



WHAT ARE THE KEY PERFORMANCE METRICS THAT AGENCIES AND COMPANIES SHOULD USE TO MEASURE REGULATORY PROCESSES AND PRACTICES TO FACILITATE THE LICENSING OF NEW MEDICINES?

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## WORKSHOP REPORT

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# WHAT ARE THE KEY PERFORMANCE METRICS THAT AGENCIES AND COMPANIES SHOULD USE TO MEASURE REGULATORY PROCESSES AND PRACTICES TO FACILITATE THE LICENSING OF NEW MEDICINES?

## Section 1: Executive Summary

### Background to the Workshop

Although regulatory performance is clearly linked to the availability of new medicines, there are many factors that can influence this performance within different jurisdictions. These factors include company strategy; regulatory policy; company time to answer agency questions; review time; available resources; review routes; pricing and reimbursement and the quality of the submission and review and decision-making processes. In addition, an agency's activities may be assessed before, during and after authorisation.

Through a number of benchmarking studies, CIRS has previously developed markers for good review practices, identified key enablers and barriers to the review of new medicines and has measured the review process and time to a product being licensed and reimbursed. Mature agencies such as US Food & Drug Administration, European Medicines Agency, Health Canada and Australia's Therapeutic Goods Administration have set themselves key qualitative and quantitative performance indicators (KPIs), against which they and their stakeholders can measure their performance. Companies have also set themselves internal KPIs to help improve and manage the regulatory process of getting medicines from development to patients globally.

Agencies in jurisdictions with emerging pharmaceutical markets are now developing their own performance metrics and are interested in what should be measured, how this is best undertaken and what role metrics have in improving their processes and practices. These measurements could serve as a barometer of change, providing active feedback on the effectiveness of changes being proposed or implemented in various jurisdictions. In today's environment, patients' access to medicines may not only be influenced by the regulatory review but also by an additional step, which can range from a simple evaluation of budget impact to a full health technology assessment (HTA) to evaluate both clinical and cost effectiveness for the healthcare system. The aim of this Workshop was to discuss which regulatory measures that companies and agencies feel are relevant in today's environment

from the time of a medicine's development to its availability to patients across different jurisdictions and how these measures could enable the quality of the processes, practices and planning of agencies and companies.

### Workshop Objectives

- Identify and provide the rationale for selecting key regulatory performance areas that agencies and their stakeholders believe should be measured and discuss how this can best be achieved
- Discuss how agencies and companies actually measure their performance and how this can enable change by improving efficiency, effectiveness and quality of processes and practices
- Recommend which key performance metrics should be used to help improve the internal performance of companies and agencies to ensure the timely availability of safe and effective medicines

### Introduction

**Dató Eisah A. Rahman**, *Senior Director of Pharmaceutical Services, Ministry of Health, Malaysia* welcomed participants to the second CIRS Workshop to be held in Kuala Lumpur. Dató Rahman reflected on the evolution of the regulation of medicine in Malaysia, where today, the consistent use of key performance indicators helps to ensure the quality, safety, efficacy and access of medicines.

### Key points from presentations

#### **SESSION: MEASURING PERFORMANCE IS AN ESSENTIAL COMPONENT OF GOOD REGULATORY PRACTICES AND DECISION MAKING**

**YUAN Lin**, *Director General, Department of International Cooperation, China Food and Drug Administration (CFDA)* spoke on the current reform of the pharmaceutical regulatory system in China. To keep pace with the rapid development of the pharmaceutical industry the Chinese regulatory system must respond to several challenges that include a heavy backlog of drug registration applications, a relatively

lengthy review and approval process and a quality gap between domestic generic drugs in comparison with international manufacturing labels. In August 2015, the Chinese State Council issued an opinion on reforming the review and approval system for drugs and medical devices. Initial results of reforms include efforts to clarify the requirements for generic medicines and to optimise their review and approval; proposed prioritised approval mechanisms to accelerate the development and launch of new drugs with clinical value and generic drugs for urgent clinical need; the optimisation of the review and approval of new trial applications and the pilot of the Marketing Authorisation Holder system, which for the first time permits non-manufacturing domestic research and development institutions to apply for regulatory approval. In 2015, 9,394 drugs were reviewed by the CFDA, which was 90% higher than the number in 2014, despite the fact that reforms had only been in progress for six months.

Whilst the specific roles of national regulatory agencies may vary, quality of process, decision making and documentation are universally essential. **Dr Tomas Salmonson**, *Chair, Committee for Medicinal Products for Human Use, European Medicines Agency* explained that the identification of relevant metrics for regulation is key for improvement as they facilitate healthy competition and enable regulators to see what they do well and what others may do better. The Heads of Medicine Agencies initiated the Benchmarking of European Medicines Agencies (BEMA) programme to assess the management systems, marketing authorisation applications, pharmacovigilance activities and inspections services of individual regulatory agencies. These assessments identify agencies' strengths and best practices as well as opportunities for improvement to enable an improved operation of the network of agencies. In addition, the selection of the "best available rapporteur team" for the EMA centralised review system is based on criteria such as the development of guidelines, overall competence and the agency's previous performance with issues such as compliance with time tables and benefit-risk templates.

Health Canada uses performance metrics to achieve a predictable review process; to allow comparisons between different individuals, units and business lines; to demonstrate transparency; to help know and manage stakeholder expectations and to be able to respond to questions and commentary about

how they do their work compared with other regulatory authorities and to deliver on their commitments to improve performance and modernise regulatory activities, including cost recovery. **Barbara Sabourin**, *Director General, Therapeutic Products Directorate, Health Canada* acknowledged that many of Canada's performance metrics - qualitative and quantitative - are common to other regulators. However, each regulatory authority works to provide a credible performance story to internal and external stakeholders, at times with metrics that are unique to their situation. In addition, data collection for performance metrics will be dependent on clear programme objectives and relevant metrics and technology and will be driven by a performance measurement culture.

Providing an industry perspective on the rationale for regulatory qualitative and quantitative performance indicators, **Dr Paul Huckle**, *Chief Regulatory Officer and Senior Vice President, GlaxoSmithKline, USA* said that regulatory agency performance measures drive development of efficient and predictable review processes that enable accurate forward planning, promote high-quality content and structure applications and more efficient reviews, identify best practices and areas for enhancement, facilitate the adoption of innovative approaches to drug development and regulatory science and accelerate the delivery of new medicines to patients and healthcare providers. In the pre-approval phase, performance measures help industry to plan and manage the complexities of global clinical development including clinical trial applications, clinical protocol development and amendments, investigator recruitment, training and meetings, ethics committee reviews, investigational drug supplies, patient recruitment and regulatory agency interactions. During review and approval, performance measures help industry plan and manage activities for new product launches across multiple markets. Regulatory performance measures in post-approval can help industry to maintain and develop products after marketing authorisation including new indications and product formulations, labelling updates, manufacturing and packaging changes, license renewals, post-approval commitments and paediatric developments.

As the primary stakeholder in the development of medicines, patients' outcomes and priorities should be considered when establishing measurements of quality for regulators. **Dr Durhane Wong-Rieger**, *President, Canadian*

*Organization for Rare Disorders* specified that regulatory performance metrics should measure the ability of regulators to achieve the goal of timely, appropriate, sustainable access to safe and effective medicines from clinical trial design to post-market monitoring and reassessment. Specifically, metrics should measure achievement of the global availability of medicines within comparable timeframes; the expansion of clinical trials into multiple regions to enable increased understanding of drug mechanisms in diverse populations and to increase global clinical experience and expertise; the reduction in delays for drug submissions and approvals, potentially through collaborative reviews and shared work; the decrease in the number of divergent decisions using the same clinical data, potentially through discussion and collaboration; the management of access through better coordination with companies, HTA agencies and payers and the use of simultaneous and parallel rather than separate and sequential processes and the development of opportunities for patient input and petition or appeal.

At the Health Sciences Authority (HSA), Singapore, product team leads are responsible to provide monthly dashboard reports of key performance indicators to senior management such as the number of applications accepted, the number under evaluation and completed, the outcomes of completed evaluations and the number of applications that met or exceeded timelines. **Dr Yee Hoo Looi**, *Acting Deputy Director – Therapeutic Products Branch, Health Sciences Authority* explained that these data are used to assess process efficiency, workload and resource balance and the effectiveness of HSA evaluation strategies. In addition, to address the need for published, transparent screening timelines to facilitate planning. HSA proposes to formulate screening target timelines inclusive of time to answer queries, introduce a cap on the number of rounds of screening queries and improve applicants' awareness of HSA requirements with the development of clear submission guidelines and checklists. HSA also proposes to review the distribution of applications according to selected evaluation routes to determine if their decision making is consistent with other regulatory bodies to further leverage the approvals of these agencies.

Performance metrics for the drug registration process at the National Agency of Drug and Food Control (NADFC), Indonesia are the percentage of drug applications per year that

receive decisions for approval, rejection or requests for additional information and the percentage of applications per year that receive final decisions within established timelines.

**Dra Nurma Hidayati**, *Director of Drug and Biological Products Evaluation, National Agency of Drug and Food Control (NADFC)* reported that metrics are tracked through a conventional manual timelines measurement and tracking system using monitoring cards and Excel spread sheets that monitor timelines in working days for the whole process from submission until final decision. Performance metrics are used at the NADFC for the development of an annual report and to review the evaluation process. A system of ongoing improvement has been implemented including the development of an electronic registration system for new drugs that incorporates a tracking system for the review that increases the transparency and traceability of the evaluation process: In addition, the evaluation process has been simplified, new drug evaluators and IT specialists have been recruited and competency has been increased through joint training with stakeholders and national and international continuing education for new and senior evaluators.

**Pia Angelique D. Priagola**, *Food Drug Regulation Officer III, Food and Drug Administration* outlined the strengths of the of the Center for Drug Regulation and Research (CDRR) at the Philippines FDA including the fact that internal and external expertise is accessible to guide different regulated areas, all regulatory functions include staff with relevant academic education and recently enacted reforms will increase staffing. In addition, the regulatory system at CDDR is ISO certified, the assessment of good manufacturing processes is part of market authorisation and a system for variations is in place. The only key performance indicator at the CDDR is the number of applications processed within target timelines. Achievements against this factor are influenced by external factors such as the quality of the dossier; that is its completeness and correctness, timing arising from company strategy and any shifts in regulatory requirements or processes. They are also influenced by internal factors including technology; that is network and infrastructure, manpower, the influx of applications and government projects.

At National Pharmaceutical Control Bureau (NPCB), Malaysia, relevant performance indicators measured in pre-and post-marketing processes at the organizational, national and

ministry level are essential to ensure the quality, efficacy and safety of registered products in the country. At the organisational level, timelines have been established for key activities such as the registration of new products, issuance of certificates of product registration; certificate of free sales and notification of cosmetics issuance of licenses for manufacturers, wholesalers and importers; issuance of clinical trial import licenses and for clinical trial exemption licenses. **Azura Abdullah**, *Senior Principal Assistant Director, National Pharmaceutical Control Bureau, Ministry of Health, Malaysia* said that timelines are tracked monthly and published twice yearly on the NPCB website. The NPCB has achieved a high rate of compliance with these timelines: 94% new drugs, biologics and generic are reviewed within the specified timeframe. In addition, an upgraded online registration system is currently under development in Malaysia, where implementation and enforcement of regulatory policies and guidelines is complemented with good practices contributing to the achievement of good performance of the organisation.

The multidisciplinary drug review team at the Taiwan Centre for Drug Evaluation (CDE) uses communication and consensus building, employing evidence-based decision making that centres on benefits and risks. The use of good review practices (GRevP) is one metric commonly used by regulatory agencies and **Dr Churn-Shiouh Gau**, *Chief Executive Director, Center for Drug Evaluation, Taiwan* reported that GRevPs that promote efficiency, quality and consistency and transparency are routinely implemented by the CDE. The measurement of review timing is another common regulatory review metric. Although the median CDE review time for new drug applications increased to 392 days by 2014, that timing improved in 2015 when the CDE invited external experts to review cases of variations and formed a taskforce team to investigate all new drug applications with extended review times. In addition, the CDE also initiated a programme to identify priority applications; that is, new chemical entities to treat serious disease representing unmet medical need and the median review timing for those priority applications decreased by 55% in a 6-month time period in 2015 from 280 days to 127 days.

**Dr John Skerritt**, *Deputy Secretary, Regulatory Services, Australian Department of Health* explained that greater regulatory performance numbers or faster timing do not always equal

better regulation and explanations of what the numbers mean are often needed. The first TGA initiative to develop measures of performance resulted in eight key performance indicators for stakeholder communication, education and satisfaction, pre- and post-market business organisation, organisation health, financial performance, statutory obligations, international cooperation and decision making. Although stakeholders were reasonably happy with this set of key performance indicators and reporting, in 2015, the Australian Prime Minister mandated a framework for all Australian regulators that focussed more specifically on generic qualitative measures of regulatory performance and resulted in six key performance indicators. Because TGA recognises that it is essential to build key performance indicators into an organisational business plan to avoid discordant sets of priorities, the agency developed a sample template for the second set of government indicators and tested it across the organisation to make sure that reporting was feasible before locking in these key performance measures. TGA is also attempting to facilitate the necessary internal cultural change to support reporting against new key performance indicators.

**Prisha Patel**, *Manager, Global Development Programme, Centre for Innovation in Regulatory Science* informed Workshop participants that CIRS has benchmarked regulatory agencies using agency-supplied data since 1995. CIRS has also used this methodology to develop benchmarking metrics for emerging market agencies, which are diverse in their practices and processes for reviews. In the Emerging Markets Regulatory Review Times (EMaRReT) database CIRS currently collects benchmarking data from international pharmaceutical companies in 18 emerging markets. These data provide companies insight into the regulatory environment; however, the insights only reflect data from multinational company's international products and do not permit the distinction of such information as company versus agency time in reviews. CIRS has also initiated the first phase of a regulatory agency benchmarking programme in which emerging market agency-supplied data was solicited from each participating agency regarding the agency's capacity and review process as well as the milestones tracked during the review process. Common agency milestones were then identified and a feasibility study was conducted using four or five products from each participating agency. Regulatory benchmarking

data can be used to identify where time is spent in the review process, to increase internal transparency, to establish programmes of internal benchmarking and to monitor the effects of change initiatives.

The mission of World Health Organization (WHO) prequalification (PQ) is to ensure timely availability of quality-assured health products for the prevention, diagnosis and treatment of priority diseases in low- and middle-income countries. **Dr Lembit Rågo**, *Head, Regulation of Medicines and other Health Technologies, Essential Medicines and Health Products, World Health Organization* stated that WHO PQ performance indicators are linked to steps of the PQ process and aim to measure the number and percentage of products going through the different steps of the PQ process and the time taken to prequalify a product. WHO has made available numerous quality-assured products to WHO Member State markets and in 2015, prequalified 112 products and three quality control laboratories. WHO PQ performance indicators are closely related to member requests and are established based on specific requirements and indicators that vary through time and members. However, WHO PQ is currently working to harmonise performance indicators with the aim of finding indicators that are relevant to the whole programme. Work on performance indicators requires continuous reflections and fine-tuning and performance indicators vary in different settings. Opportunities to harmonise terminology, approaches and core indicators of performance should be identified for the future.

The mission of the Centre of Regulatory Excellence (CoRE) of Duke-NUS Medical School, Singapore is to ensure that patients in Asia have timely access to safe, effective and high-quality therapeutic products through excellent regulation. To achieve that mission, CoRE strives to strengthen regulatory leadership through customised training to advance competencies and standards for Asian regulatory professional leaders; to develop policy and systems innovation that promotes intellectual capital in regulatory sciences and policy innovation in Asia and to establish regulatory networks as regional platforms to foster closer collaboration in regulatory science and policy and best practice. **Prof John Lim**, *Executive Director, Centre of Regulatory Excellence, Duke-NUS Medical School, Singapore* outlined some of the CoRE initiative including the conduct of a landscape analysis of regulatory systems in this region and a programme of regulatory education based on

recommendations from the CoRE Curriculum Committee comprising representatives from regulators, industry and academia. CoRE also provides a neutral academic platform for sharing innovation, best practices and open dialogue amongst regulatory stakeholders including regulators, industry and academics and collaborates with global networks and promotes regulatory convergence and thought leadership, widening the scope of available regulatory resources and expertise.

Using improvement in timelines as a measurement of regulatory performance, the Agência Nacional de Vigilância Sanitária (Anvisa), Brazil, recently assessed the results of the June 2015 reorganisation of all of the functions for the review of new drug assessments into a single office. **Ricardo Borges**, *Manager of the General Office of Drugs, ANVISA* reported that by December 2015, the queue time for applications has been reduced from 14 to 3 months and overall approval time to 506 days. New ANVISA assessment strategies also included mandatory meetings after the first request for sponsor information. An analysis of these meetings revealed that sponsors were often challenged to adapt international dossiers to Brazilian regulations because of a lack of understanding of mandatory items and ANVISA now conducts pre-submission meetings to provide advice regarding necessary dossier revisions. It is expected that approval time in 2016 will be further reduced to approximately 380 days, including a 90-day queue time, 160 days for ANVISA evaluation and 130 days for sponsor responses.

Typically, approximately 18 months before the initial submission for a product, the regulatory team at AbbVie will develop a list of possible jurisdictions where a new product might be submitted and the compound team will create submission timelines for those jurisdictions and calculate the regulatory probability of success (RPOs) for each submission. **Dr Alec Tiong**, *Head, Regulatory Affairs, Japan & Asia-Pacific, AbbVie, Singapore* said that regulatory metrics used by regions and affiliates in planning and submissions include the use of active regulatory strategy input into the global regulatory strategic and tactical plan including those strategies for the product portfolios that support the delivery of business objectives and that reflect regulatory requirements that been negotiated with regulatory agencies where applicable. A rolling update is needed for developmental plans and the metrics for the success of those plans, based

on a quickly changing regulatory environment and metrics should reflect the different conditions at global and local affiliate levels.

**Dr Neil McAuslane**, *Director, Centre for Innovation in Regulatory Science (CIRS)* reported on the results of a survey conducted among ten pharmaceutical companies and seven regulatory agencies to identify current decision-making practices for companies' decision to submit and agencies' decision to approve a new drug application and to identify how they are measuring the quality of the decision-making process and the challenges and solutions. Questions sought to identify the decision-making systems in place at agencies and companies and the framework that forms the basis of the decision-making process as well as the hurdles and biases that stood in the way of quality of decision making and how the decision making was assessed. Key results indicated that 41% of companies and 80% of agencies had a formally codified decision-making framework. Only 41% of companies and 20% of agencies undertake formal assessments of decision-making quality but 100% of companies and 88% of agencies believe that there are ways of doing this and 100% of companies and 90% of agencies believe their decision making could be improved. The majority of company and agency participants identified instances of decision-making biases within their organisation and identified hurdles to quality decision making including excessive optimism, poor assessment of uncertainty or strength of evidence and internal misalignment, previous experience biases, data availability and time pressure, lack of knowledge with regard to decision-making concepts, reluctance to discuss uncertainties or value judgements, ensuring consistent review or evaluation practices, data availability and resource constraints.

Speaking on the key factors that delay a medicine's submission and consequent access to patients, **Thuy Dang**, *Head of Regulatory Affairs Asia-Pacific/Japan Consumer Health, Bayer (South East Asia) Pte. Ltd* listed clinical trial requirements, a submission lag driven by company roll-out strategy, regulatory requirements, lack of regulatory convergence, regulatory governance issues enabling regulatory excellence and the inclusion of pricing as part of the regulatory approval process. The submission lag and delayed access could be reduced, however, by a convergence in issues such as the requirements for a certificate of pharmaceutical product, country-specific requirements related to clinical

data, chemistry, manufacturing and controls and labelling, by consistent interpretation of the guidelines by regulatory agency staff and by access to regulatory agency consultation during development and prior to submission. Most importantly, in order to reduce submission lag and ensure early patient access to medicines, industry and regulatory agency collaboration is needed to drive overall regulatory convergence.

The National Information Center on Health Services Research and Health Care Technology (NICHSR) has stated that "the impact of HTA is variable and inconsistently understood. . . even when the reporting of HTA findings is followed by changes in policies, use of a technology, or other potential indicators of impact, it may be difficult to demonstrate the causal effect of the HTA on those changes." **Dr Sorapop Kiatpongsan**, *Lecturer, Faculty of Medicine, Chulalongkorn University, Thailand* stated however, that although the impact of HTA can be difficult to measure because other factors come into play such as human resource development, economic growth and contributions. The results of HTA may be easier to evaluate when considered relative to its impact on certain issues such as regulatory policy, third party payment policy, the rate of use of a technology, clinical practice guidelines, clinician and patient awareness and behaviour, the acquisition, adoption, or diffusion of a technology and the organisation or delivery of care. Moreover, that impact can be enhanced by the use of certain strategies such as the conduct of a transparent, credible, unbiased, rigorous and well-documented HTA process, the gaining of prior commitment, where feasible, from decision makers to use HTA findings, ensuring that assessments are designed to address decision makers' questions and involving key stakeholders throughout the HTA process in a transparent, well-managed manner.

One tool for regulatory prioritisation used by the European Medicines Agency (EMA) is the accelerated assessment of products of major interest from the point of view of public health and in particular, from the viewpoint of therapeutic innovation. **Prof Hans-Georg Eichler**, *Senior Medical Officer, European Medicines Agency* explained that the maximum active regulatory time for this type of review is 150 days. However, in addition to accelerated assessment some innovative products require different, flexible pathways for regulatory assessment that can accommodate non-standard evidence development. According to

EU Regulation number 507, flexible licensing pathways for the regulation of these therapies should be used where “the benefit to public health of the immediate availability on the market ... outweighs the risk inherent in the fact that additional data are still required.” In addition, the EMA has engaged in approximately sixty procedures for early dialogue among drug developers, regulators and health technology assessment bodies, explored synergies in post-launch evidence generation between regulators and payers and initiated conceptual work in the public-private partnership project for integrated facilitated pathways, “Medicines Adaptive Pathways to Patients”.

**Dr Neil McAuslane** presented *Characteristics of emerging agency facilitated regulatory pathways* on behalf of **Lawrence Liberti**, *Executive Director, Centre for Innovation in Regulatory Science*. Examples of FRPs used in mature markets are Accelerated Assessment and Conditional Marketing Authorisation in Europe; Accelerated Approval, Breakthrough Therapy, Fast Track, Priority review in the United States and Notice of Compliance with Conditions at Health Canada. The goal of the use of these pathways is to speed the progressive development, authorisation and access to important new drugs with a positive benefit-risk balance. The importance of FRPs has also increased for emerging national regulatory authorities. Mr Liberti and associates have completed a descriptive study to assess characteristics and common elements of currently implemented FRPs in emerging national regulatory authorities in 29 countries around the world. Results showed a diversity in FRP characteristics that suggests a role for

further engagement with emerging national regulatory authorities regarding their design and implementation. Common processes could help regulatory alignment initiatives and the WHO inform the development of novel, globally aligned accelerated development and regulatory pathways for products that fulfil serious unmet public health challenges.

**Dr Murray Lumpkin**, *Deputy Director – Integrated Development and Lead for Global Regulatory Systems Initiatives, Bill and Melinda Gates Foundation, USA* discussed efforts by the World Health Organisation, the Gates Foundation, national regulatory authorities and other groups to harmonise and expedite the regulation of medicines and vaccines in low- and very-low income countries. The World Health Organization has begun to conduct abbreviated prequalification (PQ) assessment for products approved by stringent regulatory authorities. In two years, WHO has reduced PQ timing from 2.4 months to 0.5 months for products that had been approved by a stringent regulatory authority and from 10 months to 6.9 months for products that had not been approved by a stringent regulatory authority. Meanwhile, the African Medicines Regulatory Harmonisation initiative proposes to harmonise and streamline the registration process for regulators and manufacturers and creates a platform on which to build African regulatory capacity by region, leading to increased and timely access to quality products. Recent pilots of harmonised technical guidelines and requirements resulted in 40% to 60% reduction in timelines and the elimination of the spread in time of manufacturer submissions to national regulatory authorities.

## **Recommendations from across the Roundtable Discussions**

### **What are the critical key performance indicators (KPIs) that inform an agency's effective and efficient performance?**

- Agencies should measure timeliness for submissions, approvals, variations, advice, inspections and renewals; absolute timing, variability in timing and time to the first questions and the number of first-cycle approvals
- Agencies should evaluate visibility of review progression, the availability of agency personnel for consultation at key times during the development and registration processes; regular and timely public communication and provision of information via vehicles such as agency website and follow-up of industry post-approval commitments
- Agencies should assess the consistency of approved labelling with that of other jurisdictions as measured by the percentage of agreement or deviation
- Agencies and companies should provide each other with regular performance feedback regarding efficiency and quality through questionnaires or surveys
- CIRS should consider the development of an initiative to incentivise agencies and other stakeholders toward convergence or harmonisation

### **What are the key measures of quality decision making that an agency can adopt that can improve its planning and review?**

- Increase organisational awareness of the importance, benefits and impact of decision making
- Using case studies, provide organisational decision-making training
- Enlist top management in the measurement and continuous improvement of processes
- Provide transparent rationales for decisions
- Ask external stakeholders for feedback regarding decision making and carry out internal audits of decision processes

**Building a performance driven culture: How can this be defined and achieved and where do agencies start?**

- To develop standard key performance indicators for a region, CIRS should follow up it's benchmark questionnaire with more in-depth feedback, comparison and discussion with agency leadership
- Both regulators and industry have clear roles to play in the development of safe efficacious medicines and should strive for a partnership rather than an adversarial relationship
- Agencies should establish risk-based reviews with clear guidance for industry, clear agency or ministry of health governance, delegation of responsibility, established roles and expectations and peer review of recommendations by assessors
- Agencies should maintain motivation through reliance on consistent messaging of goals and expectations and acknowledgment of their achievement and establish internally and externally facing performance metrics, expectations and training, matching resources with expectations

**Company agency interactions: What are the quantitative and qualitative measures that an agency and company can use to maximise outcomes?**

- Smaller agencies should align platforms regionally to share expertise and facilitate the coordination of reviews
- Agencies should have a written process in place to ensure common interpretation across reviewers during scientific advice sessions and assessment
- Agencies should establish a standard process and key performance indicators for agency-industry interaction, including one point of entry, a procedure for escalation and documentation

**Regional alignment initiative- what should be measured and can metrics enable the process?**

- Conduct systematic research on progress and achievements of alignment/ collaborative initiatives
- Provide a discussion platform for industry and regulators to evaluate the progress of the alignment initiatives; determine what has been achieved; identify existing training opportunities or develop a training initiative for alignment or convergence initiatives

## Workshop Programme

<b>DAY 1: 3 FEBRUARY 2016</b>	
<b>SESSION 1: MEASURING PERFORMANCE IS AN ESSENTIAL COMPONENT OF GOOD REGULATORY PRACTICES AND DECISION MAKING</b>	
<b>Chair's welcome and introduction</b>	<b>Dr Murray Lumpkin</b> , Deputy Director – Integrated Development and Lead for Global Regulatory Systems Initiatives, Bill and Melinda Gates Foundation, USA
<b>Country welcome and introduction</b>	<b>Dató Eisah A. Rahman</b> , Senior Director of Pharmaceutical Services, Ministry of Health, Malaysia
<b>Current reform of the medicines regulatory system: Perspective from China</b>	<b>Director General YUAN Lin</b> , Director General, Department of International Cooperation, China Food and Drug Administration (CFDA)
<b>Measuring regulatory agencies performance: Why this is critical for strong governance and evolution of regulatory capacity</b>	<b>Dr Tomas Salmonson</b> , Chair, CHMP, European Medicines Agency
<b>What are the core qualitative and quantitative performance metrics agencies should consider and why? Health Canada perspective</b>	<b>Barbara Sabourin</b> , Director General, Therapeutic Products Directorate, Health Canada
<b>Stakeholder perspectives: Why agencies need to establish performance indicators, both qualitatively and quantitatively and how this can help medicines providers/users</b>	
<b>Pharmaceutical company perspective</b>	<b>Dr Paul Huckle</b> , Chief Regulatory Officer and Senior Vice President, GlaxoSmithKline, USA
<b>Patient perspective</b>	<b>Dr Durhane Wong-Rieger</b> , President and CEO, Canadian Organization for Rare Disorders
<b>Planning, improving, reporting – What qualitative and/or quantitative performance indicators are agencies incorporating into their practices and processes?</b>	
<b>Singapore</b>	<b>Dr Yee Hoo Looi</b> , Acting Deputy Director – Therapeutic Products Branch, Health Sciences Authority
<b>Indonesia</b>	<b>Dra Nurma Hidayati</b> , Director of Drug and Biological Products Evaluation, National Agency of Drug and Food Control (NADFC)
<b>Philippines</b>	<b>Pia Angelique D. Priagola</b> , Food Drug Regulation Officer III, Food and Drug Administration
<b>Malaysia</b>	<b>Azura Abdullah</b> , Senior Principal Assistant Director, National Pharmaceutical Control Bureau
<b>Taiwan</b>	<b>Dr Churn-Shiouh Gau</b> , Chief Executive Director, Center for Drug Evaluation

<b>SESSION 2: MEASURING PERFORMANCE – HOW CAN THIS IMPROVE PERFORMANCE FOR AGENCIES AND COMPANIES?</b>	
<b>Chair’s introduction</b>	<b>Barbara Sabourin</b> , <i>Director General, Therapeutic Products Directorate, Health Canada</i>
<b>Internal processes and practices to measure KPIs – How have these evolved in a mature agency and what recommendations should be made to agencies considering implementation of KPIs?</b>	<b>Dr John Skerritt</b> , <i>Deputy Secretary for Regulatory Services, Department of Health, Australia</i>
<b>Use of performance metrics and training to improve practices and process – what can be measured and what are the critical success factors?</b>	
<b>Measuring companies and regulators: Benchmarking through key performance indicators</b>	<b>Prisha Patel, Manager</b> , <i>Global Development Programme, CIRS</i>
<b>WHO PQ performance indicators, what they are, how do they measure them, are they reported and how do they use them to improve performance?</b>	<b>Dr Lembit Rägo</b> , <i>Head, Regulation of Medicines and other Health Technologies, WHO, Switzerland</i>
<b>Improving practices and process through mapping and training – How can this best be achieved?</b>	<b>Prof John Lim</b> , <i>Deputy Director of Medical Services and Executive Director, Centre of Regulatory Excellence, Singapore</i>
<b>Company factors that affect agency performance – how can these be best be measured and managed by agencies? Perspective from Brazil</b>	<b>Ricardo Borges</b> , <i>Manager of the General Office of Drugs, ANVISA</i>
<b>What internal regulatory metrics do companies measure themselves by /use that enable their planning, submission and understanding in getting a medicine to market globally? A company perspective</b>	<b>Dr Alec Tiong</b> , <i>Head, Regulatory Affairs, Japan &amp; Asia-Pacific, AbbVie, Singapore</i>
<b>Building quality into the decision-making process: What are the main factors that need to be considered?</b>	<b>Dr Neil McAuslane</b> , <i>Director, CIRS</i>

## DAY 2: 4 FEBRUARY 2016

## SESSION 3: ROUNDTABLE DISCUSSIONS

## Roundtable A: What are the critical KPIs that inform an agency's effective and efficient performance?

<b>Chair</b>	Prof Hans-Georg Eichler, <i>Senior Medical Officer, EMA</i>
<b>Rapporteur</b>	Dr Felipe Dolz, <i>Vice President, Global Regulatory Policy and Intelligence, Sanofi, USA</i>

## Roundtable B: What are the key measures of quality decision making that an agency can adopt that can improve its planning and review?

<b>Chair</b>	Dr Tomas Salmonson, <b>Chair</b> , <i>CHMP, European Medicines Agency</i>
<b>Rapporteur</b>	Magda Bujar, <i>Research Analyst, CIRS</i>

## Roundtable C: Building a performance-driven culture: How can this be defined achieved and where do agencies start?

<b>Chair</b>	Barbara Sabourin, <i>Director General, Therapeutic Products Directorate, Health Canada</i>
<b>Rapporteur</b>	Fraser Stodart, <i>Senior Director, Global Emerging Markets (GEMS) – Regulatory Affairs, Biogen, UK</i>

## Roundtable D: Company agency interactions: What are the quantitative and qualitative measures that an agency and company can use to maximise outcomes?

<b>Chair</b>	Prof Thomas Kühler, <i>Senior Director, Novo Nordisk A/S, Denmark</i>
<b>Rapporteur</b>	Dr David King, <i>Director, Regulatory Policy and Intelligence, Shire, UK</i>

## Roundtable E: Regional alignment initiatives– what should be measured and can metrics enable the process?

<b>Chair</b>	Dr John Skerritt, <i>Deputy Secretary for Regulatory Services, Department of Health, Australia</i>
<b>Rapporteur</b>	Sjaak Bot, <i>Vice-President, Head of EMEA Regulatory Affairs, Janssen, The Netherlands</i>

<b>Chair's introduction</b>	Prof Sir Alastair Breckenridge
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## SESSION 4: ENSURING AVAILABILITY OF MEDICINES THAT ARE SAFE AND EFFECTIVE

<b>Submission lag: What are the key factors that delay a medicine's submission and how can these be mitigated?</b>	Thuy Dang, <i>Head of Regulatory Affairs, Consumer Health Asia-Pacific/Japan, Bayer (South East Asia), Singapore</i>
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<b>Evolution of HTA agencies across Asia – Changing the access landscape – how could the impact be measured?</b>	Dr Sorapop Kiatpongsan, <i>Lecturer, Faculty of Medicine, Chulalongkorn University, Thailand</i>
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## Improving availability and meeting unmet medical need: What are the facilitated regulatory pathways that can be considered and what measures should be put in place?

<b>Mature agency perspective</b>	Prof Hans-Georg Eichler, <i>Senior Medical Officer, European Medicines Agency</i>
<b>Characteristics of emerging agency pathways: What are the key processes and substantive building blocks</b>	Dr Neil McAuslane, <i>Director, Centre for Innovation in Regulatory Science</i>
<b>Bill and Melinda Gates Foundation perspective</b>	Dr Murray Lumpkin, <i>Deputy Director – Integrated Development and Lead for Global Regulatory Systems Initiatives, Bill and Melinda Gates Foundation, USA</i>

## Section 2: Presentations

### Current reform of the medicines regulatory system: Perspective from China

**YUAN Lin**

*Director General, Department of International Cooperation, China Food and Drug Administration (CFDA)*

In 2014, pharmaceutical sales for the 1.4 billion people in China totalled Y2.5 trillion RMB and the total export volume reached \$55 billion USD, aided by more than 5,000 manufacturers and 466,000 distributors. Along with the rapid development of the Chinese pharmaceutical industry, which is now the second largest in the world, the Chinese regulatory system must also be continuously enhanced and must respond to several challenges in order to support timely public access for high-quality drugs and medical devices. These challenges include a heavy backlog of drug registration applications, a relatively lengthy review and approval process and a quality gap between domestic generic drugs in comparison with international manufacturing labels.

In August 2015, the Chinese State Council issued an opinion on reforming the review and approval system for drugs and medical

**... in 2015, 9,394 drugs were reviewed by the CFDA, which was 90% higher than the number in 2014. . .**

devices. The goals of this reform are to improve the quality of the review and approval process, address the application backlog, advance the quality of generic drugs, encourage new drug research and development and promote transparency regarding review and approval (Figure 1). In order to achieve these goals, the Standing Committee of the People's National Congress authorised the State Council to implement multiple reform measures including those that will

- promote the consistent evaluation of the quality and efficacy of new medicines,
- raise the market threshold for generic drugs,
- encourage research and development teams to increase their capacity,
- strengthen the audit of clinical trial data for completeness and authenticity,
- supplement and integrate the workforce of the Center for Drug Evaluation and issue policies to solve the backlog and accelerate the review process and
- build CFDA inspection capabilities (Figure 2).

The initial results of these reform included efforts to clarify the requirements, research methods and timetable for reference preparations for generic medicines and to optimise the review and approval procedure for these drugs, including the establishment of an electronic platform for submission and review.

In addition, the CFDA has drafted opinions on the implementation of prioritised approval mechanisms to accelerate the development and launch of new drugs with clinical value and generic drugs for urgent clinical need, including those for paediatric and geriatric populations and is acting to optimise the review and approval of new trial applications. Indeed, in 2015, 9,394 drugs were reviewed by the CFDA, which was 90% higher than the number in 2014, despite the fact that reforms had only been in progress for six months.

In order to stimulate innovative research, the

Figure 1. Goals of the reform of the China Food and Drug Authority review and approval system for drugs and medical devices.





Figure 2. Reform measures instituted by the China Food and Drug Authority.

new Marketing Authorization Holder (MAH) system is also being piloted in 10 provinces and municipalities as of November 2015. This system permits domestic research and development institutions and research personnel of Chinese nationality to apply for and obtain regulatory approval; whereas previously, only

pharmaceutical manufacturers could submit marketing authorisation applications for new medicines in China.

During the reform process, the CFDA has also paid great attention to the experience of its international peers for drug regulation and have established direct partnerships with the regulatory agencies of 60 countries and 41 international organisations and have become an active member of the International Coalition of Medicines Regulatory Authorities and the International Medical Device Regulators Forum. At the ninth International Summit of the Heads of Drug Regulatory Agencies in 2013 in Beijing, the CFDA cited cooperation, balanced development and common safety as key to strengthen international exchange and collaboration.

The CFDA looks forward to joining with international regulatory agencies to meet the challenges of pharmaceutical development and regulation and to build a global drug co-governance system with quality and innovation as its core values.

## Measuring regulatory agencies performance:

### Why this is critical for strong governance and evolution of regulatory capacity

**Dr Tomas Salmonson**

*Chair, CHMP, European Medicines Agency*

#### The elements of EU regulatory systems

From a public health perspective, European pharmaceutical regulators could be considered the gatekeepers and enablers of a system to ensure that only needed high-quality medicines with positive benefit-risk profiles reach the market. The work of these regulators must include high-quality assessment reports that are scientifically correct and transparent regarding the rationale for decision making. Whilst pharmacovigilance is important to regulation,

a life cycle approach in which regulators support early drug development, identifying key indications and patient populations is ideal. Regulators must also interact with “down-stream” stakeholders such as health technology assessors, payers, healthcare providers and registry holders and especially with patients, who as the user of medicines, represent the ultimate stakeholder.

Through their policies and processes, regulators must act to stimulate the innovation that results in access to important drugs while recognising the importance of global collaboration in today's environment in which patients do not recognise international borders in their pursuit of the best healthcare options.

Important factors for regulation include competence; that is, the expertise derived from training and experience to perform regulatory tasks. The development of and compliance with standard operating procedures, templates and benefit-risk structure are also needed to transparently communicate the methodologies used for decision making. Scientific advice to

the sponsors of medicines, coordinated when possible with advice from health technology agencies helps to ensure more efficient and timely development. Because of the centralised regulatory procedure of European Medicines Agency, compliance with timetables is also vital, in order to allow all agencies sufficient time to perform their own evaluation. Finally, the EMA system, in which all participating agencies are strengthened through work sharing and the contribution of individual competencies, stands as a model for the necessary regulatory efficiency in international collaboration.

### Measuring EU regulation

The Heads of Medicine Agencies (HMA) initiated the Benchmarking of European Medicines Agencies (BEMA) programme in 2004 to “contribute to the development of a world-class medicines regulatory system based on a network of agencies operating to best practice standards.” (<http://www.hma.eu/bema.html>). Through BEMA, HMA assesses the management systems, marketing authorisation applications, pharmacovigilance activities and inspections services of individual regulatory agencies. Rather than being a tool to compare or rank agencies or to pinpoint issues of noncompliance, these assessments identify agencies’ strengths and best practices as well as opportunities for improvement to enable an improved operation of the network of agencies. BEMA evaluation against performance indicators includes both self- and peer-review assessments in which each agency is visited by teams of specially trained assessors and results in an anonymised report stored in a central database. Three cycles of the BEMA programme have taken place, with the second and third cycle incorporating amendments based on experience based on previous cycles.

**The identification of relevant metrics for regulation is key for improvement as they facilitate healthy competition and enable regulators to see what they do well and what others may do better.**

### Selection of rapporteurs

The EMA centralised review system benefits from the friendly competition that is inherent in the independent assessments of two CHMP and two PRAC rapporteurs and the link between CHMP and PRAC ensures a life-cycle approach to regulation. The selection of the “best available rapporteur team” is based on criteria such as the regulatory agency’s previous involvement in the provision of scientific advice, development of guidelines, overall competence and the agency’s previous performance with issues such as compliance with time tables and benefit-risk templates. However, as it is also important for all national regulatory agencies to gain review expertise, an experienced rapporteur may be paired with a less practiced rapporteur for specific reviews and all jurisdictions have the opportunity for participation.

### Conclusions

Whilst the specific roles of national regulatory agencies may vary, all are part of global regulation and quality of process, decision making and documentation are universally essential. The identification of relevant metrics for regulation is key for improvement as they facilitate healthy competition and enable regulators to see what they do well and what others may do better.

## What are the core qualitative and quantitative performance metrics agencies should consider and why? Health Canada perspective

**Barbara Sabourin**

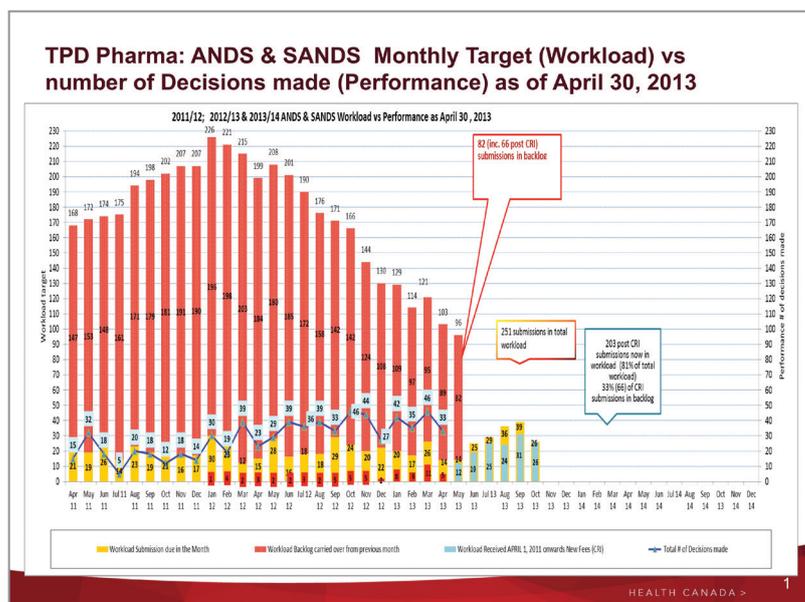
*Director General, Therapeutic Products Directorate, Health Canada*

Health Canada measures the economic contribution of the life science Industries, which entails 830 firms employing 82,500 people, creating \$35.5 billion Canadian dollars to provide regulatory context and to understand their importance to the economy and to market access.

Health Canada uses performance metrics for three primary reasons:

1. to achieve a predictable review process by knowing how well operations are managed and to help predict the outcome of process changes, to allow comparisons between different individuals, units and business lines;
2. to demonstrate that they are open and transparent about their mandate and operations as a regulatory authority to help know and manage stakeholder expectations, to be able to respond to questions and commentary about how they do their work, compared with other regulatory authorities;

Figure 3. Health Canada achieved significant progress in reducing the backlog in the review of submissions for generic medicines.



and

3. to deliver on their commitments to improve performance and modernise regulatory activities, including cost recovery.

Health Canada submission review performance is measured against targets and against other agencies to mark progress toward cost recovery review targets and to determine where change is most needed. This is not only to develop solid qualitative and quantitative performance metrics but to provide a platform for a discussion of opportunities to improve what is being measured and to analyse what fundamentals are behind performance. It is essential to build a culture of performance measurement in the organisation and to build confidence in the organisation.

In 2012-2013, Health Canada experienced a large backlog in generic drug submission reviews because of the large number of drugs losing their patent protection in the preceding time period. The agency was able to calculate a target workload that would reduce that backlog and to subsequently measure performance against that target. Accurate forecasting was essential in order for Health Canada to avoid future budgetary penalties that would be assessed for not meeting review timing targets and great progress was made (Figure 3).

Measuring the number of approved products in Canada shows the breadth of agency work. In Health Canada, approximately 13,000 medical devices, 5,300 pharmaceutical, 3,000 clinical trial decisions are made each year in addition to roughly 1,600 pharmaceutical and 5,700 medical device Special Access programme decisions.

The agency measures the overall time to market for therapeutic products in order to understand how to improve market access for Canadians. One study showed that it takes a median of 12 years including clinical trial time to develop a drug in Canada. Regulatory review takes approximately 300 days plus 55 days processing and screening time for innovative products and 180 days plus 55 days processing and screening time for generics. The Patented Medicine Prices Review Board drug price ceiling decision occurs within 6 months and the Canadian Agency for Drugs and Technology in Health Common Drug Review and Health Technology Assessment for healthcare decision makers takes 6 to 8 months. A decision by a provincial or territorial drug formulary on whether to fund the drug is made within 8 to 12 months and the drug sponsor's

**It is essential to build a culture of performance measurement in the organisation and to build confidence in the organisation.**

decision as to when to market the drug after Health Canada ranges from 0 days to over 1 year.

Health Canada conducts a quantitative review of agency performance to demonstrate that they are delivering on their commitments to improve performance and modernise regulatory activities. Every day counts during submission reviews and basic metrics include workload; volumes received; review decision times and number of decisions. Also assessed are data on review times by company, by industry association members and non-members and by drug therapeutic class, drug pipeline data and data on the median unit cost to review drugs in a fee line. Early warning indicators that review performance might be headed in the wrong direction are analysed including a sudden increase in submission volumes above a threshold for each line, the percentage of reviews above a threshold that are completed within one week of target, or go over target, an increase in review backlog above a specific threshold for each line and the number in backlog, proportion in backlog and age of backlog. Special focus is given to any fee line that receives fewer than 10 submissions per year.

Quality management principles such as those of the World Health Organization, address both an organisation's tools and the abilities of the people using them. The regulation of pharmaceuticals in Canada by the Therapeutic Products Directorate was audited in 2011 by the Office of the Auditor General of Canada, which reported that the agency had standard operating procedures, guidelines for drug reviewers, review templates, training programmes and management review of individual files but did not assess whether review procedures, guidelines and templates were consistently interpreted and applied. The Auditor General reported that "Health Canada should regularly assess whether the procedures and guidelines, which were established to ensure timely, consistent and high-quality review decisions, are interpreted and applied consistently".

Health Canada also suggests additional qualitative metrics, including tracking and reporting the top 20 submission quality issues in drug submissions to industry associations on a regular basis. The Therapeutics Product Directorate has conducted workshops with the Canadian generics industry and a national pharmaceutical sciences group on how to improve submission quality. At their

pipeline meetings with companies, Health Canada delivers the results of an internal survey tool that identifies different quality measures for submissions as well as on interactions with the regulator and formally reports these to company senior executives.

The agency also has metrics in ongoing development to gain a different perspective and to allocate resources more strategically, including those that will analyse the resources expended to for "non-review" tasks such as preparing communications items and briefing material on emerging issues related to pre-market drug submissions and post-market surveillance, compliance and enforcement and work on litigation and data integrity issues. In addition, the workload per employee, per division and per bureau will be calculated to aid in workload planning. Median review times for each submission line will be tracked by company and compared against the overall industry median time. The complexity of incoming submissions may be ranked to allocate workload more strategically.

Another way of measuring the work done by a regulatory agency is to perform a case study on the life cycle of a class of drugs. This will increase the understanding of work activities undertaken and show how activities become incremental during the life cycle of class of drugs. It will show that the approval of a drug is not the end game but the beginning of many activities which can carry on for many years. For example, the first statin, lovastatin was approved in 1988. Since then, the total number of clinical trials for statins including bioequivalence studies done by generic companies was 953. The total number of regulatory submissions was 1,801 and 654 drug identification numbers have been issued to 135 companies.

### Conclusion

Many of Canada's performance metrics - qualitative and quantitative - are common to other regulators. Each regulatory authority works to provide a credible performance story to internal and external stakeholders, at times with metrics unique to their situation. Data on internationally comparable review performance provided by neutral and respected parties such as CIRS enable national regulatory authorities to benchmark progress against other regulators where resourcing levels are similar and different. Data collection for performance metrics will be somewhat dependent on having clear programme objectives, the selection of relevant metrics and the technology and it will be driven by a performance measurement culture.

## Why agencies need to establish qualitative and quantitative performance indicators and how this can help medicines providers and users

### An industry perspective

#### Dr Paul Huckle

Chief Regulatory Officer and Senior Vice President, GlaxoSmithKline, USA

Regulatory agency performance measures drive development of efficient and predictable review processes that enable accurate forward planning, promote high-quality content and structured applications and more efficient reviews, identify best practices and areas for enhancement, facilitate the adoption of innovative approaches to drug development and regulatory science and accelerate the delivery of new medicines to patients and healthcare providers. Moreover, performance measures are beneficial across the product lifecycle.

#### Pre-approval

In the pre-approval phase, performance measures help industry to plan and manage the complexities of global clinical development including clinical trial applications, clinical protocol development and amendments,

**Coordinating varying timetables . . . adds an additional level of complexity to global product development and makes the evaluation of the predictability of those timetables essential**

investigator recruitment, training and meetings, ethics committee reviews, investigational drug supplies, patient recruitment and regulatory agency interactions. The timing for regulatory participation in this complex series of event has a clear impact on the overall efficiency of product development. Coordinating varying timetables for clinical trial approvals among jurisdictions participating in an international clinical trial, for example, adds an additional level of complexity to global product development and makes the evaluation of the predictability of those timetables essential (Figure 4).

#### Review and approval

During the review and approval of marketing applications, performance measures help industry plan and manage activities for new product launches across multiple markets including manufacturing, packaging, stability testing and global distribution networks, product labelling development and translations, pre-approval manufacturing and clinical site inspections, communications to healthcare providers and payers and advertising and promotion. Again, because of the variability in regulatory timing for review processes, predictability is key to optimise industry planning. This consistency can be encouraged through internal regulatory performance measurement such as the US FDA measurement of its timing for standard versus priority reviews against reauthorisation performance goals specified in the fifth iteration of the Prescription Drug User Fee Act (PDUFA V).

Regulatory agency performance is ideally assessed by independent third parties such the Eastern Research Group, which was contracted to conduct an independent assessment of the FDA New Molecular Entity Review programme. Using both quantitative and qualitative measures of performance, the organisation collected information and data from the FDA and industry representatives to identify benefits, best practices and areas for enhancement. To encourage high-quality submissions and first-review-cycle approvals, Eastern Research

Figure 4. Varying timelines for clinical trial approval among countries participating clinical trials.

### Predictability is Important, Heterogeneous CTA Timelines Add Complexity

Country	Regulatory Authority (RA) review time	Ethics Committee (EC) review time	RA/EC review relationship	Total Approval Time
USA	30 Days	n/a *	In parallel	From 30 days
Singapore	98 days	90 days	In parallel	98 days
Australia	50 days	50 days	In parallel	50 days
South Korea	30 days	30 days	In parallel	30 days
India	90 days	90 days	In parallel	90 days
Russia	35 days	1-6 weeks	EC approval first	77+ days
Canada	30 days	120 days	In parallel	120 days
Turkey	30 days	15 days	In parallel	30 days
Mexico	90 days	45 days	EC approval first	135 days
Brazil	90 days	90 days	EC approval first	120 days
China	265 days	60 days	RA approval	325 days

### Best Practice: First Cycle Approvals

*FDA NME program measures are intended to encourage high quality submissions and first review cycle approvals.*

Table ES-1. Applications in the baseline and Program cohorts for this study, through first two years of PDUFA V\*

Applications		Baseline (FYs 2008-2012)	Program (FYs 2013-2014)
Filed and acted upon	NME NDA	147	42
	Original BLA	72	22
	Total	219	64
First-cycle actions	Approval (AP)	120	46
	Complete Response (CR)	92	14
	Withdrawal after Filing (WD)	7	4
	Total	219	64
Percent of filed applications approved in first-cycle		54.8%	71.9%

\* NME NDAs and original BLAs received during FYs 2008-2012 and acted on by September 30, 2014 (baseline) or received and acted on during FYs 2013-2014 (Program).

From Eastern Research Group interim report March 27, 2015.

Figure 5. Internal benchmarking of first-cycle approvals at the FDA gauged the effectiveness of the New Molecular Entity programme.

measured the number of first-cycle approvals after two years of the PDUFA V New Molecular Entity programme compared with a baseline number in a previous cycle (Figure 5).

#### Post-approval

A significant amount of industry resources is dedicated to post-approval work. Regulatory performance measures in this timeframe can help industry to maintain and develop

Figure 6. Variable jurisdictional timing for the approval of safety updates for five products, 2013-2014.

### Sample of Agency Review and Approval Timelines for Label Submissions

Time between submission and approval of safety-related label update for a limited sample of 5 changes

Region	Average (days)	Shortest (days)	Longest (days)	Number of submissions
All regions (worldwide)	129	0	1393	274
European Union	197	18	349	28
N America	125	90	180	8
Asia Pacific	54	42	61	50
Latina + Mexico	93	0	550	74
Gulf	166	75	290	10
Rest of World (mostly Africa)	108	0	1393	59

Based on updates to Company Core Datasheet for 5 products in 2013-2014. Total number of submissions = 274

products after marketing authorisation including new indications and product formulations, labelling updates such as those for safety, drug interactions or special populations, manufacturing and packaging changes, license renewals, post-approval commitments and paediatric developments. As in the pre-marketing phase, predictability and consistency in individual markets are key to implementation of post-approval change. Optimal processes would facilitate greater regulatory compliance, timely implementation of changes and more efficient management of the supply chain and manufacturing processes including reduced risk of out of stock drugs, ultimately resulting in more timely availability of updated medicines for patient needs.

Planning and execution of post-approval labelling submissions in multiple markets is complex and involves multiple challenges such as the availability of certificates of pharmaceutical product or evidence of approval in a reference market, parallel or sequential variations and version control, the need to ensure continuity of supply and to minimise write-off of stocks with the old label. In addition, it is challenging to maintain consistency in labelling worldwide as safety updates reach healthcare professionals and patients at different times in different countries. For example, updates to five products in 2013-2014 necessitated 274 submissions worldwide. Timing for approval of those changes varied between 0 and 1,393 days (Figure 6). The increased visibility, consistency and predictability of review and approval times for labelling submissions facilitates better planning and execution of safety labelling updates, faster delivery of up-to-date labels to healthcare professionals and patients, improved consistency of labelling worldwide and stock planning and regulatory compliance of packs shared across markets.

## Usefulness of agencies' quantitative and qualitative performance indicators: Patient perspectives

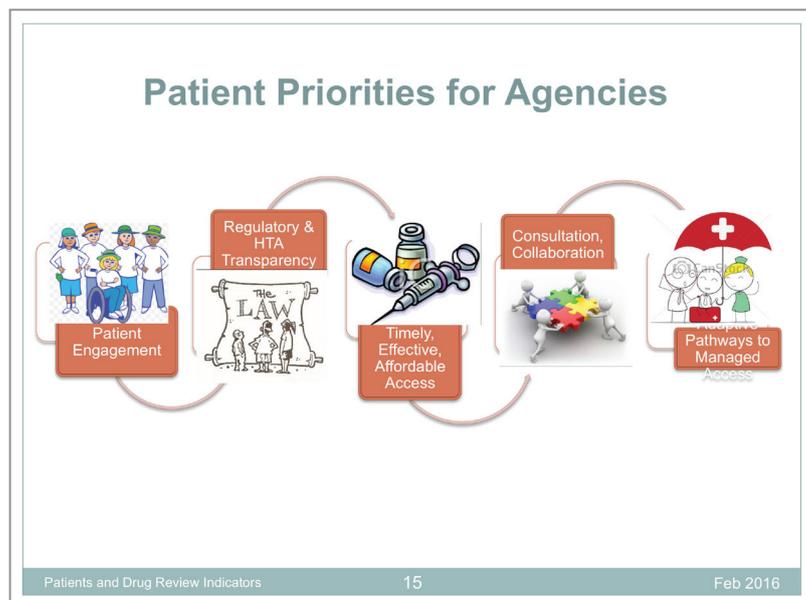
**Dr Durhane Wong-Rieger**

*President, Canadian Organization for Rare Disorders*

Despite a great movement toward transparency in recent years, regulators are not the patient's primary point of interface in their journey to obtain safe and effective medicines. Patients more typically interact with healthcare professionals, payers and other patients. However, as the primary stakeholder in the development of medicines, patients' outcomes and priorities should be considered when establishing measurements of quality for regulators (Figure 7). These priorities include timely, affordable access to individually necessary medicines and devices and participation in clinical trials. Trusted regulatory oversight is required to achieve the outcomes, especially for generics, biosimilars and locally sourced natural or homeopathic therapies. Transparency and understandability in this oversight, including rationales for decision making are achieved through clear communication processes and information.

Regulatory performance metrics should measure the ability of regulators to achieve the goal of timely, appropriate, sustainable access to safe

Figure 7. Patients' outcomes and priorities should be considered when establishing measurements of quality for regulators.



**Regulatory performance metrics should measure the ability of regulators to achieve the goal of timely, appropriate, sustainable access to safe and effective medicines**

and effective medicines from clinical trial design to post-market monitoring and reassessment. Specifically, metrics should measure achievement of

- The global availability of medicines within comparable timeframes
- The expansion of clinical trials into multiple regions to enable increased understanding of drug mechanisms in diverse populations and to increase global clinical experience and expertise
- The reduction in delays for drug submissions and approvals, potentially through collaborative reviews and shared work
- The decrease in the number of divergent decisions using the same clinical data, potentially through discussion and collaboration
- The management of access through better coordination with companies, HTA agencies and payers and the use of simultaneous and parallel rather than separate and sequential processes
- The development of opportunities for patient input and petition or appeal

Through their Citizen and Patient Involvement Group, the organisation Health Technology Assessment International (HTAi) has developed criteria for patient involvement in the general HTA process that are applicable to the general regulatory process:

- HTA organisations have strategy that outlines processes/responsibilities for those in HTA & serving on HTA committees to effectively involve patients.
- HTA organisations designate appropriate resources to ensure and support effective patient involvement in HTA.
- HTA participants (researchers, staff, HTA reviewers, committee members) receive training about appropriate involvement of patients and consideration of patients' perspectives throughout the HTA process.
- Patients and patient organizations are

given opportunity to participate in training to empower them so that they can best contribute to HTA.

- Patient involvement processes in HTA are regularly reflected on and reviewed, taking account of the experiences of all those involved, with the intent to continuously improve them.

HTAi has also developed criteria for patient involvement in individual health technology assessments that are applicable to individual regulatory submissions:

- Proactive communication strategies are used to effectively reach, inform and enable a wide range of patients to participate fully in each HTA.
- Clear timelines are established for each HTA with advance notice of deadlines to ensure that appropriate input from a wide range of patients.
- For each HTA, HTA organizations identify a staff member whose role is to support patients to contribute effectively to HTA.
- In each HTA, patients' perspectives and experiences are documented and the influence of patient contributions on conclusions and decisions is reported.
- Feedback is given to patient organizations who have contributed to an HTA, to share what contributions were most helpful and provide suggestions to assist their future involvement.

Alignment, harmonisation and mutual recognition of regulatory agencies can greatly expedite patients' access to needed medicines. Other strategies that might provide more timely availability of medicines include shared special regulatory pathways, incentives for industry to file common applications, the development of early access for compassionate use a "standard" process and the establishment of international coordination centres. Appropriate sustainable access can also be achieved through the employment of a comprehensive approach to healthcare including education, prevention, diagnosis, care and treatment; the involvement of patient advocacy groups in multiple aspects of medicine development, regulation and access and the use of a multi-disciplinary, multi-stakeholder, multi-criteria approach to medicine development.

## Planning, improving, reporting – What qualitative and/or quantitative performance indicators are agencies incorporating into their practices and processes? Singapore

**Dr Yee Hoo Looi**

*Acting Deputy Director – Therapeutic Products Branch, Health Sciences Authority*

### HSA registration process

The Health Sciences Authority (HSA) in Singapore accepts applications for new and generic drugs for pre-market approval and applications for major and minor variations to an existing product license in the post-approval timeframe. Major variations include changes in indication or dosing regimen whereas minor variations might be changes such as a package leaflet update.

#### For new drug and major variation applications

- a full dossier review of full quality, clinical and non-clinical data is conducted within 270 working days for products that have not been reviewed by any other drug regulatory agency,
- an abridged dossier review of full quality and abridged clinical data is conducted within 180 days for products that have been reviewed by one or more other drug regulatory agencies

and

- a verification dossier review of a reference agency assessment report conducted within 60 days for products that have been reviewed by two or more reference agencies.

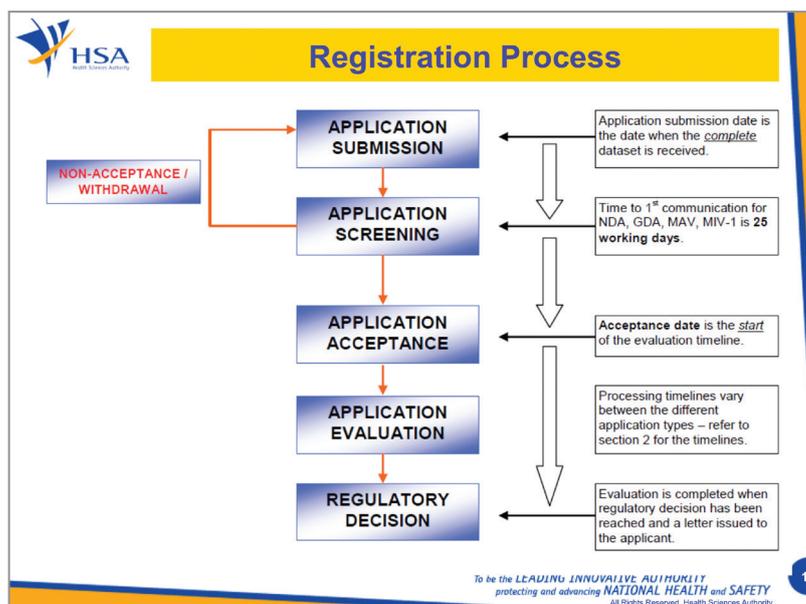
#### For generic drugs

- an abridged dossier review of full quality and bioequivalence data is conducted for products reviewed by one other regulatory agency within 240 days and
- a verification dossier review of reference agency assessment reports is conducted for products reviewed by two or more reference regulatory agencies within 120 days.

### Performance indicators

The HSA registration process consists of application submission, screening, acceptance, evaluation and regulatory decision (Figure 8). Team Leads for products are responsible to provide monthly dashboard reports of key performance indicators to senior management such as the number of applications accepted, under evaluation and completed, the outcomes of completed evaluations and the number of applications that met or exceeded timelines. These data are used to assess process efficiency, workload and resource balance and the effectiveness of HSA evaluation strategies. In addition to these quantitative measures, the listing of new drug approvals has appeared on the HAS website since 2010, permitting a qualitative assessment of HSA performance.

Figure 8. The regulatory review process at Health Sciences Authority, Singapore.



### Strategies to enhance predictability and streamline the review process

#### Screening process

To improve these observed limitations of the current system and to address the feedback provided by industry on the need for published, transparent screening timelines to facilitate planning. HSA proposes to formulate the actual screening turn-around time (TAT) based on collected data, derive a potential cap on the number of rounds of screening queries and encourage good-quality submissions. Applicants will be reminded to submit complete dossiers and to provide complete responses to queries in a timely manner in order to generate fair and representative data to reflect time required for screening of applications. Once these representative data are collected, an overall target screening TAT will be developed and a cap on the number of rounds of screening

queries will be introduced. In addition, applicants' awareness of HSA requirements will be improved with the development of clear guidelines and checklists.

#### Verification route review

To optimise the verification route for the conduct of regulatory evaluations at HSA and to increase the proportion of evaluations conducted via this method, HSA proposes to review the distribution of applications according to selected evaluation routes, examining applications for medicines that have been approved by at least one regulatory agency. HSA will assess the proportion of these applications

**Team Leads for products are responsible to provide monthly dashboard reports of key performance indicators to senior management**

for which HSA decisions differed from other regulatory agencies, allowing them to determine if their decision making is consistent with other agencies and if HSA has gained sufficient experience in the use of a confidence-based approach, to allow them to further leverage the approvals of other regulatory agencies.

## Performance measurement: Indonesia's experience

### Dra Nurma Hidayati

*Director of Drug and Biological Products Evaluation, National Agency of Drug and Food Control (NADFC)*

#### NADFC registration process

The current drug registration procedure in Indonesia was stipulated in the decree of the Ministry of Health on Drug Registration (2008) and the decree of the head of the National Agency of Drug and Food Control (NADFC) on the Criteria and Procedure to Register Drugs (2011). The latter decree instituted drug registration timelines for each evaluation path. Timelines of 100 working days for the review of new active substances (NASs) that are categorised as being life-saving or orphan drugs, or NASs for national programmes, or NASs that have been developed through clinical trials conducted in Indonesia. Timelines of 150 working days were established for NASs that have been approved by mature agencies and/or agencies that have implemented a harmonised system and timelines of 300 working days set for NASs not falling within those categories.

The two-step registration process consists of pre-registration, which has a timeline of 40 working days to determine the registration category, evaluation path and timeline and to provide a consultation on the completeness of the registration dossiers; and registration, which

consists of the submission and evaluation of dossiers according to the registration category. Clock stops are provided during agency requests for additional data or information.

#### NADFC performance metrics

Performance metrics for the drug registration process at the NADFC are the percentage of drug applications per year that receive decisions for approval, rejection or requests for additional information and the percentage of applications per year that receive final decisions within established timelines. Metrics are tracked through a conventional manual timelines measurement and tracking system using monitoring cards and Excel spread sheets that monitor timelines in working days for the whole process from submission until final decision. In addition, an electronic registration and tracking system for generic drugs has been implemented since 2014. The electronic registration and tracking system for new drugs is being developed.

Challenges to drug registration in Indonesia include the fact that the number of regulatory reviewers has remained constant despite a significant increase in the number of applications (Figure 9). In addition, there are differing perceptions between applicants and regulators regarding the measurement of process timelines and the implementation of regulations and requirements.

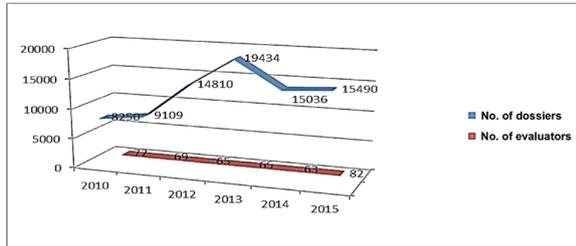
#### Conclusions

Performance metrics are used at the NADFC for the development of an annual report and to review the evaluation process. A system of

## Challenges



- The increasing number of drug applications is not aligned with the human resource addition.



- Different perspective between Pharmaceutical Industry (as drug applicant) and drug regulatory
  - On how to measure the process timeline
  - On the implementation of regulations and requirements.

2

Figure 9. The number of NADFC evaluators has not kept pace with the increase in the number of regulatory applications.

ongoing improvement has been implemented including the development of an electronic registration system for new drugs that incorporates a tracking system for the review that increases the transparency and traceability of the evaluation process: In addition, the evaluation process has been simplified, new drug evaluators and IT specialists have been recruited, furthermore, competency has

Performance metrics for the drug registration process in NADFC (2015) are the percentage of drug applications per year that receive decisions (approved, rejected, or need additional data) and the percentage of applications per year that receive final decisions within established timelines.

been increased through joint training with stakeholders as a result from Focus Group Discussion (FGD), national and international workshops/trainings and continuing education for new and senior evaluators in Indonesia and abroad.

## Performance indicators: Philippines

**Pia Angelique D. Priogola**

*Food Drug Regulation Officer III, Food and Drug Administration*

The mandate of the Center for Drug Regulation and Research (CDRR) at the Philippines Food and Drug Administration (FDA) is to ensure the safety, efficacy and quality of drug products, including new chemical entities, generic products, biotechnological products (including biosimilars and vaccines), traditionally used herbal products, herbal medicines, household remedies, over-the-counter products, medical gases and veterinary drugs and products. It is also tasked with regulating the manufacture, importation, exportation, distribution, sale, offer for sale, transfer, promotion, advertisement, sponsorship of and/or, where appropriate, the use and testing of drug products. The elements of regulatory review at CDRR are licensing and inspection of establishments, pre-marketing assessment, post-marketing surveillance, enforcement and risk communication.

Strengths of the agency include the fact that internal and external expertise is accessible to guide different regulated areas, all regulatory functions include staff with relevant academic education and recently enacted reforms will increase staffing. Philippines legislation and regulations exist to cover all regulated areas and new reforms have been initiated to strengthen the FDA. Finally, the established regulatory

**Achievements against timelines are influenced by external factors such as the quality of the dossier; that is its completeness and correctness, timing arising from company strategy and any shifts in regulatory requirements or processes.**

system at FDA is ISO certified, the assessment of good manufacturing processes is part of market authorisation and a system for variations is in place.

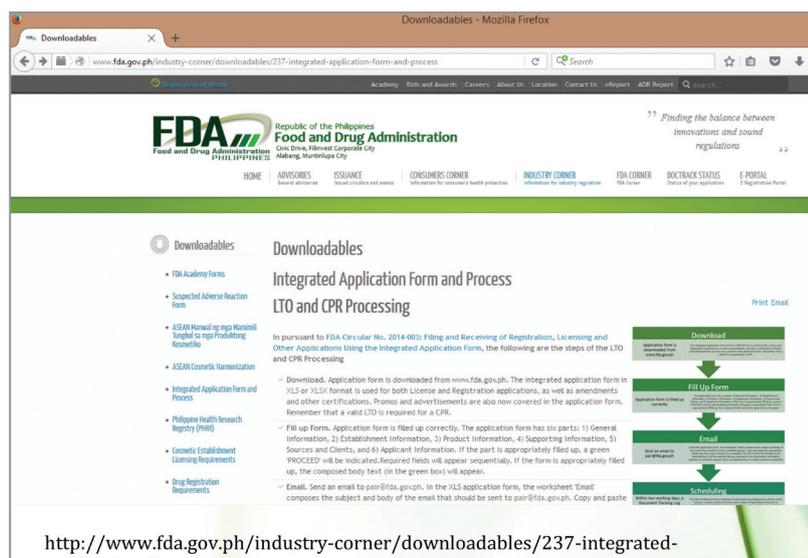
The timeline for the review of new chemical entities or major variations for existing licenses is 180 working days and for minor variations and renewals, the target timeline is 120 working days. A key performance indicator at the CDDR is the number of applications processed within those timelines. Achievements against this factor are influenced by external factors such as the quality of the dossier; that is its completeness and correctness, timing arising from company strategy and any shifts in regulatory requirements or processes. They are also influenced by internal factors including technology; that is, network and infrastructure, manpower, the influx of applications and work on government projects.

Applicants can download the integrated application form from the FDA website (Figure 10) and then submit the application dossier and proof of payment to the Public Assistance Information and Receiving (PAIR) unit on an indicated date at which time the registration clock is initiated and the registrant receives a Document Tracking Number (DTN), through which applicants may follow the progress of their application through the FDA website.

### The way forward

CDDR is engaged in continuous capacity building of its staff in terms of boosting their knowledge in the evaluation of quality, non-clinical and clinical data. It plans to disseminate and implement newly adopted guidelines and create the National Drug Advisory Committee. In addition, the agency envisions the implementation of a new pre-assessment procedure for new drug applications as well as new regulatory policies. Finally, CDDR will work to strengthen and enhance its linkage with stakeholders.

Figure 10. Applications for new drug reviews are initiated through the download of an integrated application form from the FDA website.



**Planning, improving, reporting – What qualitative and/or quantitative performance indicators are agencies incorporating into their practices and processes? Malaysia**

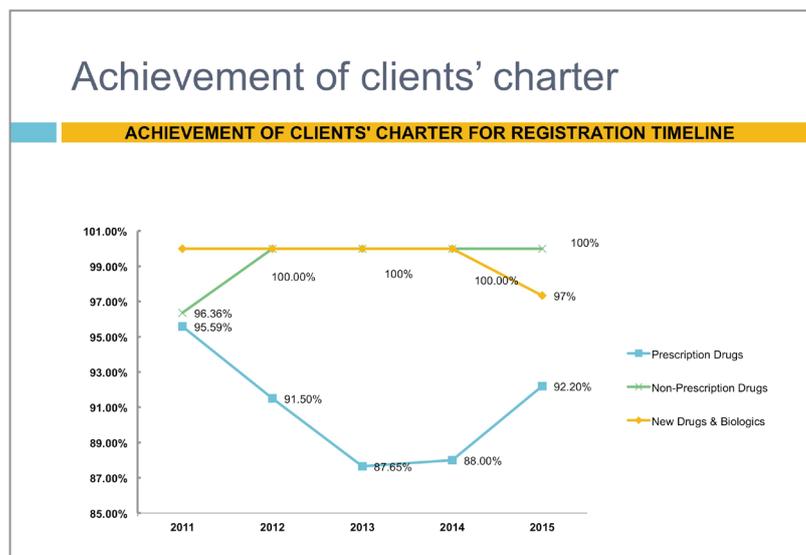
**Azura Abdullah**

*Senior Principal Assistant Director, National Pharmaceutical Control Bureau, Ministry of Health, Malaysia*

National Pharmaceutical Control Bureau (NPCB) is the regulatory authority for pharmaceuticals in the Pharmaceutical Services Division of the Ministry of Health Malaysia. NPCB core responsibilities include the registration of pharmaceuticals; that is new drugs and generics, biologics, traditional and health supplements and veterinary products; the licensing of importing and wholesaling premises, the testing of pre- and post-market samples, market surveillance and vigilance, notification of cosmetic products and other activities.

The measurement of performance, which aims to improve the management and delivery of products, is an important aspect of every organisation. At NPCB, relevant performance indicators measured in pre- and post-marketing processes at the organizational, national and ministry level are essential to ensure the quality, efficacy and safety of registered products in the country.

Figure 11. At the National Pharmaceutical Control Bureau in Malaysia, 94% new drugs, biologics and generic are reviewed within the specified timelines.



**Key performance indicators. . . should be periodically reviewed and justifications for not meeting the selected indicators should be supplemented with appropriate information.**

**Performance at the organisational level**

At the organisational level, timelines have been established for key activities such as

- the registration of new products, including
  - the full evaluation of new chemical entities, biologics and generics and the abridged evaluation of over-the-counter products and traditional and health supplements;
- issuance of certificates of product registration;
- certificate of free sales and notification of cosmetics issuance of licenses for manufacturers, wholesalers and importers;
- issuance of clinical trial import licenses and for clinical trial exemption licenses.

Target timelines for a full evaluation of prescription drugs is 210 working days and 245 working days for new drugs and biologics. For an abridged evaluation of non-prescription drugs, health supplements and traditional products, the target timeline is 116 working days for products with a single active ingredient and 136 working days for those with two or more ingredients. Certificates of pharmaceutical product and certificates of free sale must be issued within 15 days. Timelines are tracked monthly manually and online and the results are published twice yearly on the NPCB website. The NPCB has achieved a high rate of compliance with these timelines: 94% new drugs, biologics and generic are reviewed within the specified timelines (Figure 11).

Objective quality indicators are used at the organisational level. Fifteen indicators are monitored, covering different aspects of regulation; for example, the number of pre- and post-market samples analysed or the number of good manufacturing process inspections conducted. Reports of achievements according to these indicators are presented at management review meetings, which are conducted at least twice per year as a component of the Quality Management System for Malaysian Standards.

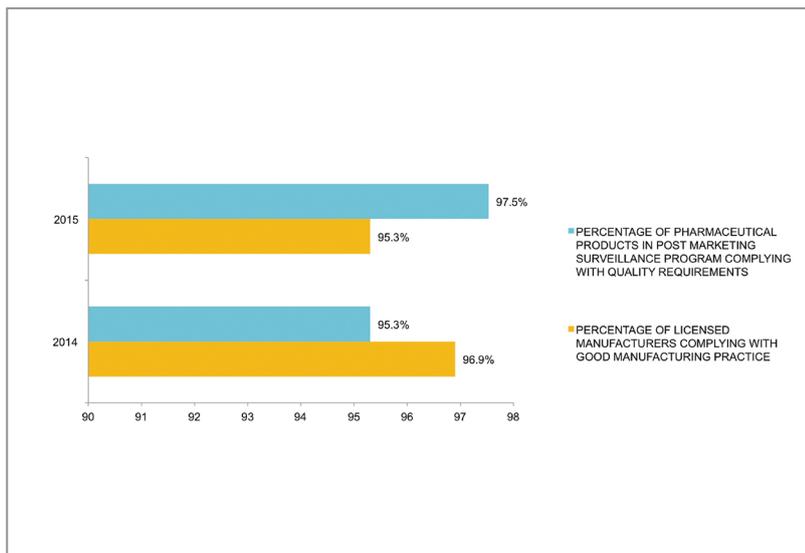


Figure 12. Examples of indicators measured at Ministerial Pharmacy Division.

### Performance at the national level

Performance indicators at the national level in Malaysia are reported under two different programmes, the National Indicator Quality Assurance Program (QAP) and Malaysian National Medicines Policy Dasar Ubat Nasional (DUNas). For QAP, the results of select indicators measured at agency and organisation level monitor performance for each division under the Ministry of Health; for example, the number of post-market surveillance samples analysed.

Endorsed in 2006, DUNas is the official document that defines and prioritises the medium- and long-term goals for the pharmaceutical sector in Malaysia. Its objective is to promote equitable access to and rational use of safe, effective and affordable essential drugs of good quality to improve health outcomes of the people.

The DUNas policy identifies the main strategies based on the goals and ensures the implementation of pharmaceutical activities in accord with targets determined. Its five major

components are Governance in Medicines; Quality, Safety and Efficacy of Medicines; Access to Medicines; Quality Use of Medicines and Partnership and Collaboration for the Healthcare Industry. Key performance indicators comprise various regulatory elements, some of which are based on World Health Organization indicators such as the number of new drugs registered and the establishment of specific guidelines.

### Indicators at ministry level

The goal of the Malaysian Government Transformation Programme is for Malaysia to become a fully developed nation by 2020. The Ministerial key result areas are measured at part of that programme and include relevant key performance indicators to be achieved and reported by respective organisations including the regulatory component or pharmacy division. These indicators are monitored by a specific units established for the Government Transformation Programme. Examples of these indicators can be seen in Figure 12.

Other performance indicators at NPCB include those showing organisational development such as the percentage of staff achieving the minimum continuing professional development or continuing professional education points or the percentage of new staff enrolled for induction courses within six months reporting to work.

### Conclusions

Measurement of key performance indicators is important for all organisations. These indicators should be periodically reviewed and justifications for not meeting the selected indicators should be supplemented with appropriate information. An upgraded online registration system is currently under development in Malaysia, where implementation and enforcement of regulatory policies and guidelines is complemented with good practices contributing to the achievement of good performance of the organisation.

## Performance measures for drug review in CDE, Taiwan

**Dr Churn-Shiouh Gau**

*Chief Executive Director, Center for Drug Evaluation, Taiwan*

The Taiwan Centre for Drug Evaluation (CDE) was established in 1998 to assist Taiwan Food and Drug (TFDA) Administration in the evaluation of medicinal products for marketing authorisation, whilst the Taiwan Drug Relief Foundation (TDRF) assists the TFDA in the post-marketing surveillance regarding drug safety and quality.

### CDE good review practices

The clinical, non-clinical and administrative multidisciplinary drug review team at the CDE uses communication and consensus building, employing evidence-based decision making that centres on benefits and risks. Good review practices that promote efficiency, quality and consistency and transparency are routinely implemented by the CDE.

In pursuit of efficiency in regulatory review, the CDE has established standard operating procedures in which the roles and responsibilities of all review team members are defined and the traceability of the review process is ensured through the provision of detailed procedures and internal timelines. Online reminder services facilitate internal productivity and the project manager, who is the

**Good review practices that promote efficiency, quality and consistency and transparency are routinely implemented by the CDE.**

contact person for the sponsor, tracks the review progress, addresses potential review process issues and resolves obstacles.

In the two-tier intra-discipline CDE system, which facilitates quality and consistency in reviews, the medical reviewer is the team leader for each application. Templates and other tools for each discipline include points to consider for specific indications and in addition to guidelines and guidances there is orientation and on-job training for reviewers. Basic and advanced educational courses, one-to-one tutoring and seminars for major review issues are also provided for reviewers in addition to case studies that facilitate the sharing of knowledge and ensure consistency among different disciplines. Senior Advisory Committee members are invited to join these discussions to enable consistency between the Advisory Committee and the CDE. Internal quality assurance activities include regular quality control meetings in which monthly case statistics are reviewed. External quality is assured through the review of external expert reports to determine if the review has covered all appropriate issues, the conclusions are supported by the reasoning in the report, if a recommendation for further amendment or request for more data is necessary, sufficient and appropriate.

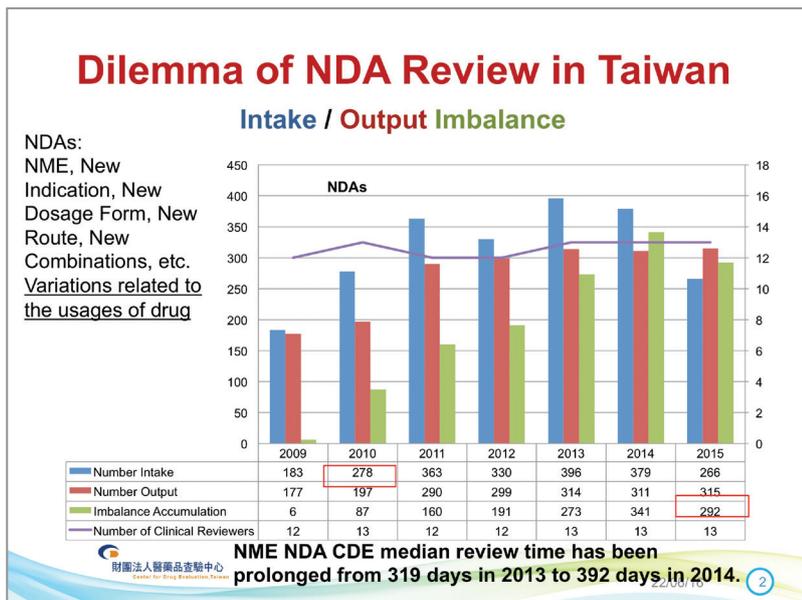
Figure 13. Three medicines were recently approved first in the world by the Taiwan CDE.

Taiwan 1st Approved Global New Drug	
Drug	Approval Time
<b>Afatinib</b> (non small cell lung cancer (NSCLC) with EGFR TK activating mutation)	<u>May 17<sup>th</sup>, 2013</u>
<b>Nemonoxacin</b> (Non-fluorinated quinolone antibiotic, mild community acquired pneumonia)	<u>Dec 4<sup>th</sup>, 2014</u>
<b>Onivyde</b> (a liposomal irinotecan, metastatic adenocarcinoma of the pancreas)	<u>Oct 22<sup>nd</sup>, 2015</u>

財團法人醫藥品查驗中心  
Center for Drug Evaluation, Taiwan

### Recent performance

Approximately 30% of submissions to the CDE are for new active substances that have not yet been approved by the US FDA or EMA and in recent years, Taiwan was the first in the world to approve three new medicines (Figure 13). Although the median review time for new drug applications increased to 392 days by 2014, that timing improved in 2015 when the CDE invited external experts to review cases of variations and formed a taskforce team to investigate all new drug applications with extended review times. In addition, the CDE also initiated a programme to identify priority applications; that is, new chemical entities to treat serious disease representing unmet medical need and the median review timing for those priority applications decreased by 55% in a 6-month time period in 2015 from 280 days to 127 days (Figure 14).



The competence of drug review in Taiwan has reached the standard of mature international agencies. The CDE is currently discussing the development of a pre-submission procedure and anticipates the development of full capacity to conduct all types of evaluations in the future.

Figure 14. The CDE initiated a programme to identify applications for priority medicines and the median review timing for those priority applications decreased by 55% in a 6-month time period in 2015.

## Key performance indicators and measures

### TGA experience and recommendations for regulators

**Dr John Skerritt**

*Deputy Secretary for Health Products Regulation, Australian Department of Health*

#### Publicly available TGA performance measures

Because the Australia Therapeutic Goods Administration (TGA) is one of few, if not the only, medicines and medical devices regulatory agencies that are fully cost recovered through industry fees and charges, there is an expectation that it will regularly report on agency activity levels, review timeframes as well as broader performance measures. Industry media analysis of these performance statistics

**Greater regulatory performance numbers do not always equal better regulation and explanations of what the numbers mean are often needed.**

often tend to focus on the numbers such as the number of products approved, withdrawn or rejected for market authorisation, the timeframes for approvals and other decision making, the total number of products and adverse event notifications.

Reports of TGA performance have been publicly available on the TGA website since 2014. These public releases undergo close scrutiny by industry, media and parliament and descriptions in external media about the reports have mostly been positive. However, when a structured review and stakeholder consultation on performance report conducted in 2015 asked users about the reports that they wanted, TGA learned that they should attempt to report fewer, more meaningful measures. They also learned that statistics can mislead and that the

regulator should recount the totals rather than the percentages of regulatory dealings and that medians (e.g. median timeframes for review) are often more informative than means. Not surprisingly, industry is often most interested in product market authorisation numbers and the transparency of regulatory data dispelled some views that industry competitors “were getting favoured treatment.”

Internally, the research allowed TGA to identify trends; for example, there were more orphan

drug applications and fewer applications for over-the-counter medications in one period that was examined. This was useful in helping set allocation of resources and despite the fact that it could not anticipate future work levels, it helped make the case for relative fees and charges. Because manual activity data collection made reporting resource intensive, an internal business case for investment in better IT systems was also made.

**BOX 1. TGA-DEVELOPED PERFORMANCE INDICATORS**

1. Stakeholder communication, education, satisfaction
  - Improved understanding of TGA's regulatory role
  - Stakeholder engagement and satisfaction with TGA consultative processes
  - Performance against TGA customer service standards
2. Premarket business operations
  - Percentage of applications processed in target timeframes:
3. Postmarket business operations
  - Time taken to complete initial review of safety signals
  - Public information on non-compliance
  - Lab testing as a result of safety issues, completed within target timeframes
  - Percentage of medical device incidents triaged and investigated in 30 days
  - Activities undertaken/public communication relating to regulatory compliance
4. Organisational health
  - Timely recruitment to key positions
  - Number of training days/ professional development of staff
  - Internal communication activities and outcomes of annual staff survey
5. Financial performance
  - Income and operating expenses relative to budget projections.
6. Statutory obligations
  - Outcomes of audits of financial statements and performance audits
  - Compliance with requests under Freedom of Information legislation
  - Reviews of decisions completed with the required timeframes
  - Contracts paid within 30 days
  - Implementation of the Government Digital Transition Policy
  - Percentage of Regulation Impact Statements that are compliant
7. International cooperation
  - Participation in international harmonisation initiatives that can be demonstrated to have ensured the international regulatory framework meets acceptable Australian standards of safety, quality and efficacy
8. Decision making
  - Percentage of substantive regulatory decisions subject to internal review, for which the original decision is revoked and substituted, without review of additional information
  - Number of matters referred to the Administrative Appeals Tribunal, where the outcome is indicative of an issue about quality of the initial decision

### Numbers and speed do not equal performance

Greater regulatory performance numbers do not always equal better regulation and explanations of what the numbers mean are often needed. For example, if 200 counterfeit medicines are intercepted in one year versus 100 in a previous year, does this mean that enforcement intelligence was better and staff were more proactive or that education and deterrence efforts were in decline or that more people decided that counterfeit medicines were lucrative? In another example, of 79 complementary medicines that underwent compliance reviews from January to June 2015 it was reported that only 20 had no compliance breaches; however, 60% of the reviews were targeted to suspect products, so the statistic is not representative of compliance by the complementary medicines industry as a whole. Just as numbers do not measure the quality of the work or interactions of the regulator with stakeholders, faster regulatory performance

is not always better and these performance data are sometimes not comparable between regulators. Recent public commentary on rapid approvals by some agencies have questioned whether the stringency of regulatory scrutiny is being maintained. But this commentary did not provide the necessary background to determine if the increase in the number and speed of approvals is the result of other factors, such as major regulators providing more feedback to sponsors during development, thereby increasing the quality of submissions or the greater use of surrogate endpoints by regulators or the acceptance of earlier stage data for oncology trials.

The first TGA initiative to develop measures of performance resulted in eight key performance indicators (Box 1)

After developing these indicators, TGA learned that many of the measures were qualitative and potentially open to dispute and that stakeholders also wanted to include a high-

#### BOX 2. AUSTRALIAN GOVERNMENT REGULATOR PERFORMANCE KPIS

1. **Regulators do not unnecessarily impede the efficient operation of regulated entities.** Regulators: demonstrate an understanding of the operating environment of industry; minimise potential for unintended negative impacts of regulation on industry; implement continuous improvement strategies to reduce compliance costs
2. **Communication with regulated entities is clear, targeted and effective.** Regulators: provide guidance that is up to date, clear, accessible and concise; consider impact on regulated entities and engage with stakeholders before implementing policies, practices or service standards; decisions and advice are provided in a timely manner, articulating expectations and the underlying reasons for decisions; provide consistent advice supporting predictable outcomes
3. **Actions undertaken by regulators are proportionate to the regulatory risk being managed.** Regulators: apply a risk-based, proportionate approach to compliance and enforcement; approach to risk is regularly reassessed to reflect changing priorities; recognise the compliance record of regulated entities
4. **Compliance and monitoring approaches are streamlined and coordinated.** Regulators: information requests only made when necessary and frequency of information collection is minimised and coordinated with other regulators; utilise existing information to limit the reliance on requests from industry; base monitoring and inspection approaches on risk
5. **Regulators are open and transparent in their dealings with regulated entities.** Regulators: Have clear and publicly available risk-based frameworks; are open to requests regarding the operation of the regulatory framework; publish performance measurement results in a timely manner
6. **Regulators actively contribute to the continuous improvement of regulatory frameworks.** Regulators: establish cooperative and collaborative relationships with stakeholders to promote trust and improve the regulatory framework; engage stakeholders in the developing options to reduce compliance costs; share feedback from stakeholders and performance information with policy departments to improve the operation of the regulatory framework

level summary of quantitative data from the performance report. Moreover, a substantial resource commitment was involved in compiling data and reporting twice annually, the cost of carrying out stakeholder satisfaction surveys was high and the results of these surveys were sometimes difficult to interpret. Despite these challenges, stakeholders were reasonably happy with this set of key performance indicators and reporting, as it was felt to portray a full picture of TGA regulation.

In July 2015, as part of the government's deregulation agenda, the Australian Government mandated a framework for all Australian regulators to articulate the Government's expectations. This framework focussed more specifically on generic qualitative measures of regulatory performance and resulted in six key performance indicators with subsidiary measures for all regulators (Box 2). Using these indicators, TGA can tailor output reporting and evidence used.

TGA recognises that it is essential to build key performance indicators into an organisational business plan to avoid discordant sets of priorities. Accordingly, they developed a sample template for the second set of government indicators and tested it across the organisation to make sure that reporting was feasible before locking in these key performance measures. TGA also appreciates that it is important to facilitate internal cultural change to support reporting against new key performance indicators. In addition, it guided the development of IT systems to enable automatic collection of much of the performance data, while recognising that many measures remain qualitative. Annual self-assessment reports must be published and external reviews will be conducted every two to three years.

## Measuring companies and regulators: Benchmarking through key performance indicators

**Prisha Patel**

Manager, Global Development Programme, Centre for Innovation in Regulatory Science

### Key performance indicators

A key performance indicator (KPI) has been defined as a “measurable value that demonstrates how effectively an organisation is in achieving key business objectives.”<sup>1</sup> Pharmaceutical companies’ KPIs might include the number of submissions or approvals achieved, the staff retention rate, company revenue, research and development expenses or the time taken to answer regulatory agency deficiency questions. Regulatory agency KPIs might comprise review timing, publication of summary bases of decision, the availability and quality of guidelines, the number and type of stakeholder communications, staff retention rate or the quality of decision-making processes.

### Regulatory agency benchmarking

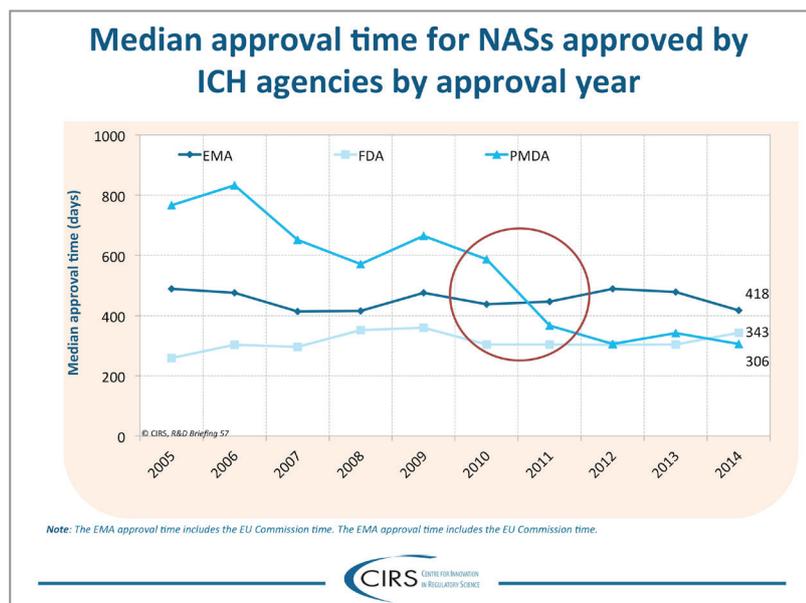
The goal of establishing benchmarks for regulatory agency performance is to remove any potential barriers for patients’ access to innovative medicines. Since 1995, the Centre for Innovation in Regulatory Science (CIRS) has benchmarked regulatory agencies using agency-supplied data. CIRS has also used this methodology to develop benchmarking metrics

**[KPIs] can be used to identify where time is spent in the review process, to increase internal transparency, to establish programmes of internal benchmarking and to monitor the effects of change initiatives.**

for emerging market agencies, which are diverse in their practices and processes for reviews.

Regulatory benchmarks for EU, Japan and the United States reported in the *CIRS R&D Briefing 57 New drug approvals in ICH countries 2005 – 2014* included information concerning the recent convergence of regulatory approval times for those three jurisdictions. (Figure 15). In addition, the Briefing discussed the 2014 decrease in the overall median approval time for EMA, which was driven largely by the decrease in company response time. It additionally suggested that review time might be further reduced through the shortening of the EU Commission timing. *CIRS R&D Briefing 56 Understanding the dynamics of China’s medicine regulatory environment* provided details concerning the enhancement of regulatory performance in Japan, starting with the formation of the PMDA in 2004. From 2005 to 2014, there was a 30% increase in the number of new active substance approvals, while the approval time for these substances was shortened by 50% from 2010 to 2014 and the drug lag was reduced by 1 year.

Figure 15. Converging regulatory approval times by ICH agencies.



### Pharmaceutical company benchmarking

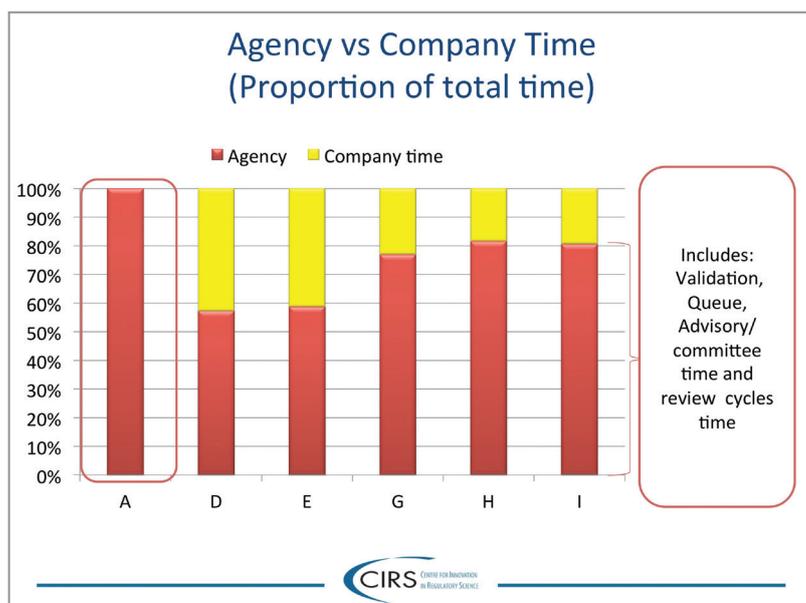
In the Emerging Markets Regulatory Review Times (EMaRReT) database CIRS currently collects benchmarking data from international pharmaceutical companies in 18 emerging markets. Using information from this database, CIRS is able to analyse trends in regulatory approval times for new active substances and major line extensions, including factors that may expedite or impede the global delivery of new medicines, facilitating the development of global pharmaceutical strategy.

EMaRReT data revealed that it took a median of 458 days from the date of submission to the date of approval for new actives substances approved in emerging market countries from 2010 through 2014. The disparity in timing for individual jurisdictions, is likely to be the result of differences in global processes and types of review models that are used. The verification assessment model requires prior recognition of an authorisation by two or more reference

or competent benchmark authorities and incorporates a verification process to validate the status of a product and to ensure that the medicine to be marketed locally conforms to the authorised product. The abridged assessment model also requires that the product has been registered by at least one reference or competent benchmark authority and conserves resources by not re-assessing the full scientific supporting data. This model focuses on aspects that must be evaluated specifically for the local environment. There are two full assessment models, that is, type 3A and 3B. In type 3A reviews, quality, safety and efficacy data are assessed in detail and there are requirements for pre-registration in another jurisdiction before an authorisation can be finalised. In type 3B reviews, a full, independent review of safety and efficacy data is carried out and information from registrations in other jurisdictions is taken into consideration but is not a prerequisite to filing or authorisation. Analysis of EMaRReT data shows that when agencies are grouped according to the type of review model that they use, the median timing for review is typically similar.

EMaRReT data are from a limited number of multinational companies' international products. Recently, CIRS collaborated with the Saudi Arabia FDA in the development of a more complete report of the timing of agency versus company portions of regulatory review.<sup>2</sup> This collaboration demonstrates the potential utility for a benchmarking programme that utilises agency-obtained information.

Figure 16. Proportion of time spent by sponsoring companies and agencies in the regulatory review process at six agencies.



### Assessing performance using regulatory agency data

CIRS has initiated the first phase of a regulatory agency benchmarking programme in which emerging market agency-supplied data was solicited from each participating agency regarding the agency's capacity and review process as well as the milestones tracked during the review process. Common agency milestones were then identified and defined for comparability. Next, a feasibility study was conducted for four or five products from each participating agency to test the usability of the milestones. To characterise the data set, qualitative information was solicited for each application including the sponsor, generic name, trade name, compound type, standard or fast-track status and therapeutic class.

The preliminary results of the study included regulatory approval times from date of submission to date of approval for four or five new active substances approved in participating jurisdictions from 2012 through 2015. The data were broken down to determine the proportion of review time that was spent by agencies compared with the time spent by companies (Figure 16); the length of time agencies spent to achieve each milestone in the regulatory review process; and the time spent to achieve each milestone in the review of fast-track versus standard submissions.

These data can be used to identify where time is spent in the review process, to increase internal transparency, to establish programmes of internal benchmarking and to monitor the effects of change initiatives. Timeliness and speed of the review is only one aspect in measuring regulatory performance. The quality of the process from construction of the dossier to the ultimate regulatory decision must also be considered and measured. This assessment guarantees expected standards, instils confidence amongst stakeholders and achieves universal acceptability of reviews.

### References

1. Klipfolio. What is a KPI? Found at <https://www.klipfolio.com/resources/articles/what-is-a-key-performance-indicator>.
2. Hajed Hashan, Ibrahim Aljuffali, Prisha Patel Stuart Walker. The Saudi Arabia Food and Drug Authority: An evaluation of the registration process and good review practices in Saudi Arabia in comparison with Australia, Canada and Singapore. *Pharm Med.* 2016;30:37-47.

## WHO Prequalification performance indicators: What are they, how are they measured and reported and are they used to improve performance?

**Dr Lembit Rägo**

*Head, Regulation of Medicines and other Health Technologies, Essential Medicines and Health Products, World Health Organization*

The mission of the World Health Organization (WHO) Prequalification Team (PQT) is to ensure timely availability of quality-assured health products for the prevention, diagnosis and treatment of priority diseases in low- and middle-income countries.

PQT is the largest of groups in the regulatory unit of (WHO) and carries out assessment of in vitro diagnostics (IVDs), male circumcision devices (MCDs), finished pharmaceutical products (FPPs) and active pharmaceutical ingredients (APIs), quality control laboratories (QCLs), vaccines and immunization devices.

Through prequalification, WHO has made a significant contribution to increasing the availability of many quality-assured products to WHO Member State markets: in 2015, for example, 17 IVDs, 37 FPPs, 13 APIs and 3 QCLs, 7 vaccines, 37 immunization devices and 1 MCD.

## Monitoring and measuring performance

WHO PQT performance indicators are designed to enable monitoring and measurement of performance: not simply what was prequalified and in what number but how long this took. In brief, the aim is to assess the (potential) impact of WHO prequalification, the difference it has made and what was required to achieve it.

Several key indicators are linked to the steps of the prequalification process and aim to measure its efficiency. For example:

- the time that WHO took to complete assessment
- the time a manufacturer took to attain prequalification of its product

Targets are linked to the indicators, to enable comparison with similar activities carried out by stringent regulatory agencies. For example:

- the target time for completion of “full” assessment of an FPP is 270 days
- the target time for completion of assessment of products that have already successfully undergone stringent assessment is 90 days
- the target time for completion of assessment of a variation to a prequalified product is 30 days.

When results for indicators are below target, investigation may be necessary to understand why. However, failure to achieve targets is sometimes readily explained. For example, the high number of inspections carried out in 2014 and the need for special data integrity investigations in 2015 stretched PQT’s capacity to the limit and therefore, also, report timelines for inspection.

## Why monitor and measure performance?

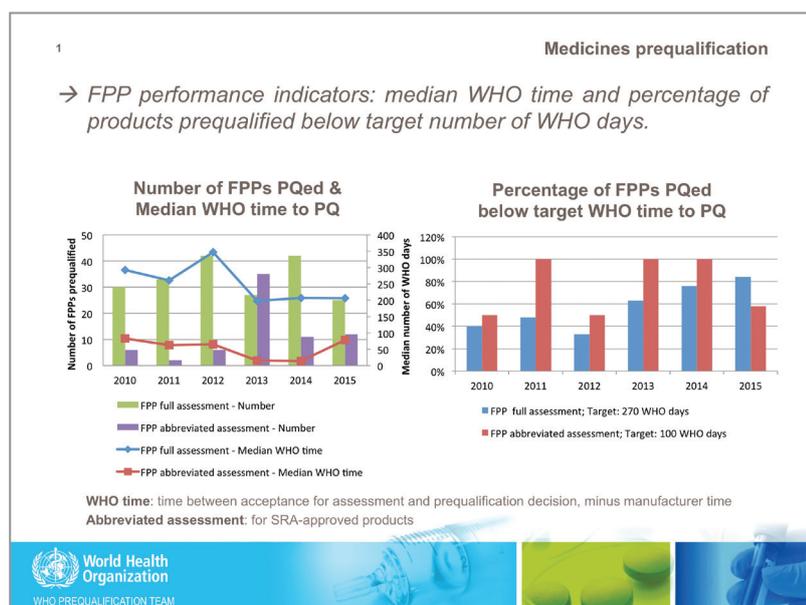
WHO PQT performance indicators are set in order to respond to the need to:

- report to Member States
- report to donors
- ensure transparency.

Measurements are compiled by a monitoring and evaluation officer using information compiled by technical groups; a data management system is in operation for each product stream that reflects the specifics of the prequalification procedure as applied to each product type.

But there may be a range of indicators that vary

Figure 17. WHO performance indicators for finished pharmaceutical products (FPP).



**Work on performance indicators requires continuous reflection and fine-tuning.**

within a product stream and through time as seen in Figure 17 for FPPS and complications arise. For example, for vaccines, the evaluation of emergency products starts before all dossier components have been received by WHO; therefore an indicator measure for such a product gives the impression that WHO is actually taking more time than usual to conduct assessment, even though the evaluation started earlier than usual and feedback to the manufacturer is provided more promptly than usual given the emergency situation.

Establishing verifiable statistics across product streams and over time has also proved challenging due, for example, to a recent change (in order to align the product streams) in the time when the WHO clock starts for vaccine prequalification, the streamlining of the IVD prequalification procedure, or the low number of products prequalified each year in some product categories. Furthermore, IVD prequalification includes an additional third component of laboratory evaluation, which is taken into account in measuring time to prequalification, making comparison with the other product streams difficult (Figure 18).

However, WHO PQT is currently working to develop performance indicators, based on harmonised terminology and aligned processes that can be applied across all product streams, thereby enabling comparisons between product streams to be made.

Figure 18. Performance indicators for in IVD prequalification timelines may be misleading as they include an additional component for laboratory evaluation.

**Future performance indicators**

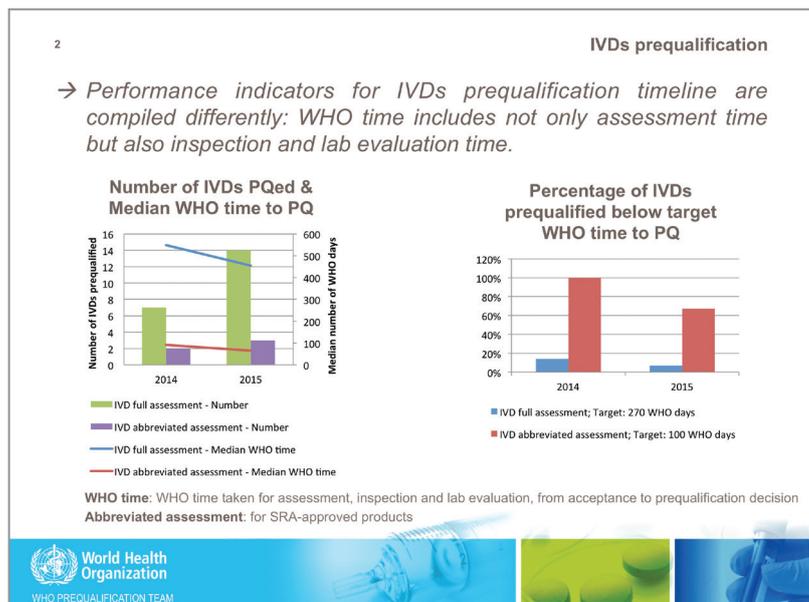
Both internal and external alignment of PQT performance indicators are called for. Internal alignment requires the alignment of prequalification processes and of major steps related to the communication with the applicant, which in turn will enable harmonisation of timeline calculation between product streams, including when the “WHO stop clock” is started and stopped. External alignment requires the identification of similarities and differences between prequalification and the registration procedures and performance indicators of SRAs.

Consideration is being given to development of a new indicator that measures WHO time between acceptance for assessment to complete review of the dossier (including provision of the full package of comments and all requests for additional data to the manufacturer). In addition, cohort monitoring could be initiated: the products accepted for assessment in a specific year would constitute the cohort for that year. Rather than focusing on measurement of timeline to prequalification, measurement would be made of the timelines for the different steps towards prequalification. This would enable capture of performance information relating not only to products that ultimately reach prequalification but also to products that are withdrawn from the process by manufacturers and also to products for which dossiers are ultimately cancelled. This would better highlight linkage between changes in prequalification processes and potential improvement of prequalification timelines, as well as better reflect the totality of work undertaken by PQT.

Investigation is also under way to determine whether an integrated data management system would be feasible.

**Looking beyond the numbers**

As already mentioned, performance indicators should be evaluated against specific targets and if targets are not reached, the cause should be investigated. But it must be recognised that many factors may influence WHO PQT performance. If the number of prequalified products is lower than expected in a given year, it may be because prequalification resources are overstretched or because a lower number of applications for prequalification was received due to less attractive markets for manufacturers. WHO PQT therefore, looks beyond the numbers, to focus on possible solutions, so that performance can improve. Indeed, work on performance indicators requires continuous reflection and fine-tuning.



## Improving regulatory practices and processes through mapping and training

**Prof John Lim**

*Executive Director, Centre of Regulatory Excellence, Duke-NUS Medical School, Singapore*

Current challenges to pharmaceutical regulatory performance in Asia include insufficient subject knowledge among regulatory professionals, fragmented regulatory requirements in different jurisdictions and the lack of networking and capacity-building platforms for regulatory science and policy innovation. Addressing these challenges requires the fostering of innovation in regulatory approaches and greater efficiency through reliance and coordination. Effective regulation of medicines entails approaches to ensure timely access without compromising quality of decisions. Regulatory policies must be continually reviewed and frameworks established for performance improvement and maintenance of relevance to overall healthcare systems. Regulatory systems must take the place of silos of regulatory functions and communication with regulatory stakeholders maintained through open dialogue and neutral platforms for exchanges, adopting a mind-set of collaboration instead of transaction.

Good implementation is key to strengthening organisational frameworks and regulatory

practices. This includes the facilitation of effective assimilation into current processes. Regulatory leadership requires the development and implementation of strategies that include plans for change management. Leaders should aim for practical and tangible outcomes, with excellence rather than perfection as the goal. They should strive to strengthen systems for robust decision-making processes and promote quality decision making. Professional development should be promoted through career progression and upgrading of skills and technical competencies. Strategies should be in place for this progression as well as to retain and grow staff and increase the talent pool.

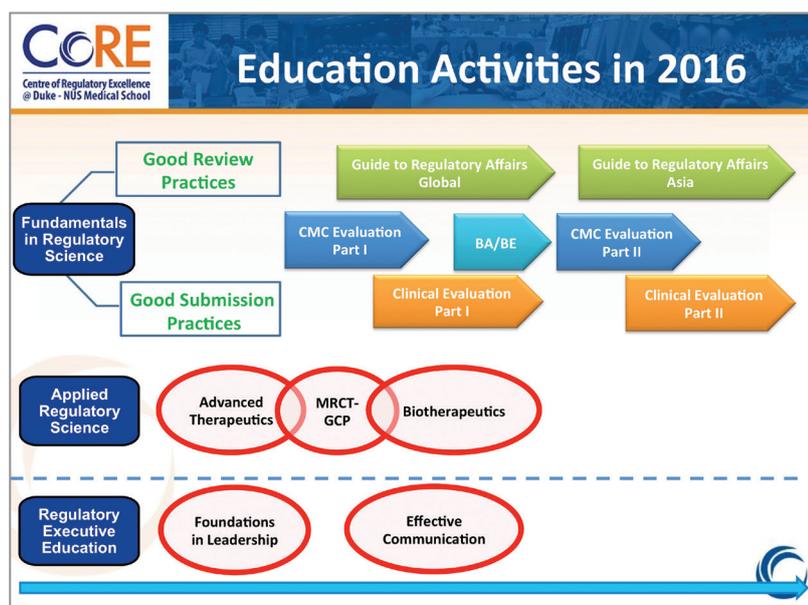
The mission of the Centre of Regulatory Excellence (CoRE) of Duke-NUS Medical School, Singapore is to ensure that patients in Asia have timely access to safe, effective and high quality therapeutic products through excellent regulation. To achieve that mission, CoRE strives to implement its strategic goals:

To strengthen regulatory leadership through customised training to advance competencies and standards for Asian regulatory professional leaders; to develop policy and systems innovation that promotes intellectual capital in regulatory sciences and policy innovation in Asia and to establish regulatory networks as regional platforms to foster closer collaboration in regulatory science and policy and best practice.

To these ends, CoRE has convened a number of advisory roundtables to identify the gaps and issues affecting performance of regulatory authorities and to provide targeted solutions for regulatory systems strengthening. Recent fact finding among stakeholders has included meetings with heads of regulatory agencies and their teams in various Association of Southeast Asian Nations countries, focus groups with representatives from multinational corporations and small-to-medium enterprise pharmaceutical and medical device companies and a survey to assess needs of regulatory professionals.

Challenges to performance identified to date include knowledge gaps, both technical skill and “soft” knowledge such as communication, crisis management, decision making, strategy planning and leadership skills. Innovation needs have been recognised including mutual recognition processes, experience sharing, policy changes and platforms for cross dialogue between regulators and industry. Educational opportunities are deficient including structured, continuous education and education that would

Figure 19. The CORE educational programme is divided into three tracks.



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foster career progression. When it exists, training is not affordable and is too US and EU centred.

With the goal of enhancing regulatory performance of ASEAN member states, CoRE will conduct a landscape analysis of regulatory systems in this region, identify performance issues and gaps within and across jurisdictions and opportunities to advance systems. This analysis will be performed through the visitation of each ASEAN country and the assessment of different stakeholders including national regulatory agencies, industry, academia and others. Outcomes will be communicated back to individual stakeholders, used to identify and prioritise action items necessary to strengthen regional regulatory capabilities and to characterize approaches for effective implementation of development programmes for regulators and industry.

A programme of regulatory education has been developed based on recommendations from CoRE Curriculum Committee comprising representatives from regulators, industry and academia. This programme consists of three tracks: Fundamentals of Regulatory Science, which is competency oriented; Applied Regulatory Science, which is proficiency and efficiency oriented; and Executive Regulatory Education, which is strategy oriented (Figure 19). The structured curriculum is in the format of the common technical document and case studies in its use. The objective of the curriculum is to educate and encourage use of a common regulatory language, to promote common

**CoRE will conduct a landscape analysis of regulatory systems in this region, identify performance issues and gaps within and across jurisdictions and opportunities to advance systems.**

understanding and application of international guidelines and to consider approaches to facilitate the implementation of guidelines into regulatory operations and processes.

CoRE education uses a blended learning approach of online learning and team-based workshops, which ensures its applicability, affordability and scalability. Using this approach, Duke-NUS medical students in Singapore outperformed their US counterparts, especially in applied skills and knowledge retention. The multi-regional clinical trial (MRCT) Workshop conducted in 2014 to train APEC regulatory staff to assess data from MRCTs is an example of the practical implementation of the programme in adult education.

CoRE convenes experts from various sectors, providing a neutral academic platform for sharing innovation, best practices and open dialogue amongst regulatory stakeholders including regulators, industry and academics. CoRE collaborates with global networks and promotes regulatory convergence and thought leadership, widening the scope of available regulatory resources and expertise.

## Company factors that affect agency performance –

### How can these best be measured and managed by agencies?

**Ricardo Borges**

*Manager of the General Office of Drugs, ANVISA*

In 2014, there was a 14-month queue time for the review of new drug applications at the Agência Nacional de Vigilância Sanitária (ANVISA), Brazil, all elements of the new drug applications were reviewed in one office and there were few early

interactions between companies and ANVISA. In June of that year, ANVISA introduced a new structure in which multiple offices separately evaluated clinical studies, active pharmaceutical ingredients, manufacturing and control, brand names and label structure and clarity, resulting in a faster, in-depth assessment. By December 2015, the queue time for applications had been reduced to 3 months and overall approval time to 506 days, comprising 217 days queue time, 161 days ANVISA time and 128 days sponsor time (Figure 20).

New ANVISA assessment strategies included mandatory meetings after the first request for sponsor information and a target timeline of 30 days to assess company replies. When the results of the mandatory meetings were

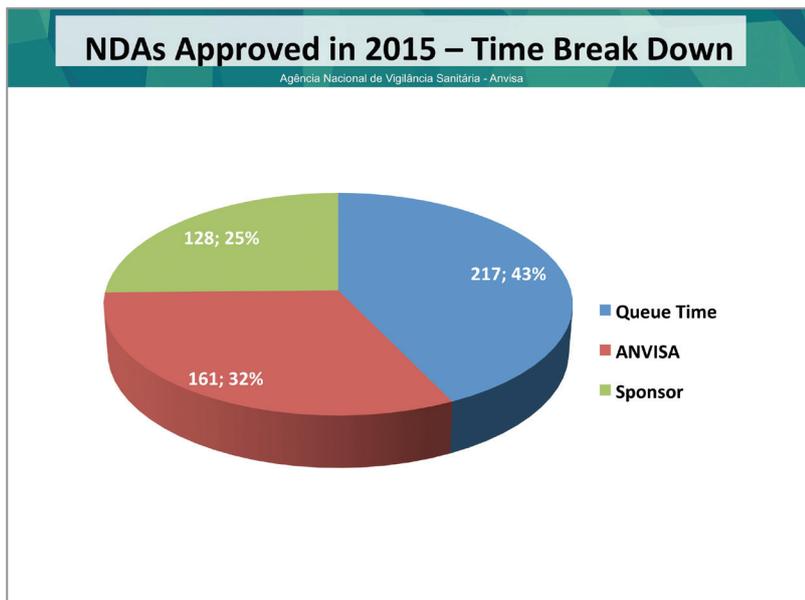


Figure 20. Approval time for new drug applications at ANVISA.

analysed, it was observed that much required information had not been previously submitted, it took longer to evaluate the sponsor response than the original submission and many sponsor requests were to discuss relatively simple points of Brazilian legislation. It was concluded that sponsors are challenged to adapt international dossiers to Brazilian regulations because of a lack of understanding of mandatory items and that sponsors often submitted incomplete dossiers because of lengthy queue times.

Figure 21. Reducing requests for sponsor information would further reduce approval times at ANVISA.

... sponsors are challenged to adapt international dossiers to Brazilian regulations because of a lack of understanding of mandatory items ...

Beginning in May 2015, ANVISA analysed all requests made by the Chemistry Manufacturing and Controls group including reasons for rejection. Subsequent meetings with sponsors highlighted dossier problems and specified needed areas of improvement for submissions. In addition, pre-submission meetings were scheduled to revise dossiers before submission.

Results from the assessment of the ANVISA reorganisation indicate that there is still room for improvement (Figure 21). For example, just one less request for information would result in a decrease of 98 days of review time (44 days sponsor; 54 ANVISA); an increase in ANVISA availability; and less queue time. It is expected that approval time in 2016 will be further reduced to approximately 380 days, including a 90-day queue time, 160 days for ANVISA evaluation and 130 days for sponsor responses.

NDA Assessment		
Agência Nacional de Vigilância Sanitária - Anvisa		
➤ Results from 2015 assessments		
	Sponsor's Time (Days)	Requests for information
Mean	128	2,67
Median	132	3,00
RSD	72	0,65

## Internal regulatory metrics for planning, submission and getting a medicine to market

**Dr Alec Tiong**

Head, Regulatory Affairs, Japan & Asia-Pacific, AbbVie, Singapore

The main purposes of regulatory metrics for industry include their ability to act as key performance indicators, monitor a development project progress, provide clear and visible reports to key stakeholders, quantify the regulatory risk level, seek opportunities to improve the working process and to adhere to compliance requirements.

### Regulatory probability of success

The regulatory probability of success (RPoS) is the probability of the approval of a new medicine. Within RPoS, the emphasis is on the potential achievement of the target product profile within the forecasted submission and approval timeline. The RPoS of a medicine reflect its designation as a standard or priority review and a starting RPoS is determined country by country and further adjustments are made during the development process based on clearly articulated assumptions.

Increases in RPoS may occur for products that attain special designations such as Priority Review (US), Accelerated Assessment (EU),

**A rolling update is needed for developmental plans and the metrics for the success of those plans, based on a quickly changing regulatory environment**

Expedited Approval (JP), Orphan Drug (US, EU and Japan), Breakthrough Designated Drug (US), Fast Track (US), or Accelerated Approval (US); Sakegaki (Japan). These are products that may be first in class, for unmet medical needs, products for which sponsors responds to regulatory questions in a timely manner or complies with regulatory advice, or products with robust clinical data. Decreases in RPoS may occur for products with safety signals that cannot be mitigated, those for which the science of the therapeutic area is evolving or unknown, those with an efficacy not superior to current standard of care, those for which the magnitude of benefit is not as expected, those with compliances or inspection issues, those for which regulatory advice was not followed, those with unmitigated technical risks or those for which there has been a change in the competitive landscape. Several assumptions are implied with RPoS; namely, certificates of pharmaceutical product (CPPs) will be available for countries requiring CPPs and technical success is assumed for US and EU submissions but not for other countries and regions.

Typically, approximately 18 months before the initial submission for a product, the regulatory team will develop a list of possible jurisdictions where a new product might be submitted and the compound team will create submission timelines for those jurisdictions and calculate the probability of successful regulatory approval for each submission (Figure 22).

Metrics for success for clinical development plans in countries outside of US and EU that require registration studies such as Japan, China and others, could include whether that country is included in the global development plan at a suitable development milestone or is included in the global clinical study or regional clinical study with the required subject numbers that will be sufficient to support product registration. Progress against global development plans is reported to senior management in a monthly metrics update.

### Local submission metrics

Preparing for local submission includes

Figure 22. A list of potential jurisdictional submissions is created for each compound and the submission timeline and potential for regulatory approval is calculated.

**“What’s Possible” – an example**

What's Possible List for [Product]						
Country / Region	Projected Submission Date	Projected Approval Date	CPP Requirements		Regulatory Probability of Success	Key Assumptions / Requirements
			Timing (Submission or Approval)	Reference Authority		
United States			N/A	N/A		
EU/EEA			N/A	N/A		
[Country 1]						
[Country 2]						
[Country 3]						
[Country 4]						
[Country 5]						
[Country 6]						
[Country 7]						
[Country 8]						
[Country 9]						
[Country 10]						

### Regulatory Submissions – an example

KPI	Target	How
<b>Registration Plan Accuracy</b>  Scope: - Dossier - New product registration - Clinical Trial Applications (if applicable)	90%	<b>Frequency:</b> Measured monthly  <b>Evaluation:</b> based on 'Latest Best Estimate Date' versus 'Completion Date' in the database - Dossier : arrived on time? - Submission: filed on time? - Approval: obtained as targeted?  <b>100%:</b> if the actual date is within 30 days of planned date <b>0%:</b> if the actual date is beyond 30 days of planned date

abbvie

Figure 23. Key performance indicators for local regulatory submissions include their consistent fulfilment of the global development plan.

translation from English to a local language, understanding local submission formats and ensuring the availability of the dossier. Regulatory metrics used by regions and affiliates in planning and submissions include the use of

active regulatory strategy input into the global regulatory strategic and tactical plan including those strategies for the product portfolios that support the delivery of business objectives and that reflect regulatory requirements that been negotiated with regulatory agencies where applicable. Local teams identify risks and mitigation plans to ensure the maximum competitiveness of the product label and the submission and approval of new drug and clinical trial applications are made according to plan (Figure 23).

#### Summary

Regulatory metrics are being widely used in different functions within pharmaceutical companies. A rolling update is needed for developmental plans and the metrics for the success of those plans, based on a quickly changing regulatory environment and metrics should reflect the different conditions at global and local affiliate levels. A good metrics system can help a company to manage research and development projects more efficiently.

## Building quality into the decision-making process:

### What are the main factors that need to be considered?

**Dr Neil McAuslane**

*Director, Centre for Innovation in Regulatory Science, UK*

Getting innovative medicines to patients requires developmental, regulatory and health technology assessment decision making. Recent CIRS Workshop participants have recommended that the quality of the decision-making processes for these functions be considered separately from the decisions themselves.

When measuring regulatory performance, the timeliness and speed of the review is only one aspect to be considered; the quality of the process, from the construction of the dossier to the ultimate regulatory decision must also be considered and measured. This quality guarantees expected standards, instils confidence amongst stakeholders and achieves the universal acceptability of the review. The quality of review decision making is critical to ensure that assessments and decisions are scientifically sound and that only safe and effective and medicines reach the market.

At a CIRS Workshop in 2004, Professor Larry Phillips, a Professor of Decision Analysis at the

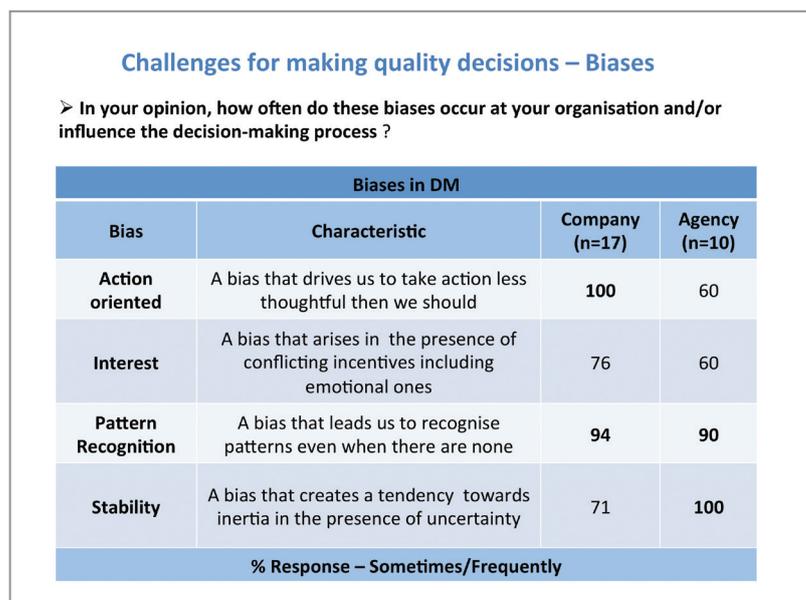
London School of Economics, discussed the “science of decision-making” saying that “. . . In an uncertain world, it is perfectly possible to make a good decision that has poor consequences and, equally, to make a bad decision and come up with a good outcome. On balance, however, the long-running use of good systems for making decisions will generally give better outcomes.”

The CIRS Quality Decision Making programme represents a natural evolution of CIRS’s work from performance metrics, good review practices and benefit-risk and currently comprises doctoral research, patient involvement initiatives and a decision-making tool.

Making good decisions in research and development, regulation and health technology assessment is critical to ensure patients’ access to innovative medicines. However, organisational decision makers are, in large part, influenced by organisational processes and procedures. Moreover, all decision-making processes are known to have a number of potential weaknesses, which usually include taking a narrow frame, biases, short-term thinking and overconfidence. These biases include action-oriented biases, which are those that drive decision makers to take actions less thoughtfully than ideal, interest biases, which arise in the presence of conflicting incentives, pattern recognition biases, which cause decision makers to see patterns where there are none and stability biases, which create inertia in the presence of uncertainty.

In a 2006 CIRS Workshop, participants outlined the broad key measures essential for building quality into review process leading to good decision making as clear and well-defined processes, consistent application and talented and well-trained people. In his programme of doctoral research, Dr Ronan Donelan interviewed 29 key opinion leaders from major regulatory authorities and the pharmaceutical industry to identify key factors influencing quality decision making. The majority of study participants indicated that current decision-making is influenced by ‘gut feeling’, ‘subjective and personal biases’ and ‘overconfidence in own judgment’. The result of this background research, is a draft set of quality of 47 decision making principles for good decision-making for the development and review of medicines which has been partially validated as a tool for assessing good quality decision making, the Quality of Decision Making Orientation Scheme (QoDOS). QoDoS items are organised into four sections,

Figure 24. The majority of survey participants identified instances of biased decision making within their organisation.



**Only 41% of companies and 20% of agencies undertake formal assessments of decision-making quality but 100% of companies and 88% of agencies believe that there are ways of doing this and 100% of companies and 90% of agencies believe their decision making could be improved.**

the organisation decision-making approach, the organisation decision-making culture, the individual decision-making competence and the individual decision-making style.

The research also revealed that quality decision making necessitates a 'structured approach', 'education and training in decision-making techniques, evaluating the importance of the options' and 'an appreciation of the impact of the decision made'. In addition, an integrated approach to quality decision making requires a systematic framework that takes into account four essential domains, namely, structure, bias, culture and impact.<sup>1</sup>

Considering the necessity of that decision framework, recommendations from a CIRS Workshop Syndicate in 2013, defined its necessary attributes as one with clear roles and responsibilities, efficiency and effectiveness, constraints biases and context and transparency, one that considers impact and helps a range of stakeholders.

Using those attributes, in 2015, CIRS conducted a survey among 17 pharmaceutical companies and 10 regulatory agencies to identify current decision-making practices for companies' decision to submit and agencies' decision to

approve a new drug application and to identify how they are measuring the quality of the decision-making process and the challenges and solutions. Questions sought to identify the decision-making systems in place at agencies and companies and the framework that forms the basis of the decision-making process as well as the hurdles and biases that stood in the way of quality of decision making and how the decision-making was assessed. Key results indicated that 41% of companies and 80% of agencies had a formally codified decision-making framework. Only 41% of companies and 20% of agencies undertake formal assessments of decision-making quality but 100% of companies and 88% of agencies believe that there are ways of doing this and 100% of companies and 90% of agencies believe their decision making could be improved.

The majority of company and agency participants identified instances of decision-making biases within their organisation (Figure 24). Other company-identified hurdles to quality decision making include excessive optimism, poor assessment of uncertainty or strength of evidence, internal misalignment, previous experience biases, data availability and time pressure. Agency-identified hurdles to quality decision making include lack of knowledge with regard to decision making concepts, reluctance to discuss uncertainties or value judgments, ensuring consistent review or evaluation practices, data availability and resource constraints. Participants also suggested solutions to these hurdles (Figure 25).<sup>2</sup>

### Conclusions

The quality of decision making is influenced by the processes and procedures within companies and agencies. The long-term use of good systems for making decisions will generally give better outcomes. Companies and agencies believe their decision making could be improved within their organisation but stakeholders need to explicitly explore quality in decision making process. The methods for measuring quality in decision making have yet to be outlined but CIRS has now initiated a programme of work to develop and validate the principles of a general quality decision-making framework, identify markers for measuring the quality of decision making and support a timely, transparent, consistent and quality process.

### References

1. Donelan R, Walker S, Salek S. *Pharmacoepidemiol Drug Safety*. 2015;24:319–328.
2. Bujar M, McAuslane N, Salek S, Walker S, *Ther Innov Reg Sci*. 2016.

Figure 25. Survey participants suggested solutions to organisational challenges to good decision making.

### Some suggested solutions to the hurdles

- **Establish or implement a structured DM framework/ method that requires values/preferences/uncertainty to be made explicit**
- **Education on decision-making concepts/theory**
- **Create an environment that encourage dissenting opinions and challenging ideas**
- **Ensure transparency and information access**
- **Have a robust system which focuses on evidence and facts**
- **Multistakeholder inclusion - including patients**
- **More formal review of decisions (both positive and negative) and process**



## Submission lag: What are the key factors that delay a medicine's submission and how can these be mitigated?

**Thuy Dang**

*Head of Regulatory Affairs Asia-Pacific/Japan Consumer Health, Bayer (South East Asia) Pte. Ltd*

### Factors affecting the global rollout of medicines

The goal of pharmaceutical companies is to provide the earliest possible global access to safe effective medicines. However, the global rollout of these therapies is driven by intrinsic, extrinsic and operational factors. Intrinsic and extrinsic factors are the properties specified in the guideline of the International Council for the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E5 that assist in the identification of appropriate treatment populations. Intrinsic genetic and physiologic factors include body weight and genetic polymorphism and extrinsic cultural or environmental factors include local medical practice and socioeconomic status. The operational factors of a sponsoring company that affect the rollout of medicines in a specific area include the size, time to completion and feasibility of required clinical trials. For example, the optimal size of a phase 3 trial may not meet the regional requirements for the number of

patient. In addition, submission to one country or region may have an effect on submission to other countries or regions.

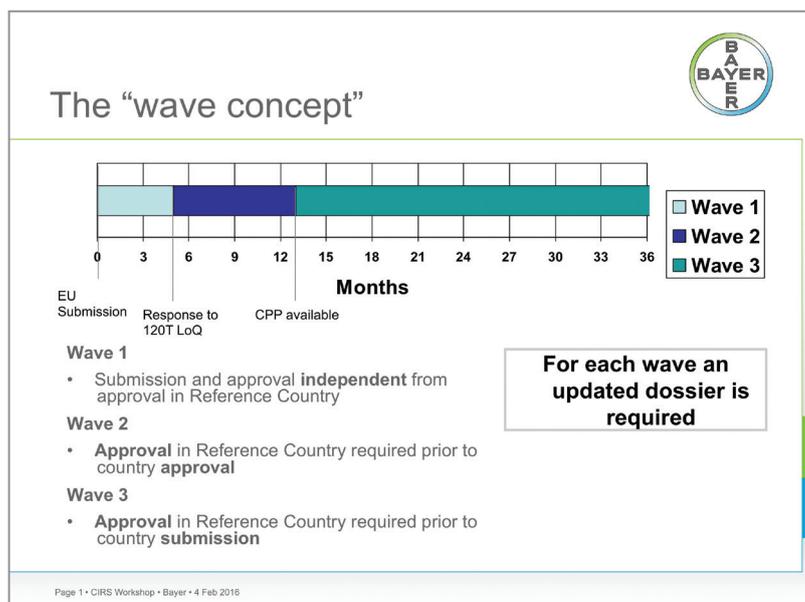
Global rollout for new medicines is often conducted in waves. In this type of submission process, wave 1 incorporate submissions and approvals that are independent from approval in reference country, wave 2 includes submissions to countries in which approval in a reference country is required prior to approval and wave 3 includes submissions to countries in which approval in a reference country is required before submission. An updated dossier is required for each wave (Figure 26).

In fine tuning global rollout strategies, companies also weight countries from a priority perspective or rank them according to their potential for market access and the respective regulatory environment. Market-driven concepts are considered such as pricing and reimbursement and peak sales potential. Strategic priorities are outlined and "must have" countries identified as well as any other countries with good growth potential and a market outlook.

Regulatory considerations influencing early access to medicines include the existence of mechanisms for compassionate access or expedited review pathways. Internal dossier management logistics typically involve submission to the United States, EU and Japan on the same day and submission to countries that do not require a certificate of pharmaceutical product (CPP) as soon as possible. Local clinical data requirements must also be considered such as bridging studies with predefined minimum sample sizes. Variability exists in the timelines for the issuance of CPPs by different health authorities and may include notarization or legalisation requirements. There may also be a need for a CPP from the manufacturing country, multiple CPPs or a marketing statement. Finally, data exclusivity and the enforcement of intellectual property and patent protection are other regulatory considerations that impact the global availability of new medicines.

Other industry considerations that might limit global access include the fact that companies may not be present in certain countries, there may be limitations on local regulatory resources or manufacturing costs may be high for certain medicines such as biologics. Region-specific data requirements, such as stability data for the Association of Southeast Asian Nation

Figure 26. Global rollout for new medicines is often conducted in waves.



(ASEAN) countries or country-specific labelling requirements may be onerous or there may be issues related to the supply chain network or market access such as reimbursement or drug listing.

### Regulatory convergence

According to the FDA,

“regulatory convergence represents a process whereby the regulatory requirements across countries or regions become more similar or “aligned” over time as a result of the gradual adoption of internationally recognised technical guidance documents, standards and scientific principles, common or similar practices and procedures, or adoption of regulatory mechanisms that might be specific to a local legal context but that align with shared principles to achieve a common public health goal. It does not necessarily represent the harmonisation of laws and regulations, which is not a prerequisite for allowing the alignment of technical requirements and greater regulatory cooperation.”

ICH reforms have resulted in the expansion of membership beyond the initial few mature markets. More involvement from regulators around the world is welcomed and expected, as different jurisdictions will be invited to join counterparts from Europe, Japan, USA, Canada and Switzerland as ICH regulatory members.

The reforms strengthen ICH as the leading platform for global pharmaceutical regulatory harmonisation and one that brings together in a

**... to reduce submission lag and ensure early patient access to medicines, industry and regulatory agency collaboration is needed to drive overall regulatory convergence.**

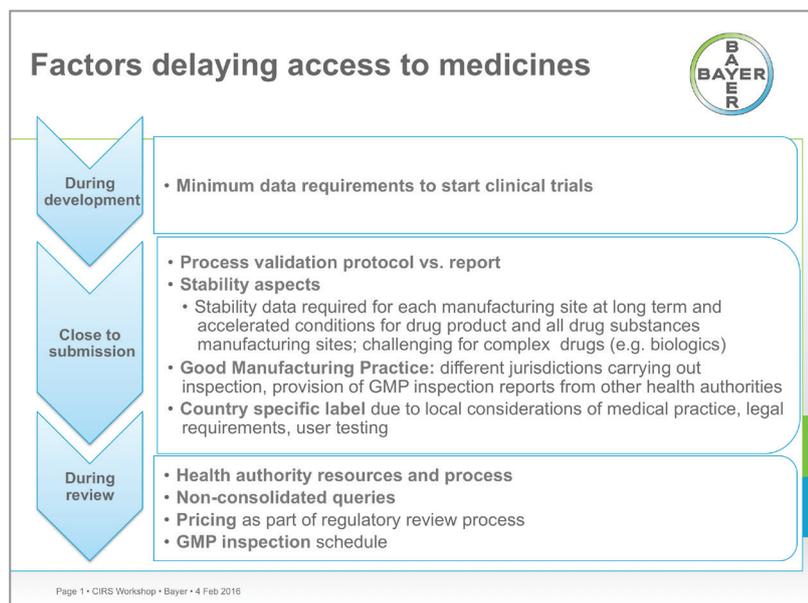
transparent manner all key regulatory authorities and industry stakeholders.

International electronic standards play a strong role in regulatory convergence. These standards include

- The Identification of Medicinal Products (IDMP), which are global standards for unique identification of medicinal products developed by the International Organization for Standardization (ISO). IDMP is an internationally accepted framework for the consistent documentation, coding and exchange of product information;
- Individual Case Safety Reports (ICSRs), which employ the ISO standard for electronic transmission in order to exchange adverse events and medication error reporting;
- The Electronic Common Technical Document (eCTD), which represents the harmonised electronic interface for the transfer of regulatory information from regulated industry to regulatory authorities. eCTD v4.0 within Health Level Seven International (HL7) incorporate new functionality such as two-way communication.

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Figure 27. Various issues can hinder availability to new medicines throughout a product lifecycle.



Active dialogue is maintained between regulators and industry in the EU. The EMA oversees the centralised authorisation procedure with the EU, providing scientific advice to companies to support research and development activities, offering targeted information to SMEs, advising on compliance with EU regulatory requirements and frequently conducting stakeholder meetings. The EMA regards the pharmaceutical industry as “one of its main stakeholders ... interactions are guided by a formal framework that rests on the principles of accountability, transparency and broad representation.”

Despite these factors that positively influence access to medicines, various other issues can delay that access throughout a product lifecycle (Figure 27).

Bayer regularly benchmarks its own performance. Key performance indicators used

by the company for regulatory submissions include the speed and quality of submissions, number of deficiency letters and types of questions, the number of simultaneous submission and approvals, the time to approval, first-cycle approval rate and the predictability of regulatory outcome. The company also measures its performance against industry peers. In a 2014 comparison with 13 other countries, the company was ranked third in discovery and first in development. Despite a research and development spending rate that was 40% below the median for other companies, the Bayer R&D success rate has increased 30% since 2009.

### Conclusions

For early access to innovative medicines, especially in areas of unmet medical need, consideration must be given to optimising a medicine's potential market access. Factors delaying early access can include clinical

trial requirements, a submission lag driven by company roll-out strategy, regulatory requirements, lack of regulatory convergence, regulatory governance issues enabling regulatory excellence and the inclusion of pricing as part of regulatory approval process.

The submission lag could be reduced by a convergence in issues surrounding CPP requirements, country-specific requirements related to clinical data, chemistry, manufacturing and controls and labelling, by consistent interpretation of the guidelines by regulatory agency staff and by access to regulatory agency consultation during development and prior to submission to optimise development programmes and dossiers submissions. Most importantly, in order to reduce submission lag and ensure early patient access to medicines, industry and regulatory agency collaboration is needed to drive overall regulatory convergence.

## Evolution of HTA agencies across Asia – Changing the access landscape –how could the impact be measured?

### Dr Sorapop Kiatpongsan

*Lecturer, Faculty of Medicine, Chulalongkorn University, Thailand*

### The need for health technology assessment

According to the World Health Organization, health technology assessment (HTA) is "the systematic evaluation of properties, effects and/or impacts of health-care technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in healthcare." HTA is one of three complementary functions to ensure the appropriate introduction and use of health technology. The other two components are regulation, which is concerned with safety and efficacy; and management, which is concerned with the procurement and maintenance of the technology during its life-cycle.

HTA is helpful because the use of limited societal resources must be prioritised and technologies purchased with those resources should be associated with value and demonstrate a level of cost and effectiveness. An evidence-based HTA decision-making process allows the decision maker to evaluate study design, costs and benefits, apply discounting and conduct a sensitivity analysis.

Evidence-based decision making can also be associated with challenges that include uncertainty and a lack of evidence. A lack of long-term data on safety and efficacy, for example, can result in the use of models that can be complex and costly to build and that may have limitations. Finally, it should be recognised, that in addition to cost effectiveness, other issues such as equity, acceptability, feasibility and competing needs must also be considered.

Established in 2010, the objective of HTAsiaLink is the collaboration between not-for-profit HTA agencies in Asia, the capacity strengthening of member organisations, the exchange of information, experience and resources and the encouragement of the use of HTA findings in decision making. Members include China, Japan, Korea, Malaysia, the Philippines, Singapore, Taiwan and Thailand.

Measuring and enhancing impact of HTA

National Information Center on Health Services Research and Health Care Technology (NICHSR) has stated that “the impact of HTA is variable and inconsistently understood. . . even when the reporting of HTA findings is followed by changes in policies, use of a technology, or other potential indicators of impact, it may be difficult to demonstrate the causal effect of the HTA on those changes.”

According to NICHSR, the impact of HTA can be difficult to quantify and results of HTA may be evaluated by considering its impacts on

- regulatory policy
- third party payment policy
- the rate of use of a technology
- clinical practice guidelines, clinician and patient awareness and behavior
- the acquisition, adoption, or diffusion of a technology
- the organization or delivery of care
- R&D priorities and associated spending levels
- data collection to fill evidence gaps identified by HTA reports
- the marketing of a technology
- the allocation of local, regional, national, or global healthcare resources
- investment decisions and
- incentives to innovate

The Health Intervention and Technology Assessment Program (HITAP), which is the HTA body of Thailand, has cited several indications of its impact including vaccine price negotiations and the expansion of cervical cancer screening program at national level; policy change to free-of-charge HIV screening for all Thai population; the use of information on social costs from alcohol abuse by a health promotion organisation to plan their activities; the suggestion by the National Health Security Office (NHSO) of the use of the three-drug instead of the two-drug regimen for the prevention of vertical virus transmission from mother to child and the agreement by the Subcommittee for Development of Benefit Package and Service Delivery (SCBP) of the NHSO to include stem cell transplantation in the benefit package pending a feasibility study.

**NICHSR: “, it may be difficult to demonstrate the causal effect of the HTA on those changes.”**

Factors that influence the impact of HTA include clinician, patient, provider organisation and environmental characteristics as well the characteristics of HTA findings. According to the NICHSR, HTA impacts might be enhanced by HTA agencies that

- conduct a transparent, credible, unbiased, rigorous and well-documented HTA process,
- gain prior commitment, where feasible, from decision makers to use HTA findings,
- ensure that assessments are designed to address decision makers’ questions,
- seek to establish formal links between producers and users of HTA,
- involve key stakeholders throughout the HTA process in a transparent, well-managed manner,
- gain input of representatives of anticipated target audiences and communication experts in planning, knowledge transfer strategies,
- anticipate the resource requirements, incentives, delivery system characteristics and other diverse factors that will influence the feasibility of implementing HTA findings and
- ensure that HTA findings are delivered on a timely basis to inform decision making, promote collaboration and transfer of knowledge and skills across jurisdictions.

### Conclusions

The post-approval phase of medicine development involves many steps and stakeholders and health technology assessment is only one piece of evidence to inform a decision. Measuring and monitoring the impact of HTA agencies is challenging but possible. Patients and policy makers should be informed and educated about HTA, cost and cost-effectiveness and collaborations between regulatory agencies and HTA agencies should be promoted.

## Improving availability and meeting unmet medical need:

### What are the facilitated licensing pathways and measures that can be considered?

**Prof Hans-Georg Eichler**

*Senior Medical Officer, European Medicines Agency*

Professor Eichler introduced the topic of facilitated regulatory pathways by asking Workshop participants to consider the healthcare needs of two patients:

- Jane, a woman in her late fifties who was recent diagnosed with advanced cancer and who has a life expectancy of approximately two years and
- John, a man in his late fifties who has a family history of cancer but who is currently in good health and who has a life expectancy of approximately twenty years.

Although on the surface it may seem logical to apply consistent, uniform regulatory processes and standards to all products, regulators must consider the best way to meet the healthcare needs of patients like Jane and John and indeed, of all patients. These needs may be best served through the prioritisation of regulatory resources.

One tool for regulatory prioritisation used by the European Medicines Agency (EMA) is

**... facilitated pathways will encompass a combination of actions and regulatory tools and are compatible with high evidence standards**

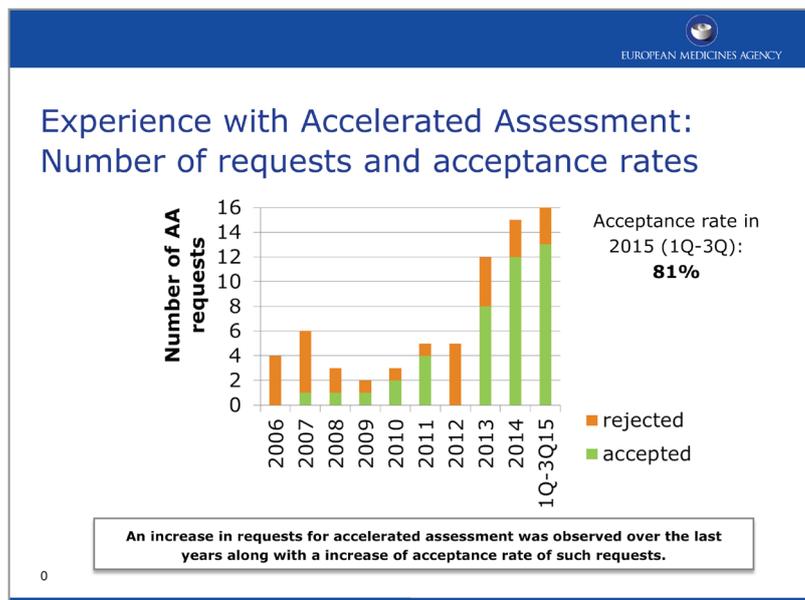
the accelerated assessment or products of major interest from the point of view of public health and in particular, from the viewpoint of therapeutic innovation. Requests for accelerated assessment must be submitted and agreed in advance of submitting the marketing approval application. The maximum active regulatory time for this type of review is 150 days. The number of requests for accelerated assessment have increased every year since 2005, as have the rate of acceptance of these requests (Figure 28).

However, in addition to accelerated assessment some innovative products require different, flexible pathways for regulatory assessment that can accommodate non-standard evidence development. For example, the benefit-risk evaluation for advanced or personalised therapies can be extremely context dependent and data for long-term outcomes are unlikely to be available. In other examples, very long observation periods are required for the benefit-risk assessment of early interception treatments, small patient numbers are common in trials of precision and personalised medicine and personalised medicine is also associated with complex therapeutic combinations.

According to EU Regulation number 507, flexible licensing pathways for the regulation of these therapies should be used where “the benefit to public health of the immediate availability on the market [...] outweighs the risk inherent in the fact that additional data are still required.” The regulation specifies that conditional marketing authorisation may be granted for these innovative products on the basis of less comprehensive data and subject to specific obligations (Figure 29)

Flexible regulatory pathways require that regulators provide operational support to medicines’ developers including intense, early dialogue with drug developers, dedicated support to small and medium enterprises and academia and faster than normal assessment. Follow-up of the specific obligations entailed in conditional marketing authorisation is also critical to avoid the unfounded public perception that the use of flexible pathways represents a lessening of regulatory standards for safety and efficacy (Figure 30)

Figure 28. Requests for accelerated assessment at the EMA: 2006-2015.



EUROPEAN MEDICINES AGENCY

## EMA regulatory tool: Conditional Marketing Authorisation

On the basis of less comprehensive data and subject to specific obligations

**Scope** (at least one):

- for **seriously debilitating diseases or life-threatening diseases**;
- to be used **in emergency situations**;
- orphan** medicinal products.

**Criteria** (all):

- the **risk-benefit balance is positive**;
- it is likely that the applicant **will be in a position to provide comprehensive clinical data**;
- unmet medical needs** will be fulfilled;
- the **benefit** to public health **of the immediate availability** on the market of the medicinal product concerned **outweighs the risk** inherent in the fact that additional data are still required.

Regulation (EC) No 507/2006

1

Figure 29. EMA Regulation EC 507: the criteria for conditional marketing authorisation.

Regulatory collaboration with downstream decision makers such as payers, prescribers and patients will also enable the success of facilitated regulatory pathways. The EMA has engaged in approximately sixty procedures for early dialogue among drug developers, regulators and health technology assessment bodies. In addition, the EMA has explored synergies in post-launch evidence generation between regulators and payers and initiated conceptual work in the public-private partnership project for integrated facilitated pathways, “Medicines Adaptive Pathways to Patients”.

Figure 30. Follow-up of specific obligations of conditional marketing authorisation is key.

Professor Eichler concluded by stating that

regulators should offer some form of “facilitated pathway” – to serve the needs of all patients, current and future. In practice, these facilitated pathways will encompass a combination of actions and regulatory tools and are compatible with high evidence standards



## Characteristics of emerging agency facilitated regulatory pathways: What are the key processes and substantive building blocks?

**Dr Neil McAuslane** for **Lawrence Liberti**

*Executive Director, Centre for Innovation in Regulatory Science*

### Facilitated regulatory pathways

Facilitated regulatory pathways (FRPs) can be defined as alternatives to standard regulatory pathways that accelerate the development, submission and regulatory review of marketing authorisations and patient access to medicines for serious diseases or unmet medical need. Examples of FRPs are Accelerated Assessment and Conditional Marketing Authorisation in Europe; Accelerated Approval, Breakthrough Therapy, Fast Track, Priority review in the United States and Notice of Compliance with Conditions at Health Canada. The goal of the use of these pathways is to speed the progressive development, authorisation and access to important new drugs with a positive benefit-risk balance.

FRPs may increase the level of communication/commitment between the developer and the agency; can give a larger role to effects on surrogate end points and move the burden of clinical benefit/longer-term safety evidence from the pre- to the post-authorisation phase. Society

must be willing to accept uncertainty about the benefits and harms of new medicines approved through these pathways because of the serious risks of the disease; the lack of effective therapies and the belief that the initial data generated are reasonably predictive of clinical benefit, despite uncertainty about the true value of the therapy.

### FRPs in mature markets

The focus of the CIRS publication, R&D Briefing 57 New Drug Approvals in ICH countries 2005-2014 was the review of medicines that underwent review through an FRP or that had received orphan status. Expedited reviews made up 58% and 50% of all NAS approvals at FDA and PMDA in 2014 and 13% at EMA. Despite differences in the use of expedited review, median approval times for these expedited reviews were similar across the ICH agencies in 2014 (Figure 31).

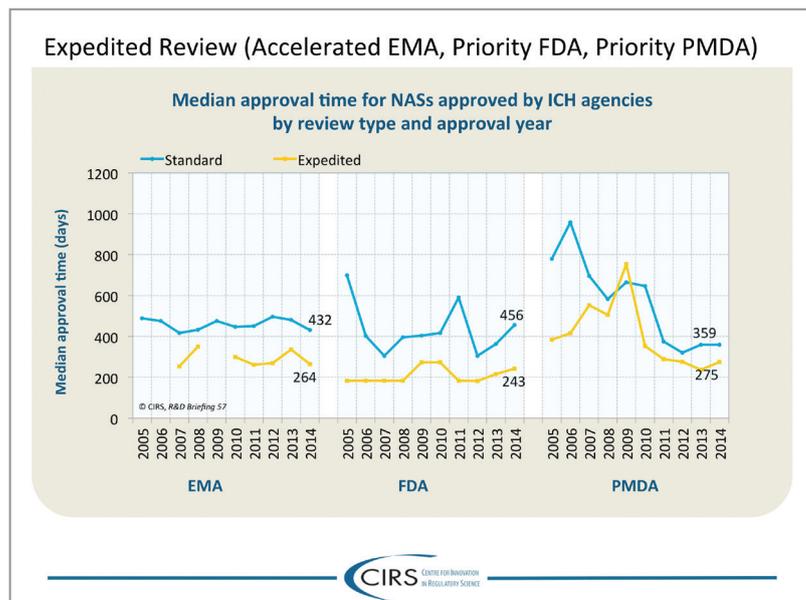
Liberti and colleagues detailed the results of a survey of 80 respondents from pharmaceutical companies, regulatory and health technology assessment agencies, patient groups and other organisations to gain insights into personal opinions regarding FRPs and adaptive licensing. Whilst 63% of survey participants indicated that US FDA FRPs are fit for purpose, EMA pathways and Japanese PMDA pathways were regarded as useful by only 13% and 7% of respondents respectively.<sup>1</sup>

### FRPs in emerging markets

With a growing portfolio of products for neglected diseases and an expanding commitment from national regulatory authorities and the World Health Organization for new treatments for local populations, the importance of FRPs has also increased for emerging national regulatory authorities. This movement has resulted in country-specific pathways to expedite the regulatory review of new medicines/vaccines for serious and unmet medical needs.

Whilst FRPs being used or piloted by stringent regulatory authorities are well characterised, no systematic assessment has been conducted of the characteristics of formal FRPs in emerging regulatory agencies. Therefore, Mr Liberti and associates have completed a descriptive study to assess characteristics and common elements of currently implemented FRPs in emerging national regulatory authorities to understand the diversity and similarities of these FRPs; to identify common processes; to help with the ongoing assessment and development of national

Figure 31. Median approval times for expedited reviews were similar across the ICH agencies in 2014.



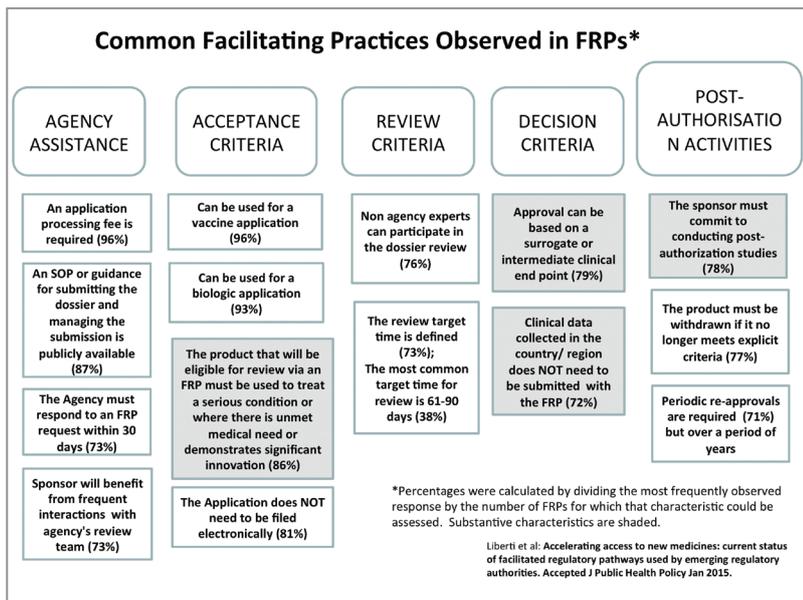


Figure 32. Some facilitating practices were common among all global agencies in the study

regulatory systems and to provide evidence for international organisations to help focus strategies for increasing regulatory capacity at emerging NRAs.<sup>2</sup> In this research, 27 FRP characteristics were assessed for 33 FRPs from 29 countries around the world.

Characteristics were categorised as procedural; that is, rules or activities related to overall process (18 characteristics) or substantive; that is, those used to determine how the evidence supports the outcome (9 characteristics). Five sequential regulatory activities were also identified:

1. those describing ways for agencies to assist the sponsor to facilitate the submission or review (6 characteristics);
2. criteria for the acceptance of the regulatory dossier (9 characteristics);

3. review process attributes (4 characteristics);
4. decision criteria (4 characteristics);
5. post-authorisation and disengagement activities (4 characteristics)

All stakeholders in medicine are on the learning curve regarding FRPs. Diversity in FRP characteristics suggests a role for further engagement with emerging national regulatory authorities regarding their design and implementation. Common characteristics were observed among surveyed agencies (Figure 32) but it remains to be determined if any of the common elements are the main decision drivers and when those characteristics assume a major role. Common processes could help regulatory alignment initiatives and the WHO inform the development of novel, globally aligned accelerated development and regulatory pathways for products that fulfil serious unmet public health challenges.

### References

1. Liberti L, Stolk P, McAuslane N, Somauroo A, Breckenridge AM, Leufkens H. Adaptive licensing and facilitated regulatory pathways: A survey of stakeholder perceptions. *Clin Pharmacol Ther.* 2015 Apr 15. doi: 10.1002/cpt.140. [Epub ahead of print].
2. Liberti L, Breckenridge A, Hoekman J, Leufkens H, Lumpkin M, McAuslane N, Stolk P, Zhi K, Rågo L. Accelerating access to new medicines: Current status of facilitated regulatory pathways used by emerging regulatory authorities. *J Pub Health Pol.* 2016 Mar 10. doi: 10.1057/jphp.2016.8. [Epub ahead of print].

## Optimising regulatory pathways in low- and very low-income countries

**Dr Murray Lumpkin**

*Deputy Director – Integrated Development and Lead for Global Regulatory Systems Initiatives, Bill and Melinda Gates Foundation, USA*

### Low- and very low-income registration

The processes for the development, regulation, and distribution of medicine in higher income countries is a closed, linear, highly regulated, proscribed system that helps ensure product quality, safety and efficacy as well as supply chain security. This is compared with an open, loosely (if at all) regulated, multifaceted, complex system in low- and very low-income (L/VLIC) countries that results in products of uncertain quality, safety and efficacy and in insecure supply chains.

To introduce a vaccine or drug in many L/VLIC countries, the product must be registered with the country’s national regulatory authority. The product also typically needs WHO prequalification (PQ) to meet the quality requirements of donors and procurers and to help assure L/VLIC suitability. Before that, the product generally needs a first registration, usually in the country of origin, or a recognised stringent regulatory authority (SRA) and often needs a Certificate of Pharmaceutical Product (CPP).

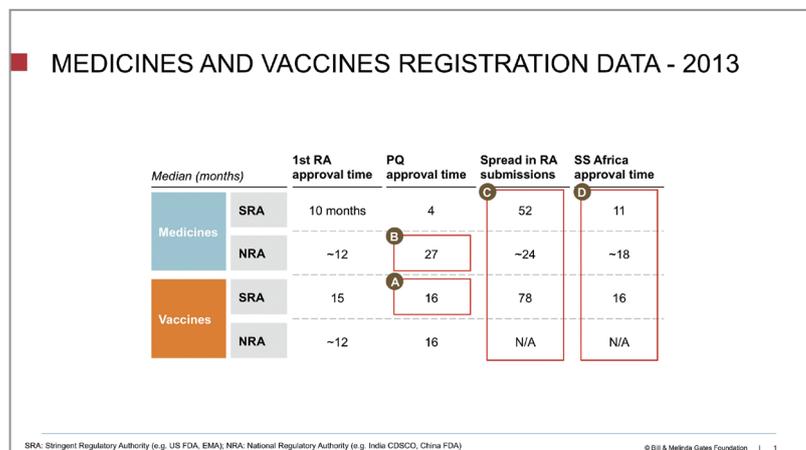
The Bill and Melinda Gates Foundation examined registration data for more than 200 medicines and vaccines to determine the timing for the various regulatory assessments a product must go through in order finally to be registered in a L/VLIC country. This, usually, three-step

assessment process includes, first, the approval by a stringent regulatory authority and/or by the national regulatory authorities in the country of manufacture, then by WHO PQ, then by the NRA in the L/VLIC. In addition there is often a very long span between first submission to an NRA in Sub-Saharan Africa and the submission to the last NRA in Sub-Saharan Africa. It was determined that the total time for all of these assessments and approvals averaged between 4 and 7 years after the completion of the development program and the initial submission to an SRA or the NRA in the country of manufacture (Figure 33). The greatest opportunities to expedite the availability of new medicines and vaccines was likely to be found in optimising some of the processes for vaccine WHO PQ, helping manufacturers from LICs understand better the international requirements of PQ, working to help NRAs rely on the working products of other trusted agencies to help inform their own decision making, both through joint reviews and work-sharing and through more regional approaches to product regulation. The rationales for some of these delays may include a lack of a business imperative, language barriers and the complexities in local registration systems.

### Facilitation of regulatory pathways

The World Health Organization has recently begun to conduct abbreviated PQ assessment for vaccines approved by SRAs. In this assessment, rather than duplicate the work performed by an SRA, the WHO PQ relies on the scientific assessment and inspection reports of the SRA but brings added value by reviewing the suitability of the product data, labelling and manufacturing for local populations. In two years, WHO has reduced PQ timing from 2.4 months to 0.5 months for products that had been approved by an SRA and from 10 months to 6.9 months for products that had not been approved by a SRA. Once products that were first approved by national regulatory authorities undergo WHO PQ, local regulatory authorities can enter into a collaborative review process with WHO, agreeing to reach a regulatory decision within 90 days (Figure 34). In this process, the local NRAs rely on the scientific assessments and inspections of WHO to inform their decision-making. Twenty-seven countries have enrolled in the collaborative process and thus far, the median time for local regulatory review as part of this process was 74 days for 105 registrations of 43 medicines.

Figure 33. Areas for improvement in timing in the registration of medicines and vaccines in L/VLICs.



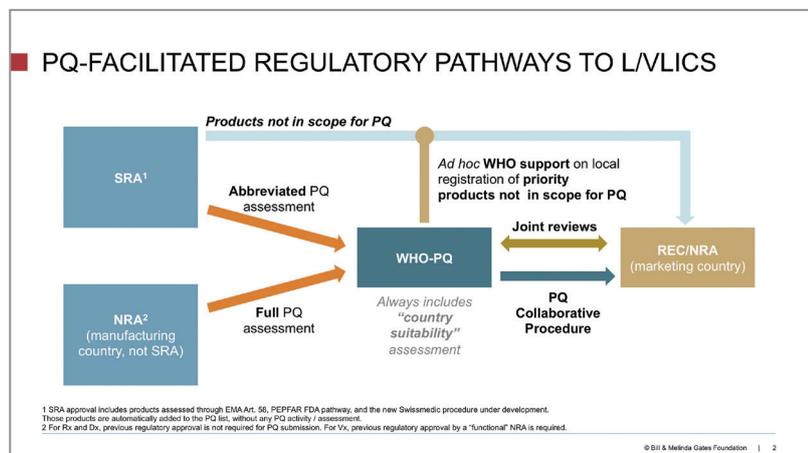
**[AMRH] proposes to harmonise and streamline the registration process for regulators and manufacturers and creates a platform on which to build African regulatory capacity by region, leading to increased and timely access to quality products.**

When measuring performance by the achievement of target times, it is critical to identify the individual timing of all stakeholders in the process; for example, WHO time versus sponsor time to answer queries posed by WHO after the initial review of the dossier. Moreover, in addition to evaluating the timing of approval cohorts, the sponsors and reviewers of medicines may wish to consider the use of performance management tools that measure “first action cohorts” such the percentage of products that came to a first decision, whether that decision is to list or to request further information versus agreed performance goals for first actions. It may also be helpful to follow first actions for products that are submitted within a calendar year (a so-called “submission cohort”) rather than the traditional “action cohort”, so that progress achieved as the result of new process improvements can be observed.

### African Medicines Regulatory Harmonisation (AMRH)

One example of the regional approach to product regulation now being taken in various part of the world, is the initiative by the East African Community (EAC) as part of the larger African Medicines Regulatory Harmonisation initiative. This effort was launched in East Africa in 2012 and includes the regulatory authorities from the EAC with supportive parties such as WHO, New Partnership for Africa’s Development, Gates Foundation, Department for International Development (UK), World Bank, Joint United

Figure 34. The role of the WHO PQ procedure in expediting the registration of medicines and vaccines in L/VLICs.



Nations Programme on HIV/AIDS, President’s Emergency Plan for AIDS Relief (US) and many others. This initiative aims to improve the fragmented system of product registration in Africa by focusing on established regional economic communities within the continent; for example, EAC and ECOWAS in West Africa. AMRH proposes to harmonise and streamline the registration process for regulators and manufacturers and creates a platform on which to build African regulatory capacity by region, leading to increased and timely access to quality products.

The initial focus is on the development of regional registration platforms with common requirements, guidelines and format, employing joint assessments and inspections, streamlined decision processes and work sharing and the pooling of resources. This optimised registration is initially for generic drugs and will be extended to other product categories such as new chemical entities, vaccines and diagnostics and extended to other regulatory functions over time such as approval of clinical trial applications and safety surveillance. After the current successes in the EAC with generic drugs and with joint assessments, the process is being extended to other African Regional Economic Communities. In the EAC, harmonised technical guidelines and requirements were developed and, after international consultation, approved at the EAC ministerial level in 2014 and implemented in January 2015. Implementation started with two pilots of the regional review and registration of seven products with a resultant 40% to 60% reduction in timeline and the elimination of the spread in time of manufacturer submissions to national regulatory authorities. Full implementation of the harmonised standards is on track.

After the successful pilots, the regional EAC product registration system was launched in January 2015 and the first joint regional review of eight dossiers was conducted in October 2015 with technical support from WHO and Swissmedic. At the time of this Workshop, four products from this cohort had already been approved by all EAC national regulatory authorities and decisions for four products were pending for sponsor response. Finally, a Pharmaceutical Model Law was adopted by African Union Heads of State in January 2016 that can now be domesticated by individual countries in Africa. This model law will allow them to have the basic legal foundation for a modern medical product regulatory system and would allow centralized registration procedures to be conducted through regional economic communities.

WORKSHOP REPORT

## Section 3: Roundtable Discussions

### Roundtable Discussion A

What are the critical KPIs that inform an agency's effective and efficient performance?	
Chair	<b>Prof Hans-Georg Eichler</b> , <i>Senior Medical Officer, EMA</i>
Rapporteur	<b>Dr Felipe Dolz, Vice President</b> , <i>Global Regulatory Policy and Intelligence, Sanofi, USA</i>

#### Background

Regulatory performance is often measured only by the time it takes to approve or reject a new medicine but there can be many factors within agencies that can influence these decisions. These factors include resources, regulatory policy, processes and practices, company time to answer agency questions, scientific assessment time, other agency time and the route used for the review.

Mature agencies have set themselves a number of key qualitative and quantitative performance indicators, against which they and their stakeholders can measure their performance. These performance measures need to be reported and utilised in order for agencies to identify what is working well and what may need improvement as well as to provide feedback to the organisation following a period of change. Agencies are interested in evaluating the impact of their changing roles in enabling medicines development throughout medicines' lifecycle and to monitor the outcome of their decision making. As such, what could be the measured key impact factors?

As emerging regulatory agencies evolve their good review practices, it is important that they also develop their own performance metrics. These measurements could serve as a barometer of change, providing active feedback on the effectiveness of changes being proposed or implemented in various jurisdictions.

At a previous CIRS Workshop, *Building quality submission and review processes and practices – Overcoming challenges and meeting expectations* in 2014 in Lima, Peru, potential KPIs suggested included timing for approval, review and scientific assessment as well as sponsors' time to answer question, communication within organisation and among stakeholders and the number of approval or rejection decisions per year.

#### Questions for consideration

The focus for this Roundtable was to identify the critical KPIs that agencies should consider as well as the benefits and hurdles for agencies in adopting these metrics. Although having these KPI is useful to monitor change, there are many factors to consider:

- What KPIs should be set to monitor an agency's progress?
- What tools should be used to monitor these KPIs?
- Should KPIs be quantitative, qualitative or a mix of both?
- What are the areas of an agency's performance that agencies and companies believe should be measured and what is the rationale for the selection?
- What are the critical internal KPIs that agencies should consider?
- Which critical KPIs are external stakeholders looking for?
- How can KPIs best be developed and implemented within agencies?
- How should internal and external KPIs be reported and what would be the main purpose?
- What impact on the agency system can these indicators have and how can they be measured?
- Should agencies also measure their impact on external stakeholders? If so, how?
- What other topics should be discussed or further investigated by CIRS?

#### Critical issues

This Roundtable agreed that key performance indicators should measure performance against

agency deliverables and ideally, both leading and lagging KPIs should be identified. Whether performance is measured quantitatively or qualitatively, the goal is predictability and transparency of regulatory process for all stakeholders. Items for measurement include regulatory talent and systems, process efficiency and output.

Suggested KPIs include timelines for submissions, approvals, variations, advice, inspections and renewals. In measuring timeliness, discriminating among agency, sponsor and other time is key. Absolute timing, variability in timing and time to the first question should all be measured as should the number of first-cycle approvals

The visibility of review progression facilitates industry planning and development and could be another valid measurement of regulatory performance as could the availability of agency personnel for consultation at key times during the development and registration processes. This availability increases company-agency understanding, reduces the number of avoidable questions and increases the likelihood of adherence to agency guidelines and advice. Regular and timely public communication and provision of information via vehicles such as agency website could also be a gauge of regulatory performance. Agencies may also be evaluated on their follow-up of industry post-approval commitments.

The consistency of approved labelling with that of other jurisdictions as measured by the percentage of agreement or deviation is another potential agency performance indicator. Agencies and industry can provide each other with regular performance feedback regarding efficiency and quality through questionnaires or surveys.

#### Recommendations

- Agencies should measure timeliness for submissions, approvals, variations, advice, inspections and renewals; absolute timing, variability in timing and time to the first questions and the number of first-cycle approvals
- Agencies should evaluate visibility of review progression, the availability of agency personnel for consultation at key times during the development and registration processes; regular and timely public communication and provision of information via vehicles such as agency website and follow-up of industry post-approval commitments
- Agencies should assess the consistency of approved labelling with that of other jurisdictions as measured by the percentage of agreement or deviation
- Agencies and companies should provide each other with regular performance feedback regarding efficiency and quality through questionnaires or surveys.
- CIRS should consider the development of an initiative to incentivise agencies and other stakeholders toward convergence or harmonisation

## Roundtable Discussion B

### What are the key measures of quality decision making that an agency can adopt that can improve its planning and review?

Chair

**Dr Tomas Salmonson**, *Chair, CHMP, European Medicines Agency*

Rapporteur

**Magda Bujar**, *Research Analyst, CIRS*

### Background

An organisation's decision abilities determine its performance and its decision making is, in large part, influenced by organisational processes and procedures. Agencies have a number of different processes, practices and frameworks that can be used to ensure that quality is built into the decision-making process, such as good review practices and a systematic structured approach to benefit-risk assessment. These ensure not just good-quality decision making but also enable consistency, transparency and confidence in the decisions that are made.

All decision-making processes are known to have a number of potential weaknesses, which can include a narrow frame, biases, short-term thinking and overconfidence and left unchecked, subconscious biases may undermine quality decision making. The science of decision making is well established, although in reality, it is a mixture of science and art. Within agencies, ten practices have been identified<sup>1</sup> as making up quality decision-making practices.

1. Have a systematic, structured approach to aid decision making (consistent and predictable)
2. Assign clear roles and responsibilities (decision makers, advisors, contributors)
3. Consider uncertainty.
4. Examine alternative solutions
5. Assign values and relative importance to decision criteria
6. Re-evaluate as new information becomes available
7. Evaluate both internal and external influences/biases
8. Apply a structured approach to ensure transparency and provide a record trail
9. Perform impact analysis.
10. Effectively communicate the basis of the decision

One way to determine whether quality decisions are being made is to assess the outcome and consequences of the decision. However, this is not often practical and can be extremely difficult to measure. Indeed, a good, well-made decision may have poor consequences and a bad decision may have good outcomes. Therefore, there is a need to ensure that processes within agencies are structured so as to enable consistency around making quality decisions. The question then, is how the process, which is separate from the outcome can, best be structured and measured to ensure quality is built into decision making.

Developing a quality management system (Say what I do, Do what I say, Prove it, Improve it) is embedded in good review practices and in a recent survey<sup>1</sup> agencies suggested possible ways to measure the quality of the decision-making process include to assess adherence against validated standards or guidelines for decision making; review the consistency of decision-making practices within an organisation; assess the degree of clarity and transparency in decision making and determine whether all the evidence (positive and negative) has been considered and to formally assess internal stakeholders' evaluation practices.

At the CIRS Workshop in Malaysia in 2011<sup>2</sup> it was recommended to delink the regulatory review process from the process of making decisions and that this separation should be explored. Although the quality of review process and the quality of decision making are of equal importance, methods for enhancing and measuring that quality have yet to be determined. The focus for this Roundtable discussion was to identify the key measures that an agency could or should consider that will enable it to measure the quality of its decision making.

### Questions for consideration

- Do any of the participants in the organisations represented at the Workshop measure the

quality of their internal decision making and if so, what tools or questionnaires are used?

- Is measuring the quality of decision making an important aspect for improving agency performance and if so why?
- What would the group perceive as being the key attributes of a quality decision-making process?
- What would be the appropriate key metrics that an agency can adopt or consider that would enable an agency to measure and improve the quality of their decision making?
- What does the group believe are the biggest challenges for agencies to develop measures for quality of decision making and what are possible solutions?
- In what ways does the group think that an agency measuring the quality of its decision making could be of benefit to other stakeholders such as companies, patients and healthcare professionals?
- Are there other topics that should be discussed here or aspects that you might suggest that CIRS research or further investigate?

### References

1. Bujar M, McAuslane N, Salek S, Walker S. Quality of regulatory decision-making practices: issues facing companies and agencies. *The Innov Reg Sci*. 2016; in publication.
2. CIRS Workshop 2011 - *Evolving the regulatory review process: What are the features which enable a transparent, timely, predictable and good-quality review*. Kuala Lumpur, Malaysia: 6-7 December 2011. [http://cirsci.org/sites/default/files/CIRS\\_December\\_2011\\_WS\\_Report.pdf](http://cirsci.org/sites/default/files/CIRS_December_2011_WS_Report.pdf)

### Critical issues

Currently most organisations do not measure the quality of their internal decision making; nevertheless, the group felt this measurement is important. Quality decision making achieves the objectives and aims of organisations for improving public health, ensures that they are working toward implementing best practices and builds trust within the organisation and among stakeholders through transparency. It's important to understand that although different groups may arrive at a different decision despite having the same data there is a need to document and understand the rationale and influences for the decision. Ultimately, more thoughtful decision making processes may lead to better decisions.

### Quality decision-making practices

The Roundtable agreed that the ten quality decision-making practices that were provided for discussion are practical, applicable and important. Some of these practices may carry more weight than others but if practices 1 through 6 are implemented, a good start can be made toward quality decision making. Before implementing these practices, however, awareness is key. The group specified some additional points for each of the practices.

1. Have a systematic, structured approach to aid decision making (consistent and predictable)
  - *Having a structured process for making decisions such as assessment, benefit-risk evaluations and decisions to approve or reject a compound is key*
  - *The decision context and any assumptions that are made should be defined*
2. Assign clear roles and responsibilities (decision makers, advisors, contributors)
  - *Distinctions must be made between these roles*
  - *Objectives need to be aligned across decision stakeholders*
  - *There is a need to separate external input from decision making by assigning roles and responsibilities – to manage expectations and avoid conflicts*
3. Consider uncertainty
  - *Stakeholders must be explicit regarding acceptability of risk*
4. Examine alternative solutions
  - *Decision makers should go beyond yes or no decision alternatives*
  - *Precedents and history must be evaluated*
5. Assign values and relative importance to decision criteria
  - *Decision makers must determine the criteria given to alternatives and decide which are key*
6. Re-evaluate as new information becomes available
  - *This action is key at all stages of process*
7. Evaluate both internal and external influences/biases
  - *These influences and biases may be difficult to measure but decision makers need to be aware, acknowledge and minimise*

8. Ensure transparency and provide a record trail
  - *There is a need to be comprehensive around subjectivity*
  - *The decision process and how the outcome was decided must be documented*
  - *The aim is to build trust internally and externally*
9. Perform impact analysis
  - *The analysis must concern the present and future impact of the decision*
10. Effectively communicate the basis of the decision
  - *Effective communication will depend on the stakeholder and how much detail is required*
  - *Communication may also have impact downstream and affect the decision processes and evidence used by health technology assessors, healthcare systems and patients*

The group agreed that decision making is challenging. Many decisions are made and decision makers must determine which facts and data are important. Going from quantitative to qualitative assessments is particularly challenging because of timing, public input and political pressure. Having legal and public frameworks can assist in the process but agencies must develop key quality measures for the decision process.

Improving decision-making quality takes time and effort but stakeholders must realise that this is an investment in public health improvement despite potential discomfort about needing to transparently justify the decision and challenges that may arise. Transparent communication is critical and the best method for articulation will depend on the stakeholders.

### Strategies

Organisations should increase the awareness of the issues in decision making in their organisation, highlighting benefits and impact

of a quality decision-making process. Top management needs to be convinced that there is value in looking at the quality of decision making and that the process should be formalised, challenged, measured and improved. Training and awareness are key. In terms of the quality decision making practices that have been identified – each practice should be illustrated, for example, in a scenario setting to further explain its practicality and meaning, applying to specific case studies to show how decisions are made. It must be recognised that there is no “right decision” but there are optimal approaches to making decisions .

Organisations should be more transparent to show how they arrived at a decision in order to build trust among stakeholders; therefore, structured decision practices and templates must be developed and implemented by organisations. Most importantly, organisations need to measure whether decision-making processes and practices are being followed and complied with by surveying external stakeholders and carrying out internal audits of decision processes.

### Recommendations

- **Increase organisational awareness of the importance, benefits and impact of decision making**
- **Using case studies, provide organisational decision-making training**
- **Enlist top management in the implementation, measurement and continuous improvement of processes**
- **Provide transparent rationale for decisions**
- **Ask external stakeholders for feedback regarding decision making and carry out internal audits of decision processes**

## Roundtable Discussion C

<b>Building a performance-driven culture: How can this be defined, achieved and where do agencies start?</b>	
Chair	<b>Barbara Sabourin</b> , <i>Director General, Therapeutic Products Directorate, Health Canada</i>
Rapporteur	<b>Fraser Stodart</b> , <i>Senior Director, Global Emerging Markets (GEMS) – Regulatory Affairs, Biogen, UK</i>

### Background

Good-quality review processes and decision making are predicated on three main items: clear and well-defined processes, consistent application and talented, well-trained people. These processes are also enabled by a performance-driven culture within agencies, in which the organisations are driven by a motivation to perform and achieve organisational success and in which employees are considered as key assets who actually undertake the activities within agencies.

Although culture per se cannot be created or driven by rules and is unique within individual agencies, there are activities that can enable the development of a performance-driven culture. These include the establishment of clarity regarding roles for each individual within the organisation and the identification of personal goals, methods for their achievement and communication how these fit into the overall activities of the agency.

Each employee needs to feel motivated and accountable for their performance and performance goals and targets need to be defined and communicated in a formal way. Areas that are often considered important in a performance-driven culture are available and visible metrics and timely feedback to and from internal and external stakeholders as well as recognition for good performance. This in turn requires organisations to have good performance management system that includes continuous evaluation, feedback, improvement and development of people and processes.

The challenges to agencies developing a performance-driven culture include defining, collecting and reporting the appropriate and relevant performance metrics as well as aligning this with appropriate incentives and training. Although metrics involving time and quantity of activity may be the easiest to implement, quality

of delivery is also an important factor to be considered in any performance-driven culture.

As agencies aspire to improve their performance, the focus for this Roundtable Discussion was the identification of activities that agencies should undertake or consider to enable a performance-driven culture to be embedded within their agency.

### Questions for consideration

- Is having a performance-driven culture important for regulatory agencies and if so why?
- How would the group define a performance-driven culture and what would the key attributes be?
- What drivers and context exist in your organisation to support a performance-driven culture?
- What are the biggest challenges for agencies to embed a performance-driven culture and what are possible solutions?
- What would an agency that wanted to evolve its performance-driven culture need to do?
- In what ways would an agency's performance-driven culture be of benefit to other stakeholders such as companies, patients and doctors?
- Are there other topics that should be discussed here or aspects that you might suggest that CIRS research or further investigate?

### Critical issues

Roundtable C agreed that along with safety, efficacy and timely patient access, quality is the fourth pillar of regulatory review and should never be sacrificed to meet timelines. Work processes, standard operating procedures and management oversight and support are vital to

accommodate a constant workload in the face of limited resources.

Acquiring and retaining competent and skilled, trained staff is critical, as is a consistent training programme. Senior staff should employ an enabling, coaching style that should be focused on key performance indicators. From an industry perspective, consistency, predictability and transparency are key in regulatory review.

This group focussed on several discussion questions.

- **Is having a performance-driven culture important for regulatory agencies and if so why? The roundtable should reflect on the presentation given during the meeting**

The group thoroughly agreed on the importance of this culture, stating that the establishment of a performance culture within agencies should originate with the Ministry of Health and should be internally motivated, with consultation from internal and external stakeholders. Performance culture should lead to a more consistent and quicker review – aiding quicker patient access. Clear key performance indicators help set expectations from external as well as internal stakeholders. Established KPIs allow comparison across similar organisations and demonstration of performance compared to these.

- **How would the group define a performance-driven culture and/or what would be they perceive as being the key attributes?**

A performance-driven culture could best be defined as collegiate and its key attributes, performance, quality, vision are visible throughout the organisation. Training and clear expectations are a part of the organisation and performance management is consistent and followed up. In this culture, cross-team sharing is practiced and knowledge sharing is key. Innovation and evolution are encouraged and fear of change does not impede change. Managers in a performance-driven culture are effective in that role and are not necessarily in a management position solely because they did well as reviewers. A clear understanding of career progression and options is essential and consistency in output and trust are required.

- **What drivers exist in your organisation and context to support a performance-driven**

#### **culture?**

Responses from individual Roundtable participants regarding their individual organisations included:

- There are broad “top down” drivers from the Ministry of Health, frequently tied to national plans. There are internal key performance indicators based on annual goals.
- KPIs are reported to the cabinet/government (Thailand).
- Ministries have a star rating (Malaysia) for performance.
- Annual performance reviews are conducted.
- What does the group believe are the biggest challenges for agencies to embed a performance-driven culture and what are possible solutions?

One solution to the challenges presented by embedding this culture would be the development of a model for convergence and mutual recognition or work sharing and trust building to accept the assessments of regional agencies. There should be governance structure, peer review and a review framework to manage risk and to ensure decisions are supported by the agency. Many agencies or ministries of health rely on external independent academics who are not bound by timelines to conduct scientific reviews. Internal standards would have to apply to these external reviewers in order to fully implement a performance-driven culture.

- **What would an agency that wanted to evolve their performance-driven culture need to do?**

Agencies that wish to develop this culture must find ways to improve submission quality. They should clearly communicate with industry regarding common submission failures and provide guidance to obviate common review issues.

Limited resources, particularly for clinical review are seen as an issue in many countries. Agencies should develop and consistently use a performance management framework, audit and review resource use, ensuring the most efficient use of resources and providing potential justification for requests for new resources. The impact of limited

resources on public health needs to be clearly communicated.

- **In what ways does the group think that an agency having a performance-driven culture could be of benefit to other stakeholders such as companies, patients, doctors?**

Externally facing key performance indicators such as training to sponsor companies on dossier content and structure would positively impact agency resource and review. Their positive impact would also extend to sponsors, who would experience fewer validation rejections and quicker and more consistent review timelines, patients, who would enjoy more rapid access to safe, effective, high-quality products and healthcare professionals, who would be assured of transparent consistent engagement with regulatory agencies.

- **Are there other topics that should be discussed here or aspects that you might suggest that CIRS research or further investigate?**

There is an opportunity for CIRS to passively influence the development of a performance-based culture by following up the benchmarking questionnaire with the provision of an opportunity for more in-depth feedback, comparison and discussion between agencies and leadership in the ministries of health. CIRS could also agree to continuously monitor and provide feedback to agencies, develop Quality Scorecards on the quality of submissions or perform an analysis of agency fees relative to resources and provided services, potentially evaluating whether increases in fees might fund enhancement or expedition of reviews. An analysis should also be performed of needed industry and agency resources for post-approval activities and descriptors of major and minor variations should be globally aligned.

#### Recommendations

- To develop standard key performance indicators for a region, CIRS should follow up its benchmark questionnaire with more in-depth feedback, comparison and discussion with agency leadership
- Both regulators and industry have clear roles to play in the development of safe efficacious medicines and should strive for a partnership rather than an adversarial relationship
- Agencies should establish risk-based reviews with clear guidance for industry, clear agency or ministry of health governance, delegation of responsibility, established roles and expectations and peer review of recommendations by assessors
- Agencies should maintain motivation through reliance on consistent messaging of goals and expectations and acknowledgment of their achievement and establish internally and externally facing performance metrics, expectations and training, matching resources with expectations

## Roundtable Discussion D

### Company and agency interactions: What are the quantitative and qualitative measures that an agency and company can use to maximise outcomes?

Chair	<b>Prof Thomas Kühler</b> , <i>Senior Director, Novo Nordisk A/S, Denmark</i>
Rapporteur	<b>Dr David King</b> , <i>Director, Regulatory Policy and Intelligence, Shire</i>

### Background

In January 2013, CIRS held a Workshop in Beijing<sup>1</sup> during which one of the Syndicates addressed the topic of "Communication between companies and agencies: How can this aid both quality of the submission and quality of the final approval decision?" CIRS asked this Syndicate group to specifically discuss how communication between companies and agencies can be utilised to enable good-quality decision making, both by companies in the decision to submit a fit-for-purpose dossier and by agencies to ensure a quality review.

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

- **Recommendations for pre-submission meetings or discussions** • Industry should be better prepared for these meeting, including having a clear objective. • Ensure the quality, clarity and transparency of communication. • Consider inviting a topic expert since affiliate representatives sometimes do not have adequate expertise. • Work with agencies where needed, develop a guideline for format of these meetings that defines their scope.
- **Recommendations for meetings or discussions during review** • Agencies should consider adopting the concept of Project Manager • Agencies should initiate a formal meeting with a sponsor if an application poses a particular challenge or is deemed not approvable; companies should be able to have a discussion and appeal a negative decision
- **Recommendations for post-decision meetings or discussions** • Create an opportunity for discussion in which reviewing teams could provide feedback to a company

on the quality of application. • Agencies should make their decision documents available on the web in an appropriate format for public use.

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

More recently, the Asia Partnership Conference of Pharmaceutical Associations (APAC) have issued "Good Submission Practice (GSubP) Guideline for Applicants" in which they highlight the importance of early company-agency interactions but emphasise that a good submission and timely review can only be achieved by keeping effective and efficient communications with the review authorities throughout the product development and registration process.<sup>2</sup>

APAC suggests the following approach to ensuring a quality interaction:

- Study and follow the defined rules (guidelines) and procedures for the meeting
- Clarify the purpose of the meeting and discussion points to be made
- Prepare good-quality meeting materials
- Discussion should be based on reasonable scientific rationale
- Prepare and circulate meeting minutes/memo on the discussion points and agreements made at the meeting
- Take appropriate follow-up measures on comments and advice received from authorities

Similarly, the WHO GRevP Guideline encourages having procedures for applicants to engage the agency, both on product development

requirements and on issues identified during the application review, so that these can facilitate the development, review and availability of medical products.<sup>3</sup>

### Questions for consideration

Using these recommendations as a starting point for discussion, this Roundtable was asked to:

- Consider if there are other important aspects of industry-agency interactions that need to be identified beyond those described above.
- Identify one or two metrics that can be used to assess the quality and the outcomes of each of the four interaction types above (and any new ones).
- Discuss how agencies and companies measure the effectiveness and return-on-time investment of their interactions. What are they measuring? If not, how could this be done?
- Discuss whether the development of a specific guidance document around company-agency interactions would be helpful to offer suggestions for approaches to enhance industry-agency interactions and to measure the value of their outcomes? If so, what would be the key elements of such a document?
- Are there other topics that should be discussed here or aspects that you might suggest that CIRS research or further investigate?

### References

1. Liberti L, McAuslane N, Patel P, Connelly P. Workshop report. *Regulatory review – How do agencies ensure the quality of the decision*. Beijing, China, 24-25 January 2013. Available at [http://www.cirsci.org/sites/default/files/CIRS\\_January\\_%202013\\_Workshop\\_REV\\_low-res.pdf](http://www.cirsci.org/sites/default/files/CIRS_January_%202013_Workshop_REV_low-res.pdf)
2. APAC: GOOD SUBMISSION PRACTICE (GSubP) - GUIDELINE FOR APPLICANTS. APAC GSubP Guideline, Final ver.20150330.
3. World Health Organization. Norms and standards. Good review practices: guidelines for national and regional regulatory authorities. *WHO Drug Information*. 2015; 29: 7-12. Available at <http://apps.who.int/medicinedocs/documents/s21799en/s21799en.pdf>

### Critical issues

This Roundtable focussed their discussions on agencies in jurisdictions with emerging pharmaceutical markets. Harmonisation among regional agencies was judged to be important by the group, as was consistency in intra-agency decision processes and heterogeneity and documentation in formal agency-industry interactions. It will be necessary

to seek input from all agencies to meet these goals, particularly to determine gaps in needed resources. Barriers to achievement include differences in medical practice among emerging market countries, the need for enabling legislation in each jurisdiction, extreme differences in capacity and capability among agencies and the lack of a link between the regulation and access to medicines.

### Strategies

Although it may be dependent on the navigation of legal barriers, harmonisation across groups of smaller agencies such as those in the ASEAN region would allow the sharing of expertise and facilitate the coordination of reviews, reducing the need for industry visits to multiple agencies. This harmonisation would be an opportunity for the sharing of scientific opinion rather than a process to give a single product approval. It would be key to have a safe harbour environment for an independent forum for discussions and to ensure minimal political and legal barriers. It would need to be determined who would facilitate the meetings but the World Health Organization coordination of meetings regarding the dengue virus provide a good example of the needed leadership. The value in this strategy lies in the ability of harmonisation to develop a common understanding, provide confidence in cooperation, help agencies to develop expertise in new technologies, increase consistency, aid in resource and capacity building and lead to increased access to new medicines and improvement in public health.

This consistency should apply across assessors and therapeutic areas and be able to be repeated and interpreted over time. Consistency provides companies with opportunities for planning. It also enables improved documentation leading to better assessment, transparency and alignment of processes, increased stakeholder satisfaction and enhance regulator reputation.

Key performance indicators and a transparent standard process detailing the conduct of agency-industry interaction should need to be established in writing including one point of entry, an established procedure for escalation and the documentation of interaction. The number of cancelled or rejected meetings should also be documented along with the rationale for their cancellation such as “meeting no longer required by company”, or “inadequate justification for meeting.” The value of these

written formalised indicators and procedures lies in their ability to decrease the number of informal interactions while increasing the quality of formal interactions, freeing up the time of assessors and building confidence in the regulatory process.

**Recommendations**

- Smaller agencies should align platforms regionally to share expertise and facilitate the coordination of reviews.
- Agencies should have a written process in place to ensure common interpretation across reviewers during scientific advice sessions and assessment.
- Agencies should establish a standard process and key performance indicators for agency-industry interaction, including one point of entry, a procedure for escalation and documentation.

## Roundtable Discussion E

Regional alignment initiatives- what should be measured and can metrics enable the process?	
Chair	<b>Prof John Skerritt</b> , Deputy Secretary for Regulatory Services, Department of Health, Australia
Rapporteur	<b>Sjaak Bot</b> , Vice-President, Head of EMEA Regulatory Affairs, Janssen, The Netherlands

### Background

Regional alignment and convergence can have different definitions depending on the context of their use. One definition that is applicable is “the process by which technical guidelines are developed to be uniform across participating authorities.” On the other hand, regulatory convergence, represents a process whereby the regulatory requirements across countries or regions become more similar or aligned over time as a result of the gradual adoption of internationally recognised technical guidance documents, standards and scientific principles and common or similar practices and procedures. This in turn leads to the potential for agencies to be able to share review of new medicines. Before alignment or convergence can occur amongst regulatory authorities, however, trust must be established, ensuring a recognised, accepted standard in the quality of the review process.

Currently there are a number of regional alignment initiatives, all with different goals and purposes, ranging from alignment in technical guidelines, improving competency through good review practices to work sharing and to undertaking joint or centralised reviews. These various types of alignment initiatives amongst agencies all have different goals. The initiatives and their success can be characterised by developing maps for each jurisdiction that identify processes and areas of best practices and need for improvement, performing a gap analysis to identify good regulatory practices or establishing internal tracking systems to measure performance against targets. The focus of this Roundtable was to discuss how to best assess the effectiveness and success of regional alignment initiatives and to identify what would be the appropriate metrics that can help monitor their evolution.

### Examples of regional alignment initiatives and their objectives

- East African Community (EAC): To utilise resources efficiently, the EAC has undertaken a joint review initiative in which each agency in the consortium has taken on tasks to develop frameworks to strengthen the regulatory review process such as develop an IT infrastructure, develop a regulatory review framework or develop good manufacturing process guidelines
- Association of Southeast Asian Nations (ASEAN): To utilise a common technical document for regulatory submissions.
- Four Agency Consortium (Health Canada, Swissmedic, Health Sciences Authority of Singapore, Therapeutic Goods Administration of Australia): To efficiently share the use of resources, working toward reviews and developing frameworks to assist in aligned decision making.
- Pan American Health Organization (PAHO): The process of evaluation and assessment of national regulatory agencies based on verification of key indicators. Agencies that reach Level 4 have demonstrated competency and efficiency in performance of the health regulation functions recommended by PAHO and the World Health Organization to guarantee the efficacy, safety and quality of medicines and can act as a regional reference authority.
- Gulf Cooperation Council (GCC): Mutual recognition procedure of regulatory drug approval within the seven gulf states

### Questions for consideration

- What are the objectives and outcomes of various types of regional alignment initiatives?
- What and how can the evolution of these initiatives be monitored?

- What parameters could be considered for assessment (e.g., type of review, number of reviewers, external/internal staff, electronic/manual tracking system)?
- How can these metrics be used to help agencies evolve their internal processes?
- What metrics can be recommended to set the stage for the development and implementation of new regionalisation initiatives?
- In relation to this Roundtable, are there other topics that should be discussed here or aspects that you might suggest that CIRS research or further investigate?

### Critical issues

Lessons have been learned from existing alignment initiatives. Despite strong political aspirations, implementation remains a challenge. In most cases, this implementation is not mandatory and is not embedded in a legal framework and strong will, such as that demonstrated by ICH is key. Moreover, country-specific requirements still exist in addition to the requirements of regional initiatives and interpretations of "common" guidelines may lead to different local requirements. There is also disparity between countries due to different organisational models, funding systems, competencies, legislative frameworks and capacity and in cases of referencing or mutual recognition, the more established agencies still repeat the assessments done by smaller countries. Finally, the existing funding model may be a disincentive for collaboration; for example, inspections may be a significant income for agencies. It has been observed that initiatives with strong functional secretariats usually perform better.

The group focussed on several discussion questions.

- **What and how can the evolution of these initiatives be monitored?**  
This Roundtable also agreed that the focus must move from discussion of regional initiatives to their implementation but realised that both political will and resources will be required as well as concrete implemented technical guidelines and arrangements such as work-sharing. The overall success of the initiatives could be measured by calculating the number of harmonised guidelines and the level of their implementation or the number of products that were approved through

referencing as the percentage of the total number of approvals.

The success of the regional initiatives from an industry perspective could be measured by the amount of referencing and mutual recognition, by the use and consistent interpretation of standard guidelines and technical standards, by transparency in expectations, by predictability in timelines and requirements and a common dossier format, Global implementation of electronic common technical document would be also be welcome, although the challenges represented by gaps in internet technology are recognised. Industry would also regard fewer required local clinical trials and faster time to market as other markers of success for regional alignment.

Success for regional initiatives for agencies would be considered from a perspective similar to industry. Ultimately, the benefit of regionalisation would be the freeing of resources that result from work sharing. A common dossier format would facilitate exchange between regulators and capacity building could result from the convergence of requirements and reliance but a certain level of expertise needs to be present to understand assessment and apply at local level and to understand the local specifics related to pharmacovigilance and labelling. Push-back from individual regulators would have to be overcome through education and inter- and intra-agency discussions. It should also be recognised that regionalisation is not a stand-alone project and implementation should begin in areas with the most critical need and would require a new business process and funding model.

- **How can these metrics be used to help agencies evolve their internal processes?**  
Small emerging agencies could make better use of limited resources and assign resources to added-value priorities. There is a need, however, for further agreement on terminology and definitions such as the difference between convergence and harmonisation.
- **What metrics can be recommended to set the stage for the development and implementation of new regionalisation initiatives?**  
The group specified that regionalisation initiatives should not start with a political

framework but rather with practical or pragmatic topics that can easily be harmonised. The success of existing initiatives should be capitalised and added value topics identified.

- **In relation to this Roundtable, are there other topics that should be discussed here or aspects that you might suggest that CIRS research or further investigate?**

CIRS should evaluate existing initiatives, identify best practices and successes and failures and determine their impact on local manufacturers and public health. Feedback should be solicited from industry regarding the progress of these initiatives, what has been achieved and potential methods for additional effectiveness. Metrics for evaluation could include the level of convergence; this a complex metric that requires the analysis of the basic principles specific to each initiative.

#### **Recommendations**

- Conduct systematic research on progress and achievements of alignment/ collaborative initiatives
- Provide a discussion platform for industry and regulators to evaluate the progress of the alignment initiatives; determine what has been achieved; identify existing training opportunities or develop a training initiative for alignment or convergence initiatives

## Appendix: Workshop Attendees

Regulatory agencies		
<b>Azura Abdullah</b>	Senior Principal Assistant Director	National Pharmaceutical Control Bureau, Malaysia
<b>Diana Silveira de Araújo</b>	Advisor of Board of Regulatory Affairs-DIREG	ANVISA, Brazil
<b>Ricardo Borges</b>	Manager of the General Office of Drugs	ANVISA, Brazil
<b>Prof Sir Alasdair Breckenridge</b>	Former Chairman	MHRA, UK
<b>Noormah Mohd Darus</b>	Senior Pharmacist / Senior Principal Assistant Director, Malaysian Health Technology Assessment Section	Ministry of Health, Malaysia
<b>Prof Hans-Georg Eichler</b>	Senior Medical Officer	European Medicines Agency
<b>Chuah Su Yin Florence</b>	Senior Assistant Director	National Pharmaceutical Control Bureau, Malaysia
<b>Dr Churn-Shiouh Gau</b>	Chief Executive Director	Center for Drug Evaluation, Taiwan
<b>Azizah Bt Ab Ghani</b>	Head, Biologics Section, Senior Principal Assistant Director	National Pharmaceutical Control Bureau, Malaysia
<b>Abed Syed Haq</b>	Director, Pharmacy Practice and Development Division	National Pharmaceutical Control Bureau, Malaysia
<b>Wesal Salem Al Haqaish</b>	Head of the Drug Registration Department	Jordan Food and Drug Administration
<b>Nurma Hidayati</b>	Director of Drugs and Biological Products Evaluation	National Agency of Drug and Food Control, Indonesia
<b>Norita Kesuma</b>	Senior Evaluator of New Drug Evaluation, Directorate of Drug and Biological Product Evaluation	National Agency of Drug and Food Control, Indonesia
<b>Dr Yvonne Khoo</b>	Senior Principal Assistant Director	National Pharmaceutical Control Bureau, Malaysia
<b>Prof John Lim</b>	Deputy Director of Medical Services	Ministry of Health, Singapore
<b>Kritsada Limpananont</b>	Drug Information Technology Group, System Development Division, Bureau of Drug Control	Food and Drug Administration, Thailand
<b>Tan Ann Ling</b>	Director	National Pharmaceutical Control Bureau, Malaysia
<b>Dr Yee Hoo Looi</b>	Acting Deputy Director – Therapeutic Products Branch	Health Sciences Authority, Singapore
<b>Merlita Pedron</b>	Administrative Officer III, Policy and Planning Service	Food and Drug Administration, Philippines
<b>Pia Angelique De Mesa Priagola</b>	Food Drug Regulation Officer III	Food and Drug Administration, Philippines
<b>Dato' Eisah Binti A Rahman</b>	Senior Director of, Pharmaceutical Services	Ministry of Health, Malaysia
<b>Barbara Sabourin</b>	Director General, Therapeutic Products Directorate	Health Canada
<b>Dr Tomas Salmonson</b>	Chair, CHMP	European Medicines Agency, Sweden
<b>Dr John Skerritt</b>	Deputy Secretary for Regulatory Services	Department of Health, Australia
<b>Anis Talib</b>	Deputy Director, Centre for Product Registration	National Pharmaceutical Control Bureau, Malaysia
<b>Xiangyu Wang</b>	Division Director	China Food and Drug Administration, China
<b>Director General Lin Yuan</b>	Director General, Department of International Cooperation	China Food and Drug Administration, China

Pharmaceutical companies		
<b>Dr Harindra Abeysinghe</b>	Vice President, Head of Asia Pacific Regulatory Affairs	Johnson & Johnson, Singapore
<b>Sjaak Bot</b>	Vice-President, Head of EMEA Regulatory Affairs	Janssen, The Netherlands
<b>Thuy Dang</b>	Head of Regulatory Affairs, Consumer Health Asia-Pacific/Japan	Bayer (South East Asia), Singapore
<b>Dr Felipe Dolz</b>	Vice President, Global Regulatory Policy and Intelligence	Sanofi, USA
<b>Rasmus Engelbrecht</b>	Senior Regulatory Intelligence Manager	Novo Nordisk A/S, Denmark
<b>Amy George</b>	Associate Director	Johnson & Johnson, USA
<b>Dr David Guez</b>	R&D Special Projects Director	Institut de Recherches Internationales Servier, France
<b>Dr Paul Huckle</b>	Chief Regulatory Officer and Senior Vice President	GlaxoSmithKline, USA
<b>Hyekyung Jin</b>	Senior RA manager, South East Asia and Korea (SEAK)	UCB / SEAK, South Korea
<b>Mahir Karababa</b>	International DRA Project Manager	Actelion Pharmaceuticals Ltd, Switzerland
<b>Dr Hiroki Kato</b>	Director for R&D	Zeria Pharmaceutical Co Ltd, Japan
<b>Dr David King</b>	Director, Regulatory Policy and Intelligence	Shire, UK
<b>Prof Thomas Kühler</b>	Senior Director	Novo Nordisk A/S, Denmark
<b>Michael Lim</b>	Market Access Director	Sanofi, Singapore
<b>Leyla Lister</b>	Head of Emerging and Regional Affiliates	F.Hoffmann-La Roche Ltd, Switzerland
<b>Dr Ashley Preston</b>	Head of Global Regulatory Science, Process, Compliance and Training	EMD Serono, USA
<b>Jin Shun</b>	Regulatory Policy and Intelligence Director, JAPAC	AbbVie, Singapore
<b>Jayani de Silva</b>	Associate Director, Regulatory Affairs APAC	Takeda Pharmaceuticals (Asia Pacific) Pte Ltd, Singapore
<b>Fraser Stodart</b>	Senior Director, Global Emerging Markets (GEMS) – Regulatory Affairs	Biogen, UK
<b>Dr Alec Tiong</b>	Head, Regulatory Affairs, Area and Affiliate, Japan & Asia Pacific	AbbVie, Singapore
<b>Kum Cheun Wong</b>	Head, Asia Pacific Policy and Liaison, Drug Regulatory Affairs	Novartis Asia Pacific Pharmaceuticals Pte Ltd, Singapore
<b>Sau Wei Wong</b>	Regulatory Affairs Director, f/Singapore	AstraZeneca Singapore Pte Ltd, Singapore
<b>Kah Leng Tan</b>	New Product Introduction Manager, Asia Regulatory Hub	GlaxoSmithKline Pte Ltd, Singapore
Academic institution, Non-profit agencies		
<b>Dr Sorapop Kiatpongsan</b>	Lecturer, Faculty of Medicine	Chulalongkorn University, Thailand
<b>Dr Murray Lumpkin</b>	Deputy Director – Integrated Development and Lead for Global Regulatory Systems Initiatives	Bill and Melinda Gates Foundation, USA
<b>Alexander Ng</b>	Health and Innovation Director	Bill and Melinda Gates Foundation, China
<b>Dr Lembit Rägo</b>	Head, Regulation of Medicines and other Health Technologies	World Health Organization (WHO), Switzerland
<b>Dr Durhane Wong-Rieger</b>	President and CEO	Canadian Organization for Rare Disorders, Canada

<b>Centre for Innovation in Regulatory Science</b>	
<b>Lawrence Liberti</b>	Executive Director
<b>Magda Bujar</b>	Senior Research Analyst
<b>Patricia Connelly</b>	Manager, Communications
<b>Dr Neil McAuslane</b>	Director
<b>Prisha Patel</b>	Manager, Emerging Markets Programme
<b>Professor Stuart Walker</b>	Founder