to questions as to how to create more predictability around decision making that cannot be easily qualified. It has been proposed that better structured quality decision-making processes may lead to more predictable decisions today and tomorrow.

What is WHO doing that can facilitate good decision-making processes?

Because health systems depend on the availability of safe, quality health products

It may need to be determined if regulatory benefit-risk assessment should consider the health systems in which products are to be used . . .

such as medicines, vaccines and medical devices, the World Health Organization actively promotes good governance and transparency in the emerging pharmaceutical sector and promotes and facilitates building nascent national regulatory systems as part of overall strengthening of health systems and step toward the goal of universal health coverage.

WHO has accumulated significant experience in assessing national regulatory systems with the objectives of identifying gaps and helping to develop institutional development plans and determining the qualifications of country authority to fulfil essential regulatory functions for the administration of vaccines. The WHO Assessment Tool for National Health Products Regulatory Systems addresses good review practice elements and is constantly evaluated for changes necessitated by the developing regulatory environment.

To help to assess national regulatory systems WHO has performed sixty-one assessments of fifty-five national regulatory systems and in 2010, the organization published a synthesis of the rapid assessment findings from national medicines regulatory authorities in twenty-six African countries. In addition, WHO facilitates information exchange and work sharing and various training courses and capacity building among regulatory agencies through such organisations as the Pan American Network for Drug Regulatory Harmonization (PANDRH), WHO Paediatric Regulators Network, the WHO Blood Regulators Network, the Medicines Transparency Alliance and the International Conference of Drug Regulatory Authorities (ICDRA).

Discussions on good review practice have been an important component of ICDRA meetings. At the 12th ICDRA meeting in Korea in 2006, specific recommendations were made.

- WHO should continue supporting country efforts to improve regulatory review processes in the context of overall improvement and implementation of good regulatory practices.
- Special emphasis should be given to helping small regulatory authorities; existing models may need to be adapted to match the resources available.

- Regulators should make efforts to implement good review practices in order to improve regulatory systems through the introduction of good regulatory practices.
- Regulators should consider the road map approach, standardised formats for dossiers, disclosure of information, use of outside consultants and quality management systems as useful tools for the improvement of review practices.

Conclusions

Good review practice is evolving to keep pace with the development of regulatory science and what is currently considered "good" may change. Basic good governance and applicable laws and regulations in the public sector, harmonisation of technical requirements and good regulatory practices underpin good regulatory decision making, hopefully resulting in better medicines (Figure 26).

Transparency of decisions – how good are agencies in communicating to their stakeholders?

Prof Steffen Thirstrup

Director of Licensing Division, Danish Health and Medicines Authority

CHMP assessment reports

The centralised regulatory procedure of the European Medicines Agency (EMA) allows one application for a new medicine to be submitted for marketing within 27 member states of the European Union. After a maximum 210-day evaluation, the Committee for Medicinal Product for Human Use (CHMP) provides an opinion on the application to the European Commission, which issues the final decision. The CHMP evaluation is a multi-step process. After an evaluation of the quality, efficacy and safety of the new product, the Rapporteur and Co-Rapporteur issue assessment reports on Day 80. Comments from other CHMP members are then incorporated into the report and by Day 120, a list of questions is forwarded to the product's sponsor. At this point, the clock is stopped while sponsors prepare their responses to the questions, which they typically provide within two months. By Day 180, the CHMP issues its opinion regarding the application, followed by and EU Commission decision within approximately three months.

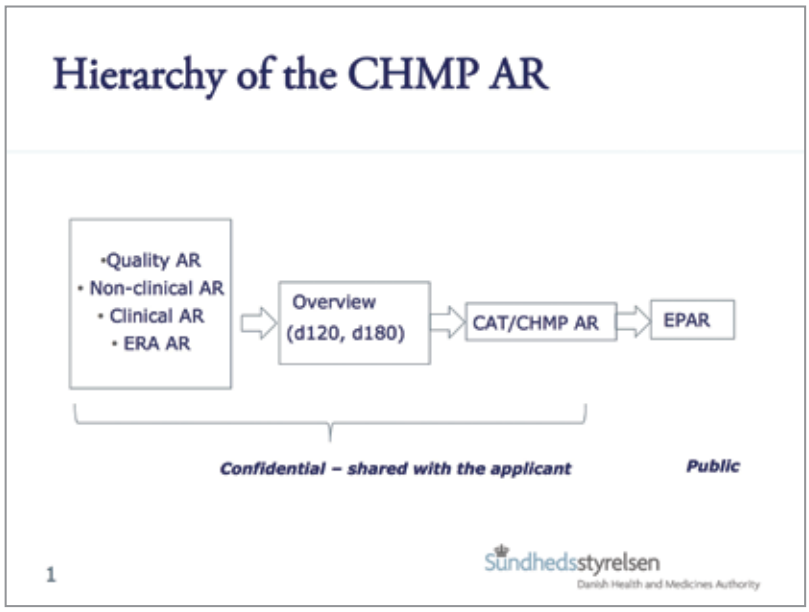


Figure 27. Full CHMP ARs are available to the sponsor of a new medicine and EPARs are available to all stakeholders after a final decision on an application has been issued. AR = assessment report; ERA = environmental assessment report; d = day; CAT = Committee for Advanced Therapies; CHMP = Committee for Medicinal Products for Human Use; EPAR = European Public Assessment Report.

A product of the regulatory evaluation of an application to market a new medicine, the Assessment Report is an important method for regulatory authorities to convey their viewpoints concerning the application to the sponsor but the volume of information contained in the documents can present a challenge for both the regulator and applicant. Regulatory agencies distil thousands of pages associated with the regulatory submission and review into a single assessment report but the size of this document continues to increase and is currently at more than 250 pages.

Full confidential assessment reports are provided to the sponsor, which include the opinions and rationale of the Rapporteurs' evaluations. In addition to the full report, after the final decision for the product has been issued, the European Public Assessment Report (EPAR), which contains the final assessment report without the confidential information is also produced (Figure 27). EPARs for all submitted applications are available on the EMA website, including those for applications that resulted in negative decisions

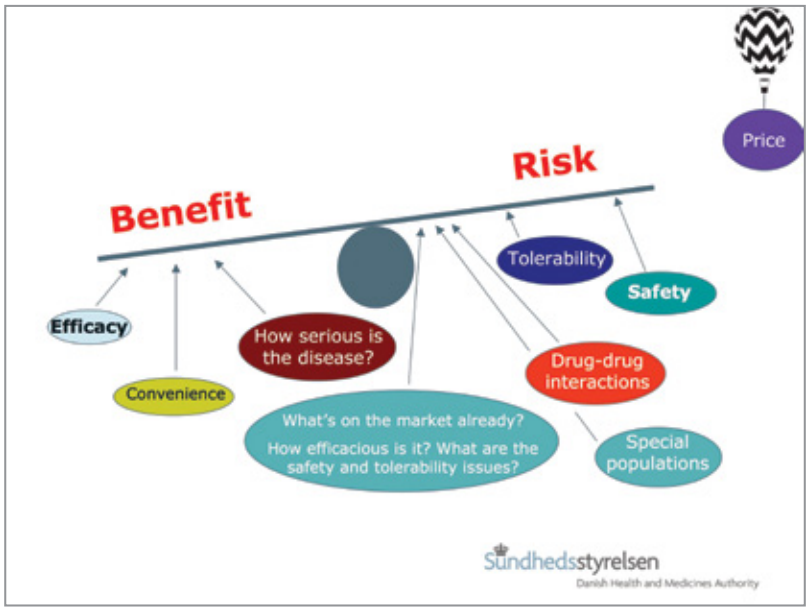


Figure 28. Many factors are applied to the benefit-risk evaluation of new medicines.

as well as for approved products. Withdrawal Assessment Reports are also available for products that were approved but subsequently removed from the market.

Regulatory transparency to sponsors can be enhanced by the sharing of assessment reports at each step of the procedure, the provision of the final list of questions and possible clarification meetings with the Rapporteurs. The rationale for decisions is reflected in the factual text in the list of questions, the assessment report and the separate section on of the assessment report on benefit-risk. Regulatory transparency to other stakeholders is ensured by the development and accessibility of the EPAR. Unlike the Summary of Product Characteristics (SmPC) or Product Information Leaflet (PIL), which provide information about a new product, the EPAR communicates the decision-making process for that product.

There is, however, a recognised potential for improvement for EPARs including the addition of input from other stakeholders such as health technology assessors. In addition, in has been proposed that the transparency of the document could be enhanced through the provision of information regarding potential conflicts of interest for experts and committee member reviewers and its usability by outside stakeholders could be improved by a reduction in the use of abbreviations and jargon. Finally, in response to criticism regarding the unavailability of clinical data for new medicines, the EMA is moving toward making this information more readily accessible to all users; however, the agency's concerns persist regarding the potential for misleading analysis of pooled data from studies with different designs.

. . . the assessment report is an important method for regulatory authorities to convey their viewpoints concerning the application to the sponsor but the volume of information contained in the documents can present a challenge for both the regulator and applicant.

Many important issues factor into the benefit-risk evaluations of new medicines conducted by regulators such as safety, efficacy, tolerability, convenience and unmet medical needs (Figure 28), However, it can be challenging to communicate the rationale for the relative importance that has been applied to these parameters by regulators. It may be useful, therefore, for regulators to employ methods for visualisation such as representing the beneficial and negative effects of a medicine as colours of a traffic signal in order to convey the medicine's overall benefit-risk profile to stakeholders, particularly to patients and other non-professionals.

Conclusions

Transparency is essential in regulatory agency communication. Currently it is primarily achieved through lengthy written documents, which can be challenging to navigate. Assessments reports and questions reflect the decision process of regulators but the rationale for the final decision may be difficult to extract. To enhance clarity of the reports, benefit-risk decision making should be summarised in a dedicated structured section of an assessment report and tools for visualisation of these concepts utilised whenever possible.

What are the future challenges, opportunities and strategies to evolving the core competency and capacity of the CDE?

ZHANG Peipei

Center Director, Center for Drug Evaluation, SFDA, PR China

The Chinese Center for Drug Evaluation (CDE) of the State Food and Drug Administration (SFDA) is a young and relatively small agency currently facing many challenges and opportunities. As detailed by Dr Feng (p 21) the CDE has undergone significant changes since its beginnings in 1985 when the review of new medicines was conducted entirely by external experts. Since 2011 the CDE has engaged in efforts to increase the transparency of the regulatory review process in China and as the number of innovative products being reviewed increased dramatically, reviews have changed from being process-based to evidence-based (Figure 29).

A number of factors have influenced the strategic direction of the CDE.

- They are the gatekeeper to public health and medicine for 1.3 billion people whose welfare must be the first consideration in all decisions.
- The CDE must promote and support innovation that will be beneficial to the Chinese population, who are an aging population with an increased life expectancy. The agency must also consider that delays in approval may increase the cost of bringing innovative products and therapies to the market, which is particularly important for the significant number of patients who may not be able to afford new medicines.
- The agency must guide the efforts of Chinese research and development to lead the way in the ongoing changes in pharmaceutical development, which include the increasing globalisation of medicine, the growth in personalised therapies and the shift from chemistry to biotechnology-based products.
- As a rapidly growing agency, the CDE must increase and enhance its resource capability.
- The right balance must be achieved between the benefits and risk of innovation.

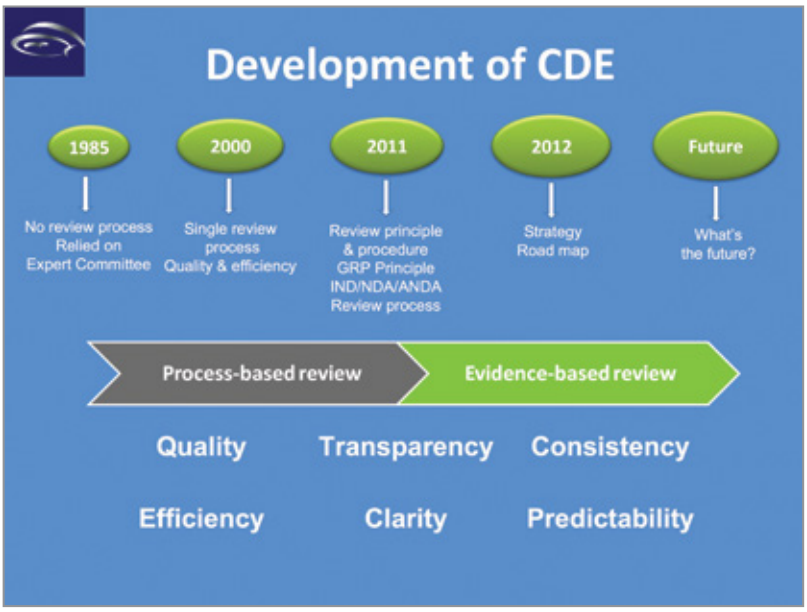


Figure 29. The Chinese Center for Drug Evaluation has undergone significant changes since it was formed in 1985.

Strategies

Regulatory science is the core driving force to promote CDE's development and high-quality standards will be maintained in data collection, analysis and discussion and decision making. Qualitative templates have been established that follow the model of the Common Technical Document. The CDE works to sustain transparent communications with sponsors, healthcare professionals and the public and to that end have developed a useful, well-organised website that provides information that includes drug safety information to the public and medical professionals and maintains communication channels with sponsors. Customer orientation is a key component of the CDE workforce development strategy.

Workforce development: Because high-quality decision making requires high-quality talent, the CDE provides training in management and leadership to its staff, working to develop professional expertise and knowledge, communication skills and learning in new technologies. Ongoing efforts are also being made to increase personnel numbers and to recruit staff of the highest quality.

Partnerships are being forged with healthcare professionals, academic institutions and scientists to bridge gaps in staffing and to share information, knowledge and therapeutic area expertise in order to better understand patient needs and to remain abreast of developments in life science.

International cooperation and the maintenance of strong communication channels with independent institutes and international experts is a CDE priority and the agency has become active participants in international meetings such as those conducted by the Drug Information Association (DIA) and the International Conference for the Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH).

Dr Zhang concluded her presentation by stating that the mission of the CDE is to protect and promote public health by ensuring safe drug use and their vision is to become an agency of international standards based on the values of openness, innovation, trust, evidence and impartiality.

Because high-quality decision making requires high-quality talent, the CDE provides training in management and leadership to its staff . . .

Appendix: Workshop Attendees

Regulatory and government agencies and academia		
Prof Sir Alasdair Breckenridge	Former Chairman	Medicines and Healthcare Products Regulatory Agency, UK
CHEN Zhen	Office Director, Office of New Drug Pharmaceutical Science	Center for Drug Evaluation, SFDA, P.R. China
CHENG Long	Senior Reviewer, Office of Management and Communication	Center for Drug Evaluation, SFDA, P.R. China
Prof Hans-Georg Eichler	Senior Medical Officer	European Medicines Agency
FENG Yi	Associate Center Director	Center for Drug Evaluation, SFDA, P.R. China
Prof Bruno Flamion	Professor of Pharmacology	University of Namur, Belgium
Dr Churn-Shiouh Gau	Executive Director	Center for Drug Evaluation
Dra Herawati	Head, Section of New Drug Evaluation Path II	National Agency of Drug and Food Control, Indonesia
Christopher Hickey	Country Director	US Food and Drug Administration, China Office
HUANG Qin	Office Director, Office of Biostatistics, CDE	Center for Drug Evaluation, SFDA, P.R. China
HUANG Xiaolong	Deputy Office Director, Office of Generic Drug Pharmaceutical Science	Center for Drug Evaluation, SFDA, P.R. China
Noorizam Ibrahim	Deputy Director	National Pharmaceutical Control Bureau, Malaysia
Juliati	Head of Section of Biological Product Evaluation	National Agency of Drug and Food Control, Indonesia
James Leong	Senior Regulatory Specialist	Health Sciences Authority, Singapore
LIU Lu	Senior Reviewer, Office of Management and Communication	Center for Drug Evaluation, SFDA, P.R. China
Dr Murray Lumpkin	Commissioner's Senior Advisor and Representative for Global Issues	Food and Drug Administration, USA
Prof Robert Peterson	Executive Director	Drug Safety and Effectiveness Network, Canadian Institutes of Health Research
Dr Lembit Rägo	Coordinator, Quality Assurance and Safety: Medicines, Essential Medicines and Health Products Health Systems and Innovation	World Health Organisation, Switzerland
Barbara Sabourin	Director General, Therapeutic Products Directorate	Health Canada
Dr Tomas Salmonson	CHMP Chair	Medical Products Agency, Sweden
Dr Won Shin	Division Director, Division of Gastroenterology and Metabolism Products, Department of Drug Evaluation	Korea Food and Drug Administration
Dra Lucky Slamet	Head	National Agency of Drug and Food Control, Indonesia
Prof Steffen Thirstrup	Head of Licensing Division	Danish Health and Medicines Authority
Gang Wang	Assistant Country Director	US Food and Drug Administration, China Office
WANG Quinli	Office Director, Office of Pharmacology and Toxicology	Center for Drug Evaluation, SFDA, P.R. China
YANG Jinbo	Deputy Office Director, Office of Clinical Evaluation II	Center for Drug Evaluation, SFDA, P.R. China
YANG Zhimin	Office Director, Office of Clinical Evaluation I	Center for Drug Evaluation, SFDA, P.R. China
YIN Li	Commissioner	State Food and Drug Administration, P.R. China
ZHANG Peipei	Center Director	Center for Drug Evaluation, SFDA, P.R. China
ZHENG Xiaoqiong	Pharmacist, Information Center	SFDA, P.R. China

Pharmaceutical industry		
Dr Stephane Andre	Head of EU/ROW Regulatory Affairs	F. Hoffmann-La Roche Ltd, Switzerland
Dr Wen Chang	Vice President, North Asia Strategy and P.R. China Regulatory Sciences	Bristol-Myers Squibb, P.R. China
Dr Rong Chen	Head of Regulatory COE, P.R. China/HK	GlaxoSmithKline, P.R. China
Thuy Dang	Global Regulatory Affairs Operational Manager	Bayer HealthCare Pharmaceuticals, USA
Dr Susan Forda	Vice President, Global Regulatory Affairs, International	Eli Lilly and Company Limited, UK
Ying Gao	Executive Director and Head of Regulatory Affairs	Merck, Sharp & Dohme, P.R. China
Dr Mark Goldberger	Divisional Vice President – Regulatory Policy and Intelligence	AbbVie, USA
Dr Florence Houn	Vice President, Regulatory Policy and Strategy	Celgene Corporation, USA
Lisa Hu	Senior Regulatory Specialist	Eisai China Inc, P.R. China
Laurence Huang	Executive Director, Regulatory Affairs	AstraZeneca Pharmaceutical Company, P.R. China
Dr Paul Huckle	Chief Regulatory Officer	GlaxoSmithKline, USA
Hiroki Kato	Director of Board	Zeria Pharmaceutical Co Ltd, Japan
Dr Thomas Kuhler	Vice President, Regulatory Policies and Intelligence	Novo Nordisk A/S, Denmark
Jie Li	Director, Regulatory Affairs	Pfizer Investment Ltd, P.R. China
Dr Zili Li	Executive Director and Head of Emerging Market Regulatory Strategy	Merck & Co, USA
Leyla Lister-Mora	Head of Emerging and Regional Affiliates	F. Hoffmann-La Roche Ltd, Switzerland
Janet Lu	Head of Regulatory Asia Pacific	Roche Holding Ltd, P.R. China
Dr Jesús Muñiz	Senior Director, Regulatory Policy and Intelligence	Shire Pharmaceuticals, USA
Sharon Olmstead	Global Head, Development and Regulatory Policy	Novartis, USA
Dr Joseph Scheeren	Head of Global Regulatory Affairs, Head of Global Development Asia	Bayer Healthcare Pharmaceuticals, P.R. China
Hidetoshi Shuto	Corporate Executive, Head of Japan Development Operation	Astellas Pharma Inc, Japan
Jennifer Tong	Associate Director - Regulatory Affairs	AstraZeneca Pharmaceutical Company, P.R. China
Dr Chris Walker	Executive Director, Regulatory Affairs	Amgen, UK
Dr Peng Wang	Chief Scientific Officer	Simcere Pharmaceutical Group, P.R. China
Dr Yamin Wang	Head, Global Regulatory Affairs, Asia Pacific	Bayer HealthCare Pharmaceuticals, Singapore
Lin Wei	Regulatory Policy and Operational Manager	Pfizer, P.R. China
Hua Zhang	Vice President, Head of Regulatory Affairs, P.R. China	Bayer Healthcare Company Limited, P.R. China

Centre for Innovation in Regulatory Science		
Patricia Connelly	Manager, Communications	
Lawrence Liberti	Executive Director	
Dr Neil McAuslane	Director	
Prisha Patel	Portfolio Manager	
Professor Stuart Walker	Founder	