EVOLVING THE REGULATORY REVIEW PROCESS:

WHAT ARE THE FEATURES THAT ENABLE A TRANSPARENT, TIMELY, PREDICTABLE AND GOOD-QUALITY REVIEW?

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WORKSHOP REPORT

CIRS Centre for Innovation in Regulatory Science

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EVOLVING THE REGULATORY REVIEW PROCESS:

What are the features that enable a transparent, timely, predictable and good-quality review?

Section 1: Executive Summary

Background to the Workshop

The functions and activities that comprise regulatory review have been found to be similar across agencies in terms of the procedures and necessary steps to assess a medicine for safety, quality and efficacy. Indeed, the requirements of a competent regulatory system have been defined as: scientific soundness legal and scientific consistency, procedural predictability and ability to adhere to time targets.

Regulatory agencies need clear and precisely defined processes, consistent application of those processes and well-trained personnel to conduct quality reviews. The presence of these attributes as well as the quality, efficiency, clarity, transparency and consistency that are the fundamental values of good review management practice (GRMP) all ensure an agency's ability to conduct a good-quality review. To maintain this ability, regulatory agencies in established markets are continuously evolving their process and practices to ensure that they are using the best tools and techniques. As agencies in countries with developing pharmaceutical markets evolve their processes, examples of good practice can be identified from agencies with more experience and the principles of GRMP which underpin a quality review in the established agencies can be adopted.

However, of all the process and practices that are in place, there are specific aspects that agencies and companies believe either enable or hinder regulatory review. Accordingly, in preparation for this Workshop, CIRS surveyed both of these stakeholders in 2011 to identify the critical factors that can facilitate or impede regulatory assessment. For agencies that are evolving rapidly but that may also have resource restriction, the survey sought to identify those key review processes and procedures that could be considered critical enablers of review.

This Workshop was held to bring together agencies and companies to identify and discuss the features of an evolving, globally consistent review process that enable the transparent, timely, predictable and good-quality evaluation of new medicines.

Workshop Objectives

- **Review approval process and practices** that can enable as well as hinder the review of new medicines
- **Identify practices and processes** for companies and agencies that underpin a transparent, timely, predictable and good-quality review of new medicines
- **Discuss and make recommendations** on the key practices and processes that should be considered or adopted as enablers for an evolving review process in the 21st century

Key points from presentations

SESSION: TRANSPARENCY IN EVALUATING NEW MEDICINES FOR COVERAGE DECISIONS SHOULD BE A COMMON GOAL

CIRS Executive Director, **Lawrence Liberti** welcomed participants to the sixth annual Emerging Markets Workshop, including international representatives from fourteen regulatory agencies and sixteen pharmaceutical companies for presentations and discussions of the evolving practice of regulatory review, particularly as it applies to countries with developing pharmaceutical markets.

The healthcare industry has become a powerful engine of economic growth in Malaysia and will play an important role in the country's plans to become a fully developed economy by 2020. **Dató Eisah A. Rahman**, *Senior Director of Pharmaceutical Services, Ministry of Health, Malaysia* outlined current and future initiatives for the country's government and economic transformation such as the institution of regulatory fast track and best practices programmes and the reorganisation, capacity building and infrastructure development of the regulatory review system.

Although the practice of clinical pharmacology continues to progress, its primary role in the development of medicines remains the same: to ensure that every patient receives the appropriate therapeutic dose.

Day 1 Chairman, Professor Sir Alasdair Breckenridge, *Chairman, MHRA, UK* discussed advances in pharmacologic precision, enabled by drug-drug interaction and special population

studies, predicting that enhancements in pharmacokinetic and pharmacodynamic modelling may result in fewer, more targeted clinical trials in the future.

The analysis of **Dr Yi Feng**, *Assistant Center Director and Director of the Office of Drug Review Management of the State Food and Drug Administration (SFDA)/Center for Drug Evaluation (CDE), China*, which was presented by **Dr Zili Li**, *Executive Director and Head of Emerging Market Regulatory Strategy, Merck & Co, Inc*, described several ongoing and planned initiatives that have been designed to optimise the capacity and capability of the Chinese regulatory review system. In 2011 the CDE was reorganised to change from a therapeutic-aligned to a discipline-aligned review structure and three important documents were issued on the topics of guiding principles and procedures, and review and decision-making pathways. Additional issues of focus for the agency include enhancement of the timeliness of activities, improving communication with stakeholders and transparency of decision-making, building a risk-based review and decision-making model and applying good review practices (GRevP). Finally, future plans include capacity building through staff education and more extensive interactions with established agencies.

As countries with emerging pharmaceutical markets become important partners in global drug discovery and development. Improvements in the predictability, transparency, timeliness and quality of the review process are needed. Providing examples of recent enhancements of regulatory review practices in emerging markets, **Dr Paul Huckle**, *Chief Regulatory Officer and Senior Vice President, Global Regulatory Affairs, GlaxoSmithKline, USA* explained that optimal global drug development can be fostered through the alignment of regulatory requirements and enhanced collaboration and effective resource utilisation among regulators through joint reviews, the exchange of scientific assessment reports, joint good manufacturing process inspection and clinical trial data recognition.

Prisha Patel, *Portfolio Manager, CIRS, UK* presented the results of the 2011 CIRS Emerging Markets Focus Study. Twelve companies provided responses and scored the attributes that enabled or impeded a transparent, procedurally predictable, timely and good-quality review; in addition, the respondents were asked to rate the performance characteristics of individual agencies relative to those attributes.

Among the elements rated as extremely valuable enablers for good review practice by all respondents were the ability to negotiate the timing of dossier submissions, the availability of transparent processes and decision making, robust information management systems, and good opportunities to engage in dialogue/interaction with the agency. Responses to the survey were in the process of being collected from regulatory agencies, and a complete report will be prepared based on the industry and agency responses.

Results of a recent study of the quality of dossier submissions for new and generic drug applications in Indonesia revealed that supportive data in these applications were not always adequate, particularly for active pharmaceutical ingredients and product development. To reach the common goal shared by industry and regulators for consistently high-quality products that will exert a positive effect on public health, **Lucky Slamet**, *Deputy, Therapeutic Products, Narcotics, Psychotropic & Addictive Substance Control, National Agency of Drug & Food Control, Indonesia*, suggested that the developers of new medicines should understand and strive to comply with guidelines and requirements such as those for good laboratory, manufacturing and clinical practices. In addition, sponsors must provide data as required by specific regulations or guidances and respond to agency questions in a timely manner, thereby building effective communication with regulators based on mutual trust.

Dr Chih-Liu Lin, *Deputy Executive Director, Center for Drug Evaluation (CDE), Taiwan* reported that the percentage of new drug application regulatory reviews that exceeded timing targets was reduced from 23% to 7% within 6 months of the introduction of the Integrated Medicinal Products Review Office (iMPRO) in Taiwan in 2011. Formerly, the administration and final resolution of each application was handled by the Taiwan Food and Drug Administration (TFDA) and the technical review and recommendations performed by the CDE, each with the oversight of separate project management teams. iMPRO combines the resource capacity of the two divisions, with unified standard operating procedures and flow control.

As the former *Executive Director of the European Medicines Agency* and the current *Director, Pharma Executive Consulting*, **Dr Thomas Lönngren** discussed methods to ensure consistency in regulatory practice from the perspective of an established agency, including

developing and adhering to practical review procedures, implementing a quality assessment system, developing a competent staff and striving for transparency in process and results. In addition, the predictability and auditability of regulatory decisions will be enhanced if the methodology used for the benefit-risk assessment of medicines becomes more systematic and consistent, using well-defined and well-valued parameters and encompasses the use of qualitative and quantitative methodologies.

Patrick O'Malley, *Senior Director, Global Regulatory Affairs – International, Eli Lilly and Company, USA* cited three aspects of regulatory review that enable the assessment of medicines: first, consultation and access, that is, the opportunity to discuss trial design, the positions of other regulators, the submission package and other key issues; second, process consistency and predictability, in which the review process, including associated steps and timelines, is well defined and consistently managed across different regulatory groups and agencies; and third, the degree of clarity and level of situational specificity of regulatory requirements. Mr O'Malley provided agency-specific examples of regulatory successes enabled by these characteristics as well as examples of challenges created by their absence.

Dialogue or communication between regulatory agencies and pharmaceutical companies should be a bilaterally positive experience that can educate, clarify or inform. However, as **Dr Murray Lumpkin**, *Commissioner's Senior Advisor and Representative for Global Issues, US Food and Drug Administration*, pointed out, dialogue is also extremely resource intensive for both parties, and like other aspects of product development, it is a process that must be well managed to be successful. Sponsors must optimise opportunities for communication by carefully considering the purpose of the interaction and reviewing, documenting and following up the results, while agencies must be accessible and engaged while maintaining objectivity.

Dr Jason Ferla, *Acting Principal Medical Adviser, Therapeutic Goods Administration (TGA), Australia* provided information on Australian Public Assessment Reports (AusPARs). Published by the TGA within one month of product approval or ninety days of product rejection, AusPARs are modelled on the similar European Public Assessment Report implemented by the European Medicines Agency, and contain data about the evaluation of a prescription medicine and the considerations that led the TGA to approve or reject an application. In addition to providing product information, the publication of such summary bases of decisions increases the transparency of and confidence in the regulatory process.

Although as **Dr Zili Li**, *Executive Director and Head of Emerging Market Regulatory Strategy, Merck & Co, Inc*, reported, the summary basis of approval varies globally in name, format and amount of content, its public disclosure is beneficial to both the pharmaceutical industry and regulatory agencies, particularly in countries with emerging pharmaceutical markets. Dr Li pointed to the summary basis of decision, as published on the Health Canada website as a model of the clear, consistent and comprehensive provision of information regarding regulatory decision making. In countries building experience in the development and regulation of new medicines, this public disclosure can serve both as an aid to company understanding of the rationale for agency decisions and as a driver for enhancement of regulatory agency capabilities.

SESSION: DRIVE TO ACHIEVE A CONSISTENT REGIONAL UNDERSTANDING - EVOLVING THE REGULATORY PROCESS – WHERE ARE WE HEADING?

Day 2 Chairman, Associate Prof John Lim, *Chief Executive, Health Sciences Authority, Singapore* summarised the presentations and discussion of the first day of the Workshop with the observation that six factors impact regulatory review: capacity, communication, collaboration, systems, stratification of risk and strategic and horizon innovation scanning. Professor Lim posed the question, Are limitations in regulatory review linked to limitations of regulatory science, agency or industry matters, or political, national or cultural factors?

Discussing his review of medical regulatory agency websites, **Dr Lembit Rägo**, *Coordinator of Quality and Safety: Medicines, Essential Medicines and Pharmaceutical Policies, World Health Organisation*, said that over the past eight years the number of regulatory agency websites has more than doubled. However, although there has been considerable improvement in the amount and comprehensiveness of the information provided, there is still room for improvement in all topics on these websites, including in key subjects such as

information for applicants, regulatory guidance, pharmacovigilance and registries of medicinal products.

The mission of the Gulf Centralized Committee for Drug Registration (GCC-DR) is to provide Gulf States of Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, the United Arab Emirates and Yemen with safe and effective medications at reasonable prices through the pre-marketing evaluation, marketing authorisation, post-marketing review, GMP inspection and the provision of technical guidelines for new medicines. **Mohammed Al-Rubaie**, *Director of Drug Control, Ministry of Health Oman*, explained that the advantages of the GCC-DR include process efficiency, transparency and harmonisation, as well as improvements in capacity, but challenges remain including inadequate staff, differences in local regulatory systems, guidelines implementation and the time-consuming registration processes.

Resource constraints in Africa result in a general lack of availability of affordable medicines The African Medicines Regulatory Harmonization (AMRH) initiative seeks to improve public health by increasing access to quality, safe and efficacious medicines for the treatment of priority diseases, through harmonising the requirements and standards and strengthening and building the capacity of local and regional regulatory systems. **Margareth Ndomondo-Sigonda**, *Pharmaceutical Coordinator, African Union – New Partnership for Africa's Development (NEPAD) Agency, South Africa* called for interested partners to join forces and support these efforts at the AMRH launch on 29 March 2012 in Arusha-Tanzania.

Chao-Yi (Joyce) Wang, *Senior Specialist, Food and Drug Administration, Taiwan*, explained that the Asia-Pacific Economic Cooperation (APEC) Best Regulatory Practice Project was developed to facilitate the adoption of good regulatory practice (GRevP) among regulatory authorities and stakeholders within APEC; reduce regulatory burden; provide patients with timely access to medicines and to provide a platform for regulatory dialogue and experience sharing. Components of the project include a survey to examine the disparities of GRevP and approaches to scientific assessments among APEC economies, a pilot study on the use of available regulatory review reports from other participating agencies, and a series of GRevP training workshops covering both pharmaceuticals and medical devices, the most recent of which was successfully held in October 2011 in Taipei City, Taiwan.

The four-agency consortium comprising Swissmedic, the Health Sciences Authority of Singapore, the Therapeutic Goods Administration of Australia and Health Canada was initiated in 2007 on the basis of a network of bilateral agreements. **Cordula Landgraf**, *Head of Networking, Swissmedic*, said that the consortium has progressed from information sharing on safety, policy, guidelines and clinical trials to labour sharing in Working Groups for the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and in completed pilots and planned projects for parallel scientific review. In addition, an electronic template for the qualitative benefit-risk assessment of medicines was developed by the consortium in cooperation with CIRS and is currently being tested by the four agencies.

Recommendations from across the Syndicates

- Before submission,
  - companies should be able to expect regulatory predictability and timeliness through the judicious use of agency consultation and dialogue, an understanding of the expected timelines, dossier requirements, legal requirements and regulatory guidelines;
  - from the agency's point of view, predictability and timeliness can be enhanced by encouraging proper training and the use of best practices sharing sessions, appropriate communication of assessment templates, a focus on local medical practices and the use of an electronic common technical document to formalise the structure of the materials presented.
- During the review process, predictability and timeliness would be encouraged through
  - the proper resourcing and training of reviewers,
  - adherence to procedural consistency,
  - use of a case management team and IT systems to track progress and timelines,
  - quality assurance systems for peer reviews,
  - the use of ongoing process improvement mechanisms,
  - the use of a standard assessment template and a defined decision-making process or framework for scientific consistency,
  - the provision of response timelines by companies and
  - companies' ability to submit accurate supporting documentation to queries and a focus on targeted areas of dossier.
- A t the time of regulatory decision predictability and timeliness can be fostered through
  - the transparency of the summary basis of the regulatory decision,
  - use of quality scorecards and metrics measurement and knowledge and sharing of best practices.

Recommendations for good-quality reviews

- Encourage alignment of review processes at the regional level, international collaboration and cross-agency training.
- Develop an inbuilt continuous improvement process through the use of "customer" surveys of both agencies and companies and the refinement and use of an independent survey such as the CIRS Quality Scorecard programme.
- Explore the separation of the quality of the regulatory review and the quality of the decision-making processes.

Recommendations for transparent reviews

- CIRS should develop a high-level description of existing Memoranda of Understanding between agencies, including topics covered therein.
- CIRS should compile a best practices document containing the elements of regulatory transparency for use in regulatory agencies in countries with emerging pharmaceutical markets, including priorities such as project management, timelines and dialogue opportunities.

Workshop Programme

DAY 1: 6 DECEMBER 2011	
Session: What are the processes and practices that can enable or hinder the review?	
Introduction to the Workshop	**Lawrence Liberti**, *Executive Director, CIRS*
Current and future drug regulation in Malaysia	**Dató Eisah A. Rahman**, *Senior Director of Pharmaceutical Services, Ministry of Health, Malaysia*
Chairman's welcome and introduction	**Professor Sir Alasdair Breckenridge**, *Chairman, MHRA, UK*
What are the expectation and requirements of the regulatory review process to deliver the needs today and for the future?	
A perspective from CDE	**Dr Yi Feng**, *Assistant Center Director, SFDA/Center for Drug Evaluation, Director, Office of Drug Review Management, SFDA/ CDE, China*
A company viewpoint	**Dr Paul Huckle**, *Chief Regulatory Officer & Senior Vice President, Global Regulatory Affairs, GlaxoSmithKline, USA*
What are the key processes and practices that are seen by companies and agencies as enablers and barriers to the review process?: Outcome of a CIRS Survey	
CIRS survey results	**Prisha Patel**, *Portfolio Manager, CIRS, UK*
Apart from resources, what are the key processes and procedures that enable a timely and predictable review?	
Developing agency 1: The role companies can play (understanding the requirements, full data provision and responding to questions in a timely manner)	**Lucky Slamet**, *Deputy, Therapeutic Products, Narcotics, Psychotropic & Addictive Substance Control, National Agency of Drug & Food Control, Indonesia*
Developing agency 2: The role of project management and target times	**Dr Chih-Liu Lin**, *Deputy Executive Director, Center for Drug Evaluation, Taiwan*
A developed agency: How to ensure consistency of practice	**Dr Thomas Lönngren**, *Independent Strategy Advisor, Pharma Executive Consulting, UK*
Company viewpoint: Examples of practices that have enabled or hindered the review	**Patrick O'Malley**, *Senior Director, Global Regulatory Affairs – International, Eli Lilly and Company, USA*
Agency-to-company and company-to-agency dialogue, pre-submission, during approval and post-approval – Is this important to an effective and efficient review process and what are the conditions?	
An agency perspective	**Dr Murray Lumpkin**, *Commissioner's Senior Advisor and Representative for Global Issues, US Food and Drug Administration*
Availability and publication of the summary basis of approval: What should be included and is publication a sign of a transparent and good quality review?	
An agency perspective	**Dr Jason Ferla**, *Acting Principal Medical Adviser, Therapeutic Goods Administration, Australia*
A company perspective	**Dr Zili Li**, *Executive Director and Head of Emerging Market Regulatory Strategy, Merck & Co, Inc, USA, Co-chair of FDA Alumni Association International Network*

Industry Panel Discussion: What are the key factors from an industry perspective that should be considered by the Syndicate Groups?	
Timeliness and predictability:	**Raj Long**, *DRA Head AMAC, GEM, LATAM, Novartis Pharma AG, Switzerland*
Good quality review:	**Dr Graham Burton**, *Senior Vice President, Global Regulatory Affairs, Pharmacovigilance and Corporate QA Compliance, Celgene Corporation, USA*
Transparency:	**Erika Eckel**, *Head of Regional Management, Regulatory Affairs, F. Hoffmann-La Roche, Switzerland*
Syndicate Sessions	
Syndicate sessions on best practices for 2020 review process	
TOPIC A: Timely and predictable review process: What does this mean and, assuming resources were not an issue, what process and procedures would an ideal agency adopt?	
Chairperson	**Lucky Slamet**, *Deputy, Therapeutic Products, Narcotics, Psychotropic & Addictive Substance Control, National Agency of Drug & Food Control, Indonesia*
Rapporteur	**Dr Raymond Chua**, *Deputy Group Director, Health Products Regulation Group, Health Sciences Authority, Singapore*
TOPIC B: Good quality review: What does this mean to companies and agencies and what are the key components?	
Chairperson	**Prof Bruno Flamion**, *Chair, Belgian Committee for Reimbursement of Medicines*
Rapporteur	**Arun Mishra**, *Director, Global Regulatory Affairs (Asia-Pacific, Japan and Emerging Markets), GlaxoSmithKline, UK*
TOPIC C: Transparency of the review process before, during and after: What should be transparent and how should it be measured?	
Chairperson	**Prof Robert Peterson**, *Executive Director, Drug Safety and Effective Network, Canadian Institutes of Health Research, Canada*
Rapporteur	**Dorte Strobel**, *Senior Regulatory Intelligence Manager, Novo Nordisk A/S, Denmark*

Day 2: 7 December 2011	
SESSION: Drive to achieve a consistent regional understanding: evolving the regulatory process – where are we heading?	
Chairman's introduction	**Associate Prof John Lim**, *Chief Executive, Health Sciences Authority, Singapore*
Feedback of Syndicate discussion	
Panel discussion: Regulators' reactions to Syndicate recommendations	
Dr In-Sook Park, *Director of Pharmaceutical Standardization Division, Korea Food and Drug Administration* **Dató Eisah A. Rahman**, *Senior Director of Pharmaceutical Services, Ministry of Health, Malaysia* **Dr Jason Ferla**, *Acting Principal Medical Adviser, Therapeutic Goods Administration, Australia* **Dr Murray Lumpkin**, *Commissioner's Senior Advisor and Representative for Global Issues, US Food and Drug Administration*	
Regulatory authority websites: What information is publically available and what is the quality of the information?	**Dr Lembit Rägo**, *Coordinator, Quality Assurance and Safety: Medicines , Essential Medicines and Pharmaceutical Policies, World Health Organization, Switzerland*
Gulf Cooperation Council Drug Registration procedure in the Middle East: What are its strengths and how does it need to evolve?	**Mohammed Al- Rubaie**, *Director of Drug Control, Ministry of Health. Oman*
African Medicines Regulatory Harmonisation: What is the status?	**Margareth Ndomondo-Sigonda**, *Pharmaceutical Coordinator, African Union - NEPAD Agency, South Africa*
APEC Best Regulatory Practice Project: An update and future direction	**Chao-Yi (Joyce) Wang**, *Senior Specialist, Food and Drug Administration, Taiwan*
Agency consortium: Evolving a work sharing model that will streamline approval and enable effective resource utilisation	**Cordula Landgraf**, *Head of Networking, Swissmedic*
Chairman's summary and close of Workshop	

Section 2: Syndicate Discussions

Three syndicate groups were asked to discuss three different aspects of enabling timely, predictable and good-quality reviews, to provide strategies to address the critical issues outlined in their discussions and to arrive at recommendations for change.

Syndicate 1	
Chair	**Lucky Slamet**, *Deputy, Therapeutic Products, Narcotics, Psychotropic & Addictive Substance Control, National Agency of Drug & Food Control, Indonesia*
Rapporteur	**Dr Raymond Chua**, *Deputy Group Director, Health Products Regulation Group, Health Sciences Authority, Singapore*
Syndicate 2	
Chair	**Prof Bruno Flamion**, *Chair, Belgian Committee for Reimbursement of Medicines*
Rapporteur	**Arun Mishra**, *Director, Global Regulatory Affairs (Asia-Pacific, Japan and Emerging Markets), GlaxoSmithKline, UK*
Syndicate 3	
Chair	**Prof Robert Peterson**, *Executive Director, Drug Safety and Effective Network, Canadian Institutes of Health Research, Canada*
Rapporteur	**Dorte Strobel**, *Senior Regulatory Intelligence Manager, Novo Nordisk A/S, Denmark*

Syndicate 1: Timely and predictable review process: What does this mean? Assuming resources were not an issue, what process and procedures would an ideal agency adopt?

Background

Timeliness and predictability are key components of a good-quality regulatory review of new medicines, not only ensuring that an agency undertakes its decision making in a way that is both legally and scientifically consistent, but that also facilitates patients' access to new medicines.

There may be many reasons for the length of a review process, which can differ among agencies for reasons including the number of reviewers, the depth of the review, the reliance on reference agency reviews, the types of questions that are raised, the time to formulate and have questions answered and the time taken to undertake scientific review versus the administrative or queue time.

However, review timeliness gives patients, healthcare providers and companies a clear understanding that access to a new medicine will not be unnecessarily delayed during the review process, and there are a number of activities that can aid a timely review. These activities include:

- setting realistic targets for each component of the review process and striving to meet those targets,
- good project management,
- clarity regarding timing of questions issued to companies and
- managing the responses to those questions.

In addition, agencies must ensure that companies understand data requirements for an initial review and the necessary format and structure of the submission.

Predictability in the review process, that is, adherence to agency-determined timing and procedural requirements and scientifically sound decision making are also critical to ensure that safe and effective medicines reach patients.

Respondents to a CIRS survey undertaken in 2011 specified parameters that enable a timely and predictable review process:

Timeliness is enabled by	Predictability is enabled by
Adherence to target timelines during review	Detailed guidelines
Availability of different assessment routes and priority review requests	Meetings during development
Defined and efficient processes	Pre-NDA/Submission meetings
Dedicated project management	The ability to track progress of an application
The ability to negotiate and the ability of regulators to give approval with the provision of providing a post-approval commitment	Detailed target times
	Consistent review assessment methods

This Syndicate was encouraged to review procedures and processes that enhance a timely and predictable regulatory review, deciding whether these parameters should be measured, either directly or indirectly, and to identify the key barriers and methods to overcome these barriers.

Key questions were considered:

- What are the critical elements of a timely and predictable review?
  - What are the stages of the review that require target timelines?
  - How do agencies and companies ensure adherence to timelines?
- Can a timely and predictable review be measured and if so, what are the metrics?
- Does having an understanding of the agency assessment template improve predictability?
- What process and procedures should agencies and companies undertake to enable a timely and predictable review?
  - Is transparency of dossier submission requirements (through publication of legislation, guidelines or pre-submission interactions) a key element?

Critical issues

Syndicate members agreed that multiple issues can impinge on a timely regulatory review. Internal factors such as the number and competency of reviewers and regulatory staff have an impact, as can lack of adherence to time targets due to limited case management and project tracking skills. Regulatory agencies may conduct complex, full evaluations or rely on the reviews of reference agencies to expedite certain types of reviews. Finally, the types and clarity of questions raised by the agency and the time required by the sponsors to answer those queries have an obvious effect on overall timelines.

As with timeliness, the number and competency of regulatory reviewers and regulatory staff, the depth of reviews and the types and clarity of agency questions all exert an influence on process predictability. An understanding by companies of processes, procedures and assessment criteria and clarity on the part of agencies in explaining these requirements in detail are absolute requirements for regulatory agency predictability as are the agency's use of a scientifically sound decision-making framework and supportive guidelines. Additionally, agencies must engage in open and timely dialogue with sponsors, ensure consistency between reviewers and submissions and achieve transparency of decision making

Strategies

Clear definitions of timeliness and predictability are required: Timeliness should encompass realistic goals that are dependent on medical need and access priority. It must be measured from submission to outcome and divided into different stages, with properly defined milestones and target timelines. Target timelines should be constructed dependent on the type of review (for example, full, abridged or verification) and should additionally incorporate consideration of the amount of required resources, both in manpower and competencies. Response time expected from the companies should be clearly defined.

Predictability requires that companies understand and comply with dossier requirements and that submissions be of good quality. It also requires agency transparency and the employment of the necessary number of reviewers with appropriate competencies, governance and accountability to patients' needs, and ensuring that reviewers are consistently using proper evaluation criteria. Predictability entails understanding that because it is dependent on individual judgement, some variability in regulatory review is unavoidable,

although it can be minimised with the use of standard quality management templates and good review and regulatory practices.

A timely and predictable timeline requires resources in terms of manpower, competency and training, the use of a standard assessment template and training for the template's use. This training must incorporate consideration of the relevance of data to specific jurisdictions. Additionally, companies should strive to adhere to scientific advice when given, and provide full and timely responses to agency queries.

Recommendations

- Before submission, companies should be able to expect regulatory predictability and timeliness through the judicious use of agency consultation and dialogue, an understanding of the expected timelines, dossier requirements, legal requirements and regulatory guidelines; from the agency's point of view, predictability and timeliness can be enhanced by encouraging proper training and the use of best practices sharing sessions, appropriate communication of assessment templates, a focus on local medical practices and the use of an electronic common technical document to formalise the structure of the materials presented.
- During the review process, predictability and timeliness would be encouraged through the proper resourcing and training of reviewers, adherence to procedural consistency, use of a case management team and IT systems to track progress and timelines, quality assurance systems for peer reviews, the use of ongoing process improvement mechanisms, the use of a standard assessment template and a defined decision-making process or framework for scientific consistency, the provision of response timelines by companies and companies' ability to submit accurate supporting documentation to queries and a focus on targeted areas of dossier.
- At the time of regulatory decision predictability and timeliness can be fostered through the transparency of the summary basis of the regulatory decision, use of quality scorecards and metrics measurement and knowledge and sharing of best practices.

Syndicate Discussion 2

Good-quality review: What does this mean to companies and agencies and what are the key components?

Background

A quality review is an essential component of good regulatory decision making. The quality of the review process from the construction of a dossier to the ultimate regulatory decision guarantees that expected standards have been met instils confidence amongst stakeholders and achieves universal acceptability of the review. This quality also ensures that assessments and decisions are scientifically sound and that safe and effective medicines reach the patients in an expeditious manner. However, despite its critical nature, quality in itself is challenging to define, although the elements of a quality review have been discussed and agreed in previous CIRS Workshops and include: the correct format for the dossier, scientific soundness of the review process, adherence to legally and scientific consistency, procedural predictability, adherence to time targets and transparency in communication among stakeholders.

A number of activities, procedures and processes are built into both agencies and companies to ensure quality. In agencies, these parameters include pre-submission advice, internal quality policies, standard operating procedures, external and internal peer reviews, auditing systems, the training and competency of staff, post-approval procedures for learning and feedback, policies, the use of electronic tracking/project management technology and having a robust agency culture and internal philosophy that fosters quality. Combined, all of these factors are known as Good Review Practices. For companies, quality parameters include dossiers that are well written, internally consistent and complete and that meet published guideline requirements for submission.

It should be understood that a good-quality dossier is not the determinant of a good-quality review process. From a regulator's perspective, having a quality review system in place helps to build a consistently good-quality review, even in the face of a relatively poor-quality dossier. However, a good quality dossier can aid the review process to be more efficient and effective.

Although processes to ensure quality can be built in and monitored internally, the objective measurement of a quality review can be challenging. Is it a measure of adherence to processes or is it also an assessment of the nature of the decision taken? Should only agencies measure quality using internal metrics or is there a role for other stakeholders in providing feedback on the processes and outcomes? It has been suggested in previous CIRS Workshops that only an understanding of stakeholder perception of the quality of a process enables an agency or company to understand those processes' efficiency and effectiveness, and that stakeholders who understand these components can better support the mission and goals of the regulator, facilitating a quality review by providing the expected input.

Key questions were considered by this Syndicate:

- How are agencies actively building quality into their reviews and what can companies do to enable this process?
- Can the quality of the review be measured and if so, what are the metrics?
- What attributes of the review should companies feed back to agencies to help improve the quality of the review process?
- What role does the quality of the submission play and how can companies aid agencies to undertake a quality review?

Critical issues

It was the consensus of this Syndicate that the quality of a regulatory review is highly dependent on the quality of the internal regulatory processes such as the supportive standard operating procedures and adherence to good review practices. Staff capacity and capability are additional important factors in review quality and as ideal performance targets should be the goal to be reached, addressing the competence of the staff through training needs as a continuous process.

Strategies

Programmes for professional development of review staff are an important factor in retaining qualified personnel and all assessors should be formally trained in concepts such as benefit-risk evaluation. Alignment of review processes should be promoted at the regional level and international collaboration and cross-agency training and the sharing of information (through appropriate legal avenues) and resources must be encouraged.

An inbuilt continuous improvement process could be developed through the use of such tools as a "customer" survey of both agencies and companies, the refinement and expanded use of an independent survey such as the CIRS Quality Scorecard programme, the use of internal and external audits, agency-to-agency review or a review of post-approval regulatory events (ie, an analysis of serious unexpected or other adverse events).

Quality documentation and the review of procedures and products through the use of assessment templates and key performance indicators should be an integral part of regulatory policies and standard operating procedures. Another option might be the use of an integrated peer review system such as an independent advisory committee. Such ongoing and scheduled reviews could enhance accountability for the regulatory review process.

Delinking the regulatory review process from the process of making decisions should be explored. Although the quality of decision making is of equal importance to the quality of review process and procedure, methods for enhancing and measuring that quality have yet to be outlined.

Recommendations

- Encourage alignment of review processes at the regional level, international collaboration and cross-agency training.
- Develop an inbuilt continuous improvement process through the use of "customer" surveys of both agencies and companies and the refinement and use of an independent survey such as the CIRS Quality Scorecard programme.
- Explore the separation of the regulatory review and decision-making processes.

Syndicate Discussion 3

Transparency of the review process before, during and post-approval: What should be transparent and how should this be measured?

Background

A transparent review process is an essential component of good regulatory decision making, as it builds trust in the review process and the decisions being made, thus enabling accountability. Internal and external communication should be a routine process in the regulation of medicines, and agencies have a number of stakeholders who require either direct information or an understanding of the agency's activities, including pharmaceutical and medical device companies, healthcare providers, patient groups, the general public, other regulators and government agencies. Such information needs to be accurate, complete, meaningful, actionable, accessible and timely.

Transparency in the review process can involve a number of activities, from sharing knowledge that provides important review information to stakeholders such as internal guidelines and standard operating procedures, to transparent communication around the content of reviews and the information utilised in making a benefit-risk decision. Transparency of process does not suggest, however, that all agencies will require or communicate similar information, nor that they will reach an identical decision about a product. Furthermore, it should be recognised that transparency does not extend to confidential information, and it is important that the confidential nature of commercial data is recognised by all parties.

There are a number of activities, procedures and processes within agencies that are built in to ensure transparency. These include operational information to ensure that processes and procedures are clearly understood by all stakeholders, decisional frameworks for the assessment of data are employed consistently, and that the resultant summary basis of decisions is made public. These factors not only aid in ensuring transparency regarding the quality of reviews, but also improve their predictability by enabling companies to understand agency requirements and how data are used to support agency decisions.

Key questions were considered by this Syndicate:

- How can transparent processes contribute to improving patient access to medicines?
- What are the key elements of a transparent review process?
- Can transparency be measured and if so, what are the metrics?
- How can agencies actively build transparency into their review and approval process?
- What tools and procedures can encourage transparent interactions?
  - Do these need to vary based on the section of the dossier being reviewed?
- What should not be transparent? Should such items as memos of understanding and proprietary process information be excluded?
- In relation to transparency, what would agencies be looking for from companies both in terms of interactions and dossier content?

Respondents to a CIRS survey undertaken in 2011 specified activities that enable a transparent review: the availability of detailed guidelines, the use of decision frameworks, the preparation and dissemination of the summary basis of approval, published quality and timeliness metrics, the availability of process information, adherence to detailed target times, the ability to have dialogue during review, the designation of an agency contact person and the capability to track progress of the submission in a transparent manner.

Critical issues

Certain details of the development and regulation of medicine are not amenable to transparency for business, legal or personal privacy reasons, such as manufacturing specifications and patient–specific data. Furthermore, implementing transparency policies is resource-intensive and could become a barrier to the fulfilment of the primary mission of regulators, that is, the efficient and timely assessment of medicines. Finally, it is not clear that it would be useful or practical for patients or other stakeholders to be informed of all aspects of the data in a submission; for example, how would patients interpret all available safety data for each new product?

It was the opinion of this Syndicate that the publication of the summary basis of the decision could be a tool to create transparency and quality, but the target audiences and therefore, the nature of the content for this

document should be considered. For example, such documentation may not always serve as a sufficient sole basis for another regulatory agency's approval of the medicine but may, for some low-risk medicines, provide sufficient background to support a decision.

Strategies

In order to prepare high-quality applications, pharmaceutical companies need to be able to follow transparent guidelines. After submission, sponsors expect that the agency will follow consistent review criteria guided by consistent internal processes and procedures, supported by communication tools to enhance regulator-sponsor discussions and a tracking system to monitor the progress of review timelines and key steps.

Agencies would benefit from advance alert of upcoming applications, to staff appropriately and prepare their internal resources. In addition, post-approval safety data should be presented to the agency in a useful format, for example, as a database rather than a static PDF, information regarding off-label use where available should be made available and information about critical queries from other agencies that have been resolved could all prove useful and valuable to regulators.

Recommendations

- CIRS should develop a high-level description of existing Memoranda of Understanding between agencies, including topics covered therein.
- CIRS should compile a best practices document containing the elements of regulatory transparency for use in regulatory agencies in countries with emerging pharmaceutical markets, including priorities such as project management, timelines and dialogue opportunities.

Panel Discussion: Regulators' reactions to Syndicate recommendations

Regulators from four jurisdictions, South Korea, Malaysia, Australia and the United States shared their observations on the Syndicate presentations on the enablers and impediments to the regulatory review of new medicines. Their comments and those of other Workshop participants have been grouped under the general classifications of predictability, quality timeliness and transparency.

Predictability

- The predictability of a regulatory evaluation is rendered more complex by the need for and input from the judgement of individual reviewers; however, there are mechanisms to ensure the quality of those judgements. Although often regulators do not have peers within their own jurisdictions, international peer review can ensure the quality of scientific endeavours. For example, although relatively resource intensive, the European centralised process of regulatory evaluation employs the excellent quality control process of combining the independent evaluation of advisors from two different jurisdictions.
- Science can inform regulators of the known risks of new products but cannot tell them whether a benefit-risk profile is acceptable within a country's specific communities or within subsets of those communities. Even when regulators in two jurisdictions completely agree on the science surrounding a new medicine, two different regulatory decisions may be rendered because of differences in community tolerance for risk or in the application of legislatively mandated risk management tools.
- It should be remembered that regulation is constrained by three different frameworks science, law and public health expectations. Of those three, science is universal but law and public health expectations differ vastly among different countries. This consideration is particularly important when regarding the regulation of medicines in countries with emerging pharmaceutical markets.

Quality

- Although post-completion evaluations of regulatory reviews would be a worthwhile mechanism for continuous quality

improvement, unfortunately development and review teams are typically quickly dispersed after a decision is rendered.

- There is often a public perception that certain societal factors such as religion or economics have played a role or should have played a role in regulatory decisions when they have not and cannot. This is particularly challenging when products are related to ethically charged issues around which society has been unable to reach a consensus.

Timeliness

- Because of the variance in medical needs among countries, setting globally optimum timelines is challenging. Agencies must work within their jurisdictions to establish realistic time targets, develop a common understanding regarding expectations for accomplishments within those timeframes and then request resources to meet those expectations.
- Agencies that rely on external evaluators because of limited resources have improved resource use but must promote the adherence to time targets by these independent evaluators. By instituting requirements for notification of new dossier submissions several months prior to the data arrival, agencies are better able to address staffing needs and adhere to stated timelines.

Transparency

- Transparency and confidentiality
  - One inconsistency in transparency is evident when regulators are precluded from providing certain information regarding new drugs in the interest of public health but that same information is easily publicly available on financial websites in the interest of economic health.
  - In fulfilment of mandates for transparency, the classification of information as confidential or non-confidential is an additional challenge encountered by regulators. In addition to proprietary trade information, industry would sometimes prefer to also classify information that might reflect negatively on their product as "confidential." This can lead to confusion regarding what should be included in the summary basis for approval.
- Transparency and audience
  - Is the objective of transparency the provision of decision-making data to the public or the fulfilment of the information-gathering needs of competitors or investors? This is a critical issue that each agency must address.
  - Establishing the audience for communication is essential as the content and format should vary between healthcare professionals and a lay audience, and even within the general public, educational levels are highly variable.
  - The current drive for transparency from consumers and government has resulted in a flood of information that may be challenging for many audiences to process. Lay audience members may require assistance in the interpretation of scientific data, for example, clinical trial results that demonstrate the achievement of an increase in treatment effect from 4% to 6% permits a sponsor to claim a 50% improvement without specifying the number needed to treat to achieve those results.
  - Training regulators in the "soft" skill of effective communication is a challenge. Scientists and lawyers are not typically trained to communicate with the general public.
- Transparency and data sharing
  - From a regulatory perspective: there is a great difference between regulators sharing data with the public and sharing data with other regulators. Typically, there is little difficulty with sharing pre-decisional or investigative information across agencies, but certain data that are considered commercially sensitive may not be shared among agencies regardless of shared confidentiality agreements or memoranda of understanding. However, agencies may argue that without access to detailed manufacturing data, those agencies are unable to maximise resource use through shared inspections.
  - From an industry perspective: in jurisdictions where intellectual property rights are not adequately protected, companies have legitimate concerns regarding sharing this manufacturing information.

Section 3: Presentations

Current and future drug regulation in Malaysia

Dato' Eisah A. Rahman

Senior Director of Pharmaceutical Services, Ministry of Health, Malaysia

Vision 2020

In 1991, former Prime Minister, Mahathir bin Mohamad outlined "Vision 2020", a plan for Malaysia to become a fully developed nation by 2020. To achieve this vision the current Prime Minister, Najib Tun Razak has laid out an aggressive developmental agenda that includes the transformation programmes and "The Tenth Malaysia Plan, 2011 to 2015". There will also be a Health System Restructuring called "1Care for 1Malaysia."

Critical elements of Malaysia's agenda for change are the Government and Economic Transformation Programmes (GTP and ETP). The GTP seeks to achieve a more effective delivery of services to the Malaysian people, moving the country towards becoming an advanced, united, and just society with high standards of living, irrespective of race, religion or region. The ETP is a comprehensive effort to convert Malaysia into a high-income nation by 2020. As part of this programme, the healthcare industry has been identified as one of the National Key Economic Areas (NKEAs), strategic sectors that will drive needed economic growth in Malaysia. A number of Entry Point Projects (EPP) involving NKEAs have been developed as part of the ETP, including EPP3, specifically focusing on Malaysian pharmaceuticals whilst promoting this via co-branding, contract manufacturing, site transfer and joint venture mechanisms. In furtherance of this goal, Malaysia has also made a commitment to complete registration process within 60 days for generics identified in EPP3, upon submission of complete product dossiers.

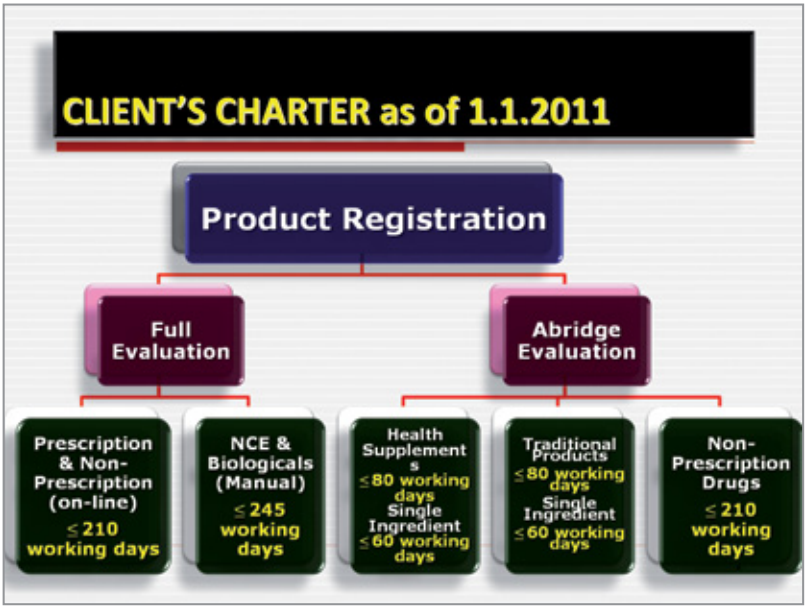


Figure 1. New regulatory timelines have been established in Malaysia.

Regulatory changes

The regulation of new medicines is also undergoing transformation in Malaysia, with liberalisation of trade policies and the implementation of fast-track procedures for therapies for life-threatening diseases. Based on a recent audit by Organisation for Economic Cooperation and Development (OECD) Inspectorate, Malaysia has satisfactorily fulfilled the requirements of the OECD Mutual Acceptance of Data (MAD) and is expected to achieve full membership of the OECD MAD for Good Laboratory Practice by 2013. Under EPP2, for promotion of clinical trials, an increase in number of clinical trials and bioequivalence (BE) studies conducted in Malaysia has been targeted.

As part of an ongoing drive for the development of regulatory best practices, the Client's Charter for the registration of medicines in Malaysia was revised in 2011 and now specifies that reviews of new chemical entities and biologicals must be accomplished within 245 working days and evaluation of a dossier for a prescription and non-prescription drugs must be conducted within 210 days, whilst an abridged evaluation for health supplements and traditional products is not more than 60 days for single ingredient products and within 80 days for products containing two and more ingredients. (Figure 1).

Other initiatives for regulatory enhancement underway include the establishment of a system of key performance indicators that drive government employees at all levels to achieve predetermined goals, as well as the certification and accreditation of BE centres for conduct of BE

. . . the healthcare industry has been identified as one of the National Key Economic Areas, strategic sectors that will drive needed economic growth in Malaysia.

study for generic medicines.

Future plans

A programme of capacity building and infrastructure improvement has been planned for Malaysia's regulatory system, possibly looking at appropriate organisation models to increase efficiency and productivity. In an effort to enlarge and enrich Malaysian regulatory expertise, opportunities for professional education, enrichment and certification will continue to be extended to regulatory officers.

Finally, for maximum achievement with limited resources, Malaysia will take full advantage of public-private partnerships and continue to promote bilateral and multilateral cooperation, including joint assessments and audits, making important strides toward the achievement of Vision 2020.

The role of clinical pharmacology

Professor Sir Alasdair Breckenridge

Chairman, MHRA, UK

Clinical pharmacology can be simply defined as what the body does to medicines (pharmacokinetics; PK) and what medicines do to the body (pharmacodynamics; PD). Sir Alasdair began his presentation by stating the equally simple goal of clinical pharmacology in medicines development: to get the right dose of the right drug to the right patient (Figure 2).

The measurement between the efficacy of a drug and the toxicity of exposure to that drug represents its benefit: risk ratio – a measurement that may differ among patients and among communities and which may be altered in response to interactions with other drugs. As Sir Alasdair noted, it is also contributes to faulty decisions about the profiles of medicines during their early drug development.

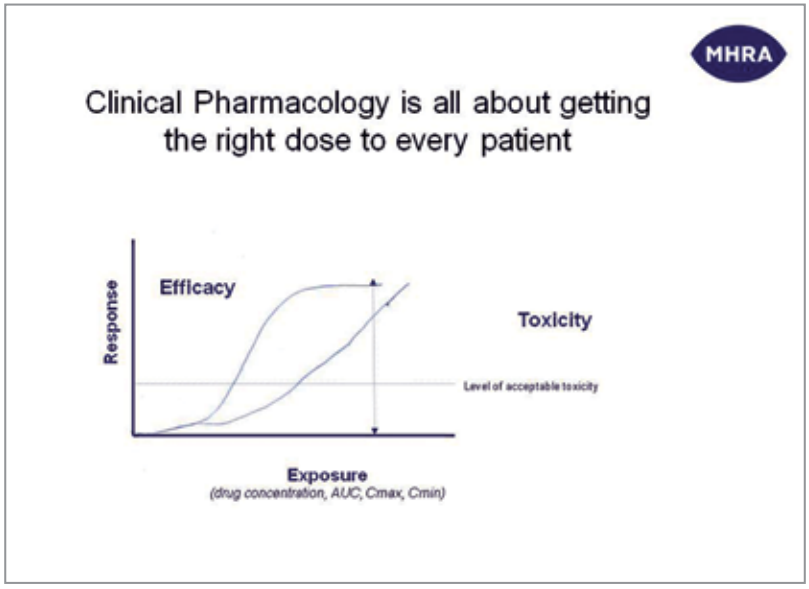


Figure 2. Determining the dose that will achieve the best response with the least harm for each patient is the goal of clinical pharmacology.

The evolution of pharmacology tools

The tools available to the clinical pharmacologist have undergone significant changes over the past several decades. In the 1960s, when many drugs still in use today were first developed, much was known about basic pharmacology, but knowledge about the receptors on which the compounds acted was very limited and the documentation of the science behind clinical pharmacology was rudimentary. By 1980, information about basic PK, such as population differences, bioequivalence and food effects while available, was largely descriptive in nature. By the year 2000, the study of PK or population pharmacokinetics was much more developed, and biomarkers were being used more commonly as a tool in drug development. The role of ethnic differences in the pharmacologic effect of a medicine was beginning to be appreciated and pharmacologists had become able to predict drug activity and interactions more effectively. Louis Shiner had published a paper in 1997 in which he coined the term "learn and confirm", two important phases of drug discovery, and which has since become a guiding force of clinical pharmacology and drug development.[1]

Sir Alasdair predicted that within the next 20 years, the science of the modelling of PK and PD and of understanding the basis for a disease itself will become more extensively developed and used more often in furtherance of the learn-and-confirm paradigm, thereby contributing to a streamlined, efficient medicines discovery

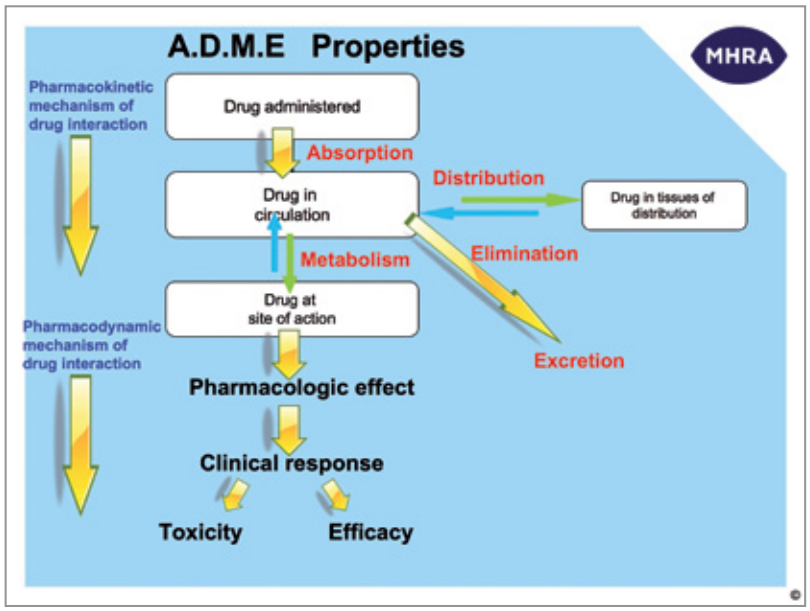
process, which limits patient exposure during the development phases.

Clinical pharmacology in drug regulation

Four of the most important supportive elements of the clinical pharmacology of a new drug evaluated by regulators are the compound's characteristics in single ascending and multiple ascending doses, its bioavailability, its potential for drug interactions and its pharmacologic characteristics in special populations.

- **Single ascending dose and multiple ascending doses** are the first studies of a drug in man and are conducted as early as possible to demonstrate the drug's safety, tolerability, PK and dose and time linearity as well as its initial PD profile.
- As drug formulations frequently change from early to later development, it must be rigorously demonstrated to the regulator (within a 90% confidence level) that the **bioavailability** of the drug has not changed with the use of a different formulation, whilst **bioequivalence** measurements must ensure that the efficacy and safety of the drug for the different formulations are also comparable.
- Studies to uncover potential drug-drug interactions that could increase or decrease the effect of drug exposure, should also be performed as early in drug development as possible, using the appropriate dose and formulation. **Drug-drug interactions** may ultimately result in PK or PD changes, as drugs are absorbed, distributed, metabolised and excreted, resulting in alterations in efficacy and potential toxicity (Figure 3). In vitro studies form a sound basis for later in vivo studies by identifying the relevant drug metabolising enzymes or transporters and the area of polymorphism of these enzymes; the most clinically important of these pathways involve CYP 2C9, 2C19, 2D6 and 3A4. Using probes, in vitro studies have shown which chemical entities cause the inhibition or induction of these pathways. In vitro data can also enable the development of reliable predictive computer models for potential drug interactions, which are now being submitted to regulatory authorities in support of in vivo data. Drug-drug interaction studies are also performed using multiple probes for a so-called "cocktail" study, designed to reflect the possible effects in patients taking multiple medicines.
- **Special populations** of pharmacologic interest to the regulator in the assessment of new drugs include patients with renal or hepatic impairment, the elderly or those in whom ethnic differences may potentially alter a drug's activity. Pharmacokinetic studies in patients with renal impairment should be conducted for drugs intended for chronic use, and the free concentration should be measured if the unbound concentration is less than 20 percent. Pharmacokinetic studies in patients with hepatic impairment should be carried out for drugs with narrow therapeutic ranges; drugs for which hepatic metabolism accounts for a substantial proportion of the elimination of the drug or the metabolite; drugs whose metabolic pathways have not been well characterised. When new drugs are to be studied in patients with ethnic differences, this should be undertaken with the understanding that differences in drug effects may be environmentally induced as well genetic in origin.

Figure 3. Drug-drug interactions may be pharmacokinetic or pharmacodynamic, as drugs are absorbed, distributed, metabolised and excreted, resulting in alterations in efficacy and potential toxicity.



Sir Alasdair concluded his presentation with the reminder that despite the growing number and sophistication of the clinical pharmacology tools that are available for the developer and regulator of new medicines, the most important function of this branch of science remains the assurance that new medicines are prescribed for appropriate patients at the appropriate dose.

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Building the regulatory review process in meeting expectations and requirements of needs today and for the future: An SFDA/CDE perspective

Dr Zili Li

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for **Dr Yi Feng**

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China as an innovation-based society

Supporting innovation in science and technology and especially in the development of new medicines is a national strategic priority in China. Indeed, the ultimate goal for several recent government initiatives is China's transformation into an innovation-based society. Cultural, organisational, capacity and capability challenges to support this transformation are now in place.

The State Food and Drug Administration (SFDA) and Centre for Drug Evaluation (CDE) have had a wide range of responsibilities for the regulation and inspection of small-molecule, biologic and traditional Chinese medicines, despite having possessed less than optimal capacity and capability to fulfil these tasks (Figure 4). Furthermore, the experience of the Chinese regulatory system has been primarily based on familiarity with the review of generic medicines, until recently expanding their experience through the assessment of innovative medicines developed to address a specific medical need.

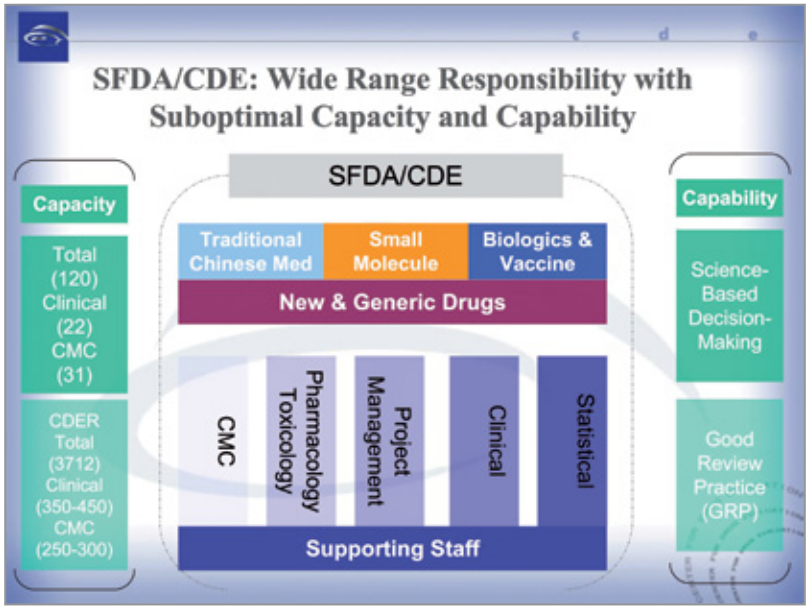

Figure 4. The SFDA and CDE have a wide range of responsibilities for the regulation and inspection of medicines, despite challenges in capacity and capability.

Opportunities for change

In 2011, several important activities transpired to advance the regulatory review process in China. First, the CDE was reorganised to develop a discipline-aligned rather than therapeutic-aligned review structure, establishing a more clear and efficient reporting configuration and division of labour. Second, the first document to focus on the provision of regulatory guidance, *Drug Review Principles and Procedures*, was issued along with two internal standard operating procedure documents on review pathways and decision-making with a foundation in a risk-based review model.

In another move toward review quality enhancement, the concept of target review timelines has been introduced in the SFDA/CDE and identified as a measure of a quality review system. Whilst taking current workload, resources and medical need into consideration, the target timeline for the review of investigational new drug applications has been gradually reduced to a total of 3.5 months for review by all stakeholders. For new drug applications, the target review timeline goal is in the range of 16 to18 months.

Although the reduction in review time is expected to be a gradual and long-term process, regulatory transparency and predictability has been enhanced by a web-based time tracking system through which the progress of a new drug application review can be traced by the sponsor. Agency-to-sponsor communication and transparency has been further augmented by facilitating industry-initiated interactions, including strategic pipeline reviews and video conferencing, and by the publication of a Summary Basis of Approval for innovative new medicines.

Additional process enhancements included:

- the creation of review templates
- the establishment of a separate quality control unit and
- the establishment of an "Office Director forum" as the means to address review policy issues.

. . . regulatory transparency and predictability has been enhanced by a web-based time tracking system through which the progress of a new drug application review can be traced by the sponsor.

Finally, review resources are now assigned based on a review's classification as single or multiple functional, parallel or sequential.

The Chinese SFDA and CDE look forward to further capacity building through a programme of direct interaction with external resources. Stage I of this programme will consist of industry-mediated educational activities. In stage II the focus will shift toward university- or society-mediated educational activities through such institutions as Yale University, the Asia Pacific Economic (APEC) group and the National Institutes of Health (NIH). In the third stage, the SFDA and CDE will engage in direct exchange with regulatory agencies in developed countries. Through all of these ongoing and planned organisational, cultural and procedural changes, the SFDA/CDE will help to ensure the timely access to innovative medicines for the Chinese people.

Expectations and requirements for the regulatory review process to deliver today and tomorrow's needs: An industry viewpoint

Dr Paul Huckle

Chief Regulatory Officer and Senior Vice President, Global Regulatory Affairs, GlaxoSmithKline, USA

The evolving role of emerging markets

Despite major advances in science and biology, pharmaceutical research and development productivity has been steadily declining over the past several decades. In fact, one recent report noted that late-stage pharmaceutical company assets decreased by approximately 20% in 2011 compared with 2010.[1] Furthermore, of the products that are successfully brought to market, only a small proportion generate profits above the cost of their development. In addition, as key product patents start to expire, the revenues that those innovative products have driven for some of the larger companies are starting to slow. At the same time, more demanding global regulatory requirements are being put into place and increasing pricing pressures brought to bear by health technology assessment agencies, payers and governments.

Because pharmaceutical research and development, manufacturing and distribution have all become increasingly global in nature, industry must have global plans for successful product development and delivery. In recognition that all resources and expertise cannot be contained within a single pharmaceutical company, there is greater use of external partnership and collaborations with small start-up companies, academia and large contract research organisations.

. . . countries such as India and China are performing increasingly advanced research and development, taking advantage of a large pool of locally trained and educated scientists with an understanding of local medical needs.

All of these changes in the pharmaceutical environment have resulted in an increased focus on the development of medicines in countries with emerging pharmaceutical markets, with one source predicting that these markets would account for one third of all pharmaceutical market growth in 2011.[2] Fundamental shifts in economic development have taken place in some of these countries, with the recognition that medicine can be a strategic driver for internal growth, as Dr Rahman has explained is currently the case in Malaysia (page 18). Other factors have also intensified concentration on pharmaceutical development in emerging markets such as increasing liberalisation in government and the resultant economic stability, reduced bureaucratisation and interventionism and the creation of new and refined systems for the registration and management of products throughout their life cycle.

Rather than acting solely as operational contributors to pharmaceutical development programmes, countries such as India and China are performing increasingly advanced research and development, by taking advantage of a large pool of locally trained and educated scientists with an understanding of local medical needs. To

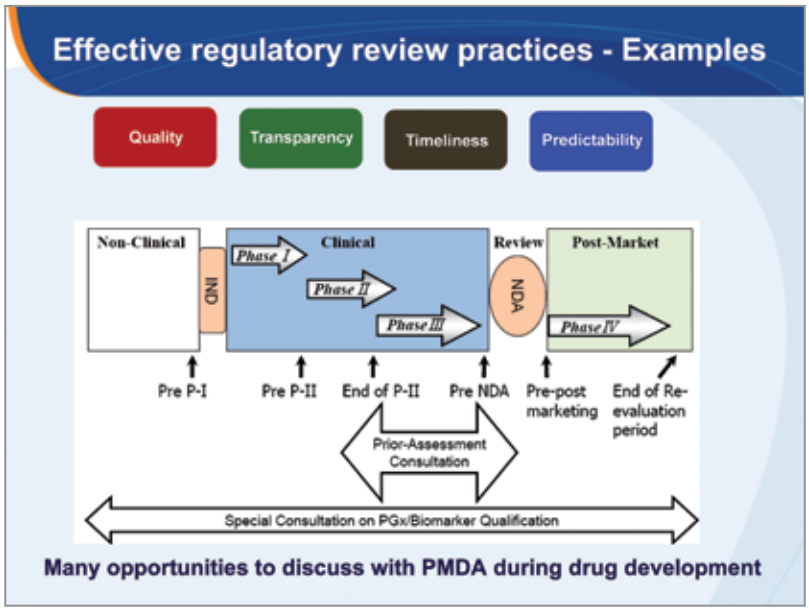

Figure 5. Multiple points for agency-sponsor interaction exist at the Japanese PMDA.

yield the maximum benefit from this new R&D globalisation, the importance of international cooperation in regulatory alignment has risen dramatically.

Alignment as a facilitator of global pharmaceutical development

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is an example of successful efforts extended toward regulatory alignment for the purpose of facilitating global drug development. Created in 1990 by regulators and industry associations to align EU, US and Japan drug registration requirements, ICH has reduced country and regional differences in technical requirements that impact availability and cost of new medicines, promoted international movement of pharmaceuticals that are safe, effective and of high quality as well as the conduct of clinical trials that meet international standards. The use of ICH guidelines has resulted in dossiers that are easier to review and analyse. They have also facilitated the exchange of information via standardised electronic submissions and resulted in better regulatory life cycle management and the reduction of resources required to prepare and maintain product dossiers.

Other bilateral harmonisation and alignment has also occurred in less traditional markets. Brazil, Argentina, Colombia and Cuba have performed joint inspections, eventually resulting in a mutual recognition agreement in November 2011. Also in 2011, the Mexican regulatory agency Commission for Protection Against Federal Health Risks (COFEPRIS) recognised good manufacturing (GMP) certificates issued by six regulatory authorities, the US Food and Drug Administration (FDA), European Medicines Agency (EMA), Portugal's National Health Surveillance Agency (ANVISA), Health Canada, Australia's Therapeutic Goods Administration (TGA) and Japan's Pharmaceuticals and Medical Devices Agency (PMDA). The East Africa Community (EAC) a harmonisation initiative of Burundi, Kenya, Rwanda, Tanzania and Uganda and the tripartite regulatory initiative among the countries of Korea, Japan and China are additional examples of recent regulatory alignment programmes.

Effective regulatory review practices

The key elements of regulatory review have been well established as quality, timeliness, transparency and predictability. Dr Huckle provided examples of recent initiatives among global regulatory agencies in emerging markets to enhance these practices.

- As detailed in Dr Feng's presentation (page 21) the SFDA/CDE has embarked on a programme to optimise regulatory review in China including specialty expertise development, a reduction in review timelines, the provision of detailed guidelines and templates and greater transparency with the ability to track applications.
- In an example of an innovative method to optimise resource use by avoiding duplication of efforts, the HSA has initiated a three-level review process in Singapore, in which a dossier is designated for full evaluation, abridged evaluation or verification, depending on whether it has been previously approved by one or more reference agencies.
- At the US FDA, recurring problems or issues identified during regulatory review, for example, the need to set accepted laboratory test methods or clinical trial designs, trigger further work or research, the results of which are subject to public discussion through advisory committees or public postings. Once publicly accepted, these new standards or tools may be used by all developers, and the US FDA often seeks international acceptance of such models, thus reducing unnecessary animal or human testing worldwide.
- At the US FDA and the Japanese PMDA there are numerous opportunities for specific

industry engagement around the nature of a research programme, the data that have been generated and the next proposed stages for development (Figure 5). This continual interaction serves to keep the agencies aware of industry development plans and ensures that sponsors' programmes are consistent with agency expectations from an early stage in development.

Challenges to regulatory review in emerging markets

Obstacles to effective regulatory review in emerging market countries remain. CIRS data show that review times in these regions are generally variable, unpredictable and in some countries, increasing. CIRS research also indicates that from 2006-2010, the majority of queries from regulatory agencies in emerging markets centred around chemistry, manufacturing, and controls (CMC), despite the fact that companies provide approximately the same data that are submitted to the US FDA and the EMA, in those jurisdictions where robust intellectual property protection systems are in place.

Resource constraints are well known in emerging market regulatory agencies; where, for example, regulators in Malaysia are responsible for the review of sixty applications, each with an average review time of six months, compared with regulators in one more experienced country, where each reviewer is responsible to contribute to the review of seven applications, with an average review time of fourteen months.

Figure 6. GSK strategy for accelerated new drug approval in Russia.

Company strategies in emerging markets

GlaxoSmithKline (GSK) has employed several strategic approaches to overcome barriers to regulatory review in emerging markets. In order to achieve Chinese participation in a multi-country phase 3 development plan, an investigational new drug application was submitted to the SFDA well in advance of applications in the United States and Europe, allowing the timely recruitment of Chinese patients into the phase 3 trial.

In another example, GSK engaged with discussions with Central Drugs Standard Control Organization (CDSCO) in India around the unmet medical need in that country for a new medicine. Multiple predevelopment meetings between GSK and CDSCO ensured the participation of Indian patients in the phase 3 trial, and a new drug application was submitted to CDSCO shortly after US approval of the drug and at the same time as the submissions to the EMA. Approval of the drug was received within nine months of submission, which was six months earlier than EU approval.

In a final example, after a new drug application was submitted in Russia two months after submission to the US FDA and EMA, approval was received within seventeen months, which was four months faster than approval in Europe. This timely approval was achieved through acceleration of local dossier translation; the justification of unmet medical need and submission without a certificate of pharmaceutical product (CPP) based on extensive local medical input; and solid research and development support for agency questions (Figure 6).

Conclusions

It has become increasingly clear that the pharmaceutical industry is now operating on a global basis, and emerging pharmaceutical markets, particularly those in Asia are becoming much more important in the discovery, research and commercialisation of products. For optimisation of this global phenomenon, however, industry requires a higher standard of predictability, transparency, timeliness, and quality in regulatory review procedures. Greater harmonisation of regulatory requirements and revised review timelines are also required to foster global drug development. Enhanced collaboration and effective resource utilisation among regulators, such as through the use of

joint reviews, exchange of scientific assessment reports, approval recognition, joint inspections and clinical trial data recognition can avoid duplicative efforts and mitigate resource constraints.

Dr Huckle concluded by remarking that an effective partnership among regulators, industry and academia can be employed to develop an implementable regulatory framework that will expedite access to medicines in countries with emerging pharmaceutical markets.

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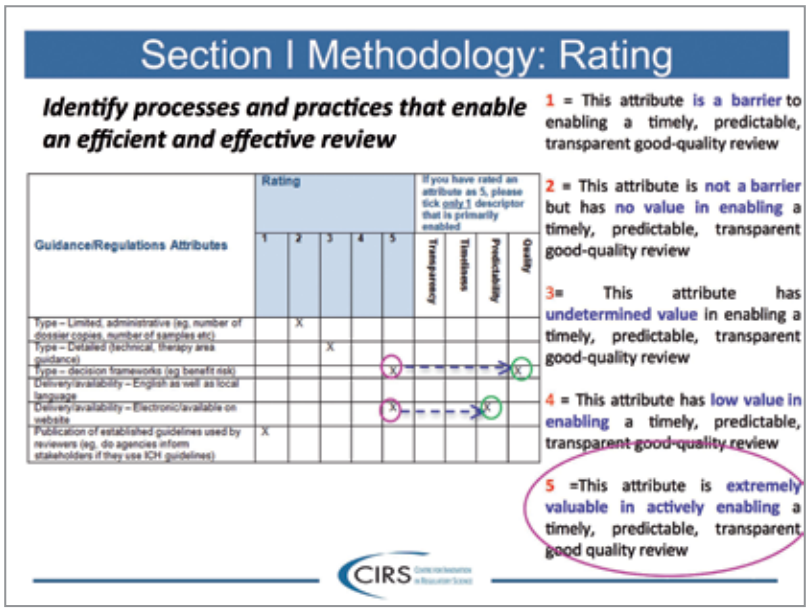
What are the key processes and practices that are seen by companies as enablers and barriers to the review process? Outcome of a CIRS survey

Prisha Patel

Portfolio Manager, Emerging Markets Programme. Centre for Innovation in Regulatory Science

In 2011, CIRS conducted a study to identify the regulatory practices, processes and procedures, which would enable the timely, predictable, transparent and good-quality review of new medicines.

Figure 7. Industry respondents rated regulatory agency attributes as being facilitative or an inhibitory to the effective review of new medicines.



Methodology

In the first section of the survey, participants were asked to identify regulatory agency attributes that acted as enablers or barriers to good review practice (GRevP). Responding companies selected attributes from the following parameters: Guidance/Regulations, Dialogue/Interactions, Transparency, User fees, Submission methods, Management systems, Training, Negotiation of document timing and Other review process attributes. Twelve responding companies rated attributes from 1 to 5, with 1 representing a barrier to GRevP; 2, a neutral factor for GRevP; 3, an undetermined factor for GRevP; 4, an enabler of GRevP of low value; and 5, an extremely valuable enabler for GRevP (Figure 7). For attributes that were identified as enablers, participants were asked to specify whether they primarily enabled the timeliness, transparency, predictability or quality of the review.

In the second section of the survey, respondents were asked to rate specific regulatory agencies for attributes that enable GRevP (transparency, timeliness, predictability, quality) from 1 to 5, with 1 being unsatisfactory; 2, poor; 3, satisfactory or fit for purpose; 4, good; and 5, excellent. For instances in which a lower score was given (1-3) respondents were asked to specify which elements of the attribute needed to be improved, whilst if a higher score was supplied (4-5), respondents were asked which of the elements of this attribute could be encouraged for use by other regulatory agencies.

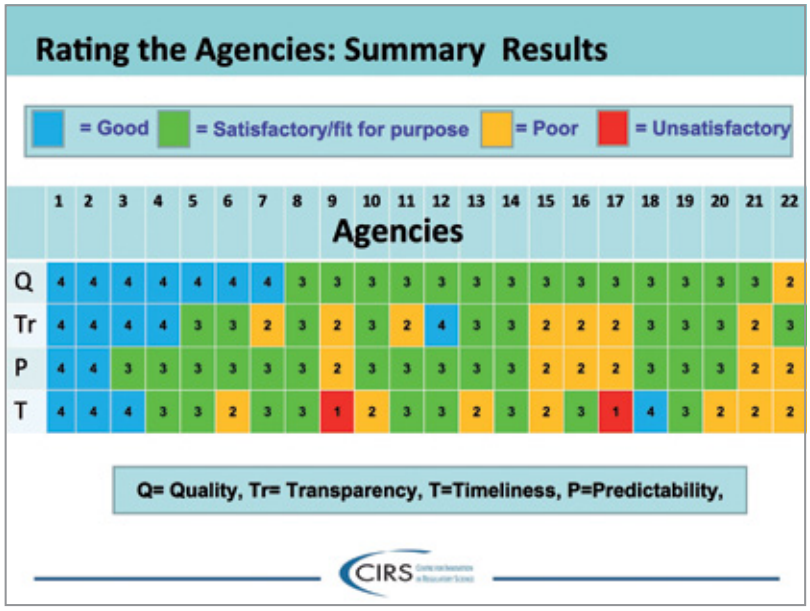
Results

The table below lists some of the results of part 1 of the survey: the attributes that were indicated as extremely valuable enablers (a rating of 5) of timeliness, predictability, transparency or quality in a regulatory review.

Table. Enablers of effective regulatory review.

Timeliness is enabled by	Predictability is enabled by	Transparency is enabled by	Quality is enabled by
Adherence to target timelines during review	Detailed guidelines	A detailed summary of approval	Agencies' adherence to international standards for requirements
Availability of different assessment routes and priority review requests	Meetings during development	A detailed description of process	The ability to negotiate patient information leaflet label
Defined and efficient processes	Pre-NDA meetings	A published decision framework	Internal training
Dedicated project management	The ability to track progress of an application	Published approval times	
The ability to negotiate and the ability of regulators to give approval with the provision of providing a post-approval commitment	Detailed target times	The ability to contact agency personnel	
	Consistent review assessment methods	The ability to conduct a dialogue with an assessor for clarification of issues raised in a deficiency letter	

Figure 8. Industry respondents rated the quality, transparency, timeliness and predictability of twenty-two regulatory agencies.



In response to the second part of the survey, nine companies rated the timeliness, predictability, transparency and quality of regulatory agencies in twenty-two jurisdictions in mature and emerging markets, and Ms Patel presented an anonymised summary of those ratings. As shown in Figure 8, after calculating the mean, the majority of responding companies indicated that the quality of review at those agencies was considered as either good or fit for purpose.

In an example of respondent comments regarding specific agency performance, one company indicated that the agency in question excelled in transparency and predictability because of "the electronic queue system, which allows companies to clearly see where their application is in terms of progress through the agency" but that this agency could improve through "better harmonization with ICH guidelines."

. . . the majority of responding companies indicated that the quality of review at those agencies was either good or satisfactory.

Next steps

Using these results, it will be possible to develop a report that will inform each agency of areas in which they excel as well as provide them with recommendations for improvement of their processes and performance. A survey has been distributed to regulatory agencies to ascertain their perspective regarding attributes that enable the review process as well as asking agencies to score the overall quality of company submissions. Once all results have been analysed a report will be developed that provides the perspectives of both stakeholder groups and that details general recommendations for improved practice.

Developing agency 1: The role companies can play (understanding the requirements, full data provision and responding to questions in a timely manner)

Lucky Slamet

Deputy, Therapeutic Products, Narcotics, Psychotropic & Addictive Substance Control, National Agency of Drug & Food Control, Indonesia

Although guided by differing missions and employing varying procedures, the goal of all regulatory agencies should be to provide an assessment of medicines for their population that is scientifically sound, legally consistent, procedurally predictable and within time targets. The National Agency of Drug and Food Control (NADFC) in Indonesia is responsible for the approval and oversight of clinical trials, the marketing authorisation of new medicines and the inspection of the processes and facilities for the production and distribution of those medicines as well as their ongoing surveillance for quality and safety.

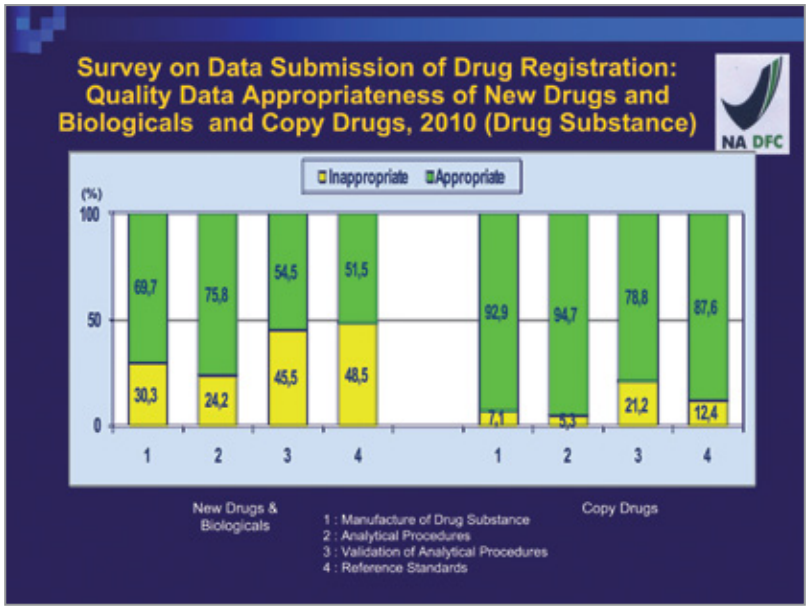


Figure 9. A survey of drug applications to the NADFC revealed deficiencies in data for drug substance in applications for new drugs.

To ensure the safety, efficacy and quality of new medicines, the NADFC adheres to the Good Review Practices (GRevP) principles of transparency and clarity, responsiveness and flexibility while aligning with international standards for efficacy and maintaining a consistency that is critical for the credibility of the agency. Assessments are made using a risk-based approach, with decisions based on scientific evidence, using standard operating procedures and post-approval monitoring. Before submission, the sponsor may receive scientific advice from the agency. After submission, the dossier is validated and sent on to a drug evaluation committee, which may consist of external as well as internal experts, depending on the disease area or treatment classification.

In Indonesia as elsewhere, however, multiple factors affect the review administration process as well as the quality of the review. For example, public health expectations for new medicines require regulators to make new lifesaving drugs available for the Indonesian people in a timely manner while maintaining an awareness of safety concerns yet striving to accomplish this with limited resources. It is the quality of submitted dossiers, however, that exerts particular influence on the administrative review process. In Indonesia, dossiers must be compliant with the Association of Southeast Asian Nations (ASEAN) Common Technical Requirements (ACTR) as well as requirements

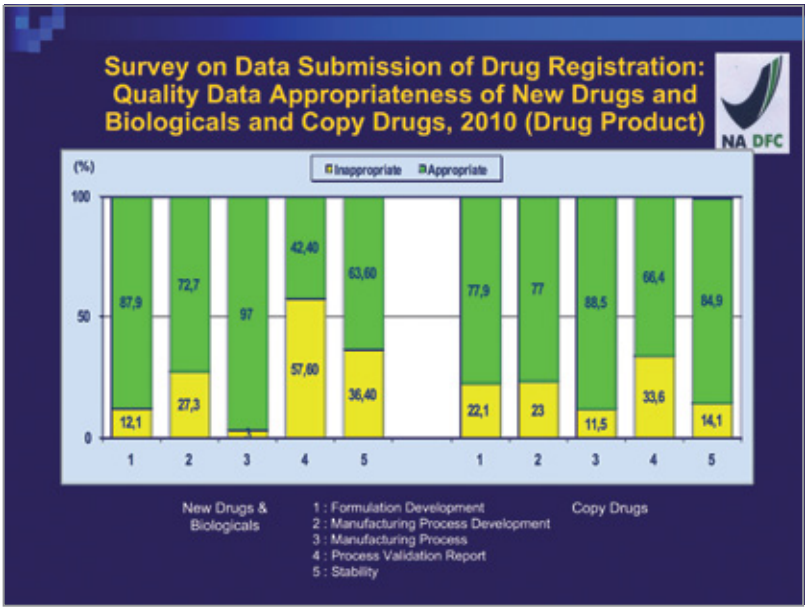


Figure 10. Data deficiencies for drug product occurred in applications for both new and generic drugs.

of the ASEAN Common Technical Dossier (ACTD). This compliance as well as compliance with Chemistry, Manufacturing, and Controls (CMC) requirements is particularly important; the agency relies on company adherence to these requirements because new technologies often require assessment of complex and comprehensive dossiers, yet often these dossiers are found to have been submitted to Indonesia in parallel with submissions to other jurisdictions but as less complete packages.

A dossier survey

A small survey of dossiers submitted to the NADFC in 2010 sought to identify whether data submitted for new and generic drug applications were appropriate to show the quality of the drug substance and the drug product. Results revealed that although the data showing quality of substance in applications for generic drugs was appropriate more than 80% of the time, the presentation of those data for new drug applications needed improvement (Figure 9).

The data for quality of the drug product, specifically process validation reports and stability data needed improvement in both new and generic drug applications, reflecting incomplete data for imported products and differences in the completeness of stability studies reflecting the unique climatic zone conditions in this country (Figure 10).

Using these survey data, a gap analysis showed that specific country requirements exist despite following regional harmonisation schemes, leading to differences in submission needs and ultimately in the product's labelling. Appropriate preclinical and clinical study results are sometimes not provided to support drug applications and there is a general lack of quality data in many dossiers, particularly data on active pharmaceutical ingredients and product development as specified by the ACTR and ACTD. In fact, there has been a lack of effective communication among stakeholders and different perspectives on the implementation of Indonesia's regulatory requirements.

. . . regulators and industry must develop the same perspectives on patient needs and work together for the common goal of improving public health.

The way forward

Ms Slamet concluded her presentation with some recommendations for ways that industry can contribute to the enhancement of regulatory reviews. To expedite effective and efficient regulatory review practices, sponsors must understand and observe requirements and guidelines and demonstrate adherence to Good Practices, whether they are Good Manufacturing Practices, Good Clinical Practices, Good Laboratory Practices or Good Review Practices. Sponsors must provide complete data as required for dossier submissions and respond to questions in a timely manner, building effective communication with regulators that is based on mutual trust. Finally, regulators and industry must develop the same perspectives on patient needs and work together for the common goal of improving public health.

Developing agency 2: The role of project management and target times

Dr Chih-Liu Lin

Deputy Executive Director, Center for Drug Evaluation, Taiwan

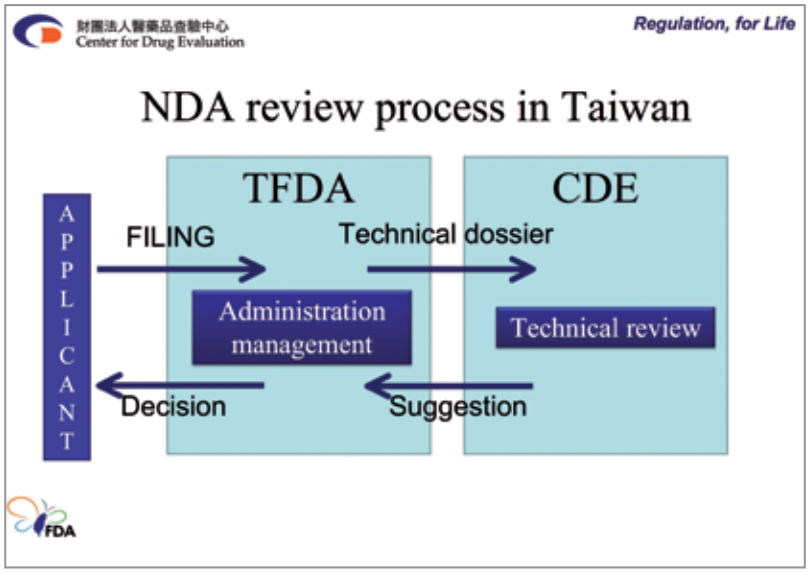
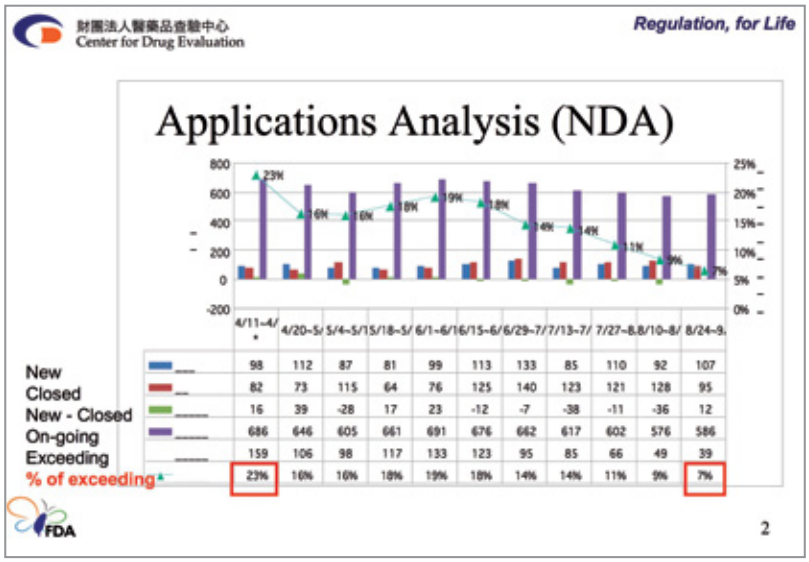


Figure 11. iMPRO manages all regulatory review applications in Taiwan.

Figure 12. The number of applications for which review exceeded timing targets was reduced from 23% to 7% with the use of iMPRO.

The Integrated Medicinal Products Review Office (iMPRO) was established by the order of the Director General of the Taiwan Food and Drug Administration (TFDA) in June 2011. Formerly, the technical review and recommendations were performed by the Center for Drug Evaluation (CDE) while the administration and final resolution of each new drug application in Taiwan was handled by the TFDA. This process, conducted in sequential steps, each under the oversight of separate project management teams, resulted in duplication of efforts, waste of resources and ultimately in a delay in review timing.



A flexible and dynamic organisation, iMPRO now manages all regulatory review-related applications and personnel, combining the resource capacity of the two divisions, with unified standard operating procedures and flow control (Figure 11). Quality control meetings are held monthly to monitor the progress of ongoing applications.

In April 2011, regulatory review by the TFDA/CDE exceeded time targets for 23% of applications. As a result of the implementation of iMPRO, by August 2011 that number had been reduced to 7%, with further reductions anticipated (Figure 12).

Therapeutic area teams have also been developed to allow further specialisation of efforts at the agency, and this new system will be evaluated and adapted as necessary in the ongoing effort to optimise regulatory review in Taiwan.

. . . iMPRO now manages all regulatory review-related applications and personnel, combining the resource capacity of the two divisions, with unified standard operating procedures and flow control

A developed agency: How to ensure consistency of practice

Thomas Lönngren

Director, Pharma Executive Consulting

As former Director of the European Medicines Agency and Deputy Director General of the Swedish Medical Products Agency, Mr Lönngren provided a regulator's perspective on consistency in the practice of regulatory review. He began by explaining that there are several aspects to regulatory consistency: legislative, procedural and scientific.

Legislative, procedural and scientific consistency

Because regulatory agencies primarily operate through government mandate, **legislative** consistency provides a necessary stability of mission and scope. **Procedural** consistency, meanwhile, allows reliable and predictable operations through the use of guidances and standard procedures. However, **scientific** consistency, that is, consistency in advice, benefit-risk evaluation and decision making, may be the most important element of consistency in regulatory review. To achieve scientific consistency, guidelines must be developed uniformly and updated in a standardised way to reflect advances in scientific knowledge. Scientific advice should not vary amongst regulators in content and format and should be recorded and tracked to ensure the development of institutional memory. Benefit-risk evaluations and decisions in the marketing and post-marketing environment should be made through established, standardised processes and procedures.

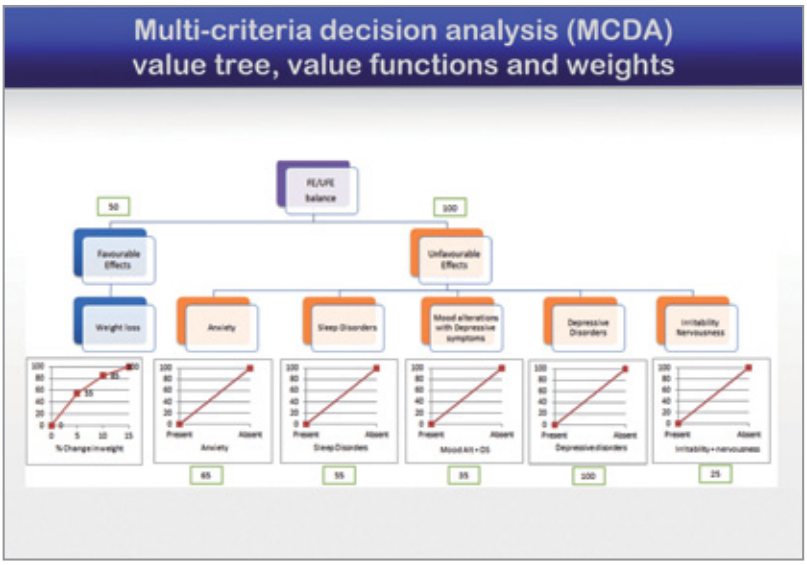


Figure 13. In this multi-criteria decision analysis the favourable effects associated with a medication are not enough to overcome its potential for unfavourable effects.

Certain general requirements ensure consistency in regulatory review including the availability of a competent staff, ongoing participation and feedback from various healthcare stakeholders, transparency in process and outcome and a system of quality assurance that incorporates peer review, constant process improvement and follow up. This last requirement, following up or tracking the clinical effects of regulatory decisions, although a significant element of quality assurance, cannot typically be implemented, however, because of regulatory agency resource constraints.

Consistency in benefit-risk evaluation

Currently, regulators make benefit-risk assessments by the sequential evaluation of data in preclinical, clinical or post-approval settings, with decisions based on varying individual expertise and a general lack of a systematic procedure to capture the values that are included in the decisions. Quoting Professor Baruch Fischhoff, Mr Lönngren explained that under these circumstances, even highly skilled, scientific decision makers can be influenced by political and media pressure: "…people assess an event's probability by how easily instances come to mind. Although more available events are often more likely, media coverage (among other things) can make events disproportionately available, inducing biased judgement."[1]

Over the past several years, there has been substantial discussion concerning the use of a systematic methodology for benefit-risk assessment in order to eliminate the potential for bias and enhance the predictability and auditability of regulatory decisions. This methodology will require well-defined parameters and could encompass the strengths of both qualitative and quantitative system approaches.

Multi-criteria decision analysis is one such methodology in which the benefits and risks of a new drug can be arranged in a value tree and assigned weights to determine the medicine's benefit-risk ratio (Figure 13). Models such as these provide a graphic, easily understandable illustration of the rationales for regulatory decision making and can be consulted for

Scientific advice should not vary amongst regulators in content and format and should be recorded and tracked to ensure the development of institutional memory.

future decisions for similar therapies, resulting in consistency of practice.

Conclusions

To ensure regulatory consistency, a competent staff, proper procedures and a quality assurance system are required. A methodologic approach should be employed in benefit-risk decision making and transparency in methodology and assessments assured. Finally, an institutional memory must be developed through standardisation and record keeping to ensure that decision making is not subject to the potential for individual bias.

Reference

1. Fischhoff, B. Risk perception and communication. In Detels R, Beaglehole R, Lansang MA, Gulliford M (Eds), *Oxford Textbook of Public Health, Fifth Edition*. Oxford: Oxford University Press; 2009: 940-952.

Company viewpoint: Examples of practices that have enabled or hindered the review

Patrick J. O'Malley

Senior Director, International Regulatory Affairs, Eli Lilly and Company, USA

Mr O'Malley provided examples of individual regulatory agency practice that facilitated or hampered good-quality review within the themes of consultation and access, process consistency and predictability, and requirements and expectations.

Consultation and access to regulators

During development and pre-submission phases, industry-regulator contact provides an opportunity to discuss trial design, target populations, statistical plans, the position of other regulators on the product or drug class, the expectations for the submission package and other key issues. As an enabler to regulatory review, this interaction can minimise the occurrence of unexpected events and is critical to facilitate industry resource management and programme investment while allowing regulators a chance to highlight specific interests and concerns. For example, the dramatic improvement in the quality, availability and consistency of consultation at Japan's PMDA has translated to a measurable decrease in review time. Consultation can function as a barrier, however, when the lack of clear advice leads to misunderstanding or when advice is not formalised or carried through to the review process.

. . . the dramatic improvement in quality, availability and consistency of consultation at Japan's PMDA has translated to a measurable decrease in review time.

Post-submission, regulator consultation and access facilitates meaningful scientific discussion about questions, issues and data interpretation surrounding a dossier. As an enabler to regulatory review, this interaction can help to ensure understanding of data, allow the most efficient use of the limited number of scientific experts and reduce the bureaucracy of document reviews and quality checks. In one such efficiency, an Australian TGA delegate's willingness to participate in a teleconference with Eli Lily and Company eliminated enormous misunderstanding based on written responses. But consultation can also hinder regulatory practice when there are language barriers, difficulties in establishing meeting timing and other logistics, or unrealistic expectations for the overburdened staff of local pharmaceutical companies. For example, the hesitation of the Korean FDA to discuss a scientific issue with non-Korean company experts resulted in the imposition of great demands on a newly hired company advisor whose expertise was in another therapeutic area.

Process, consistency, and predictability

Ideally, the review process, including understanding its associated steps and timelines, is well defined and consistently managed across different regulatory groups and agencies and established agency functions are dedicated to administrative process and project management. When practiced, this ideal enables regulators to attain target metrics and to monitor their implementation and allows companies to

prepare resources and manage internal timelines. In China, the establishment of the Office of Drug Review Management at the CDE represents an excellent beginning to enhance organisational effectiveness.

However, hindrances can occur as a result of processes when multiple regulatory agencies have responsibility for different steps in the review process or when there is a lack of a clear decision-making process, between for example, a reviewer and a supervisor or between a review division and Ministry of Health committee. As an example, Mr O'Malley described a situation in Taiwan in which, before the institution of the new project management system at the TFDA/CDE as detailed by Dr Lin (page 29), a single person involved at the final advisory committee stage overturned the recommendation of the CDE and the results of one year's review effort.

Requirements and expectations

Having an opportunity to comment on the clarity and level of situational specificity of regulatory requirements can be enabled through the implementation of a regulatory guidance system. These systems offer stakeholders the opportunity to comment on proposed regulations and increase the likelihood that dossier submissions will be complete and meet international standards. These systems can also provide a tool to communicate current thinking on scientific and regulatory topics and offer the means by which to streamline communications, conserving regulatory agency resources. For example, the recent establishment of biosimilar regulations in Korea included broad consideration of global requirements and incorporated the feedback obtained during a well-designed comment period. At the same time, there are instances in which the lack of input and discussion results in an overly rigid or standardised requirement limiting the accommodation of unique or exceptional circumstances and creates a "box-checking" administrative process. Mr O'Malley described an example in which an opportunity for the enhancement of regulatory practice in Russia was missed when a new regulatory law regarding clinical study initiatives was unfortunately enacted without guidance or feedback from industry or regulators.

Addressing individual regulatory agency practices that facilitate or hamper good-quality review by ensuring opportunities for consultation and access, process consistency and predictability, and opportunities to provide input on regulatory requirements and expectations will strengthen the global regulatory environment.

Agency-company dialogue

Dr Murray M. Lumpkin

Commissioner's Senior Advisor and Representative for Global Issues, US Food and Drug Administration

The dialogue or communication between regulatory agencies and companies can and should be a bilaterally positive event with the potential to be educational, clarifying, informative, and decisional. It is important to understand, however, that this dialogue also requires expenditure of fiscal, human, and time resources and should be carefully managed by both agency and industry to ensure a successful meeting and an appropriate use of resources.

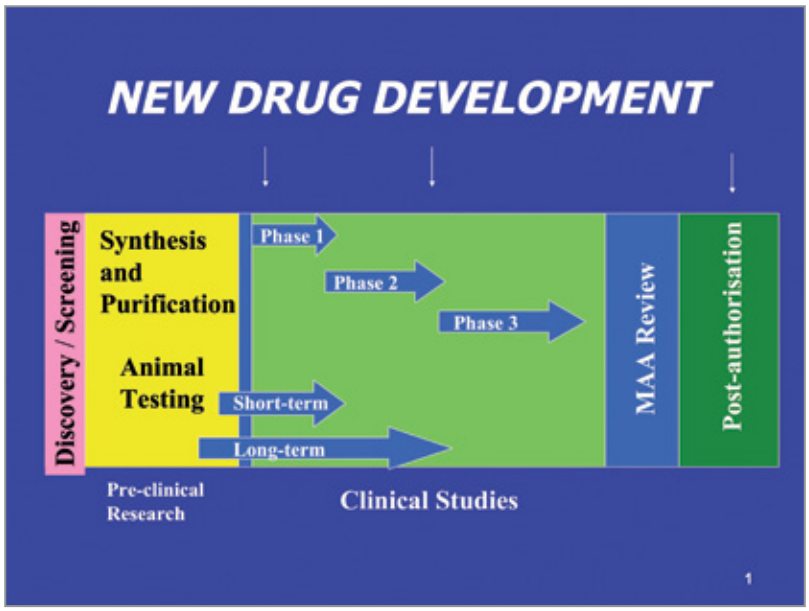
Points for consideration

Regulatory agencies are challenged to be accessible and engaged in ongoing iterative dialogue with drug companies regarding the development plans for their products without becoming potentially biased by being co-opted into a commercial development enterprise upon which the regulatory agency must later pass judgement. Generally this can be accomplished by understanding that agreeing a development programme does not imply agreement with the interpretation of the data that accrue when the plan is executed. That is why the trials are conducted and a review of the data is performed afterward. Companies and agencies must remember this difference in order to prevent misunderstandings. Furthermore, limited regulatory resources must be thoughtfully deployed to exert the greatest positive impact on public health. Often, those with whom

. . . companies requesting meetings with a regulatory agency should consider whether the meeting is truly necessary and potentially valuable and if they are prepared to accept the potential response to questions raised

companies generally wish to meet have other equally important regulatory responsibilities that compete with the time requirements for such agency-company interactions. Accordingly, companies requesting meetings with a regulatory agency should consider whether the meeting is truly necessary and potentially valuable and if they are prepared to accept the potential responses to questions raised. Additionally, it is important that the outcome/goals of the meeting expected by the company be understood by all parties and be realistic, that is, scientifically plausible and data driven. Sponsors must ensure that regulatory agency personnel with the appropriate authority and expertise have been invited to requested meetings and understand that agencies may be precluded from certain types of discussions. It should be clear to all if a meeting will be informational only or if the outcome will be decisional – and, if decisional, if it will be one where agency and company both will bound by the decisions ("special protocol" meeting in the USA, for example). Finally, all parties must understand whether there will be associated follow-up activities, and if so, what they are and who is responsible for what.

Figure 14. Meetings between regulatory agencies and pharmaceutical companies can occur throughout the development of a new drug.



Types of meetings

Agency-company meetings in the United States can occur at various points in the drug development cycle (Figure 14). The US FDA can stop the conduct of any pharmaceutical product clinical trial being conducted in the United States and place it "on clinical hold" at any time if they believe patients' safety is unacceptably being put at risk or being insufficiently monitored. Because of this, company-agency dialogue before the initiation of clinical trials, especially the initial clinical trial, can be critically important. However, because of the large number of clinical trials and the limitations of regulatory resources, such meetings should generally be limited to those concerning trials for cutting-edge technologies or those associated with special safety or manufacturing issues. Additionally sponsors must be well prepared for these encounters, which are meant to be educational for both groups.

In addition to these meetings before the initiation of the first clinical trial (in the USA, for example) regulatory agencies may also engage in a series of ongoing iterative meetings with sponsor companies during all phases of the clinical development of drugs, with the ultimate goal of accomplishing product authorisation in one review cycle, if the ultimately submitted clinical and other data support such. Companies hope that this kind of interaction will maximise the efficiency and scientific robustness of the drug development programme, while helping to ensure that compatible data will support intended product labelling and product positioning goals. For their part, agencies wish to support true innovation for the good of public health (not just another "me too" product) with the added goal of eliminating potential subject exposure to experimental drugs without the development of interpretable data and the waste of research resources on poorly designed, poorly conducted, ultimately, uninterpretable clinical trials.

Early in development, companies are well served to identify their product's target product characteristics and target desired benefit-risk profile and engage in ongoing dialogue with regulatory agencies in these regards. In addition to meetings, this dialogue may take the form of telephone communications, or sponsors may obtain necessary advice or information from agency websites or existing regulations or guidances or public advisory committee meetings.

The US FDA conducts thousands of formal meetings with companies each year, most of which involve development plans or other more acute product-related issues. Of these meetings, those that occur at the end of phase 2 may be some of the most important with respect to product development, covering such issues as final development goals and implementation and confirmation of trial designs and evaluability criteria. At this point, sponsors should seek agreement, as much as possible, regarding the requirements necessary to support the desired labelling and marketing characteristics, including the pharmacological characterisation, indications, major safety parameters and manufacturing issues.

This is also the time that consensus should be reached regarding the potential for any special review procedures such as fast-track or priority or the existence of any incentive programmes if the drug is being, for example, developed as an orphan and/or paediatric drug or a medication for a tropical disease. Companies are also encouraged to discuss and reach an understanding on the use and documentation requirements for foreign clinical trial data as primary proof for an efficacy or safety claim. This includes the methodology to establish the quality and applicability of this foreign data to local populations and medical practice.

Issues to be decided in later phase development include requirements for risk management planning, sequential development and authorisation, the timing and impact of health technology assessment studies and the likelihood that public advisory committee meetings will be convened.

Dr Lumpkin concluded his presentation by providing a list of ten critical points for sponsors to consider when requesting a meeting with regulatory agencies.

Agency-Company meetings:

Top ten considerations

1. Think ventilation: Invite the number of people originally indicated. Agencies have a limited number of conference rooms and rooms are chosen to accommodate size of group agreed initially.
2. Think building: To avoid time-wasting misunderstanding, ensure that everyone is aware of the exact meeting location, especially when agency is located in multiple buildings and sites.
3. Think lawyers: Decide if the issues to be discussed are legal or scientific. Agencies need their lawyers if legal issues are to be discussed.
4. Think level of engagement: Ensure the attendance of the proper level of regulatory agency ultimate decision maker if company desires to get agency agreement on an issue.
5. Think who is speaking for the agency: Don't hesitate to access a higher level agency participant if necessary.
6. Think deadly meetings: Ascertain the purpose of the meeting and the expected outcome and communicate these to the agency so that all are clear of the reasons for and goals of the meeting.
7. Think target product SBC: Develop a draft product description (SBC), share it with the agency and develop a meeting agenda consistent with achieving that description.
8. Think meeting summary: Use the last ten minutes of every meeting to develop consensus as to topics covered, advice received and action points and follow-up assignments.
9. Think advice: Determine whether you have been given advice or a binding agreement from the agency.
10. Think between the lines: Understand that agencies may not be able to directly reply to some questions but are often giving you the best and clearest advice they can.

Availability and publication of the summary basis of approval

Dr Jason Ferla

Acting Principal Medical Adviser, Therapeutic Goods Administration, Australia

AUSPARs

Modelled on the European Public Assessment Reports (EPARs) published by the European Medicines Agency (EMA), the Australian Public Assessment Report (AUSPAR) was introduced in December 2009. In these documents, the Australian Therapeutic Goods Administration (TGA) prepares and publishes information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or reject an application. AUSPARs are posted on the TGA website (http://www.tga.gov.au/industry/pm-auspar.htm) within one month of a product approval or within 90 days after the rejection of an application. Information on some withdrawn applications that have passed a critical point in the review process is also posted. Currently static documents, AUSPARs are prepared for the results of applications for new active substances, line extensions and major variations. The development of summaries for generic medicines and high-risk medical devices is also planned.

Fairly detailed documents, an AUSPAR contains approximately 90 pages of information about a new drug including background and international regulatory status. Quality, nonclinical and clinical findings, all evaluator and advisory committee recommendations and benefit-risk assessments are extracted from the review and summarised herein. Also included are lists of questions submitted to the sponsor by TGA and relevant sponsor answers, as well as risk management plans. Finally, the TGA decision and product information are published. The TGA has produced a guidance document that specifies which data are considered to be commercially confidential information that is not to be included in an AUSPAR such as manufacturing processes or supplier arrangements (Figure 15), and sponsors are asked to confirm that these guidelines have been observed in the AUSPARs developed for their products.

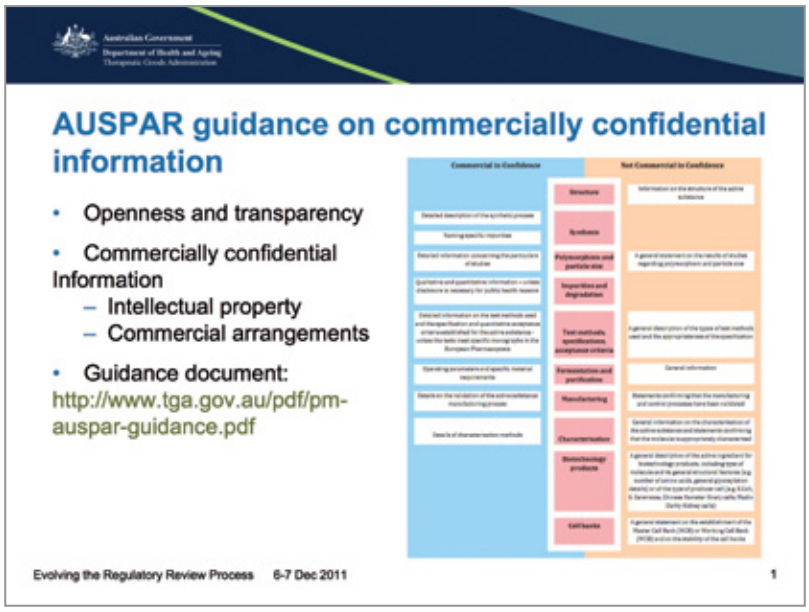


Figure 15. The TGA provides information regarding which elements of a summary basis of decision can be made publicly available.

The TGA has produced 143 AUSPARs as of November 2011 (Figure16). An evaluation of website activity reveals that new drugs generate the most public interest and for September 2011, there were 137,000 hits on the website, with 61% being generated in the United States and only 28% coming from Australia. Most feedback is from sponsors seeking information.

EMA and FDA public assessment reports

The EMA EPAR presents a summary of the grounds for the opinions of the Committee for Medicinal products for Human Use (CHMP) in favour of granting or refusing a marketing authorisation for a specific medicinal product and reflects the scientific conclusion reached by each Committee at the end of the centralised evaluation process. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125 and accessible in multiple languages, the EPAR also contains a patient-level summary, package insert, scientific discussion, benefit-risk assessment, conditions of authorisation and risk management plans. The EMA also lists the names of the rapporteur and co-rapporteur for the assessment and the evaluation timeline.

The United States Food and Drug Administration (US FDA) provides similar information to the TGA and EMA at the website Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/) but also includes a summary review for consumers, a detailed review of all the evaluation reports, environmental assessment, trade name evaluation, correspondence and a medication guide. At this website it is possible to find labels for approved drug

. . . providing information about the appropriate steps that have been undertaken to reach a regulatory conclusion fosters confidence in the regulatory process.

products; generic drug products for a brand name drug product; therapeutically equivalent drug products for a brand name; consumer information for drugs or the approval history of a drug.

As an example, a comparison of public assessment reports for a particular medication by the three agencies revealed that the US FDA report for this medication was in excess of 750 pages compared with 90 pages for the TGA report and 75 pages for the EMA version.

Summary basis of decision elements

Stating that there should be a standardised and user-friendly format for all public assessment reports that is easy to navigate and that includes a table of contents, Dr Ferla provided a list of universal report elements for consideration. A discussion and timeline of the evaluation process may prove valuable, as well details concerning the different aspects of quality, nonclinical, clinical and risk management for the product. Advice from expert committees would demonstrate an independent consideration of the submission, and other essential elements include evaluator and committee recommendations, final regulatory outcome and product leaflet information.

Additional elements that may be useful include process and approval timelines, dissenting reviewer viewpoints and responses to agency questions that are considered particularly valuable or pertinent. International regulatory status information may be a useful benchmarking or comparison tool for some agencies, and depending on whether the audience for the summary is consumer or healthcare professional, a summary or detailed scientific review could be included. Although some jurisdictions may object, identifying reviewers by name as part of the report might contribute to its transparency, whilst graphs and figures could add to a document's readability and clarity. Finally, it may be valuable to develop the assessment report as a dynamic document that could be updated as new information becomes available.

Figure 16. As of November 2011, the TGA had provided 143 public assessment reports on its website.

Why publish a summary basis of decision?

One of the most important reasons to develop and publish a summary document for a new medicine is to enhance the transparency of the regulatory process. In fact, National Medicines Policy in Australia specifies that consumers should have timely access to information on medicines. This access to unbiased representation of information stimulates broader discussion and analysis of the proper use of medicines. Furthermore, providing information about the appropriate steps that have been undertaken to reach a regulatory conclusion fosters confidence in the regulatory process. Summary documents also provide a level of detail on certain patient groups that might facilitate further study and facilitates comparisons among therapeutic choices.

Concerns or other issues to consider regarding publication include whether this represents an appropriate and efficient use of limited resources, potential litigation from publication and if there remains the potential for criticism regarding information that is excluded or included. Finally, current web-only formats, exclude stakeholders with limited or no electronic access.

Moving forward

Dr Ferla concluded his presentation by providing information regarding some developments in public summary documents worldwide. A transparency review is underway at the US FDA regarding lodgement of investigative new drug and new drug applications as well as refuse-to-file and complete response letters. The EMA has created a draft transparency policy for EPARs to increase understanding of decision-making

processes, balancing commercially confidential information, disclosure of EMA documents and methodology for benefit-risk analysis. At Health Canada, phase II of a project consultation has been initiated for streamlining and reformatting existing summary information to include a post-authorisation table of requirements and standardised approach for medicines, devices and biologicals. In Australia, actions have been taken to address two recommendations concerning public summary documents that arose from a 2010 transparency review at the TGA; one concerned the production of the guidance document on commercially confidential information, which has already been completed and the second related to providing more information on the regulatory process. This recommendation has been partially addressed through the AUSPARs, but work in this area is still ongoing.

Availability and publication of the summary basis of approval: an industry perspective

Dr Zili Li

Executive Director and Head of Emerging Market Regulatory Strategy, Merck & Co, Inc, USA

Co-chair of FDA Alumni Association International Network

The Summary Basis of Approval for pharmaceutical products varies globally in name, format and amount of content. Known as the *Summary Basis of Regulatory Action* by the US FDA Center for Biologics Evaluation and Research (CBER) and the *Reviewers Report* by the US FDA Center for Drug Evaluation and Research (CDER), this document is called the *Summary Basis of Decision* by Health Canada, and as reported by Dr Ferla and others, the *European Public Assessment Report (EPAR)* by the EMA and the *Australian Public Assessment Report (AUSPAR)* by the Australian TGA.

Figure 17. The Summary Basis of Decision as published on the Health Canada website is an example of transparent, accessible communication regarding regulatory agency decision making.

These summaries, which are produced as the result of a legislated mandate in United States and Europe, but through agency initiative in Canada and Australia, also differ in the amount and detail of their content. Dr Li pointed to the Summary Basis of Decision, as published on the Health Canada website as a model of the clear, consistent and comprehensive provision of information regarding regulatory decision making (Figure 17).

Additional differences exist in the area of public disclosure policies. Health Canada and TGA, for example have indicated that certain aspects of drug submissions should not be disclosed in any public summary document, whereas the US FDA has taken the position that under certain circumstances, no information regarding some dossiers should be publicly disclosed.

These documents are available electronically.

Irrespective of designation, content or format, the public disclosure of the Summary Basis of Approval is beneficial to both the pharmaceutical industry, patients, healthcare professionals and regulatory agencies, particularly in countries building experience in the development and regulation of new

. . . the Summary Basis of Approval . . . can serve both as an aid to company understanding of the rationale for agency decisions and as a driver for enhancement of regulatory agency capabilities.

medicines, where it can serve both as an aid to company understanding of the rationale for agency decisions and as a driver for enhancement of regulatory agency capabilities.

Dr Li concluded by remarking that publication of the results of the review of clinical trial applications might yield similar benefits and would be a worthwhile topic of discussion for stakeholders in future international healthcare.

Chairman's Introduction Day 2

Assoc Prof John Lim

Chief Executive Officer, Health Sciences Authority, Singapore

Professor Lim summarised the presentations and discussion of the first day of the Workshop with the observation that six factors impact regulatory review.

Regulatory agency **capacity**, that is, not only the number of staff, but their expertise and experience, exerts an important effect on regulatory review. Transparent **communication** between industry and agencies serves to provide information regarding processes and procedures as well as to enhance understanding of the context of overarching issues and strategic goals of both groups. International **collaboration**, in which expertise and work are shared across jurisdictions and organisations benchmark their performance against the best practices of their peers maximises the use of limited regulatory resources

Quality **systems** can also have a significant effect on regulatory review; that is, methods for measuring organisational value and accomplishments such as key performance indicators and external and internal audits and advisory systems enhance the consistency of review practices. Rather than apply the same standards to all new drugs, the capacity to **stratify** a product based on its likely benefits and risks is another important way to allocate manpower in an efficient manner to submitted dossiers. Finally, **strategic horizon scanning** capabilities within agencies and companies can inform and drive the level of innovation required to develop practical solution to important issues as they emerge.

Are limitations in regulatory science linked to limitations of regulatory science, agency or industry matters, or political, national or cultural factors?

Professor Lim questioned whether and to what extent limitations in regulatory review are linked to limitations of regulatory science, agency or industry matters, or political, national or cultural factors. Encouraged by qualitative enhancements that have taken place in the field of pharmaceutical development and review over the past several years, he stressed the ongoing need for commitment, vision and courage on part of agencies and industry and suggested that new stakeholders, who have the means and the capacity to affect quantitative changes be invited to participate in future workshops and other forms of dialogue.

Regulatory authorities websites: What information is publically available and what is the quality of information?

Dr Lembit Rägo

Coordinator, Quality Assurance and Safety: Medicines

Essential Medicines and Pharmaceutical Policies, World Health Organization

The World Health Organization (WHO) promotes and supports building national regulatory capacity through many layers of activities. These activities can be general in nature, such as promoting good governance, or more specific, such as assessing specific national regulatory authorities, providing technical assistance through a variety of activities and training courses or monitoring progress using assessment tools or focussed projects.

An example of a specific programme to promote regulatory excellence, the WHO Good Governance for Medicines (GGM) programme was launched in 2004 with mandates that included the increase of transparency and accountability and the promotion of ethical practices among medical regulatory agencies. The GGM offered a technical support package to participating agencies consisting of a transparency assessment and the development and implementation of a GGM framework. As part of the GGM programme, a number of high-level assessments of the transparency and vulnerability to corruption of national regulatory systems were published from 2004-2010, providing a general overview of agency strengths and weaknesses.

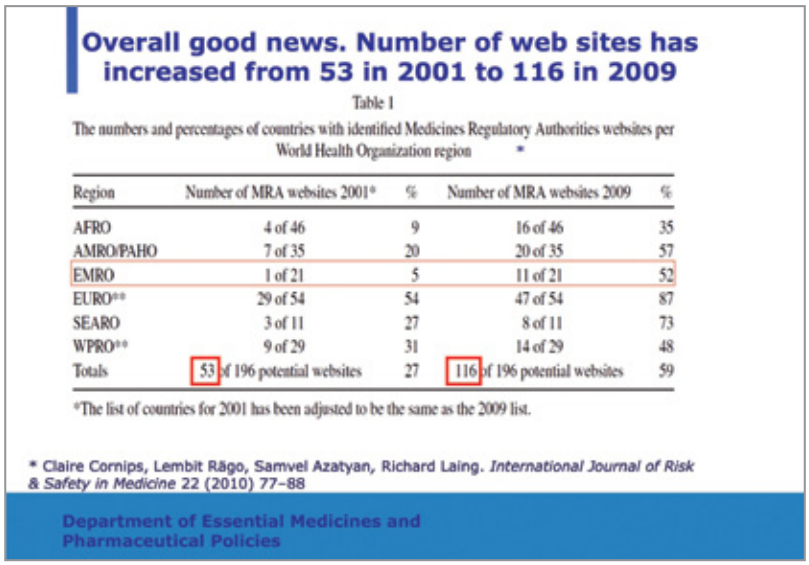


Figure 18. The number of websites among the 51 jurisdictions in the WHO study more than doubled from 2001-2009.

WHO and regulatory websites

In another effort to enhance good governance in pharmaceutical regulation, after a 2000 WHO survey demonstrated that only 50 pharmaceutical regulatory authorities across the globe offered regulatory information resources via a website,[1] WHO established a model website in order to assist member states in website creation. A follow-up research project was undertaken in 2009,[2,3] using essentially the same parameters as were employed in the earlier survey to enable comparison of websites during the two time points. General website criteria studied included user friendliness, navigability, speed, search capability, frequency of updates, languages, publications, instructions for applicants and links.

Results of the study revealed excellent progress: the number of websites increased from 53 in 2001 to 116 in 2009 (Figure 18). In the African region for example, there was only four regulatory websites of a possible 46 in 2001 and in 2009, that number had increased to 16. The most dramatic change, however, was seen in the eastern Mediterranean region, where there had been only 1 website for 21 countries in 2001, but increasing to 11 by 2009. Starting with a comparatively higher percentage of websites in 2001 (29 of 54 countries), the European region further increased this number to 47 out of 54 regions in 2009, representing the region with the highest percentage in the study. An obvious correlation was found between website presence and per capita income level (Figure 19).

However, even though regulatory websites had improved in terms of quantity, the study revealed the need for ongoing qualitative improvement. Although the percentage of user-friendly sites increased from 29% in 2001 to 43% in 2009, it was found that more than half of sites could be organised in a more user-friendly, logical and attractive way. The presence of good site maps had increased from 28% in 2001 to 71% in 2009, but the navigability of sites appears to have deteriorated overall: almost 60% of websites were assessed to have been easy to navigate in 2001, while only 35% were evaluated as easily navigable in 2009. This circumstance may have been due to significant increases in site information, leading to complexity in logical organisation.

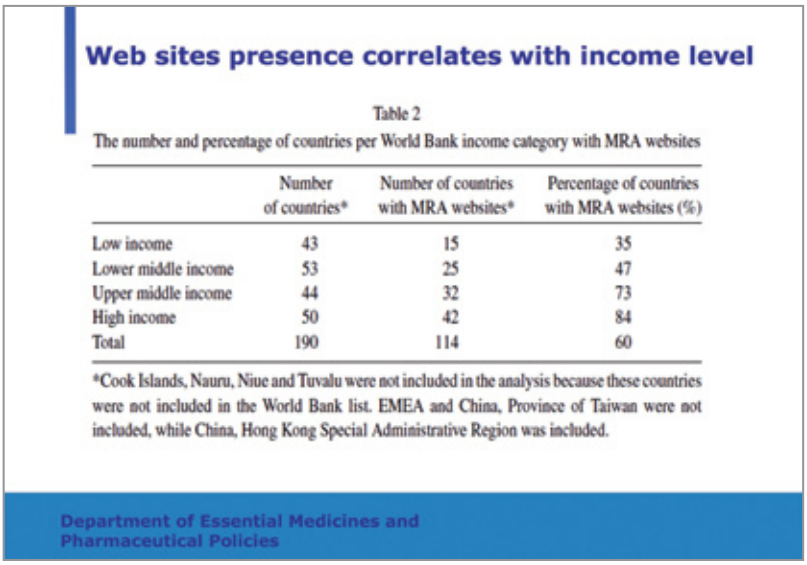


Figure19. In the 2009 WHO study, county website presence was correlated with higher per capita income.

The percentage of websites without adequate contact information declined from 29% in 2001 to 10% in 2009. However, it was noted that many of the websites could improve their contact information by providing the names of contacts for specific activities in addition to central contacts. In 2009, 27% of websites provided good information on organisational structure, including an organogram and an overview of the responsibilities or activities per department. This percentage is lower than the 41% reported in 2001.

A database of registered medicinal products was available on 14% of websites in 2001. This percentage rose to 37% in 2009, a promising, but not yet an adequate representation. Virtually no websites provided information on orphan drugs, cancelled marketing authorisations, and products under special post-marketing surveillance monitoring, unlike for example, the United States FDA website, which gives comprehensive information about these topics. Websites with listings of licensed manufacturers rose from 6% in 2001 to 37% in 2009, and lists of licensed wholesalers, distributors and pharmacies remained uncommon, rising from 6% in 2001 to 18% in 2009. Clear instructions for marketing authorisation applicants were included in 47% of websites in 2001 but did not increase significantly (49% of websites) in 2009. Although the number of websites with good information on import and export of medicines has doubled to 18% in 2009, this percentage is still low.

Safety has become an important consideration for all agencies and this is reflected in the observation that in 2001, 80% of assessed websites did not provide adequate information on how to report adverse drug reactions, or did not publish safety alerts. In 2009, only 18% of websites were scored "inadequate" on this item and 41% of the websites had sections on pharmacovigilance rated as "good."

Many web sites (33%) were still only available in the national language in 2009. Only 28% of websites were partly available in English in addition to the national language(s), and often key functions such as the information for applicants, medicinal products database, or search engines were not available in this language. Of note, there were five countries with websites only available in English rather than the national language: Morocco, Philippines, India, Malaysia and Singapore.

. . . even though regulatory websites had improved in terms of quantity, the study revealed the need for ongoing qualitative improvement.

Conclusions

From 2001 through 2009, the number of countries with regulatory websites as studied in WHO research surveys more than doubled. The jurisdictions that have maintained websites have demonstrated considerable improvement in the content and comprehensiveness of the information provided and parameters such as sitemaps, updates and mission statements, which were missing in 2001, are now more adequately addressed. However, there is still room for improvement in all fields covered in these web sites, including key subjects like information for applicants, regulatory guidance, pharmacovigilance and registries of medicinal products. This review also identified information gaps that need to be addressed in the future.

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Regulatory collaboration in the Gulf Cooperation Council states

Mohammed Al- Rubaie

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In 1981, the Gulf Cooperation Council (GCC) was established through an agreement among Bahrain, Kuwait, Oman, Qatar, United Arab Emirates and Saudi Arabia, covering a total population of 38.6 million inhabitants. The Council's scope includes work in domains of healthcare, economics, political information and education, and its ministers meet twice yearly. Although Yemen is not a GCC member, it does participate in a number of committees.

The GCC for Health Ministers coordinates activities and communications between the Ministers of Health of member countries, organising conferences, seminars, and training and implementing procurement programmes for pharmaceutical products, conducting field surveys and research and assessments of healthcare systems and strategies.

GCC-DR

Approved in 1999, the Gulf Centralized Committee for Drug Registration (GCC-DR) registers pharmaceutical companies and their products through the joint coordination of evaluations of scientific safety, efficacy and quality. The GCC-DR committee consists of two members nominated by each state and the executive office board is chaired by the Director General, who is responsible for supervising the work of the Board and following up the resolutions and recommendation of the Health Minister Council. The scope of the GCC-DR includes pre-marketing evaluation, marketing authorisation, post-marketing review, GMP inspections and the promulgation of technical guidelines. The activities of this group are financed by contributions from member states and cost recovery fees paid by industry.

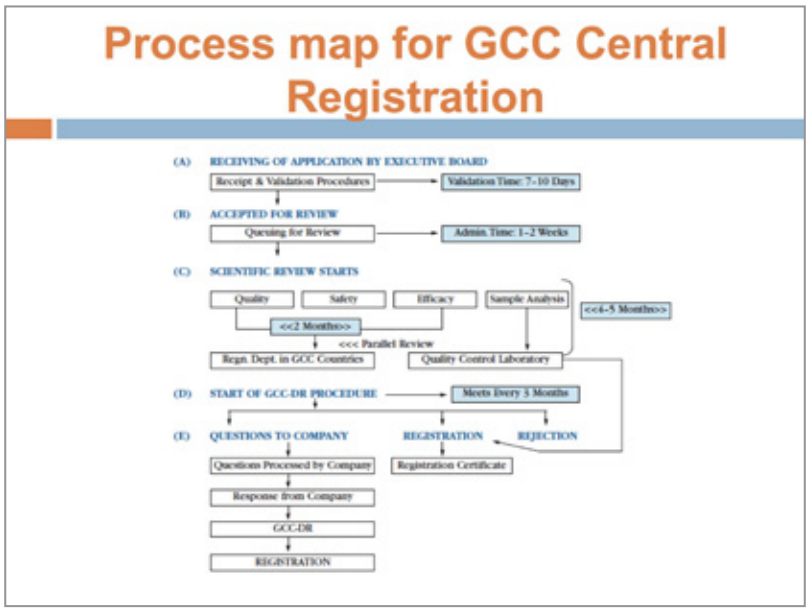
The GCC-DR primarily uses International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) guidelines as the basis for developing regional directives as well as other international guidelines including those of the World Health Organization (WHO). National technical documents are also used as the basis for harmonisation and as reference material. After being developed by a working group, a draft guideline is circulated to all member states for comment and posted on a website to solicit comments from stakeholders. Once adopted by the GCC-DR, final approval must be granted by the Council of Health Ministers.

GCC-DR communications include an updated website, presentations and promotions in national and international congresses or conferences and meetings with healthcare professionals, industry associations, individual companies and the media. In addition, the GCC-DR organises workshops on specific topics. Although there is no officially structured training programme within the GCC-DR initiative, each member state is responsible for providing training for their regulators and the Executive Office has organised training in the areas of good manufacturing process and post-marketing surveillance.

GCC-DR procedure

Dossiers and product samples must be submitted to the GCC-DR secretariat at the Executive Office and copies are forwarded to member states for review (Figure 20). Two GCC-DR members are designated to submit an evaluation report, and analysis samples are sent to GCC-DR-accredited laboratories. If a registration certificate is issued, the company is instructed to complete the registration process in each GCC-DR country. In order to produce

Figure 20. The process for dossier submission and review in the GCC States.



The harmonisation of processes and guidelines and shared workload facilitated by the GCC-DR system increases the transparency, efficiency, capacity and quality of the regulatory process.

medicines, manufacturers must possess a license granted through a successful good manufacturing process inspection by the GCC-DR.

GCC-DR advantages and disadvantages

The harmonisation of processes and guidelines and shared workload facilitated by the GCC-DR system increases the transparency, efficiency, capacity and quality of the regulatory process.

However, despite the availability of this work-sharing system, the GCC-DR continues to be challenged by an inadequate number of staff in the face of a steadily increasing number of new drug applications, resulting in longer than planned for regulatory review times. Other obstacles include differences in regulatory systems among the member countries and diverse activity timelines sometimes complicated by the inconsistent application of guidelines. Mr Al-Rubaie remains confident, however, that the shared resources and expertise of the Gulf States will allow the member states to continue to make significant progress in their efforts to enhance the regulatory review of new medicines.

The African Medicines Regulatory Harmonization Initiative

Margareth Ndomondo-Sigonda

Pharmaceutical Coordinator, African Union - NEPAD Agency, South Africa

Every country is obliged to regulate the trade of health products to ensure its citizens have access to quality, safe and efficacious treatments but resource constraints can make these obligations difficult to fulfil. As many as 90% of African National Medicines Regulatory Authorities (NMRAs) lack the capacity to guarantee quality, safety, and efficacy,[1] whilst sponsors and manufacturers face a landscape of diverse regulations, frequent delays, and limited transparency. As a result of these issues, needed health products are often not available or affordable in low-income countries, and substandard and counterfeit medicines pose public health and economic risks.

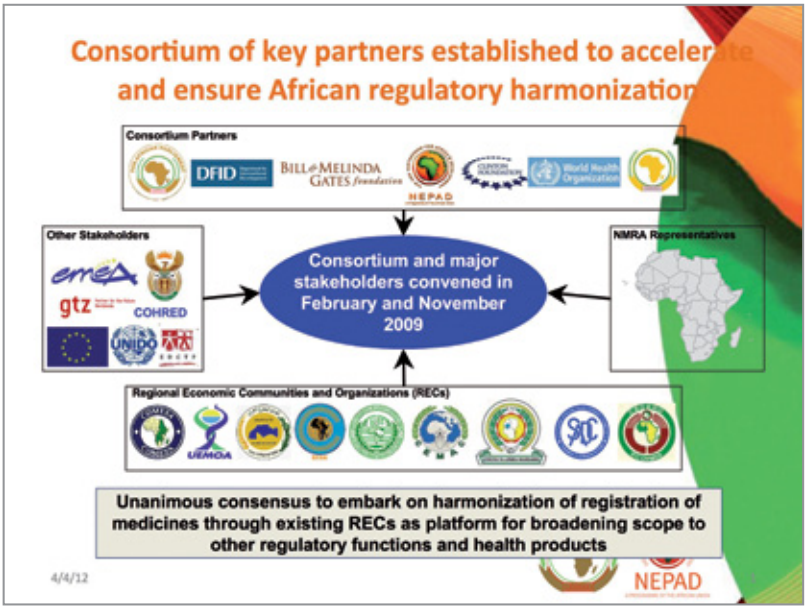


Figure 21. A Consensus meeting organised by the AMRH Consortium in Johannesburg, South Africa in February 2009.

In order to address these challenges, the African Medicines Regulatory Harmonization (AMRH) initiative was initiated at a New Partnership for Africa's Development (NEPAD) and Pan-African Parliament (PAP) consultation meeting in February 2009, which was hosted in collaboration with their Consortium partners, namely the World Health Organization, Bill & Melinda Gates Foundation (BMGF), UK Department for International Development (DFID) and the Clinton Health Access Initiative (CHAI). The meeting attracted representatives from nine of the continent's Regional Economic Communities (RECs) and organisations and over 40 NMRAs (Figure 21). This provided a strong endorsement for the consensus plan that emerged and hence the approach that RECs and NMRAs are now taking. The approach has been to conduct situation analysis of medicines regulation and harmonisation across the RECs; and thereafter support the development of regional project proposals to expedite and strengthen medicines registration through regional harmonisation and collaboration. The role of AMRH partners therefore is to mobilise political support, financial and technical resources needed. The overall aim is to improve

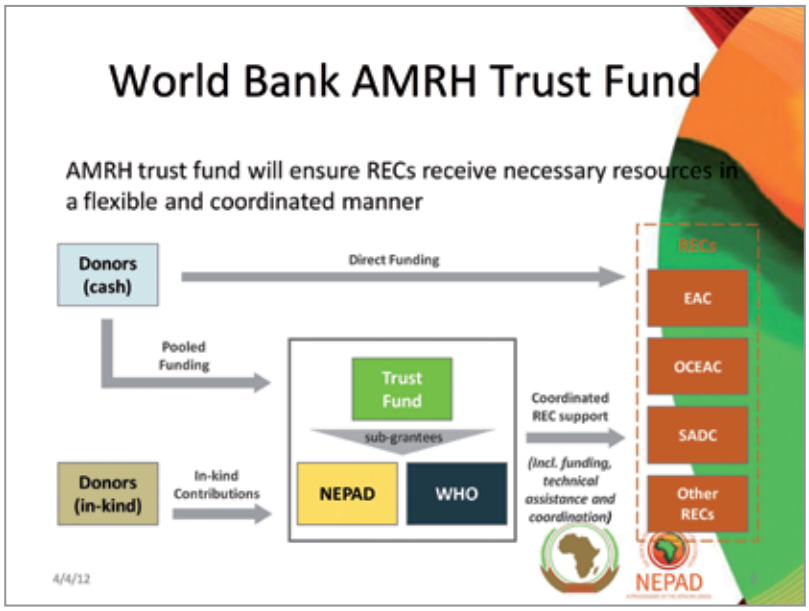


Figure 22. AMRH financial governance is managed through a trust fund.

public health by increasing access to quality, safe and efficacious medicines for the treatment of priority diseases. Specifically, the AMRH initiative aims to reduce the time taken to register essential medicines by countries in the African continent.

AMRH builds on the existing political mandates, plans and progress at continental and regional levels. Countries and RECs tailor their objectives and activities to their own specific needs, circumstances and preferences in line with the major objectives of the programme. The AMRH initiative focuses on near-term steps to promote the registration of generic medicines, with the ultimate goal of expanding the initiative to encompass other health products and regulatory functions.

Thus far, roughly 85% of Sub-Saharan Africa is covered by the AMRH initiative and project proposals for medicines registration harmonisation are at different stages of development. The project for East African Community is ready for funding and project launch is expected to take place early 2012.

Critical milestones identified by AMRH include the development and implementation of harmonised registration requirements and standards; the development of regulatory capacity and the strengthening of regulatory systems.

AMRH is planning to develop exchange programmes among national medicines regulatory authorities within and outside the continent and to establish Regional Centres of Regulatory Excellence.

Currently, member states in the African continent operate independently and each country has its own technical requirements for registration. The AMRH vision is the harmonisation of registration requirements, formats and procedures for the evaluation of medicine, harmonisation of good manufacturing practice (GMP) guidelines and inspection procedures . Eventually, it is the expectation that joint evaluations, shared assessment and inspection reports and mutual recognition agreements in Africa will be put into place, ultimately leading to a centralised procedure for registration of medicines through regional economic communities, whilst ensuring national sovereignty in registration decisions. In terms of governance and management, the AMRH Advisory Committee, composed of regulatory authority representation from regional economies, AMRH partners, industry and civil society, provide advice on AMRH implementation, and the World Bank Trust Fund manages a multi-donor trust fund, ensuring that regional economic communities receive resources in a flexible and coordinated manner (Figure 22)

To build capacity and strengthen regulatory systems, AMRH is currently working with various partners conducting regulatory training programmes in Africa with a view to establish harmonised training curricula, certification system and evaluation of training programmes. The aim is to move from the existing ad-hoc training arrangements based on donor funding to a more cost-effective and sustainable mechanism using the existing NMRAs and academic institutions in the African regions. The initial goal is for member states to collaborate on training programmes for the evaluation and registration of medicines, GMP inspections and quality and management systems (QMS). In the short term, AMRH is planning to develop exchange programmes among national medicines regulatory authorities within and outside the continent and to establish Regional Centres of Regulatory Excellence. Long-term plans include the engagement of academic institutions to offer post-graduate courses in regulatory science. Finally, the AMRH East Africa community (EAC) project, which will be launched in Tanzania in March 2012, will serve as a pilot for learning and sharing experience among African economic communities.

AMRH provides an excellent platform for benchmarking regulatory review process and practices and increasing the regulatory workforce in Africa, thereby making an important contribution to the continent's social and economic development.

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APEC best regulatory practice project: An update and future direction

Chao-Yi (Joyce) Wang

Senior Specialist, Food and Drug Administration, Chinese Taipei

Established January 2010, the Taiwan Food and Drug Administration (TFDA) is administered through three regional centres and comprises seven divisions: Risk Management, Planning and Research, Food Safety, Drugs and Biotechnology Products, Medical Devices and Cosmetics, Controlled Drugs, and Research and Analysis. The central mission of the TFDA is to ensure consumer access to safe and effective products through a risk analysis of those products. The Centre for Drug Evaluation (CDE), a cooperative non-governmental institution, performs the technical evaluation of new drugs and provides recommendations for licensure to the TFDA.

Good practices based on those of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH) are followed throughout the process of medical products registration in Chinese Taipei (Figure 23):

- Good Laboratory Practice (GLP) during the drug discovery and preclinical phase;
- Good Clinical Practice (GCP) during the clinical trial time period;
- Good Review Practice (GRevP) during drug registration
- and Good Manufacturing (GMP), Pharmaceutical Inspection Co-operation Scheme (PIC/s) practice and Good Pharmacovigilance (GPvP) practices after drug registration.

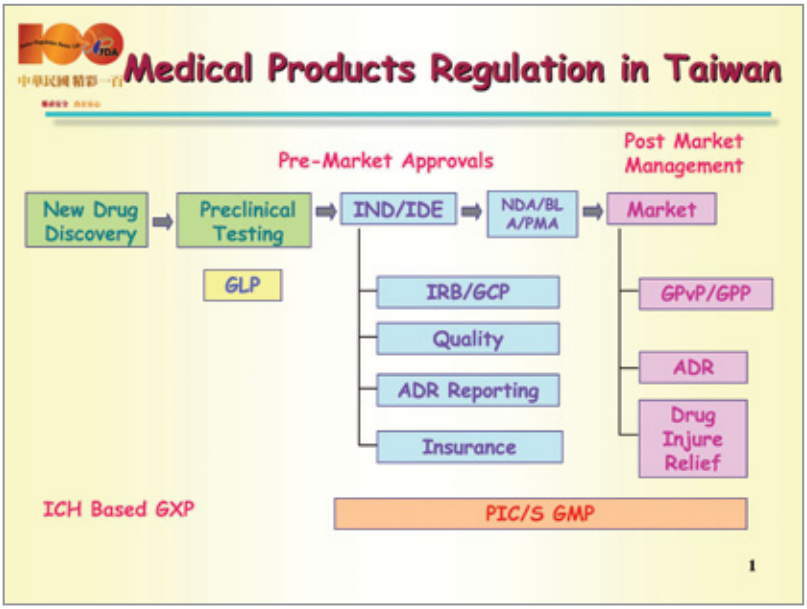


Figure 23. Good practices are employed throughout the product development life cycle in Chinese Taipei.

In addition, Chinese Taipei is one of only three countries in the world to establish a Drug Injury Relief Foundation, which provides financial compensation to patients who experience serious adverse events associated with the use of an approved medicine.

TFDA best regulatory practices are supported by the Asian Pacific Economic Cooperation (APEC) Regional Harmonization Steering Committee (RHSC) strategic framework, which seeks to reach regulatory convergence in APEC economies by 2020. This framework employs a coordinated approach, in which priority work areas are identified through needs assessments derived from diagnostic workshops, and a roadmap for the promotion of best practices is developed that specifies individual projects that will contribute to overall goals (Figure 24).

An element of the framework, the APEC Good Review Practice (GRevP) Roadmap, endeavours to achieve best practices in the review of medicines, which are based on efficiency, quality, clarity, transparency and consistency as well as to accomplish the acceleration of mutual recognition through the enhancement of mutual trust between member economies. Challenges to the implementation of this roadmap exist, however, including a lack of conformity in review practices and the need to dynamically update agency processes in response to the ongoing

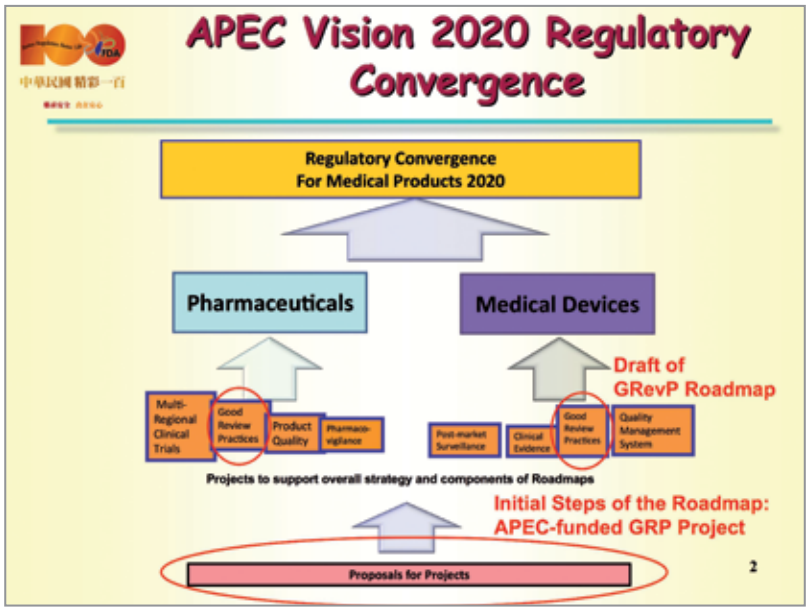


Figure 24. The APEC RHSC strategic framework, which seeks to reach regulatory convergence in APEC economies by 2020.

emergence of complex new medical products. Execution will also require no-tariff measures to eliminate trade barriers and to accelerate the provision of good-quality medicinal products to all patients in APEC countries.

The TFDA has outlined a four-step process for the facilitation of GRevP.

- Step one, which will take place from 2011 through 2012, will consist of an assessment and capacity building, setting the foundation for APEC convergence. During this period, regulatory system gaps will be identified and a prioritised list of needs and activities will be developed.
- Step two, which will occur from 2011 to 2014, will further advance the process of convergence. A strategic programme will be outlined that will include training workshops and information sharing. GRevP documentation will also be developed.
- Step 3, scheduled to take place from 2012 to 2015, will assess the effect of GRevP training, evaluate performance readiness and execute an audit programme.
- Step 4, occurring from 2015 through 2020 will be the time frame during which the implementation of GRevP will be evaluated, the goal of regulatory convergence among APEC economies attained and recommendations for further harmonisation issued.

. . . it is hoped that the project will demonstrate the importance of good review practice to a well-functioning regulatory system and lead to changes in review behaviour and amendments in regulatory practice policy.

An initial step for implementation of the Roadmap, The Best Regulatory Practice for Medical Products for Trade Facilitation project, was funded by APEC in December 2010 and is co-sponsored by Canada, China, Indonesia, Korea, Malaysia, Mexico, Peru, the Phillipines, Thailand and the United States. Key objectives for this programme are the promotion of awareness and adoption of GRevP to reduce regulatory burden and achieve timely market access for new medicines. It is further expected that the project will provide a platform for regulatory dialogue and experience and information sharing among regulatory authorities, establishing mutual confidence in assessment reports and an appreciation of how the reports of other trusted agencies can be systemically used to improve the overall efficiency and effectiveness of the product assessment process. Finally, it is hoped that the project will demonstrate the importance of GRevP to a well-functioning regulatory system and lead to changes in review behaviour and amendments in regulatory practice policy.

The project will consist of three components: a survey to examine disparities in GRevP and approaches to scientific assessments among APEC economies and to collect data on current practice by participating agencies; a pilot study on the voluntary use of available regulatory review reports from other participating agencies; and a series of three- to five-day GRevP workshops, covering both pharmaceuticals and medical devices, to be held in Chinese Taipei in 2011 and 2012. The Centre for Innovation in Regulatory Science (CIRS) has assisted APEC in implementing the first component of this process.

The first GRevP training workshop was held in October 2011 in Chinese Taipei with the goal of contributing to regulatory practice and interagency cooperation through a common understanding of the importance of GRevP and sharing best practices among participants from Canada, China, Indonesia, the Republic of Korea, Mexico, Chile, Chinese Taipei, Japan, Malaysia, Peru, Singapore, United Kingdom, the Philippines, Thailand and the United States. The next workshop will be convened in Chinese Taipei in October 2012.

The Four-Agency Consortium: Evolving a work-sharing model that will streamline approval and enable effective resource utilisation

Cordula Landgraf

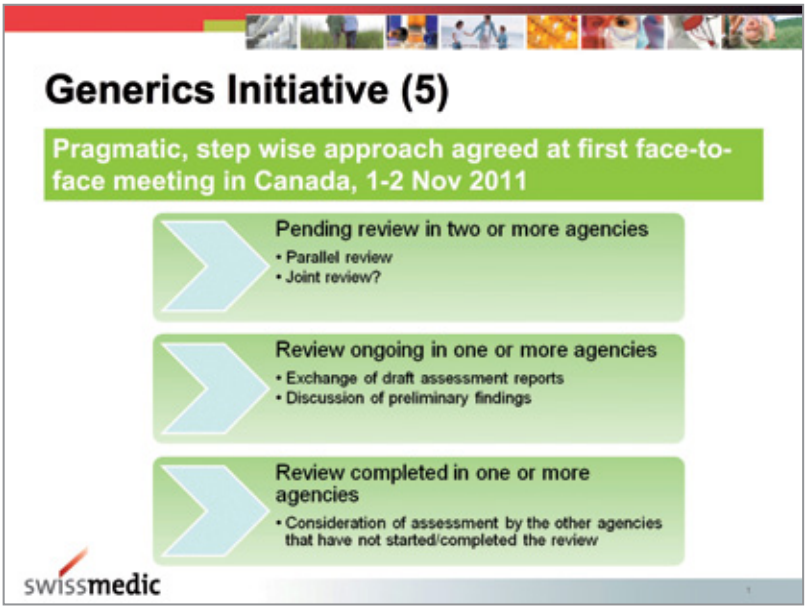
Head of Networking, Swissmedic

In 2007, a Consortium was formed among four regulatory agencies, Health Canada, Swissmedic, Australia's Therapeutic Goods Administration (TGA) and Singapore's Health Sciences Authority (HSA) with the common goal of evolving a work-sharing model that will streamline approval and enable effective resource utilisation.

The partnership was initiated on the basis of an established network of bilateral agreements among the four agencies that permitted the exchange of confidential information. A detailed work plan was then developed that started with the sharing of information which provided a platform to exchange knowledge and expertise on topics such as policies, processes and guidelines as well as early access to important safety data, such as product recalls and information regarding counterfeit medicinal products.

This programme of information sharing is ongoing and has since been complemented by a plan for future work sharing among Consortium members. Initial pilot programmes of work sharing in the form of bilateral parallel review have been completed. In the pilots, which required prior applicant agreement, two agencies exchanged assessment reports, analyses and findings, but in the end, each agency took its own decision. The goals of these first pilots were to gain knowledge about the processes applied by other agencies while building confidence in the other agency's work.

Figure 25. Generic medicines for which regulatory review is pending, ongoing or completed are being selected for work sharing among Consortium members.



Specific work-sharing initiatives within the Consortium include initiatives in New Chemical Entities (NCE) and Biologics, generics and benefit-risk assessment as well as participation in the International Conference on the Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH).

The New Chemical Entities and Biologics Initiative

The Consortium has employed a step-wise approach to implement the NCE and Biologics initiative, starting with the bilateral exchange of assessment reports. The goal of the project is the development of confidence in the processes of the other agencies and an analysis of similarities and differences that occur within the region. The potential benefits that can be accrued as a result of this specific initiative are insights regarding the review processes, practices and standards of the participating consortium authorities and the identification of similarities and differences. It allows the Consortium to benefit from one agency's area of expertise and provides for the informed decision making which results from peer expert discussion. Finally this initiative serves as a potential basis for future enhanced collaboration and work sharing.

Within this initiative, a pilot project of parallel review has been completed between HSA and Swissmedic, and assessment reports have been exchanged. A secure electronic platform for the exchange of confidential documents was established and contact points within the agencies were identified as well as a list of products that may be suitable for future parallel review. The parallel review process itself was determined to be an excellent platform to share technical knowledge and to learn about another agency's evaluation procedures. Furthermore, the interactive discussions were appreciated by reviewers at both agencies and the general findings were consistent between the countries. Differing review cycles and timing, however, were found to be challenging to participants, and it was decided that they should be more aligned in future projects.

The Generics Initiative

Part of an international collaborative model for the review of generic drugs, this initiative was begun among Consortium members in 2010. Generic medicines were identified as a priority for exploring work-sharing opportunities because of agency backlogs, the often simultaneous submission of generic medicine applications and the expectations for similar international regulatory requirements. Potential benefits anticipated for this initiative include a savings in resources through a decrease in duplicative work and a reduction in the review backlog with the reallocation of resources to more high-risk applications. It is additionally foreseen that the peer-review process may result in more thorough assessments, with greater sharing of quality and safety data, the potential to incorporate diverse scientific viewpoints, increased consistency in regulatory and scientific decisions and enhanced predictability. Finally, this collaboration can result in potentially faster market entry and greater availability of generics, leading to reductions in healthcare costs.

A pragmatic, step-wise approach was agreed at the first face-to-face meeting of participants in Canada in November 2011. Similar to the NCE and Biologics Initiative, a secure platform for the exchange of documents and contact points within the Consortium were established. Completed assessment reports for specified generic drugs were then exchanged among the agencies to familiarise participants with the other agencies' processes and practices as well as to to identify potential points of convergence and challenge. The outcome of a comparative analysis revealed that criteria for the assessment of generic medicines were similar among Consortium agencies, with differences among participants related to

- stability data owing to Singapore's different climatic conditions;
- the acceptability of the reference product, that is, the TGA requires that a reference product originate in Australia, whereas the HSA, Health Canada and Swissmedic allow the reference medication to originate from another market if certain conditions are fulfilled;
- and patents, the regulation of which is not within the scope of some agencies such as Swissmedic but which does lie within the purview of others such as Health Canada.

Potential scenarios for work sharing in this initiative are being constructed through the identification of generic applications awaiting review at each agency for products for which review is pending in two or more agencies or ongoing or completed in one or more agencies (Figure 25).

The Benefit-Risk Initiative

The Consortium has also initiated a project in collaboration with the Centre for Innovation in Regulatory Science (CIRS) to develop a qualitative framework for the benefit-risk assessment of new medicines that will allow a systematic standardised approach to the appraisal during regulatory review and post-marketing evaluation. It is anticipated that the framework will also facilitate the opportunity for joint or shared reviews among the four agencies and enhance the transparency and consistency of decision making. This project will permit each agency to perform a critical appraisal of their own processes for benefit-risk decision making in the light of a better understanding of the approaches and decision-making processes of other agencies. Other benefits include the development of a template with the potential to be used for improved communication of the outcome of benefit-risk assessment to the public and to be used as a basis to move from parallel to joint review.

An electronic template has been developed and is currently being tested in the benefit-risk evaluation of a product that has been approved by all four agencies. In this examination, each agency will complete the assessment using the template, after which a comparison of the findings and analysis of the template suitability will be conducted and necessary fine tuning performed.

ICH participation

Health Canada and Swissmedic (as representatives of the European Free Trade Association, EFTA) are observers in the ICH process, whereas TGA and HSA have participated in some ICH Expert Working Groups (EWGs) since ICH processes were opened to non-

. . . it is hoped that the project will demonstrate the importance of good review practice to a well-functioning regulatory system and lead to changes in review behaviour and amendments in regulatory practice policy.

ICH regulators in 2010. At the second joint caucus during the ICH meeting in Seville, Spain in November 2011, there was an exchange of information and discussion among Consortium members regarding ongoing EWG efforts. In expectation of the achievement of reduced workload through the sharing of efforts, Consortium members anticipate that participation in this new initiative area will continue to intensify.

Conclusions

The first steps and pilot projects of the Consortium are successfully underway and principle fields of cooperation have been defined and are monitored in the Consortium work plan. These efforts have been revealed as a good basis to establish long-term cooperation in the achievement of shared workload and the efficient use of resources. Preliminary discussions regarding joint review of new medicines by Consortium members have taken place but the models remain to be further elucidated.

Appendix: Workshop Attendees

Regulatory and government agencies and academic institutions		
Siti Aida Abdullah	Deputy Director, Product Registration	National Pharmaceutical Control Bureau, Malaysia
Mohammed Hamdan Al-Rubaie	Director of Drug Control	Ministry of Health, Oman
Prof Sir Alasdair Breckenridge	Chairman	Medicines and Healthcare products Regulatory Agency, UK
Agnes Chan	Regulatory Consultant, Pharmaceuticals and Biologics Branch	Health Sciences Authority, Singapore
Ya-Ting (Fia) Chen	Associate Technical Specialist	Taiwan Food and Drug Administration
Dr Raymond Chua	Deputy Group Director, Health Products Regulation Group	Health Sciences Authority, Singapore
Dr Jason Ferla	Acting Principal Medical Adviser	Therapeutic Goods Administration, Australia
Prof Bruno Flamion	Chair	Belgian Committee for Reimbursement of Medicines, Belgian National Institute for Health and Disability Insurance
Dra. Herawati	Head, Section of New Drug Evaluation Path II	National Agency of Drug and Food Control, Indonesia
Dr Christopher Hickey	Country Director	US Food and Drug Administration, China
Noorizam Ibrahim	Deputy Director	National Pharmaceutical Control Bureau, Malaysia
En-Ling Lan	Associate Technical Specialist	Taiwan Food and Drug Administration
Cordula Landgraf	Head of Networking	Swissmedic
Associate Prof John Lim	Chief Executive Officer	Health Sciences Authority, Singapore
Dr Chih-Liu Lin	Deputy Executive Director	Center for Drug Evaluation, Taiwan
Dr Murray Lumpkin	Commissioner's Senior Advisor and Representative for Global Issues	US Food and Drug Administration
Margareth Ndomondo-Sigonda	Pharmaceutical Coordinator	African Union - NEPAD Agency, South Africa
Dr Chang-won Park	Team Leader, Off-label Evaluation TF Team, Drug Evaluation Department	Korea Food and Drug Administration
Prof Robert Peterson	Executive Director	Drug Safety and Effective Network, Canadian Institutes of Health Research
Dr Lembit Rägo	Coordinator of QSM	World Health Organisation, Switzerland
Dató Eisah A. Rahman	Senior Director of Pharmaceutical Services	Ministry of Health, Malaysia
Lucky Slamet	Deputy, Therapeutic Products, Narcotics, Psychotropic & Addictive Substance Control	National Agency of Drug and Food Control, Indonesia
Sue Kim Tan	Regulatory Specialist, Pharmaceuticals & Biologics Branch	Health Sciences Authority, Singapore
Dr Meir-Chyun Tzou	Director	Taiwan Food and Drug Administration
Chao-Yi (Joyce) Wang	Senior Specialist	Taiwan Food and Drug Administration
Pharmaceutical companies and consultancies		
Jayanthi Boobalan	Regulatory Lead	Pfizer (Malaysia) Sdn Bhd, Malaysia
Dr Graham Burton	Senior Vice President, Global Regulatory Affairs, Pharmacovigilance and Corporate QA Compliance	Celgene Corporation, USA
Vicky Chang	Regulatory Affairs Manager	Astellas Pharma Taiwan Inc, Taiwan
Zhao Rong Chen	Head of Regulatory Centre of Excellence	GlaxoSmithKline China/HK, China

Richard Cheung	Regulatory Affairs Senior Manager, Head, Regulatory Affairs & Safety, Asia-Pacific	Amgen (Asia) Limited, Hong Kong SAR, China
Helen Cho	Director	Bristol-Myers Squibb Company, South Korea
Erika Eckel	Head of Regional Management, Regulatory Affairs	F Hoffmann-La Roche, Switzerland
Dr Paul Huckle	Chief Regulatory Officer and Senior Vice President, Global Regulatory Affairs	GlaxoSmithKline, USA
Hiroki Kato	Director of Board, Clinical Research	Zeria Pharmaceutical Co Ltd, Japan
Huey Yiing Lee	Regulatory Affairs Manager	Bayer Co (Malaysia) Snd Bhd, Malaysia
Dr Zili Li	Executive Director and Head of Emerging Markets Regulatory Strategy	Merck & Co Inc, USA
Thean Soo Lo	Director	Janssen-Cilag Asia Pacific, Singapore
Raj Long	DRA Head, AMAC, GEM, LATAM	Novartis Pharma AG, Switzerland
Dr Thomas Lönngren	Independent Strategy Advisor	Pharma Executive Consulting, UK
Arun Mishra	Director, Global Regulatory Affairs (Asia-Pacific, Japan and Emerging Markets)	GlaxoSmithKline, UK
Patrick O'Malley	Senior Director, Global Regulatory Affairs - International	Eli Lilly & Company, USA
Dorte Strobel	Senior Regulatory Intelligence Manager	Novo Nordisk A/S, Denmark
Dr Yamin Wang	Head, Global Regulatory Affairs, Asia Pacific	Bayer HealthCare Pharmaceuticals, Singapore
Adrian Waterson	Asia Pacific Regional Director	AstraZeneca, UK
Dr Hua Zhang	Director, Worldwide Regulatory Strategy Asian Region	Pfizer, China
Centre for Innovation in Regulatory Science		
Patricia Connelly	Manager, Communications	
Lawrence Liberti	Executive Director	
Dr Neil McAuslane	Director	
Prisha Patel	Portfolio Manager	
Professor Stuart Walker	Founder	