REGIONAL ALIGNMENT IN ASIA PACIFIC:

WHAT NEEDS TO BE IN THE REGULATORY SCIENCE "TOOLKIT" TO ENABLE GOOD REGULATORY DECISION MAKING

WORKSHOP
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WORKSHOP REPORT

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The Institute has a distinct agenda dealing with regulatory affairs and their scientific basis, which is supported by an independent Advisory Board of regulatory experts.

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What needs to be in the regulatory science "toolkit" to enable good regulatory decision making

Section 1: Executive Summary

Background to the Workshop

Regulatory agencies are rising to meet the challenge posed by the reality in which companies are not only undertaking global clinical trials but are also looking to make their products available to patients worldwide in a timely, often almost simultaneous fashion. In the developing pharmaceutical markets this has put pressure on the evolution of regulatory policy, infrastructure and resources, while in established markets resource implications along with the duplicative nature of some of the work is resulting in an increasing emphasis on collaboration and sharing of resources where possible. As more agencies look to take a science-based approach to regulation and risk-based decision making, a common regulatory language is being developed as well as clarity around the resources required to approve and monitor new medicines. This has lead agencies to begin to discuss and work out how to cooperate in order to share information and activities, such as safety data and inspections, as well as exchange of staff. In addition, some agencies are looking to the exchange of assessment reports. Challenges to collaboration include differences in skill sets, experience and processes between agencies. The key question therefore is, what are the underpinning components of good regulatory decision making and what are the regulatory science tools that can be used to ensure a timely, high-quality, predictable and transparent process whilst ensuring an effective and efficient use of resources?

The key question therefore, is what are the underpinning components of good regulatory decision making and what are the regulatory science tools that can be used to ensure a timely, high-quality, predictable and transparent process whilst ensuring an effective and efficient use of resources?

The objectives of this Workshop were to:

- **Discuss good risk-based regulatory decision making** and what the components are that need to be built into the review process
- **Identify current initiatives/approaches** and understand how these are enabling the decision making process from companies and agencies perspective
- **Recommend what should be in the regulatory science "toolkit"** and how best this can be used as part of the regional alignment initiatives

The Workshop and its Syndicate Discussion Sessions provided a comprehensive look at and recommendations for the use of three key tools that can form the basis of a good regulatory decision making strategy: a Quality Scorecard for the assessment of dossiers and their reviews, a simple, standardised benefit-risk framework, and the foundational elements that can underpin the sharing of assessment reports among stakeholders. Each of these was addressed within the broader context of moves towards regionally harmonised regulatory activities.

Day 1, Part 1 Chairman, Dr Thomas Lönngren, *Former Director, European Medicines Agency*

Good decision making is linked to the use of a consistent, regionally acceptable science-based good review practices. Several speakers described the key elements of best practices that can be implemented by agencies, whether in developed or emerging markets.

Presentations

Dr Satoshi Toyoshima, *Senior Advisor, Pharmaceuticals and Medical Devices Agency (PMDA), Japan* reported on the status of the five components of the PMDA four-year action programme for new drug reviews: improving the consulting service and review system; promoting global drug development; improving measures for ensuring public safety and reassurance; strengthening international programs including collaboration with Asian regulators; and advancing regulatory science within the agency, industry and academia.

The holistic paradigm of the United States Food and Drug Administration for ensuring the safety and efficacy of drugs throughout their life cycles was described by **Dr Christopher Hickey**, *Director, China Office, U.S. Food and Drug Administration (FDA), China* which consisted of good review management principles and practices, oversight of post-market drug safety and harmonisation and collaboration with other regulatory authorities

Noting that the quality of regulatory decisions are dictated by their accuracy, predictability and transparency, **Dr Zili Li**, *Emerging Markets Regulatory Strategy and Policy Lead, Merck & Co Inc, USA* detailed the quality measures, continuous improvement initiatives, training and education of assessors and communication efforts being undertaken by thirteen regulatory authorities in the Emerging Markets to meet these goals.

As the Chair of the Asia Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC), **Mike Ward**, *Manager International Programs Division, Health Canada* detailed important new developments taking place within APEC in advancing regulatory harmonisation and cooperation, including the ratification of a multi-year strategic plan, moving from individual effort to more collective, coordinated and more effective action. A project plan to be implemented during 2011-2012 includes the development of a training program, a good review practice toolkit and a framework for the use and exchange of regulatory information.

According to **Dr Won Shin**, *Division Director, Korea Food and Drug Administration*, good review practices, training and international and regional cooperation are the most important platforms on which to build trust and partnership across agencies. This partnership is particularly important in the development of the rapidly growing Asian pharmaceutical market, which represents both the largest portion of the global population and an environment that highly encourages research and development.

Dr Neil McAuslane, *Scientific Director, CMR International Institute for Regulatory Science*, explained that because no agency works in isolation and because they are being judged by their stakeholders, timely, high-quality, predictable and transparent processes for the measurement of performance such as the Institute's Regulatory Benchmarking and Quality Scorecard programmes can help underpin good regulatory decisions, create a basis for improvement and aid in more predictable decision making.

At Swissmedic, performance measurement is directly related to strategic goals and they have measures related to employees, process, finance, stakeholders and mandate, the results of which are reported as a balanced scorecard. **Dr Petra Dörr**, *Head of Management Services and Networking* reported that benchmarking information can be used to support strategic planning discussion with stakeholders, and at Swissmedic such data have been used to support requests for additional resources to maintain global competitiveness.

Dr David Jefferys, *Senior Vice President, Global Regulatory and Healthcare Policy, Eisai Europe Ltd. UK* provided an industry wish list for regulatory performance by an agency: rapid assessment and outcome determination; pragmatic, proportionate, justified decisions; balanced and transparent benefit-risk assessment; and predictability. Judging an agency's performance by metric benchmarking, however, is complicated by the fact that performance targets reflect different country regulatory systems and involve different definitions.

Day 1, Part 2 Chairman, Professor Sir Alasdair Breckenridge, *Chairman, MHRA, UK*

Presentations

Following the Scientific Advice obtained from a regulatory agency is one of the strongest predictors of regulatory success yet identified; how to best provide this advice in a consistent manner that can drive both regulatory and reimbursement decisions remains a matter of discussion. As the former Chair of the Scientific Advice Working Party (SAWP) of the Committee for Medical products for Human Use (CHMP) **Professor Bruno Flamion**, *Chairman, Belgian Committee for Reimbursement of Medicines (CTG/CRM), Belgium* reported that receipt of unfavourable scientific advice from the SAWP is a negative factor toward achieving marketing authorisation in the EU if the company does not change its development plans accordingly. The SAWP would welcome the opportunity to provide parallel scientific advice with other regulatory bodies and expects that it would be provided in collaboration with key European HTA and payers organisations in the near future.

Dr Supriya Sharma, *Director General, Therapeutic Products Directorate, Health Canada* discussed the contribution of Good Review Practices (GRPs) to a well-functioning regulatory review system and to inter-agency cooperation. Although good

regulatory review is a highly subjective concept for which there is no easy measure, there are ten hallmarks that point to an independent, objective, scientific and timely analysis of information relevant to a marketing application. A good review is knowledge-based, uses critical analyses, identifies signals, investigates issues, makes linkages, considers context, involves consultation, and is balanced, thorough, and well documented.

During the course of this Workshop, it became clear that streamlining the regulatory process by sharing regulatory assessment reports is a win-win proposition for agencies in the Asia Pacific region. According to **Dr Meir-Chyun Tzou**, *Director, Division of Drugs and New Biotechnology Products, Food and Drug Administration, Chinese Taipei*, such collaboration will save resources, lead to better review quality and earlier approval of and access to medicines. A pilot study of best regulatory practice has been proposed to be conducted by APEC in 2011-2012.

Dr Joseph Scheeren, *SVP, Head of Global Regulatory Affairs. Bayer Healthcare, Pharmaceuticals Inc, USA* agreed that regulatory dialogue and sharing regulatory reports has many advantages and will allow a more efficient use of resources and earlier access to medicines. The chief challenges to this sharing will be language and standardisation barriers and a framework for partnership is required.

Dr Christina Lim, *Deputy Group Director, Health Products Regulation Group, Health Sciences Authority (HSA), Singapore* explained that although HSA does use information from other agencies in their decision making, the primary challenges in obtaining the best value for the exchange of regulatory reports are a lack of access to the data set submitted to other agencies in support of an application, the lack of avenues to seek clarification, and industry's expectation that regulatory approval in other countries would lead to HSA approval.

There is a clear need for a better understanding of why different agencies come to different conclusions when faced with essentially identical application data; this is a particularly challenging issue for regulatory agencies that are under growing pressure to increase transparency and accountability for their decision making. **Professor Stuart Walker**, *Founder of the Institute*, described the efforts underway to develop an international, structured, systematic and standardised benefit-risk framework as an essential part of the regulators' transparency armamentarium. He presented a summary of the seven steps of such a framework currently being developed by the Institute.

CONCLUSION

Day 2 Chairman, Professor Robert Peterson, *Executive Director, Drug Safety and Effectiveness Network. Canadian Institute of Health, Canada* concluded the Workshop presentations by reminding the audience that the primary objective of regulatory agencies is the timely, predictable review of new medicines, permitting market entry of products with a positive benefit-harm profile while demonstrating value to national or regional healthcare systems. Strategies to accomplish this objective successfully in an increasingly complex global environment include regional harmonisation, scientific advice prior to submission, measuring performance, and use of GRP and a benefit-risk framework. Strategies for efficiencies meanwhile, include sharing regulatory assessment reports, parallel reviews, multinational regulatory consortia, use of other regulator's decisions and regional safety surveillance.

General Recommendations Across Syndicates

1. To assess the real-world benefit in the Emerging Markets, the Institute should conduct a Workshop to explore the integration of a benefit-risk framework between regulatory and HTA bodies designed specifically for use by emerging market agencies
2. Conduct a pilot study including Indonesia, Malaysia, Philippines and Thailand in the implementation of a benefit-risk framework that would focus on steps 1-4 and 7 of the Institute's model
3. Encourage further progress in the work of the Institute's benefit-risk 4-Agency Consortium (TGA, HSA, Swissmedic, Health Canada) to serve as a model to other agencies
4. Using comments provided by the Syndicate, the Institute should reorganise the current survey by employing a more streamlined approach and by reducing the number of questions and then mapping them to broader categories; that is, using a bottom-up versus a top-down approach
5. Pilot the revised Quality Scorecard with selected emerging market agencies
6. Link the revised Quality Scorecard with the Asia Pacific Economic Good Review Practice (APEC GRP) initiative
7. Conduct a survey to review and understand the content and availability of assessment reports, determining the rationale for each agency's preferred format and the relative value of individual sections
8. Carry out a survey of agencies to understand their prioritised areas of resource constraint, identifying the strategic goal of resource needs and use, and acquiring feedback on what level and types of assessment would add the most value
9. Propose a submission and review model that formalises and defines a new review process using existing assessment reports and that includes a risk-based approach for assessments of new products with significant complexity or issues. Consider fees and timing incentives
10. Establish a secretariat or steering committee to oversee the steady advance and cooperation with agencies and sponsors; a pilot initiative between APEC Life Sciences Innovation Forum and the Institute is suggested

Workshop Programme

Day 1: Wednesday 26th January 2011	
Session: Evolution of good regulatory science and practice – Is this the key to successful regional alignment and effective use of regulatory resource?	
Chairman's welcome and introduction	**Dr Thomas Lönngren**, *Former Executive Director, EMA*
Good regulatory decision making: What are the key components that build predictability into the process?	
PMDA	**Dr Satoshi Toyoshima**, *Senior Advisor, Pharmaceuticals and Medical Devices Agency, Japan*
US FDA Viewpoint	**Dr Christopher Hickey**, *Director, China Office, U.S. Food and Drug Administration, China*
Industry Viewpoint	**Dr Zili Li**, *Emerging Markets Regulatory Strategy and Policy Lead, Merck & Co Inc, USA*
Regional harmonisation initiatives: Is there a need to have a good regulatory science platform on which to build trust and partnership across agencies and if so how can this be achieved?	
View of the Regional Harmonisation Steering Committee	**Mike Ward**, *Manager International Programs Division, Health Canada*
Agency Viewpoint	**Dr Won Shin**, *Division Director, Korea Food and Drug Administration*
Measuring performance across regulatory agencies: What can and should be measured?	
What measures can be used across agencies?	**Dr Neil McAuslane**, *Director, Institute for Regulatory Science*
Improving agency performance – What needs to be measured?	**Dr Petra Dörr**, *Head of Management Services and Networking, Swissmedic*
Why should regulatory agencies measure performance?	**Dr David Jefferys**, *Senior Vice President, Global Regulatory and Healthcare Policy, Eisai Europe Ltd, UK*
Session: Risk-based decision making	
Chairman's introduction	**Professor Sir Alasdair Breckenridge** , *Chairman, MHRA, UK*
Scientific advice/consultation during development – A critical component in the regulators armament to improve the regulatory outcome and decision making process?	**Professor Bruno Flamion**, *Chairman, Belgian Committee for Reimbursement of Medicines (CTG/CRM), Belgium*
Good regulatory review practice – What are the guiding principles and is this a critical success factor for across agency co-operation?	**Dr Supriya Sharma**, *Director General, Therapeutic Products Directorate, Health Canada*
Sharing assessment of regulatory approval or assessment reports – could this be an effective way for agencies in Asia Pacific to use regulatory resources?	
Agency Viewpoint	**Dr Meir-Chyun Tzou**, *Director, Division of Drugs and New Biotechnology Products, Food and Drug Administration, Taiwan, R.O.C*
Industry Viewpoint	**Dr Joseph Scheeren**, *SVP, Head of Global Regulatory Affairs, Bayer Healthcare, Pharmaceuticals Inc, USA*

Enabling the acceptability of other agency reviews – What are the critical success factors?	**Dr Christina Lim**, *Deputy Group Director, Health Products Regulation Group, Health Sciences Authority, Singapore*
Development of a benefit-risk framework in the regulatory review of medicines	**Professor Stuart Walker**, *Founder CMR International Institute for Regulatory Science*
What needs to be in the regulatory science 'toolkit' to enable good regulatory decision making? Summary of key points	**Professor Robert Peterson**, *Executive Director, Drug Safety and Effectiveness Network, Canadian Institute of Health, Canada*
DAY 2: Thursday 27th January 2011 - Closed Meeting for invited participants	
Chairman's introduction	**Professor Robert Peterson**
Syndicate session discussions	
Syndicate A: Benefit-risk balance Discussion on benefit-risk evaluation and what the development of a standardised structured pro forma for different types of regulatory review (verification, abridged, full) in the emerging markets encompasses	**Chair: Dr Lucky Slamet**, *Deputy for Therapeutic Products, Narcotics, Psychotropic and Addictive Substance Control, National Agency of Drug and Food Control, Indonesia* **Rapporteur: Jerry Stewart**, *Regulatory Policy Head Emerging Markets, Pfizer Inc, USA* **Facilitator: Professor Stuart Walker**, *CMR International Institute for Regulatory Science*
Syndicate B: Scorecard on the review and dossier submitted A review of the Scorecard developed for ICH countries and a discussion of how this could be used to aid emerging market countries and what parameters need to be included and excluded to ensure value to the agencies and companies	**Chair: Mike Ward**, *Manager International Programs Division, Health Canada* **Rapporteur: Carolyn Maranca**, *VP, Global Regulatory Affairs – Asia Pacific and Latin America, Johnson & Johnson PRD, USA* **Facilitator: Neil McAuslane**, *CMR International Institute for Regulatory Science*
Syndicate C: Sharing assessment reports for the review of new medicines Assessment reports provide key insights into the rationale for the approvals of a new medicine. Sharing assessment reports among agencies may in theory assist in the review process, thereby streamlining time to final decision. The use of a standardised report template could be key to meeting reviewers' expectations and contributing to a consistent and high-quality review. This syndicate discussed what needs to be place for this to occur and what such a document would look like	**Chair: Dr Herng-Der Chern**, *Executive Director Center for Drug Evaluation, Taiwan, R.O.C* **Rapporteur: Patrick O'Malley**, *Senior Director, International Regulatory Affairs, Eli Lilly & Co, USA* **Facilitator: Lawrence Liberti**, *CMR International Institute for Regulatory Science*
Syndicate feedback and discussion	
Chairman Summary and Institute next steps	

Section 2: Syndicate Discussions

Three syndicate groups were asked to discuss topics centred on regional alignment in the Asia Pacific region and elements of the regulatory science "toolkit" that enable good decision making. Syndicates developed recommendations for action centred on three core topics: standardising the assessment of benefit-risk, applying dossier Scorecards to the Emerging Markets, and determining best practices for sharing dossier assessment reports.

- **Syndicate 1:** A discussion on benefit-risk evaluation and what the development of a standardised structured pro forma for different types of regulatory review (Verification, Abridged, Full) in the Emerging Markets might encompass
- **Syndicate 2:** A review of the Quality Scorecard developed for countries participating in the International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and discussion of how this could be used to aid Emerging Market countries and what parameters need to be included or excluded to ensure value to the agencies and companies
- **Syndicate 3:** An analysis of shared assessment reports: Assessment reports provide key insights into the rationale for the approvals of a new medicine. Sharing assessment reports among agencies may in theory assist in the review process, thereby streamlining time to final decision. The use of a standardised report template could be key to meeting reviewers' expectations and contributing to a consistent and high quality review. As agencies move to share assessment reports what needs to be in place for this to occur and what would such a document look like?

The Chairpersons and Rapporteurs for the groups follow:

Syndicate 1	Chair:	**Dr Lucky Slamet**, *Deputy for Therapeutic Products, Narcotics, Psychotropic and Addictive Substance Control, National Agency of Drug and Food Control, Indonesia*
	Rapporteur:	**Jerry Stewart**, *Regulatory Policy Head Emerging Markets, Pfizer Inc, USA*
Syndicate 2	Chair:	**Mike Ward**, *Manager International Programs Division, Health Canada*
	Rapporteur:	**Carolyn Maranca**, *VP, Global Regulatory Affairs – Asia Pacific and Latin America, Johnson & Johnson PRD, USA*
Syndicate 3	Chair:	**Dr Herng-Der Chern**, *Executive Director Center for Drug Evaluation, Taiwan, R.O.C*
	Rapporteur:	**Patrick O'Malley**, *Senior Director, International Regulatory Affairs, Eli Lilly & Co, USA*

Syndicate 1: Benefit-risk balance

Background

A number of regulatory agencies are working on methodologies to standardise the benefit-risk evaluation of new medicines and to communicate the results of this evaluation to stakeholders. Professor Stuart Walker and the CMR International Institute for Regulatory Science (the Institute) have developed seven steps for the evaluation of benefit-risk for agencies undertaking full dossier reviews. Some agencies require approval in another market before conducting some form of abbreviated assessment within their own country. As agencies in the emerging markets improve their science-based risk assessment of new medicines, they will continue to face the need to evaluate the dataset to ensure the benefit-risk balance for their local population, a critical component of good regulatory decision making.

The objective of this syndicate group was to evaluate the seven steps for making a benefit-risk decision and to discuss and recommend how this process may be adapted to enable the different regulatory approval pathways (full approval, abridged and verification methods) used commonly within Emerging Market agencies.

Outcome of discussion

Critical issues

- A proactive Emerging Markets benefit-risk plan: Although benefit-risk evaluations are currently part of the regulatory review process in most Emerging Market countries, a formal codification would add structure, could improve the transparency of the overall assessment and facilitate inter-agency exchange of assessment reports. Countries with developing pharmaceutical markets should not wait for the US FDA or the European Medicines Agency to implement a fully defined benefit-risk framework before initiating their own work in this area
- Integrating benefit-risk throughout a product life cycle: To better understand a medicine's effectiveness, there should be a post-approval plan to study benefit-risk in "real-world" settings
- Link between HTA and regulatory assessments: Structured benefit-risk analysis can act to bridge regulatory and health technology assessment needs, as they are ultimately intertwined in public policy and stakeholder expectation
- Benefit-risk in the approval pathways: A formal benefit-risk assessment is part of the full and abridged but not the verification versions of Emerging Markets regulatory assessments and therefore, the use of a consistent framework will facilitate communication around this process
- The Institute model and Emerging Markets: In the construction of a benefit-risk framework for use in Emerging Market countries, consideration should be paid to the use of steps 1-4 and 7 in the model developed by the Institute. The complexity and resource-intensive nature of steps 5 (weighting of the benefits and the risks) and 6 (visualisation of the data), however, may render them beyond the capabilities of less experienced authorities

Recommendations

1. To assess the real-world benefit in the Emerging Markets, the Institute should conduct a Workshop to explore the integration of a benefit-risk framework between regulatory and HTA bodies designed specifically for use by emerging market agencies
2. Conduct a pilot study including Indonesia, Malaysia, Philippines and Thailand in the implementation of a benefit-risk framework that would focus on steps 1-4 and 7 of the Institute's model
3. Encourage further progress in the work of the Institute's benefit-risk 4-Agency Consortium (TGA, HSA, Swissmedic, Health Canada) to serve as a model to other agencies

Syndicate 2: The dossier and review quality

Background

A quality review is an essential component of good regulatory decision making. Quality itself is very difficult to measure, but performance indicators that can make up both a quality review and a quality submission have been developed. As agencies in emerging markets and in particular Asia develop their regulatory process and procedures and adopt good review practices, how can the concept of the Scorecard be adapted and what are the key components and needs?

The objective of this group was to discuss both the implications and the potential of the Quality Scorecard methodology already developed by the Institute and to make recommendations on changes needed for implementing the Scorecard in the Emerging Markets as well as potential use of the Scorecard to improve agencies' reviews and companies' submissions.

Outcome of discussion

Critical issues

- Scorecards and the Emerging Markets dossier: The general cconsensus was that Quality Scorecards are an appropriate element of the

regulatory toolkit, providing the opportunity to build confidence and trust among agencies by gaining a clear understanding of each ones strengths and weaknesses. However, many questions must be answered relative to their practical use, the goal of transparency among agencies and industry, and their relative place in the review process. It must be decided, for example, if Scorecards would be used only for the evaluation of new molecular entities or for all applications, including those for generic medicines and whether data collection would be prospective or retrospective, and which of these approaches would have less impact on the limited resources of Emerging Market agencies

- Added complexity of scorecard approach in Emerging Markets: In addition to rating the quality of the dossiers received from sponsors, health authorities may need to rate the quality of information received from other health authorities (assessment reports)
- Anonymity pros and cons: Although respondents may be more open and less guarded if Scorecards are anonymous, attributed responses may foster more open communication among all stakeholders
- Risk management plans must include strong compliance components
- Communication strategies are needed to engage stakeholders in the process, including developing partnership with patients in supporting the development of a new release model
- Different incentive strategies for all stakeholders must be considered
- Exclusivity, pricing/reimbursement issues need to be addressed by the HTA early during the development process

Recommendations

1. Using comments provided by this Syndicate, the Institute should reorganise the the current quality survey tool by employing a more streamlined approach and by reducing the number of questions and then mapping them to broader categories; that is, using a bottom-up versus top-down approach
2. Pilot the revised Scorecard with selected Emerging Market agencies
3. Link the revised Scorecard with the Asia Pacific Economic Good Review Practice (APEC GRP) initiative

Syndicate 3: Sharing assessment reports for the review of new medicines

Background

Assessment reports provide key insights into the rationale for the approvals of a new medicine. Sharing assessment reports among agencies may, in theory, streamline the review process and thereby expedite time to final decision. The use of a standardised report template could be key to meeting reviewers' expectations and to contributing to a consistent and high-quality review.

The objective of this Syndicate was to discuss what needs to be place for agencies to share assessment reports.

Outcome of discussion

Critical issues

- Differences in format and content of assessment reports: Assessment reports are highly variable in substance and level of detail. The extent of documentation of decision rationale and the details of the question and answers that were addressed during the review process can be lacking
- Timing of global applications: It was felt that although it is the sponsor's intent to achieve approval as quickly as possible, reliance on the use of completed assessments could lead to delays in regional submissions and perhaps even their approval. Challenges

to sharing these reports include varying levels of agency expertise, different visions of the agencies with regard to their role in international approval processes, and the language in which the report is written may create a barrier for easy international use). Implementation of the sharing of reports requires agency and industry commitment and therefore, the incentives for both sponsors and regulators should be defined.

Recommendations

1. Conduct a survey to review and understand the content and availability of assessment reports, determining the rationale for each agency's preferred format and the relative value of individual sections
2. Carry out a survey of agencies to understand their prioritised areas of resource constraint, identifying the strategic goal of resource needs and use, and acquiring feedback on what level and types of assessment would add the most value
3. Propose a submission and review model that formalises and defines a new review process using existing assessment reports and that includes a risk-based approach for assessments of new products with significant complexity or issues. Consider fees and timing incentives
4. Establish a secretariat or steering committee to oversee the steady advance and cooperation with agencies and sponsors; a pilot initiative between APEC Life Sciences Innovation Forum and the Institute is suggested

Section 3: Presentations

Day 1, Part 1

Chairman's welcome and introduction

Dr Thomas Lönngren

Former Executive Director, European Medicines Agency (EMA)

In this first session, presentations and discussions centred on the tools that build predictability into regulatory decision making. Certain key competencies are required to build this reliability, the first of which is guidance as to how to interpret and apply the legislation into practice. Next, regulatory administrative and scientific procedures must be established for the consistent review of regulatory dossiers along with mechanisms to resolve issues and questions surrounding the safety, efficacy and quality of the medicines under review. Regulatory decisions must be made that are high-quality, scientifically driven, efficient, timely and predictable, all of which require resources and specific competencies. The European Union is addressing these needs by developing tools, such as a benefit-risk framework to develop processes that support more transparent predictability in decision-making. Outcomes research, investigating the activity of medicines in real-world settings, is another tool that will allow us to follow up regulatory decisions to determine whether observations of efficacy in a controlled environment are consistent with the reality of clinical practice. Finally, the consistency that evolves through the experiential benefits of institutional memory will provide the next generation of regulators with a practical basis to interpret and apply the established policies and methodologies.

The pharmaceutical market continues to evolve, offering new challenges and opportunities. Regulators formerly evaluated medicines that were produced, researched, and marketed within their regulatory jurisdiction, using distinct legislation, procedures and competencies relevant within that region. Although in the current global pharmaceutical market this is generally no longer the case, and many of the drugs that are introduced into one territory have been researched or manufactured in other parts of the world, it is still our responsibility as regulators to control the safety, efficacy, and quality of these medicines for our constituents.

The road map created for the European Medicine Agency over the last ten years focussed on ways to best allocate resources and develop the competencies required to address the growing needs of global regulatory collaborations. The focus of this Workshop on regional alignment continues in this same strategic direction, and the experience of the EMA, as the most well-developed regional collaboration in the history of pharmaceutical and regulatory development suggests that regional alignment may be the best way to facilitate global cooperation.

New drug review programme in PMDA

Dr Satoshi Toyoshima

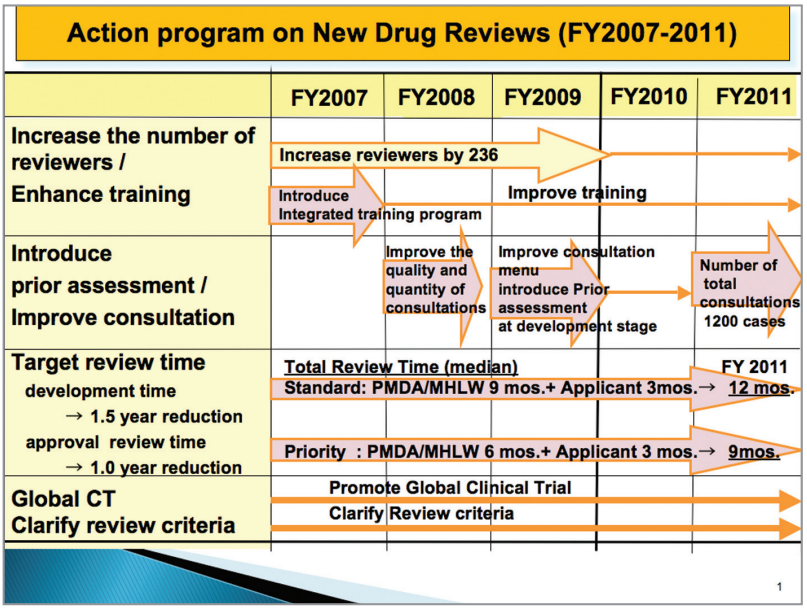
Senior Advisor, Pharmaceuticals and Medical Devices Agency, Japan

The Pharmaceutical and Medical Devices Agency (PMDA) of Japan has established five new basic policies and objectives to be achieved during the period of 2009 through 2013 to facilitate the medicines development process in Japan:

- Improve the consulting services and review system
- Promote global drug development
- Improve measures for ensuring public safety
- Strengthen international programmes including collaboration with Asian regulators
- Advance the application of regulatory science to drive the activities of the PMDA

Improve consulting services and review system

In order to improve the pre-approval scientific consultation process and to make the review system more timely, the PMDA has increased its review staff by 236 in 3 years, approximately doubling the number of personnel reviewing new drugs; the total number of staff is expected to reach 751 by the end of fiscal year 2013.



Additionally, the agency has established an integrated training programme for these new reviewers and embarked on a pre-NDA review consultation pilot programme and a programme of special consultation on pharmacogenomics, focusing on issues that include biomarker qualification.

Promote global drug development

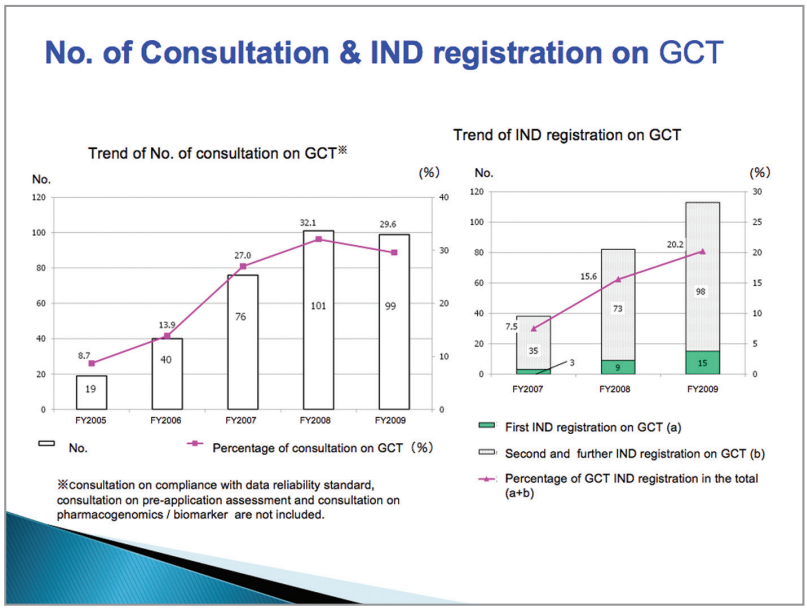
To accelerate new drug development and eliminate the drug lag in Japan, simultaneous global development for new drugs has been proposed whenever possible. In furtherance of this goal, two publications have been issued to inform how these processes are supported. The first, "Basic Principles on Global Clinical Trials" (http://www.pmda.go.jp/operations/notice/2007/file/0928010-e.pdf) included recommendations for sponsors to incorporate Japan in global drug development programmes, recruit Japanese patients and discuss the details of proposed global drug development programmes with the PMDA. To standardise general review policy, avoid inconsistent decision making, establish clear check points in the review and to accelerate review time, "Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drug," (http://www.pmda.go.jp/english/service/pdf/points.pdf) was published by the PMDA in 2008. Japan has markedly increased the number of global clinical trials (GCTs) since 2007, in almost all therapeutic areas. This has resulted in an important shift from primarily phase III trials, to most of these GCTs now being conducted as part of phase II programmes.

Improve measures for ensuring public safety

The PMDA's integrated service offerings include the development and review of safety measures throughout a product's life cycle; these include predictive and preventive safety measures for new medicines that have benefitted by improvements in the system for analysing adverse event reports. The number of staff in the Office of Safety has increased by 100 since 2009 and the agency envisions that safety systems will be further strengthened by increased cooperation with international regulatory bodies.

Strengthen international programmes

PMDA's international relationship strategy was formulated to advance basic policies for overall international activities. Targets to be achieved include strengthening cooperation and building collaborative relations with the



United States, Europe, other Asian countries and relevant international organisations; proactively participating in international harmonisation activities and further contributing to such activities; and improving and strengthening the provision of international information.

Advance the application of regulatory science to drive the activities of the PMDA

Regulatory science attempts to standardise the products of science and technology for human use. Relative to pharmaceuticals and medical devices it is defined as the scientific study of the implementation of state of the art regulatory and other administrative policies based on life science and advanced scientific research. To make a final decision on approval of pharmaceuticals and medical devices carries some degree of risk. The task of regulators is to determine whether the potential risk of a medicine is outweighed by it potential therapeutic benefit and the decision needs to address issues of access, safety and economics. Regulatory science provides a framework within which these decisions can be made.

PMDA acts as a bridge between academic and regulatory science and stimulates each relevant organisation to contribute to the advancement of public policy. PMDA promulgates regulatory science by promoting a graduate school programme, cooperating on the development of infrastructures for clinical research and providing training and information on research activities. Dr Toyoshima concluded by emphasising that it is essential for regulators to work together in a responsible manner based on scientific principles by fostering close communication among industry, academia, and other international regulatory authorities.

FDA's regulation of drugs: A holistic paradigm

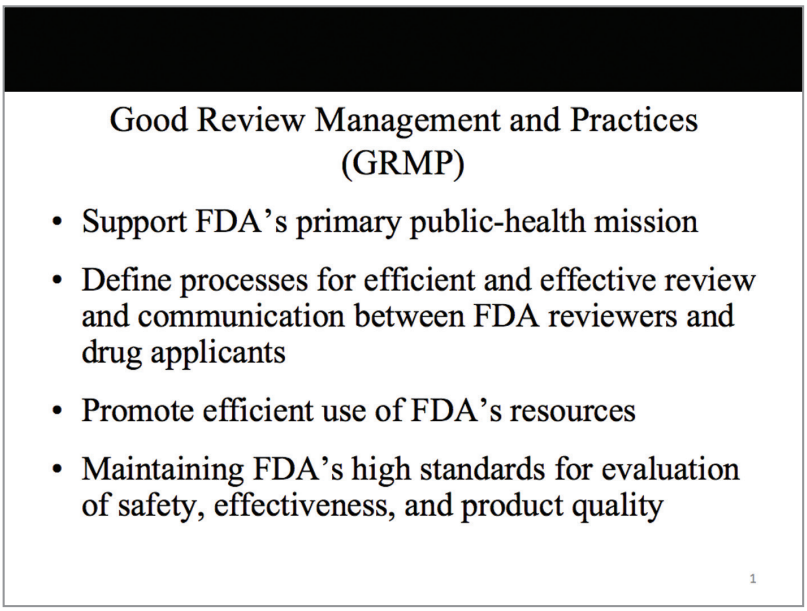
Dr Christopher Hickey

Director, China Office, United States Food and Drug Administration, China

Good review management: Principles and practices

In recent years the FDA has endeavoured to manage best practices of drug review and to implement key principles into day-to-day practice. These principles and practices support the agency's primary public-health mission, define processes for efficient and effective reviews, provide a framework to enhance communication between reviewers and applicants, promote efficient use of resources and underlie the FDA goal to main the highest standards for the evaluation of safety, effectiveness, and product quality. The fundamental values that underlie good management review practice are quality, efficiency, clarity, transparency and consistency.

Through planning, the agency has clearly identified timelines for deliverables that are needed to continuously implement these principles. One of the key factors for meeting review deadlines is the receipt from the sponsor of complete applications at the time of submission. The importance of cross disciplinary teamwork with the Center for Drug Evaluation and Research (CDER) and communication across different disciplines is now emphasised even more than in past years; review teams include a variety of disciplines such as clinicians, pharmacologists, chemists, statisticians, microbiologists, immunologists and management experts. Work distribution throughout the review cycle is examined carefully with an attempt to anticipate extra work that may be required for particular applications. The ongoing involvement of the sponsor as well as transparency in interactions is stressed.

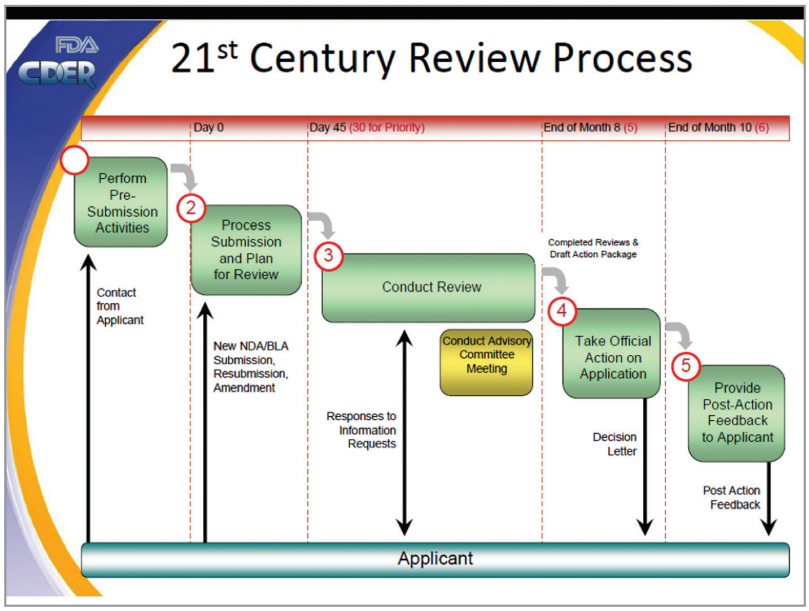


Communication is strongly encouraged throughout the review process as well as active involvement and response during review. In fact, the FDA emphasises enhanced interaction of the entire review team across disciplines and timely communication with applicants centralised within the agency, especially at key junctures and not in an ad hoc fashion, is the goal. Advisory committees play a key role in supporting this review process. CDER policy dictates that most, if not all new drug and biologic license applications that involve a new molecular entity will be discussed at a public meeting of an advisory committee, providing transparency for the review process as well as important input from experts and the public. The role of patients and advocacy groups is considered crucial in drug development and approval.

This new review model was applied to all applications beginning in 2009 and extensive training of the review staff in this new process and with teamwork skills continues. A steering committee audits specific applications to measure the performance of review teams for those deliverables. The agency is close to meeting its performance goals, and strives to improve these measurable elements on an ongoing basis.

Oversight of post-market drug safety

The oversight of the post-approval safety of new medicines is a key area of FDA focus, with the goal of bringing the same level of attention, priority and project management to the issues of post-approval surveillance as those exacted on drug review, ensuring that all appropriate disciplines and experts are involved. The agency now has the authority to require studies at the time of approval or after approval (based on the collection of new safety information), although the requirement needs to be based on



scientific data, and is limited to specific purposes. This allows a new medicine to be introduced that may in the past not have been as quickly approved, albeit with specific requirements for careful surveillance. The well-known limitations of clinical trials as they relate to the broader population, the use in the most appropriate indication and the difficulty ensuring a response when compliance cannot readily be monitored further underscore the importance of post-approval surveillance.

The importance of timely communication to the public and greater transparency about the reasons that underlie regulatory decisions has also assumed importance for the FDA. Further, overseeing the life-cycle of medicine development means that over-the-counter and generic medicines as well as the relevance and role of new prescription medicines must also be considered on an ongoing basis and this regulatory assessment needs to occur through the product life cycle.

Harmonisation and collaboration with other regulatory authorities

The efforts undertaken by the ICH have been key in the area of global cooperation, especially in the area of the development of common technical documents (CTD). The CTD facilitated a consistent and timely review across agencies and helped to ensure transparency by providing a predictable format for dossiers with a consistent order of information and data submitted. It has also assisted the public and industry in their understanding of the review process and regulatory decision making, as well as with intra-regulatory interaction and harmonisation.

In the area of inspections, the efforts of the Chinese regulatory agency may be more mature than that of some international counterparts, and Chinese inspectors have joined with FDA staff on a number of occasions, enhancing each other's collaboration, understanding and capacity. The FDA has several pilots that have helped to enhance efforts in the area of information exchange and predictability, working with overseas drug producers primarily in India and China to secure the quality of the supply chain. Several international inspection pilots are ongoing with the EMA and the TGA of Australia to assess whether the results of inspection conducted by these authorities can be shared.

As the FDA expands its horizons in China, it is crucial that its work is built on the foundation of strong science and strong evidence, which ultimately form the basis for predictability in regulatory decision making.

Good regulatory decision making: What are the key components that build predictability into the process? An industry perspective

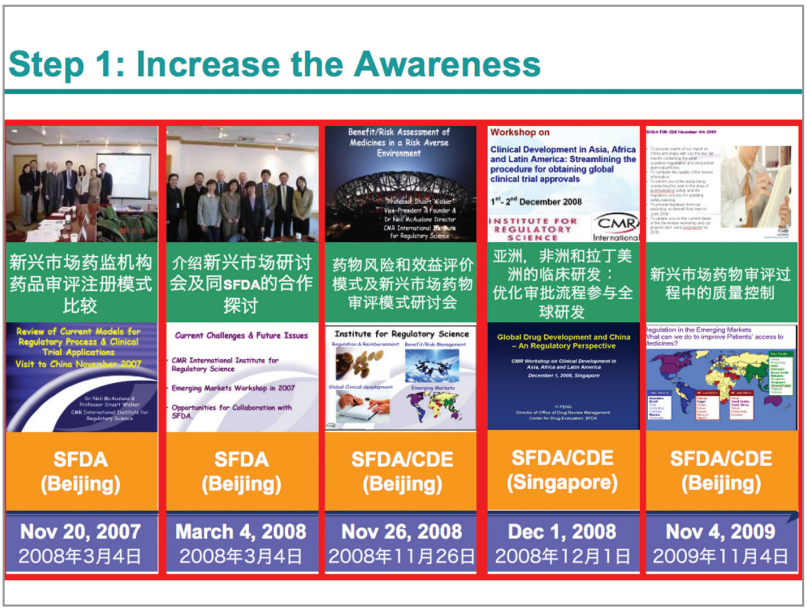
Dr Zili Li

Emerging Markets Regulatory Strategy and Policy Lead, Merck & Co Inc, USA

Key components

The first step in defining good regulatory decision making is to identify the objective of those decisions, but it is important to understand that the identified objectives may be dependent on stakeholder perspective. Members of industry for example, may regard a positive regulatory review outcome for their product as the primary goal and highly value opportunities for agency communication and engagement to that end. Other stakeholders may consider the timeliness or quality of regulatory decisions as primary objectives of good regulatory decision making.

Considering "correct" decisions as the benchmark of the quality of a regulatory system is problematic, because two agencies faced with the same data set frequently arrive at disparate decisions. Transparency, which is often cited as another indicator of quality decision making, is more of a process than an end result. Predictability, however, is key for industry, and consistency of the implementation of the factors that underlie good decision making sets a foundation for this predictability, particularly in emerging pharmaceutical markets.



Emerging market agency comparisons

Good decision making requires capable people to make decisions grounded in solid science. These decision makers also follow a process defined by laws and regulations to help them resolve issues both influenced by subjective judgement and sound science. Regulatory agencies in developed markets typically have a multipurpose mission to protect public health and ensure drug safety while also advancing public health by ensuring that innovative effective products are safely delivered and information regarding the use of these products is adequately disseminated to the public. Emerging market agencies on the other hand are focused on their role as guardians of public health and safety, and as such may be risk averse. Fostering innovation does not generally play a role in their decision making (particularly in those countries that have a requirement for a certificate of pharmaceutical product). Approval in China for example, is more likely for a product that has been approved in the United States and then assessed in Chinese trials that generate required local data; although these findings may take three to five years to collect, the data help provide the confidence required by the regulator to form a decision about the product's benefit for the local population.

Meeting all regulatory expectations and requirements is not a guarantee of regulatory approval in countries with emerging pharmaceutical markets, however, because of the unpredictability of single-pathway systems that have not been designed to accommodate situations such as generics, technology transfer or joint venture applications.

The way forward

Communication with emerging market agencies regarding quality measurements, available tools and best practice models in other regulatory systems may be key to their optimisation. For example, the Institute has made several visits to the State Food and Drug Administration (SFDA) in China over the past 4 years, introducing models of quality measurement and illustrating data comparison derived from surveys of numerous emerging market agencies. The results of questions posed to these agencies were discussed with the SFDA, revealing efforts made by these agencies in relation to implementing quality measurements, continuous improvement

initiatives, training and education for assessors along with ways that they are now looking to enhance the communication of information to the public.

In response to these results and other inputs, the SFDA has recently reorganised and a newly created division is responsible for quality control, consistency in decision making and industry appeals. In June 2010, a formal internal training programme in drug development and regulatory science was established, and in August 2010, the first open advisory committee meeting was held for the approval of the H1N1 vaccine. The next step in development for China and for other emerging markets will be to develop an understanding of the rationale behind the use of good regulatory review tools, processes and procedures so that they can be applied appropriately under varying circumstances in the best interests of local public health.

Although it is expected that implementing regional alignment in the Asia Pacific region will be a long-term process, recent agreements reached between Japan, China, and Korea are encouraging developments. The next steps are likely to result from shared data and increased intra-agency exposure and knowledge sharing.

Regional alignment in Asia Pacific – a perspective from the Chair of the Asia Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC)

Mike Ward

Manager International Programs Division, Health Canada

International cooperation

International cooperation is increasingly an essential part of our daily business in an interconnected, global world. It is not undertaken for its own sake, however, but should contribute to public health and innovation by strengthening the efficiency and the effectiveness of regulatory authorities. Increased efficiency and effectiveness in turn translate into more informed, timely decisions, coordinated actions between regulatory authorities in terms of addressing safety and compliance issues, more efficient use of resources, and finally the adoption of best practices that incorporate risk-based approaches.

There is much effort underway internationally, regionally and at the economy or country level to strengthen the capacity and efficiencies of national regulatory authorities. But goals for international cooperation and the methods for achieving those goals must be clearly defined and interagency dialogue should addressed whether such efforts are as effective as they could be and what role the Asia Pacific Economic Cooperation (APEC) organisation can play in advancing such efforts.

The coordination of efforts is becoming increasingly important in achieving the desired outcomes. Cooperative regulatory efforts should, whenever possible, be directed towards multilateral networks, maximising time investment and its impact. Where this is not possible or appropriate, the efforts of regulatory bodies and international organisations should nonetheless be complementary to the extent possible, with the goal of promoting synergies and avoiding duplication of effort. To achieve this goal there are a number of prerequisites; first, strategic discussions must take place among

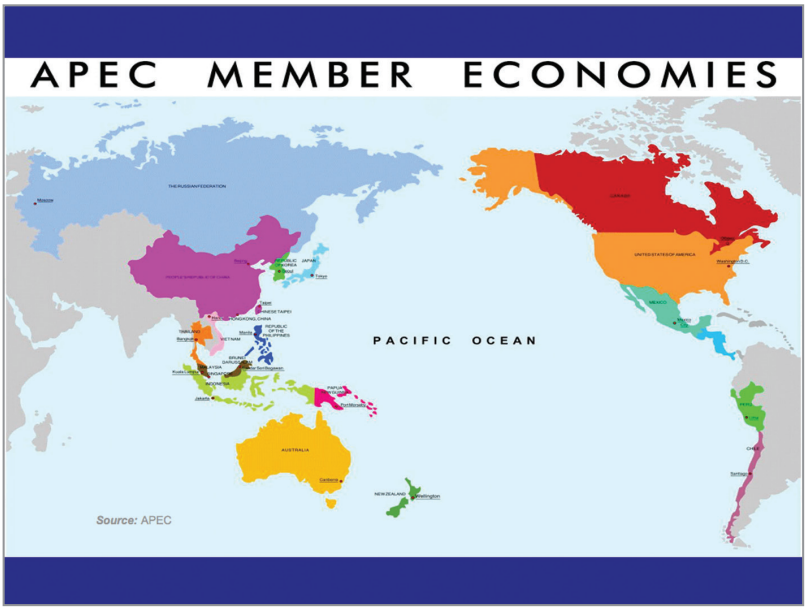
interested parties, including the World Health Organization, and second, a mapping exercise must be conducted of what is taking place in terms of cooperative efforts, harmonisation and capacity building.

APEC

Created in 1989, the goals of APEC are to promote trade, sustainable economic growth and the prosperity of its 21 member economies through policy alignment and economic and technical cooperation. It operates on the basis of non-binding commitments, open dialogue, and equal respect for views of all participants, and decisions are by consensus.

Within APEC, the Life Sciences Innovation Forum (LSIF) is a tri-partite initiative involving government, industry, and academia that was created in 2002 in recognition of the importance of promoting public and economic health improvement through life sciences innovation. Rather than produce harmonised guidance, LSIF promotes the use of existing international guidelines, most notably those of the ICH and the Global Harmonization Task Force (GHTF). A voluntary basis for engagement ensures the participation of interested economies committed to cooperation. Collective and individual action allows concerted efforts between economies as well as discrete engagement at an economy level.

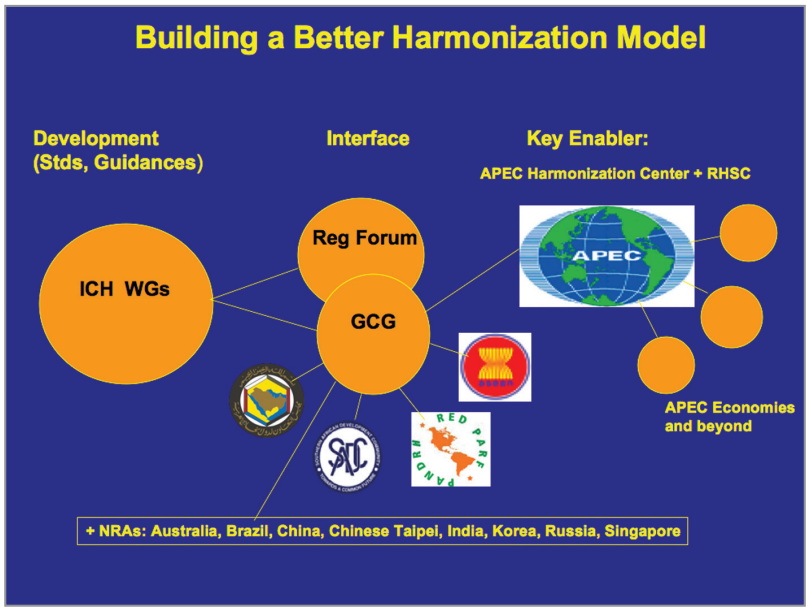
Training has been a key focus of the LSIF over the last number of years, and it has sponsored a successful series of workshops aimed at promoting a better understanding of international guidance related to the development, registration and surveillance of pharmaceuticals and medical devices. Training is typically delivered to a group of countries, including some outside the APEC region, which is a model that has been found to produce maximum return on time and cost investment.



The APEC Harmonization Center is an APEC-wide resource to enhance and sustain harmonisation and capacity-building efforts by conducting research and surveys, providing educational programmes such as workshops, publishing and web posting, and establishing networks and exchanges between experts and institutions at centres of excellence. It operates under the authority of the LSIF with the direction from the Regulatory Harmonization Steering Committee (RHSC) and an international advisory body.

The RHSC was created to promote a more strategic, effective, and sustainable approach to harmonisation by proactively identifying and prioritising projects seen to be of greatest value to regulators and to the regulated industry within the APEC region. Further, the RHSC establishes or strengthens linkages with harmonisation initiatives such as, ICH, GHTF and the Asian Harmonization Working Party, to promote complementary actions and most effective use of resources. Inaugurated in June 2009, achievements thus far include the development of an overall strategic action plan, operating procedures for the steering committee with a multi-year planning cycle, a permanent secretariat in Seoul and a series of successful workshops. Two recent workshops led to a series of recommendations to address the challenges of multiregional clinical trials, including continued research on ethnic factors in clinical development in China, Japan and Korea, targeted training and the use of standardised reporting templates. All of this is in an effort to move away from ad hoc, individual actions to a collective strategic approach to consistent regulatory requirements, reviews and processes.

Some of the enablers that would promote effective cross-agency cooperation in Asia-Pacific are common standards and approaches, a shared alignment of political and institutional will, building the overall regional capacity in resource and expertise, continuing to develop strong trust in each other's activities, and the development of appropriate tools that facilitate cooperation and allow for information exchange such as memorandums of understanding, confidentiality



agreements, virtual networks and secure IT platforms, transparency initiatives, growth plans for the public availability of information, and a concerted, sustainable effort guided by goals, strategies and business cases at the national, regional, and international level.

Considerations required when addressing ways to implement harmonisation strategies include a true understanding of the intent of the respective guidelines, and translation, not only in terms of languages, but also in concepts that may be country specific and unique. Because each APEC member economy's national regulatory agency differs in its resource readiness, number, expertise and training of personnel and infrastructure, existing regulations, policies and guidelines may need to be adapted rather than simply adopted by each agency. For example, the common technical document facilitates more timely filings, the use of a common regulatory language, and encourages the application of good review practices, but also involves the review of an amount of information that exceeds the capacity of some jurisdictions. Therefore, an adaption of the CTD format may be more relevant to a specific member economy that the wholesale adoption of the CTD guidance. The LSIF has sponsored workshops on clinical trial assessment and good clinical practice inspection for industry and regulatory authorities that moved training beyond a basic understanding of the ICH guidelines to their application from a regional regulatory perspective.

Summary

In summary, there have been important new developments within APEC in advancing regulatory harmonisation and cooperation in a more strategic, sustainable, and effective manner, directed towards concrete, complementary actions; the ultimate goal being a consistent contribution to each economy's public health and the support of innovation in an increasingly challenging regulatory environment. Next steps for APEC are to finalise and implement the two-year project that will be led by Chinese Taipei consisting of a training programme, a good review practices toolkit and a framework for the use and exchange of regulatory information.

Regional harmonisation Initiatives

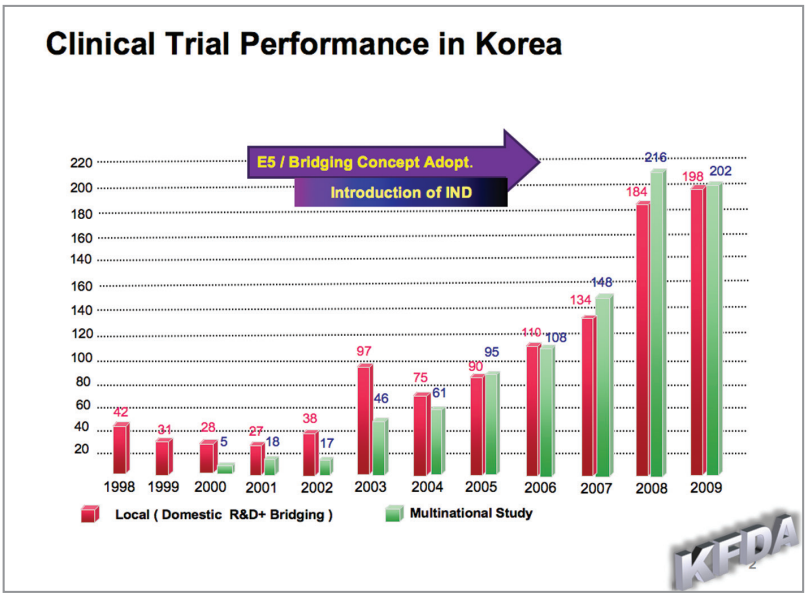
Dr Won Shin

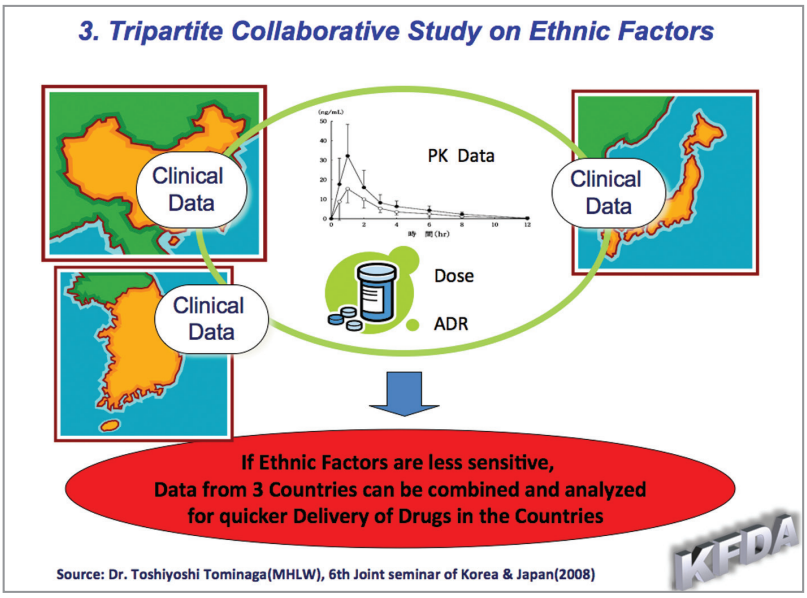
Division Director, Korea Food and Drug Administration

Dr Shin noted that three key factors are required to build a platform for a trusted partnership across regulatory agencies: good review practices (GRP), training, and international and regional cooperation.

Good review practices

The necessary elements of GRP are documentation and standardisation, a training programme and disclosure of review results. The Korea Food and Drug Administration (KFDA) provides those elements, having established a programme of GRP in 2004, standardised all processes, and provided a training programme for reviewers and disclosure of review results after approval. Standard operating procedures, review templates, and guidelines for standardisation and documentation of process format, content and management have been enacted to improve the quality, efficiency, transparency and consistency of product review.





Training

Training is one of the most important components needed to set the stage for the harmonisation of standards and regulatory practices among national regulatory authorities, especially in the emerging markets. Consequently many short- and long-term in-house training programmes are made available to KFDA reviewers. Government-supported international training fellowships represent opportunities for KFDA staff to gain first-hand experience in international regulatory programmes at agencies such the US FDA and Health Canada.

The APEC Harmonization Center was established in Seoul, Korea in 2008 under the authority of the APEC LSIF to promote regulatory reform and harmonisation, with workshops planned to occur every two or three years for approximately 600 attendees from government, industry, and academia from 17 APEC economies.

To improve practices related to vaccine development, especially vaccine regulation and quality production, a series of training courses is offered by selected training centres. KFDA was designated as a World Health Organization (WHO) training centre for this programme in 2007, and approximately 50 good manufacturing processes (GMP) inspectors from 12 countries have participated in this training programme to date.

International and regional cooperation

Another important factor enabling Asia-Pacific regional harmonisation is international and regional cooperation activities coordinated through organisations such as ICH and WHO and through regional cooperation initiatives as the Tripartite Ministers Meeting held among Korea, China and Japan. Through this latter meeting, agreements have been reached to promote clinical trials and develop medicines through such efforts as joint research on ethnic factors in clinical trials and the establishment of a working group to exchange clinical trial information among these countries.

KFDA has also participated in more than twenty collaborative activities organized by WHO to establish international standards for biological reference materials, and this participation has assisted in the harmonisation of testing methods and the promotion and evaluation of testing capacity.

Conclusion

Emerging markets in countries such as China, Brazil, Turkey and Korea accounted for 51 percent of the total pharmaceutical market in 2009. Clinical trials are rapidly increasing in Korea, and approximately half of the 400 clinical trials currently underway are part of multinational clinical programmes. In fact, Asia represents the largest portion of the global population; Asia has a favourable research and development environment in terms of speed of development, cost and quality, and on the basis of its commitment to widely implement good review practice, training and international and regional cooperation. Dr Shin concluded by noting that Korea has an excellent scientific platform on which to build trust and partnership across agencies.

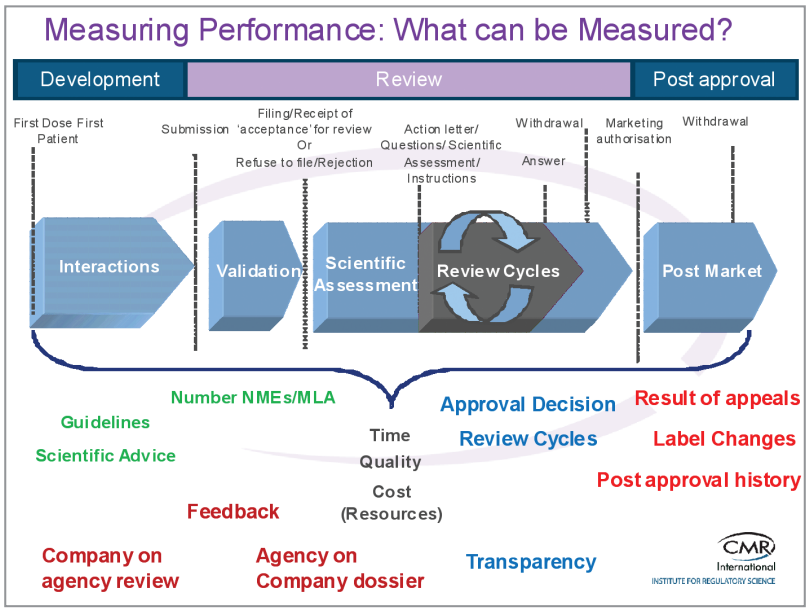
What measures can be used across agencies?

Dr Neil McAuslane

Director, Institute for Regulatory Science

As the first of three speakers in a section of the Workshop called *Measuring Performance Across Regulatory Agencies*, Dr McAuslane began by providing some background information. In 1997, Ferdinand Sauer, the Executive Director of a relatively new agency, the European Agency for the Evaluation of Medicinal Products (now the European Medicines Agency; EMA) spoke at a CMR Workshop Assessing the Regulatory Review Process, saying: "In the same way that companies judge each other's performance so, whether they like it or not, agencies are judged by both companies and the public. If this is going to happen it is important to know on what basis comparisons are made, whether they are fair and what can be learnt from the outcome. Hence there is a need for performance indicators."

When comparing across agencies, the tangible common elements that can be considered in relation to a quality regulatory review include right format, scientifically sound, legally and scientifically consistent, procedurally predictable and within time targets. As agencies have evolved, it is possible to identify both qualitative and qualitative measures in terms of activities and processes being undertaken by the agencies pre-submission (during development), review and post-approval. (see figure).



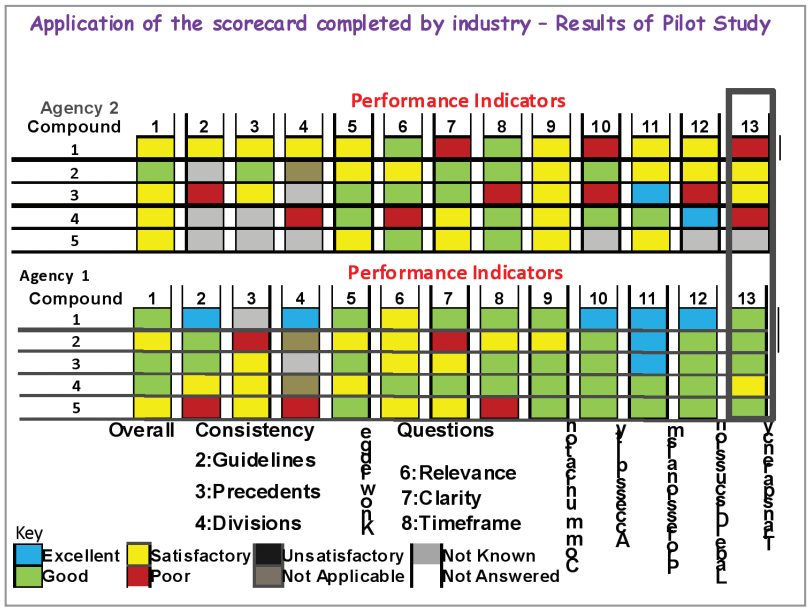
In addition, some agencies are trying activities undertaken in areas like scientific advice pre-submission and evaluating the outcome of the review process for companies that seek advice compared to those that do not as well as the outcome for companies who take the advice compared to those that do not.

Measuring performance allows the setting of realistic internal goals and objectives, permits comparisons with other agencies, provides information for the improvement and development of performance, enabling agencies to gain insight into the ways in which the regulatory process could be more effective and efficient.

Programmes for performance measurement and improvement

The Institute has continually conducted activities to help improve regulatory and industry performance and improving patient access to medicines through benchmarking programmes, process mapping of the approval process, establishing Quality Scorecards to improve regulatory submission and review, developing a framework for the benefit-risk assessment of medicines and creating process maps to characterise the confluence of regulators, sponsors and health technology assessment.

Begun in the mid 1990s, the objectives of the Institute programme to benchmark regulatory processes were to encourage systematic measuring of the processes which occur during the review of new drug marketing authorisations; to accurately compare the processes used by these authorities in the review of new drug marketing authorisations thereby encouraging the sharing of information on common practices in order to learn from others experiences; and to provide benchmarking data which can be used by regulatory authorities to define performance targets and focus on ongoing performance improvement initiatives. Since 1997, the Institute has undertaken a benchmarking exercise in which submissions of new active substances have been reviewed by five agencies (Australia TGA, Health Canada, European Medicines Agency, Swissmedic and US CDER, FDA) across the same milestones. Data from the FDA and EMA have been gathered from public domain sources and verified by the agencies whilst other agencies have provided



the information directly. This data set has provided to agencies comparative information regarding approved, withdrawn, rejected and refuse-to-file products and enabled the sharing of experiences.

Because the benchmarking programme has established common milestones, it is possible to observe that even mature agencies vary in the time it takes to accomplish similar activities, and this is, in part, due to the differences in approaches. For example, unlike other agencies, at CDER, there is no validation stage between the receipt of dossier at the agency and the start of scientific assessment. The number of days, therefore, between receipt of a dossier and initiation of scientific assessment is 0 at CDER compared with 24 to 113 days at other agencies. A review of benchmarking data such as these allows the agencies to have conversations about their different processes.

The Institute has begun translating these benchmarking activities for use within the emerging markets, concentrating on documenting the time to approval of new medicines, which is important to industry in terms of planning and building predictability. It is also important, however, to understand the reasons behind these numbers; that is, what are the processes and how do they impact timing. Review process maps for individual emerging market agencies are being developed thorough conversations, interviews and surveys, and this work is ongoing.

Timeliness and speed of the review is only one aspect in measuring regulatory performance. Quality of the process from construction of the dossier to the ultimate regulatory decision must be considered and measured. This quality guarantees expected standards, instils confidence amongst stakeholders and achieves universal acceptability of reviews. It is also critical for ensuring that assessments and decisions are scientifically sound and that only safe and effective and medicines attain approval.

The Institute's Quality Scorecard system was initiated to improve the quality of dossier submission and regulatory review. In this programme, industry's dossier submissions are scored by agencies in relation to application format, technical content communication/ transparency, and scientific competency to help the sponsor understand the results of the review and learn from the outcome in order to implement improvements for future dossiers. At the same time, industry scores agencies on the quality of their reviews in terms of consistency, communication/transparency, information in relation to the assessment reports, as well as scientific competency with the objective of establishing an open exchange of views on the conduct of the review as well as empowering the agencies to look to undertake quality improvements both locally and internationally.

A feasibility and pilot study of the Scorecard system have been conducted over the last four years, for purposes of validation, with the participation of Swissmedic, Health Canada and Australian TGA and seven companies. Because not all the parameters within the Scorecard have equal weight, the Institute is now developing a "balanced" Scorecard as a way of more completely interpreting the information to feed back to both agencies and companies.

Summary

Because no agency works in isolation and is continually being judged by its stakeholders, comparative information that can be used to develop timely, high quality, predictable, and transparent processes that support the effective and efficient use of resources can help underpin good predictable regulatory decisions and create a basis for improvement of practice.

The Institute has established several methodologies for assessing time and quality across regulatory agencies from which it is possible to identify learn and compare successful practices in a relevant context and to gain insights into methods for process improvement.

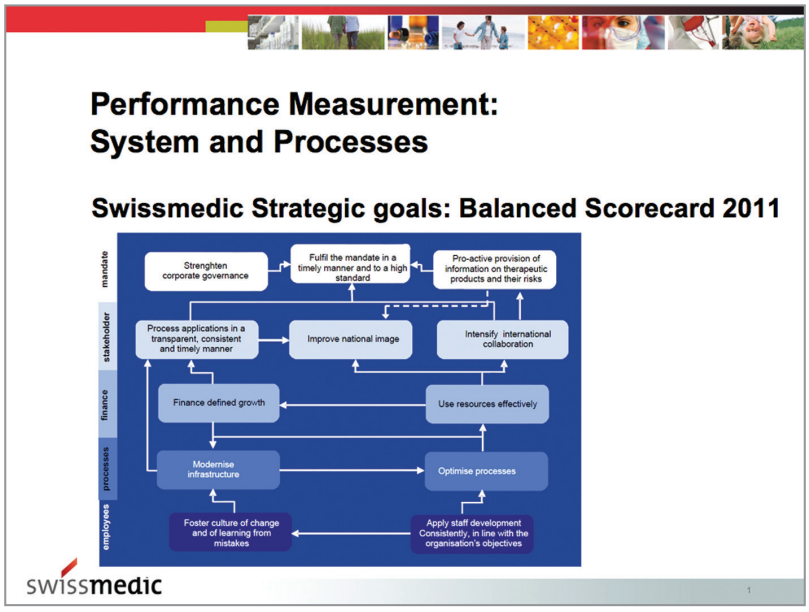
Improving agency performance: What needs to be measured?

Dr. Petra Dörr

Head of Management Services and Networking, Swissmedic

Performance measurement

Swissmedic is the independent, central supervisory authority for therapeutic products in the Swiss federal government. At Swissmedic, corporate governance is clear and transparent: on the basis of a four-year mandate from the Federal Government, a service agreement with the Department of the Interior establishes yearly performance targets. The Strategic Plan, just revised for 2011- 2014, sets guiding principles and strategic goals, displayed in the form of a balanced Scorecard. Measurements for the achievement of these strategic goals are defined and implemented through special projects. Biannual reports for the Department are produced, with quarterly reports to a Council. Quarterly reports include financial, stakeholder, product, performance, processes, quality management and human resources indicators and specify percentage change in numbers compared with the previous year. Target values will be set for the individual indicators and deviations from these target values highlighted. Individual projects are subject to a system of project control and monthly reports to a Management Board. An Annual Report is also published.



The overarching strategic goal for 2011-2014 is to fulfil the government mandate in a timely manner and to a high standard. Another goal is the modernisation of the infrastructure, which is expected to also help improve performance.

Measurements of performance at Swissmedic include assessments of input, output, quality and efficiency. Examples of input measurements are the number of adverse event reports received, the number of applications for marketing authorisation, the number of requests for information and income. Output measurements might include the number of applications approved or measures in market surveillance; performance, the percentage of cases completed within a given timeframe; and quality, the number of complaints received, quality of documentation or execution from internal audits. Efficiency is measured through time or cost expended, based on the type project. It is expected that an advanced planning and schedule system in marketing authorisation to be introduced in 2011 will increase planning capabilities as well as capacity.

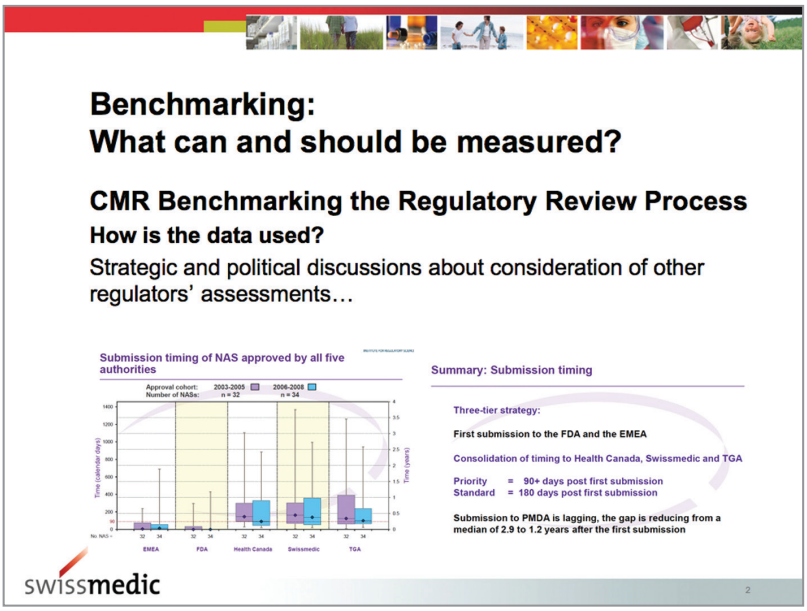
Information technology tools will assist in the planning and implementation and reporting on an individual basis.

Benchmarking

Several types of benchmarking activities are undertaken within the agency. These include process benchmarking to identify and observe best practices, performance benchmarking to assess competitive positioning, strategic benchmarking to observe how others compete, and financial and functional benchmarking. Benchmarking data are being used by regulatory agencies to identify best practices and to document long-term outcomes to support the development of performance improvements. Agencies can also measure the impact of process or structural changes such as staff increases and use benchmarking data as an input in strategic planning or political discussions.

Examples of benchmarking processes cited by Dr Dörr included the Institute's benchmarking of the regulatory review process, as detailed in the presentation by Dr McAuslane. Dr Dörr suggested several enhancements to this programme including yearly reports, online data entry and consideration of an expansion of the programme to include additional countries and a focus on products in addition to new chemical entities currently being assessed.

In another example, the goal of the EU Heads



of Medicine Agency benchmarking project is to contribute to the development of a world-class system for medicinal products based on data provide by a network of agencies. These groups are cooperating to identify best practice standards and by using benchmarking as a methodology of assessing internal performance improvement. Swissmedic has used the questionnaire from this programme in their internal audit process.

Finally, benchmarking data have been used for several different strategic and tactical purposes at Swissmedic:

- Functional benchmarking has been performed as an element of a project to analyse research allocations
- Data showing decreasing performance relative to other agencies in the wake of a hiring moratorium during a period of increased workload were used to support a request for additional resources
- Data showing that the difference in approval times between submissions to Swissmedic and to EMA of between three and six months demonstrated that the system of review could cause a delay in the access of innovated medicines in Switzerland

Dr Dörr concluded by characterising benchmarking as a useful management tool, in which the timely availability of data enables timely actions. Swissmedic focuses on benchmarking performance and processes; the availability of benchmarking information is also important to support strategic planning discussions with key stakeholders.

Why should regulatory agencies measure performance?

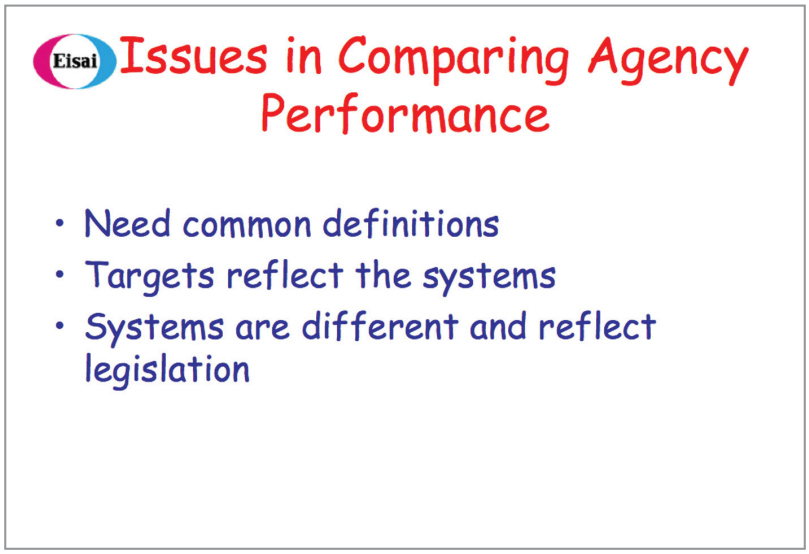
Dr David Jefferys

Senior Vice President, Global Regulatory and Healthcare Policy, Eisai Europe Ltd, UK

Many stakeholders in pharmaceutical development have an interest in measuring the performance of regulatory agencies: industry (companies and trade associations), the patients, health technology assessment agencies, government bodies, healthcare providers and professional associations. Among the aspects that can be measured are quantitative timelines, quality of the process, outcomes, and the added value that the review process contributes to the overall process.

From a company perspective, performance measurements should reflect the need for both the rapid assessment of new medicines and the rapid rendering of pragmatic, proportionate, justified decisions. Industry seeks not simply a benefit-risk assessment, but a balanced benefit-risk assessment that places in perspective the needs of all stakeholders. Above all, these stakeholders value both a predictable quality approach and resulting predictable timelines, because predictability reduces costs and increases efficiency, which are beneficial to health service and to improving patient access to medicines. Predictability also facilitates the global strategies necessary for the increasingly common, simultaneous global filing of dossiers and the parallel HTA assessments.

Trade associations are interested in the "bigger picture" and focus on slightly different measurements, such as overall performance and trends. Ultimately, the level of resourcing available at specific regulatory agencies can be addressed to ensure their optimal efficiency.



It is important to establish if the information contained in published performance statistics is sufficiently granular. Understanding the broad nature of "failure" statistics, for example, is necessary when failure may be defined by various diverse measures. The data are frequently complex and require common definitions for understanding and true transparency. Timing for example may be expressed in terminology such as clock-off periods and net or gross times. Furthermore, it should also be recognised that different legal and legislative constraints in various systems can impact agency performance.

One of the great recent achievements of the EMA has been the realisation of standardised, predictable timelines that allow the optimal use of resources. The Japanese PMDA has also achieved a high level of timeline predictability. The US FDA has been more variable in timeline predictability and productive discussions regarding the revisions to Prescription Drug User Fee Act (PDUFA) timelines are now taking place.

Eribulin experience

Dossiers for eribulin, a microtubule inhibitor with anticancer activity, were simultaneously submitted on 31 March 2010 to the PMDA, US FDA and EMA. The US authorisation was received on 22 November 2010, while the EMA opinion was given 20 January 2011. Although this appears to be a difference of two months, because of the effect of Easter, the EU timetable was not initiated until 22 May. So in effect, both agencies have been running almost the same timelines. In Japan, the PMDA approval was given in April 2011.

The expected timelines were met and exceeded by all three agencies, the FDA, EMA and PMDA and although the labels that were granted were nearly identical, regulatory agency questions received after dossier submission were extremely different despite having received similar pre-submission scientific advice. Furthermore, post-authorisation commitments varied between regions.

The Future

Market access has become a complex, multilayered environment in which assessment is now regional as well as national and in which outcomes analysis has assumed a priority role. There will be more collaboration and partnership in medicine development and it must be determined how to take that forward in terms of ensuring a quality dossier coupled with a quality review process. Risk sharing will be an important topic to explore as it is debated if patients, regulators, and HTA agencies are willing to share the risk of expedited approvals. Public health will ultimately benefit if a template is established for the evaluation and communication of a new medicine's benefit and risk.

Performance targets can be used by regulators to encourage and reward industry innovation, respond to public health imperatives and unmet medical needs in both developed and developing countries, and facilitate early approval models. Therefore, we must be careful that target metrics are not misused to distort priorities or to reduce the quality and effectiveness of dossier reviews.

Chairman, Day 1, Part 2

Sir Alasdair Breckenridge

Medicines and Healthcare Products Regulatory Agency, UK

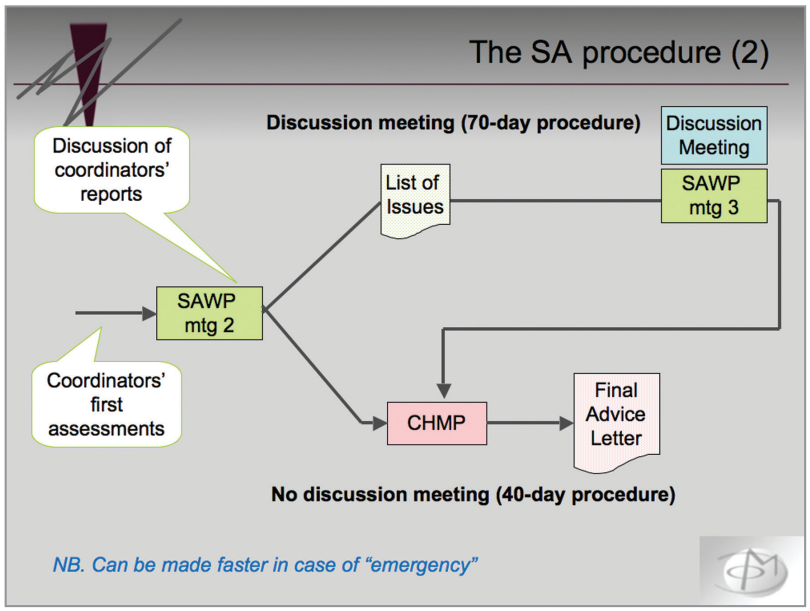
Scientific advice during drug development

Professor Bruno Flamion

Former Chair, Scientific Advice Working Party (SAWP) of the CHMP (EMA), Chair, Belgian Committee for Reimbursement of Medicines (CTG-CRM), Professor of Physiology & Pharmacology, FUNDP Namur, Belgium

The Scientific Advice Working Party (SAWP), a standing working party of the CHMP, is a multidisciplinary expert group with 28 members elected from a short list of national regulatory agency assessors and agency-related academic experts, based on their complementary scientific competencies. It includes three members of the Committee for Orphan Medicinal Products and three members of the Committee for Advanced Therapies.

Modelled after the CHMP, each SAWP procedure is taken on by two coordinators, with assessments compared and commented on by other members. The role of the SAWP is flexible and not limited to giving advice to companies on specific product-development related issues. It is also empowered to act on behalf of the CHMP and to advise on non-product related issues, for example, on a new statistical approach or on the validation of a new scale. It also provides advice on the qualification of novel methodologies and provides a platform for many scientific activities such as reflection workshops and meetings or pilot projects on multi-stakeholder consultation. All advice is provided on a voluntary basis.

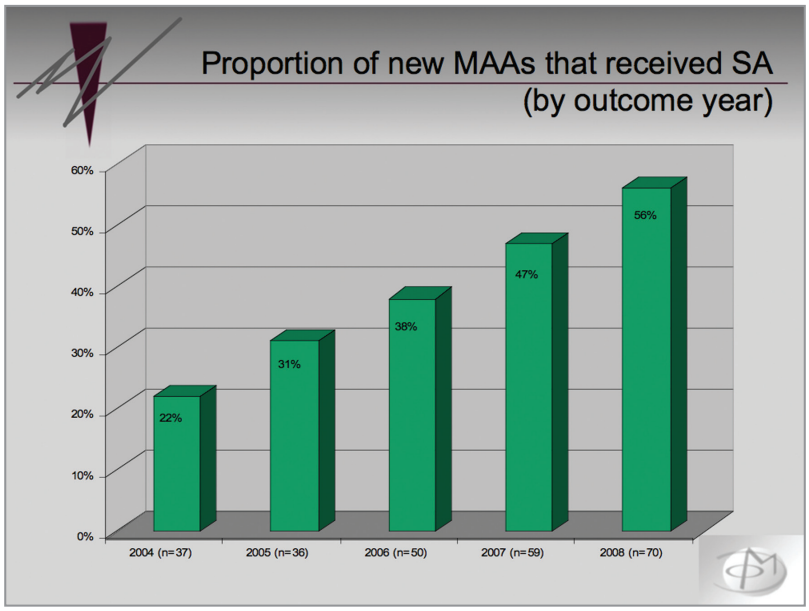


The SAWP works within an established procedure, taking approximately 70 days to render a decision. The process can be expedited under unusual or emergency circumstances, for products demonstrating unexpected clinical activity. A meeting between SAWP and the sponsor may occur before a final decision is reached under circumstances such as a major disagreement with a sponsor's plans or a discrepancy in reports or a lack relevant guidance documents; or it may be obviated in cases of a potential therapeutic breakthrough or orphan medicinal product. In general, companies come approximately twice for scientific advice during the development of a product (mean number of requests is 1.7).

There is the potential for SAWP to provide advice parallel with other agencies if requested by the sponsor and approved by the other agency. To date, only parallel US FDA advice has been requested. The FDA accepts these parallel scientific advice meetings "in lieu of PDUFA meetings" and they are chaired on a rotating basis.

Overall, the instances of scientific advice are steadily increasing, and approximately two thirds of marketing authorisations are now preceded with scientific advice. Centralised scientific advice is not incompatible with national advice and many member states in Europe still give national scientific advice under slightly different conditions. It may be helpful for companies to have several advices at national levels, and then a more general European advice, especially in those cases where a consensus is difficult to reach.

The influence of SAWP scientific advice has not been limited to single products, but has also a broad effect on triggering new guidelines and prompting adjustments to existing guidelines. SAWP workshops have been extremely successful, especially those that were organised in connection with EFPIA on biomarkers, adaptive designs, modelling, and



paediatrics. The central questions, however are, does scientific advice actually help companies achieve marketing authorisation more reliably or more quickly, and does it help them improve their decision-making process during drug development?

SAWP members recently published the results of a retrospective analysis of products submitted after sponsor compliance with scientific advice (vs no advice) demonstrating that following scientific advice had a strong positive association with successful approval.[1]

As to scientific advice accelerating market authorisation, the EU Commission has specified the need for a positive benefit-risk balance at the time of marketing authorisation, regardless of whether it is a conditional or a normal approval. The SAWP receives approximately 30 requests per year for expedited conditional approval. In discussions regarding these requests, sponsors are asked similar questions: Does the plan fulfil an unmet medical need? How will you demonstrate the positive benefit-risk at a time when the development plan is incomplete? What kind of data will you be able to provide after marketing authorisation and how will the interim analysis be designed in terms of timing, analysis and trial integrity? Based on these considerations, it is not clear whether scientific advice is accelerating the development of medicines.

Tolvaptan (for hyponatremia), TachoSil (for haemostasis), eltrombopag (for idiopathic thrombocytopenic purpura) and degarlelix (for testosterone suppression) are four examples of therapeutics recently approved by the CHMP on the basis of surrogate endpoints that had been preapproved by guidance from scientific advice. Scientific advice is also critical to the development of biosimilars, where there are no specific guidelines, and therefore complex discussions result in commitments that are made on a case-by-case basis.

Whether scientific advice improves sponsors' decision-making during development is at this point unknown and may benefit from benchmarking research as to whether, for example, earlier advice would reduce attrition or streamline the development process. In an example of scientific advice that had a direct impact on a company's decision making, one company sought to develop a product to treat chronic kidney disease in type II diabetes patients, with the change in albuminuria as the clinical trial endpoint. SAWP did not consider that a reduction in albuminuria can currently be accepted as a primary endpoint because the cause-effect relationship has not been completely proven. The company was advised that if intended to pursue albuminuria as a surrogate endpoint for a pivotal trial, this surrogate endpoint should first be validated using the appropriate EMA procedure. This is a procedure that has been ongoing for several years, usually in parallel with the FDA and will end in either of two ways: either confidential scientific advice will indicate that future studies will be required for the surrogate marker qualification, or a public opinion will indicate that it is qualified.

In a second case, the CHMP agreed that a panel of cerebrospinal fluid biomarkers or a "biomarker signature" based on low amyloid-beta 142 and high Ti-tau levels in the cerebrospinal fluid is a predictive factor for progression from minimal cognitive impairment to Alzheimer's disease. This decision can be used as an enrichment tool by companies who would like to develop anti-Alzheimer products at a very early stage as the result of a broad consultation which may not have been possible though normal scientific advice.

Finally, we should be aware that in the EU, the added hurdle of comparative efficacy or effectiveness is increasingly considered an important feature beyond marketing authorisation. This comparative added value

is currently evaluated by health technology assessment bodies and national reimbursement systems across Europe. Early consultation, between regulatory bodies and those organisations assessing this added value has begun and the EMA is taking part in an ongoing multi-stakeholder consultation organised by Tapestry Networks along with HTAs, patients, and payers from other member states – France, Germany, Italy, Netherland, Sweden, and the UK, which is raising interesting questions and identifying parallel needs between regulators and HTA representatives.

Conclusions

- Scientific advice or early consultation at EMA will continue to be available on a voluntary basis
- The advantages of this system overweigh the shortcomings, and create a horizontal platform for the CHMP across therapeutic domains
- Unfavourable scientific advice is a negative factor toward achieving marketing authorisation if the company doesn't use the advice to change their plans. We are currently analysing whether companies that change their plans following scientific advice achieve similar success rate as for other products
- The impact of scientific advice on decision making within companies or on the speed of drug development is unknown at this stage.
- Qualification of novel methodologies/ biomarkers is a novel, important role of scientific advice, often performed in parallel with FDA and which can directly impact on innovation. Groups such as the Critical Path Initiative, or the Innovative Medicines Initiative can benefit from the experiences of the SAWP
- Parallel scientific advice or qualification exercises are important, and welcomed by EMA, not only with FDA but with other regulatory agencies.
- In the near future, broader scientific advice could be given in collaboration with the key health technology assessment bodies or payers organisations

Reference

1. Regnstrom F et al. *Eur J Clin Pharmacol.* 2011;66:39-48.

Good regulatory review practice – What are the guiding principles and is this a critical success factor for across agency cooperation?

Dr Supriya Sharma

Director General, Therapeutic Products Directorate, Health Canada

The extent to which regulatory authorities fulfil their mandate in a timely, effective and consistent manner can have significant impact on access to medicines, public health, product development costs and promoting an environment conducive to research and innovation. At issue is the contribution of Good Review Practices (GRPs) to a well-functioning regulatory review system and to interagency cooperation.

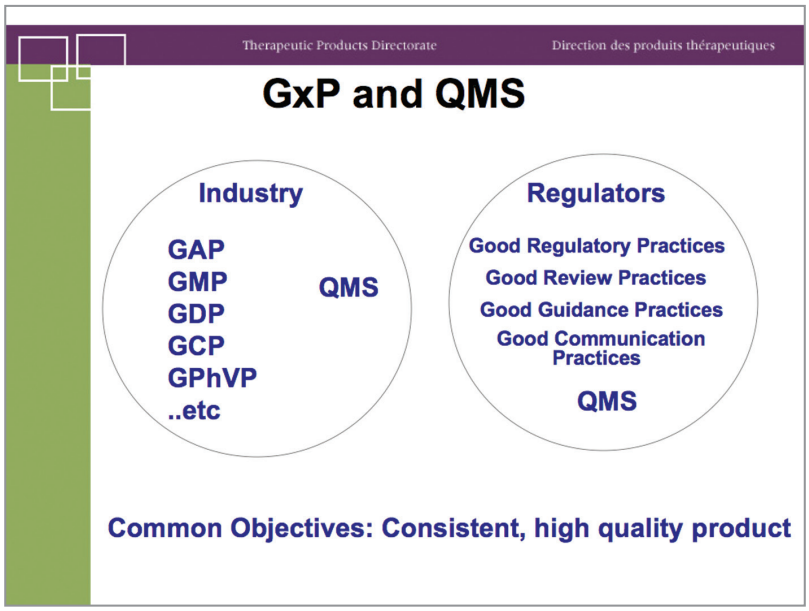
The importance of GRPs

Conformity with Good Review Practices needs to encompass elements of quality, efficiency, clarity, transparency and consistency. However, the issue of conformity is highly subjective, with conflicting stakeholder expectations, cultural differences, disparity in process, and continually changing context in terms of time, scientific advice, knowledge and technology. An ideal review is independent, subjective, defensible, well documented, clear, concise, and consistent; however, these goals may be difficult to accomplish in reality.

Health Canada has established The Ten Hallmarks of a Good Review.

A good review:

1. Is learned: "question your knowledge"
   - A good review is knowledge-based and reflects scientific and regulatory state-of-the-art. Reviewers come into a review with a background of knowledge and will acquire additional knowledge during that review
2. Uses critical analyses: "question their knowledge"
   - A reviewer should not accept anything at face value, but rather critically appraise information by questioning the scientific integrity, relevance and completeness of data and proposed labelling, as well as the sponsor's interpretation
3. Identifies signals: "find the needles in the



haystack"
- Highlights potential areas of concern identified by the company

4. Investigates issues: "dig deep when necessary"
   - Provides both company's and reviewers' in-depth analyses and findings of critical study reports
5. Makes linkages: "realize everything is connected"
   - Provides integrated analysis across all aspects of the application, managing connections between review teams and to other products in the same therapeutic class
6. Considers context: "see the big picture"
   - Places the data, conclusions, risk-benefit analyses and suggested risk management strategies of both the company and reviewers in context of proposed conditions of use
7. Involves consultation: "ask, ask, ask"
   - Reflects input from those (internal and/or external) with expertise relevant to various aspects of application
8. Is balanced: "play fair"
   - A good review is objective and unbiased
9. Is thorough: "sink your teeth in and don't let go"
   - Reflects adequate follow-through by reviewers of all issues
10. Is well-documented: "assume you are going to court"
    - Provides well-written and thorough accounts of findings and conclusions provided by sponsor and reviewers' own evidence

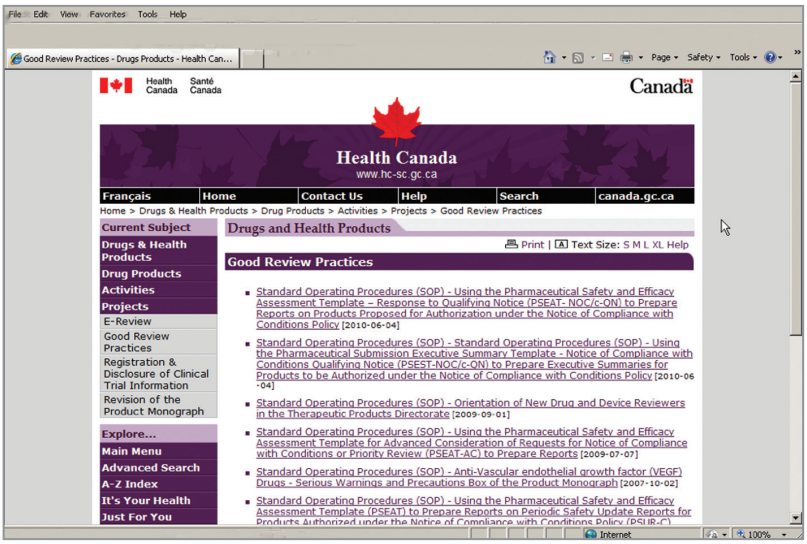
Regulatory review is a complicated, lengthy process that is often learned through the experience of a mentor. Given the long development pathway, the potential importance of medicines to patients and the risks involved, the final decision has significant consequences. However, there are a finite number of reviewers, and with current limitations in time, energy and resources, taking the most skilled reviewers offline to do more coaching, mentoring and supervising for new reviewers is a challenge.

Good review practices are not a panacea. They cannot and perhaps should not take the art out of review, but should provide those involved in review and decision-making process with the best possible support and tools for ensuring consistent, science-based assessments that comply with legal requirements.

There are many advantages to implementing a GRP system including an enhanced review process and increased interaction between assessors and industry. These systems can enable more effective training, minimise the risk of critical omissions and increase consistency in assessing dossiers.

While no single definition of GRP exists, common elements include principles, procedures and templates related to the review process, including its management, peer review, use of internal and external advisors and interactions with sponsors. Orientation and training for staff and management are linked to defined competencies. Information and experiences are centralised in established repositories. GRPs are a part of a continual improvement process, enabling the conduct of internal quality audits, self-assessments, analyses of feedback from stakeholders, post-approval analysis with other authorities and industry management reviews, and allowing the results to be used to take corrective action or introduce improvements to the review process and decision-making.

The internal Health Canada website is a repository for GRPs, SOPs, templates and orientation, and foundation and specialty training courses. At regularly held discussion sessions, reviewers meet and share ideas with colleagues outside of their organisations or therapeutic areas. Feedback from these sessions is used to improve GRP courses. GRPs and SOPs are also available on the public Health Canada web site.



The timeliness and quality of review are both important in measuring regulatory performance and Health Canada has participated in a number of Institute multi-agency benchmarking studies. Its most recent exercise involved a scorecard evaluation of industry and agencies (see Dr McAuslane's presentation). The feedback from these exercises has been used in the development of internal processes, in discussion with stakeholders, and to validate statistics from other sources.

Standardised GRPs promote trust and confidence, enabling the sharing of information with other regulatory authorities and other stakeholders. There is growing recognition of the importance of GRPs to regulatory cooperation. The recently approved APEC project on GRPs for drugs and devices includes three complementary components: training on GRPs, the development of a common framework and a plan for promoting GRPs, and a framework for the exchange and use of regulatory reviews. GRPs also rated highly in terms of impact of review quality measures in a 2006 survey of eleven established agencies conducted by the Institute.

The reality: Health Canada's GRP experience

Despite their importance, GRPs have not played a major role in terms of facilitating the interactions of Health Canada with other agencies. Major enablers of cooperation have included:

- Harmonisation initiatives and the adoption of similar or common standards
- Equivalence- and confidence-building exercises
- Implementing a platform for common training and scientific exchange
- Longstanding personnel exchanges and collaborative history facilitated by confidentiality arrangements

This then, raises the question regarding the contribution of GRPs: given the amount of effort required to standardise the cognitive, analytic process for review, how important are GRPs in promoting interagency cooperation and the use of one another's review outputs? More fundamentally, is it even appropriate to try to standardise the creative cognitive process?

However, we likely have not yet optimised the use of GRPs. Internal discussions around how to take best advantage of reports from other agencies contributed to the identification of those components of Canadian applications considered critical to our domestic review process. This, in turn, contributed to early discussions around GRPs and to the importance of using international evaluation reports within a GRP framework. Toward this end, Health Canada is currently developing a framework, procedures and training programme on the use of evaluation reports from other agencies within a GRP context, is contributing to the APEC project on GRPs and the exchange of regulatory information, and has participated in a recent CDER Forum on the FDA review of sitagliptin and pre-International Conference of Drug Regulatory Authorities discussions on these same topics.

The evolution and implementation of GRPs within agencies coupled with the increasing need to leverage one another's resources and experience will become increasingly important. This does not mean that decisions of different agencies will be the same. There is a need to distinguish the science-based procedures for the assessment of quality, safety and efficacy from the broader benefit-risk considerations specific to a particular country and health care systems. This also does not mean that one size or approach to GRP will fit all agencies. The use of alignment rather than harmonisation and the implementation of different approaches grounded in best practices is more likely. Although we are in fact able to develop unlimited SOPs, templates, training, and a variety of sophisticated tools for regulatory review, colleagues from authorities with fewer resources want to know how much effort they should put in to standardising GRPs, and to what level of detail? It remains to be decided how important GRPs are in ensuring a high-functioning regulatory system, and how important they are in building trust and confidence and in facilitating cross-jurisdictional cooperation.

Sharing assessment of regulatory approval or assessment reports – Could this be an effective way for agencies in Asia Pacific to use regulatory resources?

Meir-Chyun Tzou

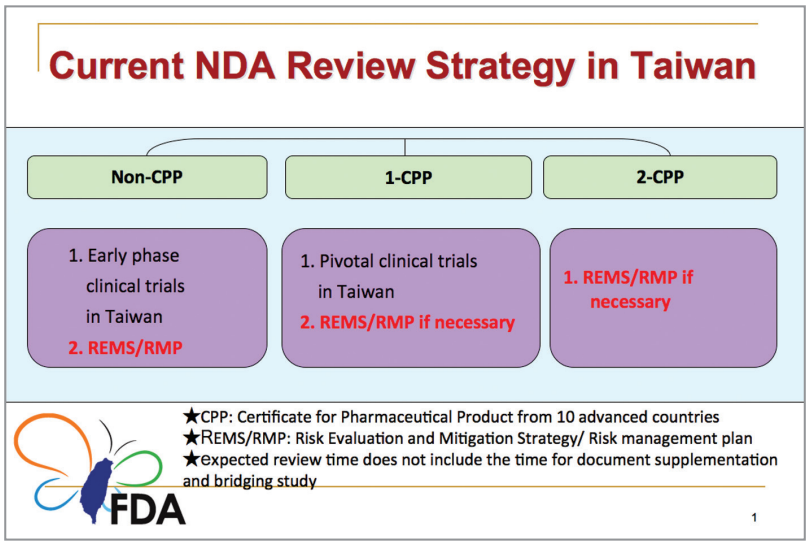
Director, Division of Drugs and New Biotechnology Products, Taiwan FDA

Dr Shin noted that three key factors are required to build a platform for a trusted partnership across regulatory agencies: good review practices (GRP), training, and international and regional cooperation.

Organisation of the TFDA

Established in January 2010, the Taiwan FDA (TFDA) was formed though the merger of four organisations to integrate and optimise the use of available resources. TFDA now comprises seven major divisions. One of those divisions, the Division of Drugs and New Biotechnology Products regulates all new drugs and biologics. As in most countries, the TFDA provides services for premarketing approval and post-marketing surveillance adhering to guidances including Good Laboratory Practice (GLP), Good Training Practice (GTP), Good Manufacturing Practice (GMP), and Good Vigilance Practice (GVP) in accordance with international standards.

For New Drug Applications (NDAs) the TFDA Review team performs the evaluation, in some cases consulting with an advisory committee, and then prepares an assessment report, after which the TFDA renders a final decision. For Investigative New Drugs, the process is the same except that the Review Team includes members of the Centre for Drug Evaluation (CDE)



Regulatory challenges

Taiwan faces the ubiquitous global challenges of today's medicine regulators: limited resources, an overwhelming workload, increasing scientific complexity of the proposed new products and heightened expectations from all stakeholders. In Taiwan, as elsewhere, these challenges must be met to establish the confidence around the uncertainty of the safety of a new medicine. Slower approvals may result in the so-called "drug lag" but expedited reviews may ultimately result in increased drug withdrawals as occurred in the United States after the Prescription Drug User Fee Act (PDUFA) was passed. Global medicine development adds further complexity to the review process with issues in supply chain management, the effects of ethnicity, and cultural considerations.

Potential solutions to avoid the duplication of efforts in the global review of medicines include the use of international standards such as those developed by the ICH or the Global Harmonisation Task Force (GHTF). Other tactics are the mutual recognition of different countries, such as that afforded by the European Union (EU) or the Association of Southeast Asian Nations (ASEAN) or non-binding partnerships such as the APEC Harmonisation Project. Finally, adopting a common platform for the administrative requirements for the use of the Certificate of Pharmaceutical Product (CPP) can also obviate duplication of labour.

Beginning in 2010, the TFDA instituted several changes to processes and procedures to accelerate the NDA review mechanism. Because of a growing review capacity and the added review experience of the CDE, CPP requirements have been relaxed. For applications already approved by reference country agencies such as the US or EMA, streamlined review processes may be available, with the TFDA focussing on issues such as ethnic sensitivity or specific local requirements.

Sharing assessment reports

The overall advantages of sharing assessment reports among regulatory agencies include the optimisation of transparency, efficiency, predictability and consistency in the review of medicines. GRP in general can be enhanced

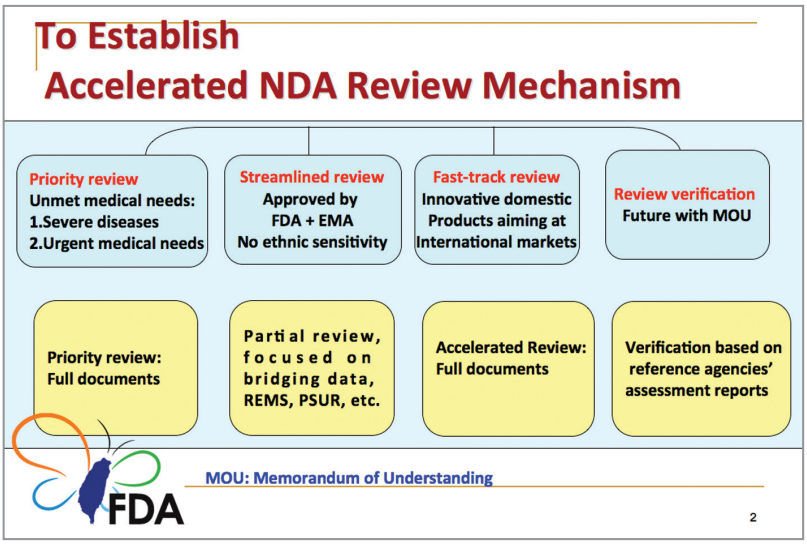
through group discussions and interactions that accompany the exchange of these reports. Differences in benefit-risk decisions and safety evaluations can be compared and contrasted, and responsibility and risk can be shared though public or private partnerships. Finally, shared reports can result in the best use of limited resources and ultimately in the expedited availability of medicine to patients.

However, there are several potential reasons why agencies may not be in a position to share assessment reports. Confidentiality issues, the use of differing review approaches and templates, or even simply a lack of confidence in other agencies' assessment procedures can present challenges. Although the US FDA, EMA or PMDA assessment reports that are available on the web are good references, ethnic sensitivity issues, lack of local safety data, different approval indications based on different scientific considerations or different medical practice environments can limit their value to other agencies.

APEC Best Regulatory Practice Project

Partnership in harmonisation is the mission of the APEC Best Regulatory Practice Project, a two-year APEC programme led by Chinese Taipei, and co-sponsored by ten APEC countries. The goal of this project is to build the capacity of regulatory science though a series of GRP workshops for regulators and related research projects.

The APEC Pharmaceutical Evaluation Report (PER) scheme follows the success in sharing assessment reports of the PER Scheme (1979-2000), which supported the EMA Centralised Procedure. A pilot study of the APEC PER scheme is being developed in which NDA assessment reports for several marketed products approved by a number of regulatory agencies will be exchanged with the permission from the license holders. The experience of these case studies in GRP, the development of common review templates and the impact of administrative requirement will then be evaluated.



Pilot case study

A selective norepinephrine reuptake inhibitor was approved by the US FDA in 2002, the EMA in 2004 and the TFDA in 2006. The sponsor granted permission to share all TFDA regulatory information regarding this product with the exception of CMC with other agencies for purposes of this exercise.

The review team comprised reviewers with differing areas of expertise. Periodic safety update reports (PSURs) were requested from the US and EMA and a bridging trial was required to be conducted in Chinese Taipei, the data from which indicated significant superiority for the drug. Potential differences in AUC levels of the drug in Asian populations and liver toxicity and suicide ideation data from US patients were evaluated, found not to present a significant clinical risk but these were nevertheless noted in the final TFDA approved label. This process allowed for the efficient use of local manpower by focusing the reviews on local issues.

TFDA future perspective

Chinese Taipei next plans to conduct a survey of the current status of bilateral agreements among different countries, and to plan pilot studies of shared assessments. In addition to sharing review reports, the TFDA hopes to collaborate on the study of ethnic issues through retrospective data surveillance, establish a consensus on bridging studies and enable fast track review of new drug applications. Pharmaceutical regulatory networking will be enhanced by joint training programmes, sharing information and communication and potentially harmonising report formats and data requirements and the establishment of a reviewer exchange programme among agencies.

Regulatory cooperation in Asia Pacific: An industry perspective

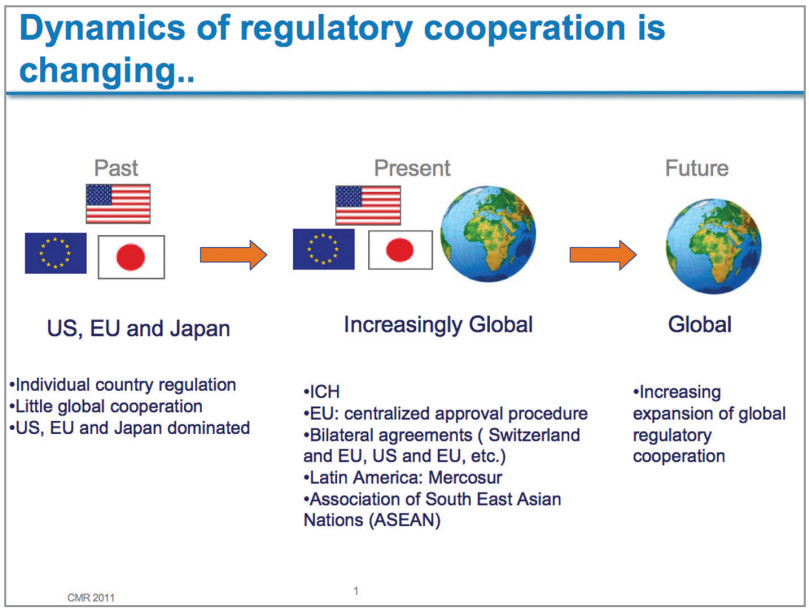
Dr Joseph Scheeren

Senior VP, Head, Global Regulatory Affairs, Bayer HealthCare Pharmaceuticals

Transparency in decision making, increasingly demanded by patients and other healthcare stakeholders, is an important goal for today's health authorities. Inroads have been made toward this goal, with much information being publicly available on the Internet. Evidence of these activities includes the US FDA Summary Basis of Approval (SBA) and the European Public Assessment Reports (EPARS). Advisory committee meetings can be observed live online or transcripts and videos ordered later and clinical trials databases contain publicly available information regarding the design, implementation and results of clinical trials.

The US FDA would like to make complete response letters publicly available, although for confidentiality reasons, industry would prefer that this information be made publicly accessible after drug approval. The EMA is also pushing transparency to next level by making the reports in the approval dossier open to public access.

Underlying this trend toward transparency is the fact that scientific and regulatory complexity is growing with the need to assess new healthcare technologies and novel therapeutic approaches.



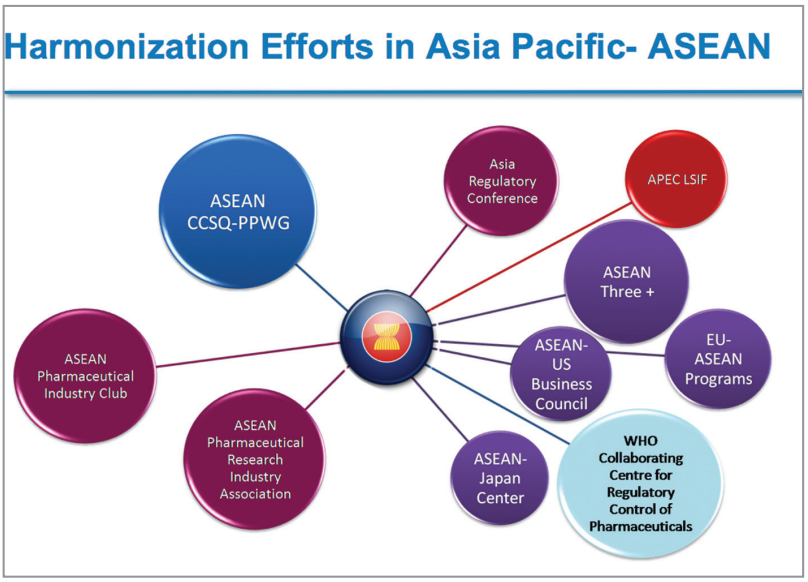
Requirements for evidence-based medicine and information are increasing and the need to address rapidly evolving globalisation challenges are ever intensifying. In the face of all these changes, companies and agencies are expected to accomplish more with fewer resources. One solution is to maximise the opportunities for collaboration, including the sharing of assessment reports.

Dynamics of regulatory cooperation

In the 1990s, Europe, the United States and Japan, who then collectively represented approximately 80% of the worldwide pharmaceutical market, drove the ICH initiative. Presently, the ICH block has a predominant place in the overall spectrum of ongoing collaborations, but many other countries, particularly Brazil, Russia, India, China, Mexico, South Korea, and Turkey are becoming increasingly involved in global development and regulatory activities. As the trend toward sharing information grows to potentially include these and other important economies, it will hopefully lead to better and earlier access of innovative medicines on a global basis.

There are many types of collaboration initiatives going on in addition to the ICH global efforts, such as the Pharmaceutical Inspection Cooperation Scheme (PICS), which the United States has recently joined. On a regional basis, there is the Pan-American Network for Drug Regulatory Harmonization (PANDRH), the Association of Southeast Nations (ASEAN), Asia-Pacific Economic Cooperation (APEC), the Gulf Central Committee (GCC) for Drug Registration and Africa Medicines Regulatory Harmonization Initiative. Bilateral agreements are also expanding and within the Institute's own activities, there is an initiative going on between Canada, Switzerland, Australia and Singapore to establish procedures to standardise benefit-risk assessments.

There are several drivers of regulatory cooperation including the benefits of exchanging regulatory expertise and manpower, sharing guidance on legislative documents, providing a framework for joint evaluation of dossiers and inspections, and ultimately, improving access to new and innovative medicines. Each of these drivers is focussed on improving the predictability of the review process and speeding access to safe and effective medicines.



The EU experience

In the early 1980s, the European community consisted of individual health authorities, all with their own different approval processes, language, and assessment reports, coming often to very different conclusions. These processes eventually evolved into a multistate procedure, which was later called the Mutual Recognition Procedure, or decentralised procedure, the goal for which was the mutual recognition by the group of the regulatory approval of a new medicine by one of its member states. This goal has not yet been fully achieved. The construction of a standardised regulatory file, the precursor of the ICH common technical document, was one of the building blocks that permitted the effective communication between the different authorities. In the centralised procedure begun in the early 1990s, joint assessments by a Rapporteur and a co-Rapporteur resulted in a better understanding of each country's methods for reviewing medicines. This procedure permits more rapid, thorough evaluation of drugs, making them available to all EU patients at the same time. Meanwhile, the local requirements for health technology assessments impose an additional step before patient availability such that the goal of simultaneous availability has not yet been achieved.

The US FDA came under scrutiny by patient organisations in the midst of the AIDS epidemic in the late 1980s, when patient advocates demanded that the FDA make new treatments more readily available. This led to the first US cooperation with the EU. Today there is a close collaboration between the EU and the United States, progressing toward parallel scientific advice, drug development and risk management. However, differences in medical practice and in healthcare system environments mean that this collaboration does not always result in the same regulatory decisions.

Current status in Asia Pacific

The Asian Pacific region is a patchwork of independent countries, all with their own language, medical culture, healthcare systems, approval procedures, local pharmaceutical companies and local traditional products. New products can be reviewed through the local approval systems either after the approval in the EU, US or Japan, based on a Certificate of Pharmaceutical Product or before approval if certain prerequisites are met. Regulatory guidelines are not well developed in many Asian countries. Each authority with limited resources often evaluates products independently, which leads to a diversity in approval timelines, duplication of efforts, increased cost, and slowed access and reduced patent life. Although collaborative activities are taking place, these efforts will benefit by being unified within a core partnership to drive forward the Asian voice within the overall regulatory community.

Industry perspective

As health authorities increasingly share assessment reports and enhance transparency of their processes and results, there are some important points to consider. Language barriers may result in a lack of usability of publicly available information and additional resources may be required to work within a common language, which is most likely to be English. Decision-making processes differ: data analyses are performed differently in each jurisdiction, the benefit-risk components are disparately weighed and valued by each authority and regulatory timelines therefore, are variable. Extrinsic and intrinsic country and regional difference will continue to exert an influence on decision making.

Conclusions

The sharing of assessment reports will benefit access to new medications in Asia. Beyond this, a sharing of processes to better understand each other's viewpoints and the use of robust benefit-risk and partnership frameworks are required to align review processes. The realisation of a close collaboration not only in the Asian space, but well beyond on a global level will allow the more efficient use of resources and ultimately benefit patients everywhere.

Enabling the acceptability of other agency reviews: What are the critical success factors?

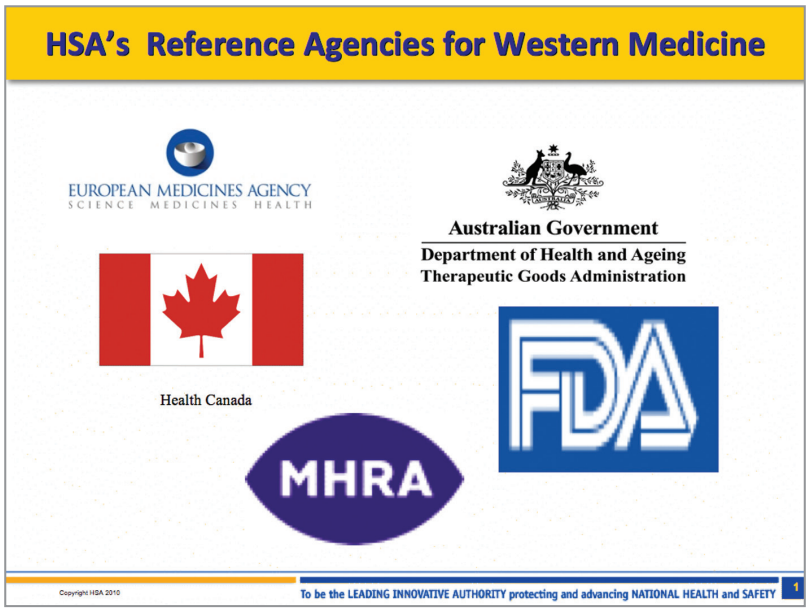
Dr Christina Lim

Deputy Group Director, Health Products Regulation Group, Health Sciences Authority

Medicinal products regulation in Singapore

The Health Products Regulation Group of the Health Sciences Authority (HSA) ensures that western medicines in Singapore are wisely regulated to meet appropriate standards of safety, quality and efficacy. There are about 40 reviewers working on approximately 150 new drug applications, 200 generic applications, and 3,000 post-approval variations each year. HSA performs evidence-based risk-benefit assessments, based on current scientific knowledge, local considerations and international standards. To optimise the work process with limited resources, HSA leverages evaluations done by competent regulatory agencies and/or HSA's reference agencies: Australia's Therapeutic Goods Administration, the European Medicines Agency, Health Canada, the United Kingdom Medicines and Healthcare products Regulatory Agency and the United States Food & Drug Administration.

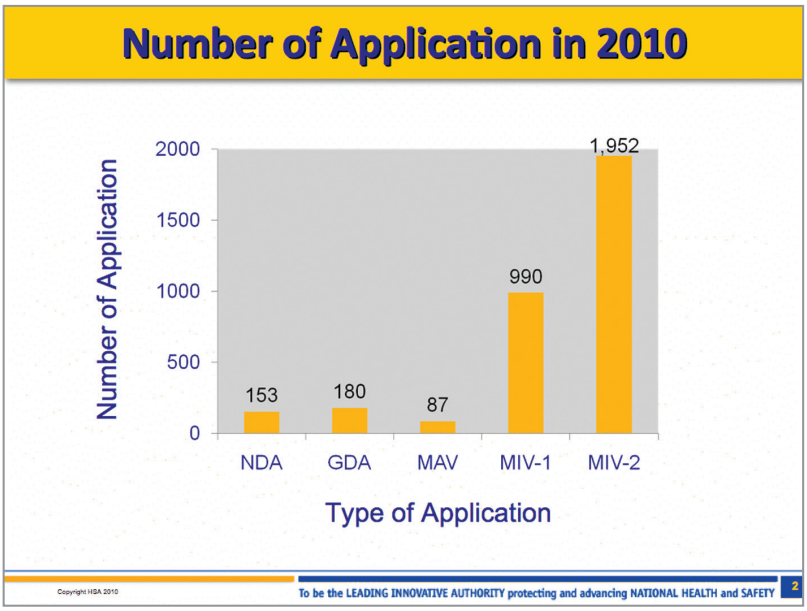
HSA offers 3 evaluation routes for New Drug Applications and companies can opt for the evaluation route that best fits their business plan.



Western medicines that have not been approved by any regulatory agency at the time of submission should be submitted to HSA via the Full Evaluation Route, and the target processing time is approximately 270 working days excluding stop-clock. Western medicines that have been evaluated and approved by at least one competent regulatory agency could qualify for the Abridged Evaluation Route, whereby HSA leverages the assessment of the nonclinical and early-phase clinical studies by a competent regulatory agency. This evaluation route takes approximately 180 working days excluding stop-clock. In the Verification Evaluation Route, HSA leverages the approvals by HSA's reference agency, and this route takes approximately 60 working days excluding stop-clock. To qualify for the Verification Evaluation Route, a medicine must be approved with similar indications by at least two of HSA's reference agencies. For a medicine submitted via the Verification Evaluation Route, the company must provide the full set of assessment reports from the chosen primary reference agency, and the application must be submitted within three years from the date of approval by the primary chosen reference agency. The Verification Evaluation Route is not open for biological medicines, for medicines that have been rejected by or withdrawn from any regulatory agency, or for medicines requiring a more stringent assessment as a result of differences in local disease patterns or medical practices.

HSA offers Abridged and Verification Evaluation Routes for generic drug applications. To qualify for the Verification Evaluation Route, the application must be approved by at least one of HSA's reference agencies and submitted within 2 years from the date of approval by the chosen reference agency.

HSA uses information from other regulatory agencies to understand regulatory assessments and decisions. The information is also used to streamline the work processes and improve work efficiency from pre- to post-market activities. Before using post-approval surveillance information from other regulatory agencies, HSA first determines whether the source of the product is the same as the source of the product registered with the HSA. While HSA uses information from other regulatory agencies to assist in their work, HSA also conducts independent assessments in all pre- to post-market activities. For example, in the recent review of cardiovascular risk associated with rosiglitazone, HSA performed an independent



review of the adverse event reports received and of the medical usage in Singapore, and also reviewed the analysis performed by the US FDA. Ultimately, HSA's decision was to restrict the use of the drug to patients whose glucose levels could not be controlled effectively with other medicines, and the drug was not withdrawn from the Singapore's market.

Critical success factors for accepting other Agency reviews

Guidelines and standard operating procedures specify the conditions under which information from other agencies can be used, and these conditions are also incorporated into HSA's assessment templates. There is ongoing communication between management and staff to ensure that staff are cognisant of the necessary background information regarding the country and agency providing the information, such as the legal provisions, regulatory process, and the healthcare reimbursement and social structure of the reference agency. When reviewing other agencies' assessments it is equally important that reviewers understand that agency's regulatory principles, how they structure their product information documents and what dataset was submitted in support of the regulatory decision.

HSA does face regulatory challenges, including the lack of access to full datasets for an analysis done by an individual agency and a lack of an avenue to seek clarification with agencies with which there is no memorandum of understanding. HSA must also manage the expectations of sponsors who expect approval for applications approved by HSA's reference agencies. HSA uses information from other regulatory agencies as a guideline to inform its own independent assessments and decision making. All regulatory decisions are agency specific, taking into consideration the local patient, medical, legal and environmental factors.

The development of a benefit-risk framework in the regulatory review of medicines

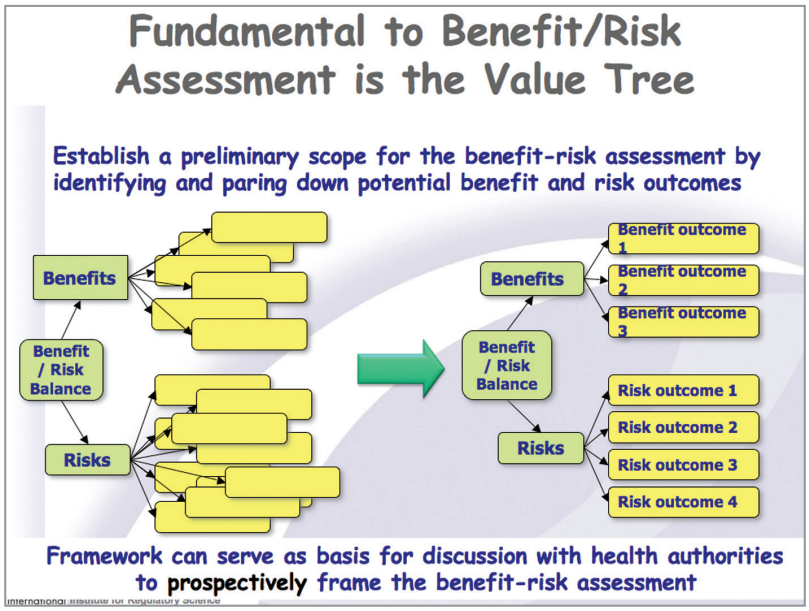
Professor Stuart Walker

Founder of CMR International Institute for Regulatory Science

The need for benefit-risk assessment

In the "Project 2020 Survey", conducted by the Institute in 2010, representatives of various disciplines within industry were presented with 39 scenarios that might affect medicines development; they were asked which they felt would be important in the year 2020, which represented a priority to their companies and on which they felt their company could exert influence. The results revealed that the most important issue to the respondents was the development of a common framework for benefit-risk assessment, including the communication used for the review of dossiers and to convey the results to stakeholders.

The balance of benefits and risks is not only greatly affected by the perspective of the stakeholder but is also dynamic and subject to change. Approximately 25 years ago, it was suggested that the benefits and risks of potential medicines could be represented on a matrix in which a product with high benefits and low risks would be ideal to submit to regulatory assessment, one with high risks and low benefits would be eliminated from development and one with high benefits and high risks might be considered in cases of life-threatening diseases with unmet therapeutic options. It has emerged since then that the position of new medicines on such a matrix is not stable but is fluid in terms of



benefits of risks that emerge in real-life use.

In a 2009 Institute Workshop presentation by Dr Paul Huckle, he discussed the results of an analysis of products reviewed by the US FDA and the EMA from 1995 to 2009, which showed that there were 31 products approved by the FDA that had a negative outcome from the EMA and 24 products approved by the EMA with a negative outcome from the FDA. Reasons for the negative outcomes included the need for more data, or clinical trial design, or safety/efficacy concerns, but for none of these products, was a full benefit-risk analysis available. Therefore, the need for a better understanding of why different agencies come to different conclusions when faced with essentially the same application data is an important reason to develop a standardized benefit-risk framework.

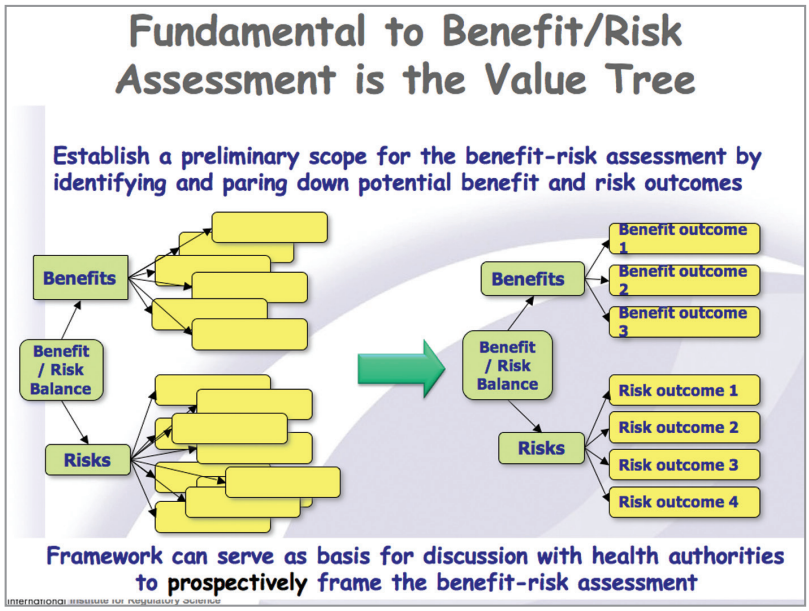
Other reasons include the need for a system that is sufficiently dynamic and flexible that it can be developed with experience, with the potential that its application could be extended to include the views of a wider range of stakeholders including reviewers, pharmaceutical industry members, physicians, payers and patients. Development of this framework would reflect the acknowledgement that current approaches are somewhat inconsistent, not only on the part of regulators, whose decisions can be inconsistent and may lack transparency, but also on the part of companies, whose data and submissions on benefits and risks are not always presented in a coherent and well-structured manner. Development of such a framework would serve to satisfy the increasing pressure on agencies to increase transparency and accountability and to establish a paper trail to explain how decisions are reached.

A benefit-risk framework is required that is able to take into account the data that are in the marketing application or that are otherwise available to regulatory agencies. No additional analyses of source data or meta-analyses should be required. The framework should closely match the practices of current regulatory agencies for benefit-risk assessment (qualitative or quantitative). It should have the ability to be used throughout a medicine's development, initial registration and post-approval periods, and be able to be independently validated. Finally, the framework should be applicable to all types of medicines, including vaccines, biologics and over-the-counter drugs.

Current regulatory and company initiatives

Professor Walker noted that there are several reports on the development of a benefit-risk framework have been generated by Institute activities that stakeholders may wish to consult. *Measuring benefit and balancing risk: Strategies for the benefit-risk assessment of new medicines in a risk-averse environment*[1] from 2008, *Strategies for communicating benefit-risk to decision makers: Explaining methods, findings and conclusions through a common approach*[2] from 2009 and *Refining the benefit-risk framework for the assessment of medicines: Valuing and weighing benefit and risk parameters*[3] from 2010.

These publications discuss a number of important ongoing initiatives in the area of benefit risk: Professor Larry Phillips, Professor of Decision Analysis at the London School of Economics, has been consulting to the EMA with Xavier Luria, Eric Abadie, Thomas Lönngren, and others, to develop a system that he believes is workable and achievable within Europe. Dr Theresa Mullen and others from the FDA have also developed a framework for the United States. The Institute initiated the 4-Agency Consortium study involving Swiss Medic, Health Canada, TGA in Australia, and HSA in Singapore, who are interested in developing a framework for purposes of carrying out joint reviews. The Benefit Risk Assessment Team (BRAT) initiative, is being carried out by Dr Bennett Levitan from Johnson and Johnson, Dr Becky Noel from Eli Lily, and others, and a recent publication provides insight into their approach.[4] Individual pharmaceutical companies are also involved in studies of novel approaches to benefit-risk frameworks.



Although all of these frameworks and models differ, one fundamental aspect of similarity is the use of a "value tree." The value tree helps to establish a preliminary scope for a benefit-risk assessment by identifying and paring down potential benefit and risk outcomes for an individual product. After identifying all relevant benefit and risk criteria, those that are most likely to contribute to the benefit-risk balance are selected and then valued through a ranking or weighting. Next, the product under investigation, the comparator and the placebo are scored relative to the established benefit and risk criteria. Finally, in the expert judgement step, the combination of values and weights determine the final benefit and risk assessment.

Using this multi-criteria decision analysis (MCDA) approach enhances the consistency, 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. Furthermore, reviewing the approaches used to making regulatory decisions on marketing authorisation applications enables learning from these experiences. The MCDA framework also allows the achievement of a better understanding and more rational explanation of why different agencies reach different conclusions on the basis of the same data. It provides a training tool for both industry and regulatory authorities as they develop and assess new products, allowing industry to take a rational, objective view of the data in their submissions and determine what might need to be strengthened or clarified. Lastly, it will allow the carrying out of a more balanced and objective benefit- risk assessment during post-authorisation, where there is a tendency to emphasise adverse event reporting as opposed to benefit risk assessment.

Visualisation is paramount in the communication of benefit-risk information to all stakeholders: pharmaceutical companies, regulatory authorities, payers, doctors, pharmacists and patients. To explain the seven steps in the critical path for benefit-risk assessment, Professor Walker used the example of a scenario created by Dr Bennett Levitan at the June 2010 Institute Workshop.

- **Step one** is to establish the decision context. In the Workshop scenario, the task was to develop a structured benefit-risk assessment of a hypothetical statin used for the primary prevention of atherosclerotic cardiovascular disease. In the Workshop, information was evaluated from the perspective of the patient, sponsor and regulator to determine differences and similarities to risk assessment.
- **Step two** is the development of a value tree, in this case listing all possible benefits relevant to prevention of cardiovascular disease, such as prevention of cardiovascular death or hemorrhagic stroke, and identifying other beneficial effects, not only of the statin under investigation, but for alternative marketed therapies. Then potential risks were listed, such as myopathy, liver damage, kidney failure or other effects that had been identified from the pivotal studies.
- Step three is to provide a rationale for the inclusion of benefit-risk criteria. In the Workshop exercise, rationales were provided from each of three stakeholders perspectives.
- Step four is to establish the value of the benefits and the risks, using either a quantitative or qualitative approach.
- Step five, which is regarded as the most difficult and most critical step of the assessment, is the weighting of the benefits and the risks.
- Step six is the visualisation of the data. For this step in the Workshop scenario, Dr Levitan created a forest plot showing the occurrence of events in patients using the hypothetical statin compared with those not treated, showing the likelihood of the occurrence of benefits and harms in each group.

- Step seven is applying the expert judgement made by the assessors, looking at all of the relevant data in a systematic, logical way in order to come to the final conclusion and recommendation, which in the case of this hypothetical scenario, whether to recommend the statin or not.

Professor Walker concluded by stating that an important objective of the Institute over the next three years is to develop an international, structured, systematic and standardised approach to benefit- risk assessment, which will be of particular value in the exchange of assessment reports, and which will bring consistency and predictability to the assessment of new medicines. He quoted Professor Bruno Flamion regarding the use of such a framework: "In my view, it is undisputable that the application of an MCDA-based model to the benefit-risk assessment of new medicinal products would help regulatory bodies display their decision criteria and would thus bring increased transparency to the regulatory decisions."

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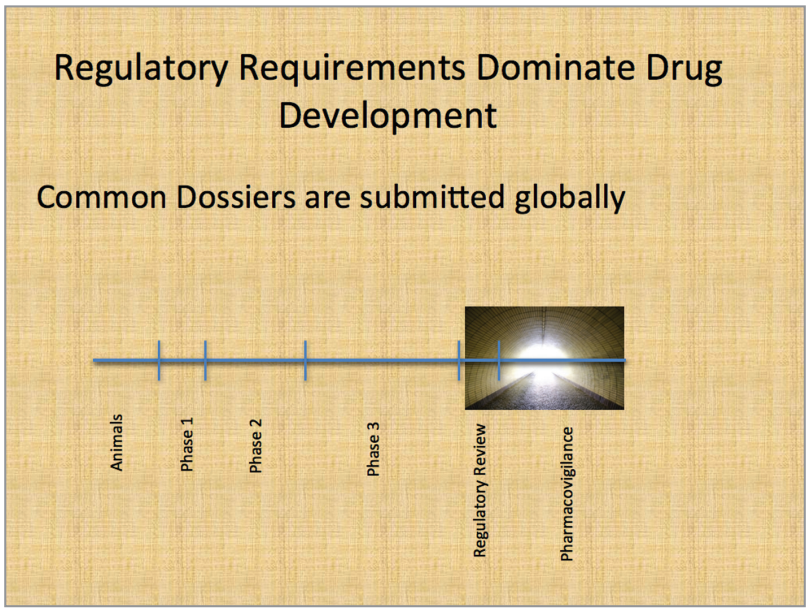
4. Levitan BS, Andrews EB, Gilsenan A, Ferguson J, Noel RA, Coplan PM, Mussen F. *Clin Pharmacol Ther.* 2011;89:217-224.

A regulatory science toolkit (in summary)

Professor Robert Peterson

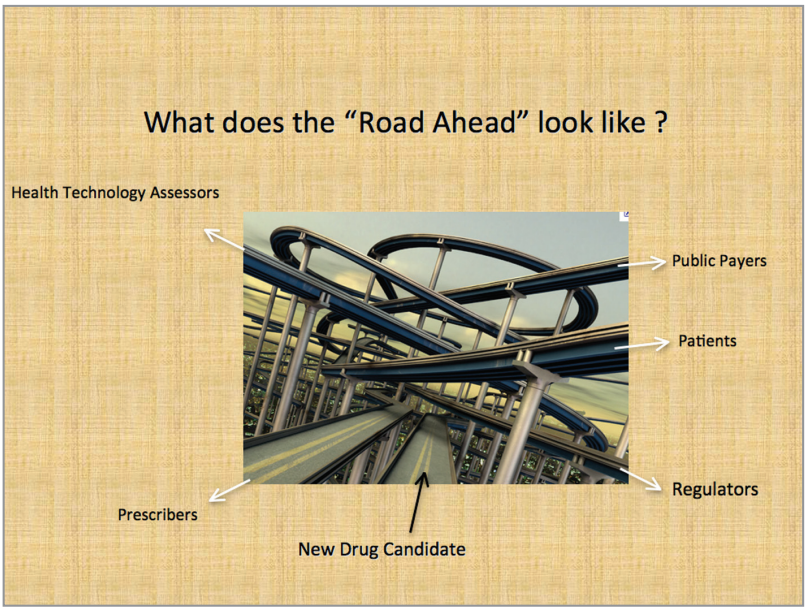
Executive Director, Drug Safety and Effectiveness Network, Canadian Institutes of Health Research, Canada



Meeting the objectives of regulatory review

There is strong concurrence among healthcare stakeholders that the provision of timely, predictable reviews permitting the market entry of products with a positive benefit-harm profile is an important objective for regulators. In this case, the term "harm" is used, as opposed to "risk" for purpose of clear communication, as "risk" is a complex function that connotes at least the likelihood of an adverse event as well as the seriousness of the event. Patients, especially those with serious illnesses, are frequently called upon to balance the risks of their disease versus the risks of potential therapies. Because these harms are communicated to them by regulators, sponsors and healthcare providers, these professionals must consider ways to modify their approach to conveying this information.

Providing high-level scientific advice and appropriate submission guidance to Sponsors through face-to-face meetings are also essential regulatory goals. Ongoing product life-cycle responsibilities were an important topic of discussion at this Workshop, where the challenges for regulators to be prepared for premarket assessments of innovative products while continuing to define regulators' preparedness for premarket assessments ongoing product lifecycle accountabilities was discussed.



Finally, regulators from Emerging Markets at the Workshop detailed a strong and clearly defined public health responsibility that has been assigned to the regulator, beyond that of being a "product gatekeeper." The value of regulatory assessments to national or regional healthcare systems is demonstrated, when assessment reports are made available to decision-makers in other jurisdictions.

Once such regulatory objectives are clearly defined, regulatory organisations must be aligned with these objectives in two broad categories. First, human resources within agencies must be able meet the responsibilities of the traditional regulatory approach of preclinical advice, clinical trial evaluation, premarket review and post-market safety surveillance. Second, the nature of quality systems within agencies must allow the organisation to internally and externally validate the level that they are able to meet the responsibilities of timely review, risk-based resource allocation, transparency of decision making and training.

Strategies for success

A strategy for regulatory success discussed at the Workshop, particularly with regard to a number of small or medium-sized agencies, is regional harmonisation and the sharing of assessment reports. This sharing takes place at many different levels, from a Memorandum of Understanding or national-level agreement to less formal arrangements governed by internal agency policies. Sharing competencies provides an efficient and economical way for manufacturers and sponsors to enhance the regulatory submission and review processes.

Pre-submission scientific advice or consultation given by smaller agencies may differ from that provided by larger or more established regulators who are resourced to offer scientific advice based upon the distinctive competency that they have acquired through interactions with many types of products and different manufacturers. Smaller agencies' advice is often related to ways for sponsors to successfully navigate national or regional regulatory requirements, whether that involves a careful discussion around local issues such as the use of CPPs, shared access to external assessment reports, or requirements for bridging studies.

The frequent measurement of performance allows for internal adjustments to be made within an organisation, and for the opportunity to identify and examine best practices.

One strategy for success that has been frequently linked to the predictability of the outcome of a regulatory review is the incorporation of Good Review Practices. Another tool, the benefit-risk framework, has to encompass not just the assessment of harms and measurement of efficacy that was established within the restricted environment of a drug development programme but also the effectiveness of the medicine in clinical reality. Patient protests in the midst of the AIDS epidemic in the 1980s clearly indicated impatience with the careful, extensive and sometimes redundant reflection upon evidence for efficacy, leading to a change that was not just related to the regulatory resources, timelines and improvements in business practices, but also to an important cultural change regarding regulatory expectations. Typically, once an application has been reviewed and found to contain substantive evidence that meets predetermined thresholds of efficacy, safety and quality, it will be approved. Healthcare systems will from that point on determine the value of that product based upon its value in comparison to other products on the market or unmet needs. The ability to coordinate these determinations will facilitate access to a new medicine.

Strategies for efficiencies

With the advent of the European Union, sharing regulatory assessment reports, parallel or shared reviews, and multinational regulatory consortia

have allowed regulators from small or medium-size agencies to come together and work in a fashion that is respectful of their national requirements and expectations but at the same time be highly efficient, sharing resources to reach a mutual objective. Use of other regulators' decisions requires substantive confidence building and an understanding of and agreement with the reference country's review practices. GRPs serve as the platform underlying this confidence. Finally, shared regional safety surveillance activities provide amplification of data for authorities with small populations or with slow uptake of new medicines, thereby allowing them to make better informed decisions for their unique populations.

Regulatory requirements dominate development

Regulatory requirements are imperative to the drug development process and these are often effectively addressed through requests for scientific advice early in the drug development programme. Dossiers that are submitted globally can be made to comply with regional requirements conveyed through scientific advice.

Recently, the traditional approach of advancing from a phase two to phase three drug development programme, with the attendant timing gaps and lengthy phase two dosing investigations, have been questioned. Rather, mounting evidence indicates that these issues may be addressed effectively through the use of adaptive randomisation trial designs, whereby multiple dosages within a range are tested with a resultant Bayesian likelihood that the best dose providing the measured outcome will fall within a narrow range. In an adaptive trial design environment, a phase two study can seamlessly move into phase three. The resultant effect can be a comprehensive profiling of the product using a more efficient development approach.

Evidence requirements today

Health technology assessment (HTA) is a new reality in drug development that has emerged as a key factor in drug access over the past several years. HTA involves different requirements, reviews, and levels of evidence than a regulatory assessment and focuses on a more comprehensive benefit-harm assessment intended to assess the real-world use of a product. The health technology assessor needs to know what a medicine's effect will be in the full target population. Such evidence requirements often lead to modifications in clinical trial designs to accommodate the needs of these decision-makers. Decision analysis methodology allows the extrapolation of clinical trial results beyond the regulatory requirement-defined clinical trial population through the use of network meta-analysis and other developing methods.

Payers meanwhile require pharmacoeconomic input that allows them to make judgements based on utilities such as quality-adjusted life years, and public payers operate from different perspectives and business models than private payers. Additionally, prescribers or the healthcare decision makers who are attempting to balance one therapy versus another and patients who are becoming more informed and involved in healthcare decisions have often unique evidence needs to assist in their decision making.

The responsibility to meet today's challenges in bringing new safe and effective medicines to patients while demonstrating value to national healthcare systems must be met by all stakeholders and will rely on the evolution of a new regulatory "toolkit" of approaches to help inform cogent, evidence-based and value-based decision making.

Appendix: Workshop Attendees

Regulatory and Government Agencies		
Prof Sir Alasdair Breckenridge	Chairman	Medicines and Healthcare Products Regulatory Agency, UK
Dr Herng-Der Chern	Executive Director	Center for Drug Evaluation, Taiwan, R.O.C.
Dr Osamu Doi	Chief Executive	Pharmaceutical and Medical Device Regulatory Science Society of Japan
Dr Petra Dörr	Head of Management Services and Networking	Swissmedic
Prof Bruno Flamion	Chairman	Belgian Committee for Reimbursement of Medicines (CTG/CRM), Belgium
Dr Christopher Hickey	Director, China Office	US Food and Drug Administration, China
Dr Christina Lim	Deputy Group Director, Health Products Regulation Group	Health Sciences Authority, Singapore
Dr Thomas Lönngren	Former Executive Director	European Medicines Agency
Dr Huei-Xin Lou	Acting Director, PBB Branch, Health Products Regulation Group	Health Sciences Authority, Singapore
Prof Robert Peterson	Executive Director, Drug Safety and Effectiveness Network	Canadian Institutes of Health Research
Dr Lembit Rägo	Coordinator, Quality Assurance and Safety: Medicines (QSM)	World Health Organization
Dr Supriya Sharma	Director General, Therapeutic Products Directorate	Health Canada
Dr Won Shin	Division Director	Korea Food and Drug Administration, South Korea
Dr Lucky Slamet	Deputy for Therapeutic Products, Narcotics, Psychotropic and Addictive Substance Control	National Agency of Drug and Food Control, Indonesia
Dr Satoshi Toyoshima	Senior Advisor	Pharmaceuticals and Medical Devices Agency, Japan
Shigeki Tsuda	Senior Executive Director	Pharmaceutical and Medical Device Regulatory Science Society of Japan
Dr Meir-Chyun Tzou	Director, Division of Drugs and New Biotechnology Products	Food and Drug Administration, Department of Health, Taiwan, R.O.C
Dr Brenda Bun Uratani	Associate Director, China Office	US Food and Drug Administration, China
Mike Ward	Manager, International Programs Division	Health Canada
Industry		
Dr Cliff Burford	Manager, Regulatory Affairs	Taiho Pharmaceutical Company, Japan
Dr Graham Burton	Senior Vice President, Regulatory Affairs Pharmacovigilance and Corporate QA Compliance	Celgene Corporation, USA
Zhao Rong Chen	Head of Regulatory Centre of Excellence	GlaxoSmithKline, China
Dr David Guez	Director Medical Innovation and R&D Coordination	Institut Recherches Internationales SERVIER, France
Dr Ziqun Han	Manager, Regulatory Policy and Intelligence	Abbott Laboratories, UK
Laurence Huang	Executive Director – Regulatory Affairs	AstraZeneca Pharmaceutical Co Ltd, China
Dr Paul Huckle	Senior Vice President, Global Regulatory Affairs	GlaxoSmithKline, USA
Dr David Jefferys	Senior Vice President, Global Regulatory and Government Relations	Eisai Europe Ltd, UK

Hiroki Kato	Director	Zeria Pharmaceutical Co Ltd, Japan
Satoshi Kato	Manager	Zeria Pharmaceutical Co Ltd, Japan
Satoshi Kawaoto	Head, Drug Regulatory Affairs Department	Novartis Pharma KK, Japan,
Dr Satoshi Koike	Representative Director	Amgen Development KK, Japan
Dr Zili Li	Emerging Markets Regulatory Strategy and Policy Lead	Merck & Co Inc, USA
Carolyn Maranca	Vice President, Global Regulatory Affairs – Asia Pacific and Latin America	Johnson & Johnson PRD, USA
Tomoharu Miyagawa	Manager	Zeria Pharmaceutical Co Ltd, Japan
Keiichiro Mori	Senior Director, Regulatory Affairs, Development, Japan	Pfizer Japan Inc, Japan
Patrick O'Malley	Senior Director, International Regulatory Affairs	Eli Lilly and Company, USA
Dr Hironobu Saito	Director, Group 2, New Drug Regulatory Affairs Department	Daiichi-Sankyo, Japan
Dr Joseph Scheeren	Senior Vice President, Head of Global Regulatory Affairs	Bayer Healthcare Pharmaceuticals Inc, USA
Jerry Stewart	Regulatory Policy Head Emerging Markets	Pfizer Inc, USA
Shinji Sugimoto	Manager, Medical Quality Assurance Department	Yakult Honsha Co Ltd, Japan
Etsuko Usui	Manager, Regulatory Policy	Novartis Pharma KK, Japan
Mayumi Yamada	Associate Manager	Astellas Pharma Inc, Japan
Masahiro Yamashita	Manager	TORAY Co Ltd, Japan
Academic institutions		
Prof Koji Kawakami	Professor and Chairman, School of Medicine and Public Health	Kyoto University, Japan
Dr Mamoru Narukawa	Associate Professor	Kitasato University Graduate School of Pharmaceutical Sciences, Japan
Consultancy groups		
Anthony Baker	Senior Partner and Vice President, NDA Group	NDA Group, UK
John Reynolds	Head, Business Development	NDA Group, UK
Kenji Yasuda	Representative Director	PharmaKnowledge Initiative Co Ltd, Japan
CMR International Institute for Regulatory Science		
Patricia Connelly	Manager, Communications	CMR International Institute for Regulatory Science
Lawrence Liberti	Executive Director	CMR International Institute for Regulatory Science
Dr Neil McAuslane	Director	CMR International Institute for Regulatory Science
Prisha Patel	Portfolio, Manager, Emerging Market Programme	CMR International Institute for Regulatory Science
Professor Stuart Walker	Founder	CMR International Institute for Regulatory Science