Facilitating the review of new medicines through risk-based evaluations:

How can a stratification process be utilised to achieve an effective use of resources?

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WORKSHOP REPORT

CIRS Centre for Innovation in Regulatory Science

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Section 1: Executive Summary

Background to the Workshop

Despite vastly differing resources and capacities among regulatory agencies worldwide, the engagement in duplicative work regardless of resources limitations has been identified by the World Health Organization as a common factor among these agencies. In fact, as the development of new medicines and advanced therapies becomes increasingly important, not all agencies have the needed advanced skills and mature regulatory systems to conduct a relevant review of these treatments; this is complicated by the observation that the majority of the WHO member states do not have fully functional effective regulatory systems.

As countries develop their regulatory capabilities, an evolution to a more risk-based evaluation approach has been suggested, which moves away from the prescriptive approach in which any agency repeats a full review. Risk-based stratification of submissions and of the related decision-making process addresses both compliance and product risks. These stratifications can be implemented across the life cycle of new medicines as well as generics, addressing evidence requirements for marketing authorisation during the manufacturing and inspection processes through to post-marketing compliance and review of variations. These prioritised risk-based approaches are being developed across mature and maturing agencies.

Not only are countries looking to improve access through conditional or accelerated approvals for products to address serious and life-threatening diseases for which there are few, if any, effective therapies but many agencies are also looking to leverage/rely on work undertaken by reference agencies to help inform their own regulatory decision making. This enables them to stratify the evaluations of new medicines allowing them to use verification or abridged processes that can be informed by prior assessments, thereby focusing their resources on the benefit-risk and suitability assessment of the product for their jurisdiction and on other value-added activities within their jurisdiction that only they can perform.

Indeed, the continuing limitations of adequate resources within regulatory agencies have the potential to drive greater focus toward risk-based evaluation, focusing on what is locally critical versus what can be leveraged from other trusted authorities, leading to improved allocation of scant local resources and improved medicine availability This can be seen in the increasing role of WHO prequalification and its collaborative and joint review processes with NRAs, or where regional alignment or work-sharing initiatives are being developed. These approaches allow agencies time to build their regulatory technical capacity in line with their mission and funding but at the same time enable patient access to good quality medicines that are safe and effective. However, implementation of these prioritisation approaches face a number of legal, political, methodological, cultural and organizational challenges, which may be mitigated through appropriate decision-making frameworks and practices.

This Workshop built on previous CIRS global development workshops as well the work being undertaken by various groups in the areas of good regulatory and review practices and focused specifically on the risk-based prioritisation of the review process for new medicines.

Workshop objectives

- Identify the **current risk-based prioritisation evaluation models of decision making being used for the review of medicines** and what are believed to be the benefits and hurdles of utilising these in the review of new medicines
- Discuss **the frameworks and decision-making practices that need to be in place to enable** effective and efficient prioritised risk-based decision making
- Make recommendations on practical and acceptable review models to **evolve and ensure success of risk-based evaluation approaches to decision making** that allow agencies to focus on value-added activities and provide timely patient availability to good quality medicines that are safe and effective

Key points from presentations

SESSION: MODELS AND APPROACHES TO RISK-BASED REVIEW AND DECISION MAKING: ADVANTAGES AND BARRIERS TO STRATIFICATION

As countries across the world face serious economic and political challenges, regulators look to enhance their contribution to improving global health. **Patrícia Oliveira Pereira Tagliari**, *Head of International Affairs Office, ANVISA, Brazil,* welcomed Workshop participants to this meeting to discuss the use of risk-based regulatory evaluations, potentially allowing agencies to maximise the use of limited resources and to especially focus on those activities that can add value and ensure more rapid authorisation of products for local populations.

Considering the terms *risk stratification* from the title of the Workshop, **Session Chair Prof Hans-Georg Eichler,** *Senior Medical Officer, European Medicines Agency* encouraged Workshop participants to consider differentiating new medicines by evaluating the potential *benefits* that might be accrued through their use against their potential to be associated with *harms*, even while understanding the *uncertainty* that might surround both of these parameters.

National regulatory authorities are under mounting pressure to improve performance and facilitate timely access to safe, effective and quality medicines and other health technologies. This task has become more challenging due to globalisation, increasingly complex technologies and growing public expectations. **Mike Ward**, *Coordinator, Regulatory Systems Strengthening, Essential Medicines and Health Products, World Health Organization (WHO)* emphasised that WHO has long supported regulators in low- and middle-income countries in fulfilling their mandates through the development of norms and standards, promotion of regulatory convergence and harmonisation, training, capacity building and increasingly, by supporting the best use of resources through collaboration, reliance and recognition. Since 2013, 189 products have been approved through the use of WHO collaborative procedures, which are voluntary for manufacturers and national

regulatory authorities and do not interfere with national decision-making processes. Interested agencies sign a confidentiality undertaking, commit to follow principles of the process and strive to register the product in 90 days. WHO shares detailed outcomes of its assessment and inspections with interested regulators to support decision making in exchange for an accelerated registration process.

There is a need for a framework that describes the use of flexible systems that offer the benefits of timely assessments of safe and effective medicines while protecting the public health in all jurisdictions. **Lawrence Liberti,** *Executive Director, Centre for Innovation in Regulatory Science* proposed a four-step framework to assess agencies' regulatory environment, capabilities and capacities to determine the most appropriate facilitates regulatory pathway (FRP). The first step in the approach is to understand the environmental preparedness of the agency, based on domains that describe an agency's mandate, governmental structures, capacity, competency, available decision-making tools and post-authorisation capability. In the second step, the status within the agency of detailed process criteria such as dossier acceptance requirements, review elements, decision criteria and post-authorisation abilities are examined. Step 3 gives agencies tools to assess all of the items in steps 1 and 2 plus additional aspects. As a result of that assessment, a tier-based approach can be used to categorise the agencies based on their readiness to implement an FRP process. Finally, step 4 provides a pathway for agencies to determine the most relevant FRP for their use based on their tiered capabilities.

Singapore has designed a regulatory system based on its risk threshold, regulatory capabilities, national policies and international developments in regulatory convergence. According to **Agnes Chan,** *Director of Therapeutic Products Branch, Health Sciences Authority (HSA), Singapore,* risk-based evaluation is a pragmatic approach that enables HSA to optimise limited resources effectively while ensuring robustness in its decisions. By recognising agency limitations, identifying elements in the benefit-risk assessment that are critical in the local context and bridging reference agency assessments to the Singapore population, HSA is able to leverage the work of larger agencies without compromising the robustness of decisions made for the people of Singapore. It has been key for the agency to identify gaps and use its regulatory capability in order to bridge benefit-risk assessment done by reference agencies to the local Singapore context. Capabilities to perform independent evaluation remain strategically critical and this ensures support for regional biomedical research and development growth.

Adj Prof John Skerritt, *Deputy Secretary for Health Products Regulation, Department of Health, Australia* pointed out that Australia is the only known country where international regulatory cooperation with "comparable overseas regulators" is government policy. Criteria were proposed by the TGA Review Panel to define comparable overseas regulators and each of these criteria is independently necessary. These regulators should regulate for a demographic that is broadly representative of the Australian population and have similar health outcomes, adopt ICH guidelines, have a credible and consistent track record of approving safe and effective medicines, conduct de novo evaluations of dossiers for all medicine types, require peer/ independent assessment of evaluations, employ evaluators with the necessary technical and clinical expertise, have access to un-redacted evaluation reports and where applicable, individual patient data and communicate and prepare evaluation reports in English. Integration of collaboration between regulators will

take time and more effort at first but in time, there will be benefits for industry, regulators and patients including faster market access and lower costs, reduced workload, less duplication and earlier access to medicines.

The Regulatory Affairs Team of the Bill and Melinda Gates Foundation seeks to accelerate access to quality products in target countries by supporting the regulatory aspects of the development, approval and lifecycle management of vaccines, drugs, diagnostics and other global health technologies. **Dr Shyam Bhaskaran,** *Program Officer, Regulatory Affairs, Bill & Melinda Gates Foundation, USA* said that building on principles of reliance, process re-engineering and regionalisation, the major focus of the programme to date has been on registration, optimising the prequalification process to be predictable, accountable and transparent, expanding the prequalification collaborative procedure and supporting regulatory regionalisation through such groups as African Medicines Regulatory Harmonisation, Caribbean Community and the Association of Southeast Asian Nations. Other regulatory efforts have centred on monitoring national regulatory authority and regional economic community metrics, strengthening national regulatory authority value-added capacity in targeted countries, developing WHO Guidance on Good Reliance Practices and global regulatory communication, training and sharing of best practices. Expansion is ongoing into the clinical development area with a regional approach to clinical trial and ethics committee authorisation and oversight in Africa and the development of WHO Guidance on local Clinical Trial Requirements. Delivery and surveillance activities will include improving safety and surveillance activities in low- and middle-income countries, the regulatory components of supply chain integrity and regulatory oversight of vaccine chemistry, manufacturing and control variations.

Togi Junice Hutadjulu, *Director of Drugs and Biological Product Evaluation, NADFC* reported that a simplification of the evaluation process for applications for new drugs that have been approved by mature agencies using reliance mechanisms is underway in Indonesia that is expected to reduce the authorisation timelines from 150 to 100 working days. The criteria of the reliance mechanism include medicinal products with similar indications and dosing regimens that have been approved by at least three mature agencies with published assessment reports from these three agencies. All aspects of the products' quality, including but not limited to the formulation, manufacturing sites, release and shelf-life specifications and primary packaging must be identical to that currently approved by the reference agencies. In addition, the product must not need a more stringent assessment as a result of differences in local disease patterns and/or medical practices; for example, as this might impact some anti-infection, anti-virus, anti-malaria or tuberculosis drugs. By applying these reliance mechanisms, evaluations will focus on country-specific requirement for excipients on animal origin, stability studies and product information and labelling. In addition, a paperless *online* system for NDA submission will be initiated in mid-2017, which is expected to enhance the expediency and transparency of the evaluation process and provide a tracking mechanism for product sponsors.

SESSION: WHAT ARE THE PRACTICAL FRAMEWORKS THAT AGENCIES HAVE OR NEED TO HAVE IN PLACE TO ADOPT MULTIPLE PATHWAYS TO PRIORITISE MEDICINES EVALUATION?

Dr Petra Dörr, *Head of Communication and Networking, Deputy Director, Swissmedic* initiated the session by reminding participants that regardless of level of maturity or capabilities, all regulatory agencies are limited by

available resources and must prioritise activities to accomplish their mandates and goals and regularly re-evaluate those allocations.

The Caribbean Community (CARICOM) comprises a diverse group of countries with a combined population of 17 million people. Unfortunately, regulatory capacity in these countries is limited. However, as **Dr Charlie Preston**, *Advisor, Regulatory System Strengthening in Medicines and Other Health Technologies, PAHO, Trinidad* explained, efforts are ongoing to strengthen regulatory capacity. Using a regional approach to regulatory review, the Caribbean Regulatory System of the CARICOM Regional Public Health Agency carries out assessment activities for eligible products and is looking to perform pharmacovigilance and post-market surveillance. Reliance on reference authorities allows the abbreviated review of already approved products and the use of verification procedures based on the World Health Organization Prequalification by stringent regulatory authorities process. Agencies can then focus on the highest priority regulatory needs such as essential generic medicines, which may be less complex in terms of regulatory science.

Gugu Mahlangu, *Director-General, Medicines Control Authority, Zimbabwe* discussed ZaZiBoNa in the context of the South African Development Community (SADC) Collaborative Medicines Registration Initiative. The original participants Zambia, Zimbabwe, Botswana and Namibia have since been joined by South Africa and Swaziland (an observing member). The objectives of the initiative are to cooperate in the assessment and inspections for medicines' registrations with the goal of reducing workloads, shortening timelines to registrations, developing mutual trust and confidence in regulatory collaboration and developing a platform for training and collaboration in regulatory fields. In just 3.5 years of operation, more than 154 products have been evaluated through the ZaZiBoNa process and 90 out of 154 have been finalised, with the remaining 64 products pending responses from manufacturers. The median time to recommendation has been 9 months, which corresponds to the target time for the process. No initiative that is similar to this cost-effective collaboration has delivered these kinds of results in such a relatively short period.

The International Federation of Pharmaceutical Manufacturers Association (IFPMA) approaches regional alignment of regulatory review in multiple ways. **Dr David Jefferys,** *Senior Vice President, Eisai and Co-Chair, IFPMA* explained that the Association supports appropriate regulatory capacity building and training and as a standing member of ICH, IFPMA also backs ongoing regulatory convergence and harmonisation. Activities that IFPMA regards as being key in this area include the development of the *Good regulatory review practices: guidelines for national and regional regulatory authorities* by the Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee and the World Health Organization. However, as the number of accelerated reliance approvals increases, the majority of industry resources are now focussed on lifecycle management. A risk-based approach to medicines' regulation would reduce duplication, decrease resource use and help maintain medicine availability.

Speaking on the use of a benefit-risk or decision-making framework to enable consistency within and across regulatory agencies, **Dr Neil McAuslane,** *Director, CIRS* reported that there is a general agreement that there is a need for a structured, standardised, systematic approach to the benefit-risk assessment of medicines

using a framework that should ideally be feasible and practical within the regulatory review process. The use of a framework could also facilitate trust and understanding of benefit-risk assessments, which are necessary for regulatory authorities that wish to work together and collaborate within a region in joint and shared reviews; a framework provides value to agencies conducting both abridged and verification reviews where there is reliance to some degree on the assessment by reference agencies. Stakeholders in medicines' development and health technology assessment have suggested that decision making can also benefit from the use of frameworks. Among the solutions to challenges in decision making that emerged in a recent CIRS study among pharmaceutical companies and regulatory agencies, participants suggested establishing or implementing a structured decision-making framework and ensuring transparency and information access.

As explained by **Mario Alanís Garza**, *Director General de Asuntos Internacionales, COFEPRIS,* COFEPRIS has benefited from its programmes of reliance in terms of cost, time, resources, industry productivity and access to medicines and believes that further discussion and agreement on generally accepted reliance concepts and modalities would add to those benefits. In the COFEPRIS regulatory reliance model, authorised third parties support the health agency in risk assessment while facilitating processes and authorisations. In addition, COFEPRIS unilaterally accepts good manufacturing process certifications issued by the US, Brazil, Canada, Japan, Australia, South Korea, Switzerland and the EU. Equivalence agreements are also recognised for new drugs from the US, Canada, Australia, Switzerland and the EU and for medical device registrations issued by the US FDA, Health Canada and Japan. To develop COFEPRIS as a regulatory Center of Excellence, the agency established collaborations with regulatory agencies, industry and academic institutions for the research and development of new knowledge. COFEPRIS also created an electronic platform for the dissemination of information and the development of a network of areas of excellence, ensuring free access to health information, obtained the recognition of WHO, documented and published good regulatory practices for COFEPRIS as well as for research, industry and academic centres and developed a national and international network of partners interested in supporting the Centre of Excellence and its activities.

The Good Registration Roadmap was initiated in 2011 when good review practices (GRevP) was endorsed as a priority work area by the Asia Pacific Economic Cooperation Life Science Innovation Forum Regulatory Harmonization Steering Committee (APEC LSIF-RHSC) and Chinese Taipei was named as its champion. **Chao-Yi (Joyce) Wang,** *Director, Division of Medicinal Products, Taiwan Food and Drug Administration* said that the goals of this project are to promote the concept of good registration management (GRM) and to enhance the mutual trust needed for regulatory convergence among the APEC member economies by 2020. The first action toward the envisioned completion of the Roadmap in 2020 was the conduct of a gap analysis survey of APEC members. Following the survey, *Good review practices: Guidelines for national and regional regulatory authorities* was adopted and published by the World Health Organization in 2015. In 2016, *Good Submission Practice Guidelines for Applicants* was endorsed by the APEC LSIF-RHSC and in 2017, the Taiwan Food and Drug Administration (TFDA) was endorsed as a formal APEC GRM Centre of Excellence by the LSIF-RHSC. GRM could serve as critical components in enabling agencies to undertake a risk-based review process. Good submission practices enable applicants to understand the principles of a good submission and strengthen their core competency in understanding the nature of the benefits and risks of

products and benefit-risk analyses when preparing for submission. Good review practices enable regulators to understand the principles of a good review, strengthen their knowledge and skills for risk-based analysis in reviewing a medical product application, enhance their competency in critical thinking, facilitate the determination as to whether an application permits a conclusion about benefits and risks and allow the application of a review strategy to understand benefit-risk profiles.

Claudiosvam Martins Alves de Sousa, *Manager, Office of Safety and Efficacy Assessment of Synthetic Drugs, ANVISA, Brazil* detailed the current and future processes for the registration of medicines in Brazil. As a former observer and current standing member of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Brazil endorses the ICH vision of reducing unnecessary duplication and facilitating faster access to new products, including implementation of the common technical document for medicines registration and other ICH Guidelines. It is envisioned that CIRS will be a partner to ANVISA in its efforts to improve its review process through structured systematic standardised approaches to the benefit-risk assessment of medicines, a stepwise implementation of good review practices and the better use of available resources, especially existing international tools and strategies, which can be adapted for the Brazilian environment to improve the review process for drug registration.

In a discussion of the management of safety after the approval of drugs and vaccines, **Dr Lembit Rägo**, *Secretary-General, Council for International Organizations of Medical Sciences, Switzerland* emphasised the importance of effective collaboration between authorities in the area of safety and pharmacovigilance at the global, regional and sub-regional levels. Because regulatory authorities have responsibility for their populations, all jurisdictions should have at least basic pharmacovigilance capacity when approving new complex medicines. Each national jurisdiction must carefully study and understand the risk minimisation activities of reference authorities and appreciate the adjustments that may be needed in those activities for their national setting. Working Groups of the Council for International Organizations of Medical Sciences (CIOMS) CIOMS have produced multiple publications in this area, most recently the *CIOMS Guide to Active Vaccine Safety Surveillance* provides a structured approach to identifying and analysing specific vaccines safety knowledge gaps, while considering all available sources of information, in order to determine whether active vaccine surveillance is an appropriate solution.

Recommendations from across the Roundtable Discussions

- Regulatory agencies should consider the criteria categories of *products, facilities, evaluation processes* and *an evaluation of strengths and weaknesses* in developing a risk-based regulatory review.
- Regulatory agencies should communicate key drivers for the adoption of a risk-based regulatory review, including high-quality and timely decision making, faster access, best use of resources and the development of a collaborative environment between regulators.
- Regulatory agencies should communicate key opportunities for the adoption of a risk-based regulatory review, which include the prospect to build on the knowledge and expertise from other agencies, the ability to respond to emergency situations, accountability by agencies and companies to establish clear commitments, the identification of the relevant aspects of product evaluation that should be strengthened in a particular country.
- Ensure that any guidelines or best practice guide for risk-based regulatory review include: agreed timelines, types of products to be addresses, acceptable certifications from good reference agencies, reliance on good review practices, clear information regarding roles and responsibilities for compliance, transparency from regulators regarding protection of intellectual property, identification of regulatory activities suitable for reliance practice such as product testing and good manufacturing practice audits and the strengthening of post-approval safety.
- CIRS should compare assessment templates used by countries utilising reference country assessment reports.
- The performance of reliance models should not just be measured by speed of review; CIRS should assess whether abbreviated reviews have resulted in subsequent safety or quality issues.
- CIRS should highlight the need for reform relative to CPP availability from reference countries, including electronic availability and the subsequent acceptance by regulatory agencies.
- Develop model instruments or tools to guide the establishment and conduct of the regional alignment initiative
- There should be ongoing documentation of current models of regional alignment initiatives.
- Establish clarity regarding long-term expectations for regional alignment initiatives.
- Address regulatory knowledge gaps through capacity-building programmes.
- Donors should invest capital for the development of regional alignment initiatives and the support of capacity-building programmes.
- Develop national, regional or independent guidance documents to describe objective criteria that might be considered by regulatory agencies for each review pathway and the technical data requirements for industry for each pathway.
- Conduct a mapping exercise research project of existing timelines for each pathway to establish suggested target timelines for agencies.
- Apply reliance approaches for post-approval changes**.** It would be useful to have a survey or mapping of models or experiences describing mechanisms in place for implementing risk-based approaches for post-approval changes based on reliance or other efficiencies.
- Regulators should avoid the historic mistake of solely focussing on post-approval safety and consider how best to evaluate effectiveness. They should additionally focus on better communication with patients as one of the key stakeholders in medicine, potentially through social media or other avenues of education.
- Electronic healthcare records should be built in such a way that this essential real-world data for efficacy and safety can be collected for use in decision making.
- Regional centres should be developed or expanded so that pharmacovigilance data can be shared for decision making and mutual pre-notifications of post-licensing activities can occur.

PROGRAMME

DAY 1: 8 MARCH 2017

SESSION: MODELS AND APPROACHES TO RISK-BASED REVIEW AND DECISION MAKING: ADVANTAGES AND BARRIERS TO STRATIFICATION	
Chair's welcome and introduction	**Prof Hans-Georg Eichler,** *Senior Medical Officer, European Medicines Agency*
Country welcome and introduction	**Patrícia Oliveira Pereira Tagliari**, *Head of International Affairs Office, ANVISA*
Risk-based approaches to the evaluation of new medicines: What does this mean and why should countries consider such an approach?	**Mike Ward**, *Coordinator, Regulatory Systems Strengthening, Essential Medicines and Health Products, World Health Organization*
What are the different risk-based evaluation models/approaches that agencies can consider or adopt? What are their main advantages and possible barriers?	**Lawrence Liberti**, *Executive Director, CIRS*
Introducing risk-based evaluation methods into the review process – Practical experience and key considerations	**Agnes Chan,** *Director of Therapeutic Products Branch, Health Sciences Authority, Singapore*
Work-sharing versus information sharing – What are the practical consideration an Agency needs to consider?	**Adj Prof John Skerritt**, *Deputy Secretary for Health Products Regulation, Department of Health, Australia*
Stakeholder perspectives: Why should agencies establish risk-based approaches and how could stakeholders enable the process? NGO perspective	**Dr Shyam Bhaskaran,** *Program Officer, Regulatory Affairs, Bill & Melinda Gates Foundation, USA*
Country approaches to risk-based evaluation – Prioritisation based on reference agency approval: What are the opportunities and barriers within their country?	
Agency Viewpoint - Colombia **Agency Viewpoint** - Indonesia – (Path I, II and III) –	**Dr Javier Guzman**, *Director General, INVIMA* **Togi Junice Hutadjulu**, *Director of Drugs and Biological Product Evaluation, NADFC*

SESSION: WHAT ARE THE PRACTICAL FRAMEWORKS THAT AGENCIES HAVE OR NEED TO HAVE IN PLACE TO ADOPT MULTIPLE PATHWAYS TO PRIORITISE MEDICINES EVALUATION?	
Chair's introduction	**Dr Petra Dörr,** *Head of Communication and Networking, Deputy Director, Swissmedic*
Regional approaches to risk-based evaluation – Rationale, considerations, opportunities and barriers How are these maximising capacity, enabling competence and improving patient access to new, safe and effective medicines?	
Caribbean Community (CARICOM)	**Dr Charlie Preston**, *Advisor, Regulatory System Strengthening in Medicines and Other Health Technologies, PAHO, Trinidad*
Zambia, Zimbabwe, Botswana and Namibia, (ZaZiBoNa)	**Gugu Mahlangu**, *Director-General, Medicines Control Authority, Zimbabwe*
What do companies see as the advantages and barriers in regard to regional alignment review models?	**Dr David Jefferys,** *Senior Vice President, Global Regulatory, Government Relations, Public Affairs and European Product Safety, Eisai Europe Ltd, UK*
Utilization of a systematic structured benefit-risk or decision making framework to enable consistency within and across agencies	**Dr Neil McAuslane,** *Director, CIRS*
Communication and transparency of decision making by agencies - How can assessment reports, inspection reports and other work products of other agencies be used most effectively?	**Mario Alanis Garza,** *Director General de Asuntos Internacionales,* COFEPRIS, Mexico
Good registration management (GRP and GSP) as critical components to enabling agencies to undertake a risk-based review process	**Joyce Wang,** *Director, Division of Medicinal Products, Food and Drug Administration, Chinese Taipei*
Prioritisation: Balancing the evidence available within the submission and local jurisdictional requirements – What are the practical/scientific issues that agencies face?	**Claudiosvam Martins Alves de Sousa,** *Manager, Office of Safety and Efficacy Assessment of Synthetic Drugs, ANVISA, Brazil*
Managing safety post-approval: What do agencies using risk-based approaches need to consider?	**Dr Lembit Rägo**, *Secretary-General, Council for International Organizations of Medical Sciences (CIOMS), Switzerland*

DAY 2: 9 MARCH 2017

SESSION: ROUNDTABLE DISCUSSIONS, FEEDBACK AND PANEL DISCUSSIONS

Roundtable discussions	
Roundtable A: What are main criteria utilised in defining "risk based" and what need to be the key considerations?	**Chair: Catherine Parker,** *Director General, Biologics and Genetic Therapies Directorate, Health Canada* **Rapporteur: Jorge Azar,** *Area Regulatory Director LA, AstraZeneca, USA*
Roundtable B: What are the main internal considerations, policy challenges and opportunities for individual agencies to incorporate a risk stratification-based decision-making approach to the review of new medicines?	**Chair: Adj Prof John Skerritt**, *Deputy Secretary for Health Products Regulation, Department of Health, Australia* **Rapporteur: Dr Catherine Burgess,** *Senior Director, Head of Emerging Markets Regulatory Affairs – Pipeline, Takeda, USA*
Roundtable C: What are the main internal considerations, policy challenges and opportunities that agencies need to address in order to take a regional approach to the joint/shared review of new medicines?	**Chair: Lahouari Belgharbi,** *Director General, Center of Excellence For Regulatory Sciences (RS), Good Regulatory Practices (GRP) and Good Regulatory Management (GRM),* COFEPRIS*, Mexico* **Rapporteur: Gugu Mahlangu**, *Director-General, Medicines Control Authority, Zimbabwe*
Roundtable D: What are companies looking for in agencies or regions that might use a risk evaluation-based approach – What would a successful system look like?	**Chair: Dr Janet Vessotskie,** *Head of Americas, Regulatory Policy and Intelligence, UCB, USA* **Rapporteur: Cammilla Horta Gomes**, *Health Regulations Expert, ANVISA, Brazil*
Roundtable E: Managing risk post-approval: What are the roles and responsibilities of companies, agencies and other stakeholders?	**Chair: Prof Hans-Georg Eichler,** *Senior Medical Officer, European Medicines Agency* **Rapporteur: Maria Cristina Mota,** *Director – Scientific Regulatory Policy and Intelligence- Latin America, AbbVie, USA*
Chair's Introduction	**Prof Sir Alasdair Breckenridge**
Feedback by roundtable rapporteurs and discussion	
Panel reflection from roundtable session – What are the next steps in the implementation of risk-based evaluations, by jurisdiction or regionally? Viewpoints from:	**Dr David Jefferys,** *Senior Vice President, Global Regulatory, Government Relations, Public Affairs and European Product Safety, Eisai Europe Ltd, UK* **Dr Charlie Preston,** *Advisor, Regulatory System Strengthening in Medicines and Other Health Technologies, PAHO, Trinidad* **Renato Porto**, *Director, ANVISA* **Dr Petra Dörr,** *Head of Communication and Networking, Deputy Director, Swissmedic* **Dr Shyam Bhaskaran**, *Program Officer, Regulatory Affairs, Bill & Melinda Gates Foundation, USA*
Chairman's summary and close of Workshop	**Prof Sir Alasdair Breckenridge**

SECTION 2: PRESENTATIONS

Risk-based approaches to the evaluation of new medicines: What does this mean and why should countries consider such an approach?

Mike Ward, *Coordinator, Regulatory Systems Strengthening, Essential Medicines and Health Products, World Health Organization*

National Regulatory Authorities (NRAs) are under mounting pressure to improve performance and facilitate timely access to safe, effective and quality medicines and other health technologies. This task has become more challenging due to globalisation, increasingly complex technologies and growing public expectations. Nowhere are these challenges more acute than in low and middle income countries (LMICs). WHO has long supported regulators in LMICs in fulfilling their mandates through the development of norms and standards, promotion of regulatory convergence and harmonisation, training, capacity building and increasingly, by supporting the best use of resources through collaboration, reliance and recognition. Experience to date has helped characterise the benefits, challenges and potential evolution of such initiatives in accelerating in-country regulatory decisions.

WHO principles are aligned with recommendations from the 14th (Singapore, 2010) and 17th (Cape Town, 2016) International Conference of Drug Regulatory Authorities:

- Importance of reliance, transparency, trust and good regulatory practices
- Take account of one another's work with a view to improving the efficiency of the global regulatory system
- Commit resources to form cooperative networks based on uniform standards
- Engage with regional and international initiatives promoting harmonisation, information sharing as tools for improving timely access to medicines and medical products

WHO principles stress that weak or inefficient regulatory systems do not serve the interests of consumers, patients, industry or healthcare systems. All regulatory systems should be science based, respect international standards and best practices and adopt an approach that focuses on what cannot be done by others while leveraging the work of other trusted NRAs and regulatory networks. Collaboration should lead to mutual benefit and measurable public health.

Collaboration is defined as a process that enables independent individuals and organisations to combine their human and material resources so they can accomplish objectives that are difficult to bring about alone.[1]

Various terms have been used in literature to describe this process of coming together such as *partnership*, *alliances, collaboration* and *teamwork*.[2, 3] A key success factor for collaborative mechanisms is that the impetus for the collaboration should come from within the community (ownership). Collaborative relations should be based on senior management/institutional support and investment, mutual trust and respect, good communication, clarity of roles and designated responsibilities, formalization of the relationship, professional efficacy and sufficient distribution of power. Collaborative initiatives include, the WHO Pre-qualification (PQ)

and Collaborative Procedures and regional initiatives such as in the East Africa Community (EAC) and Zambia + Zimbabwe + Botswana + Namibia (ZaZiBoNa; see page 36).

Reliance and *recognition* are often-used terms in regulatory documentation but lack formal definition. *Reliance* is an act whereby a regulatory authority in one jurisdiction may take into account/give significant weight to work performed by another regulator or other trusted institution in reaching its own decision. *Recognition* is the routine acceptance of the regulatory decision of another regulator or other trusted institution. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B. Both *reliance* and *recognition* reflect the concept of relying on or taking account of the output of other agencies (single or as part of regulatory network) or organisations to reduce or inform the regulatory undertakings of an agency. Sovereignty maintained in both cases.

Reliance can be used during normal operations when resources are insufficient to perform required functions or to reduce unnecessarily duplicative work. Reliance can also be used during emergencies to provide timely access to therapies through use of evaluations performed by another NRA or other trusted institution (including WHO Prequalification) to facilitate decision making. Some elements of regulatory oversight can be shared through reliance including evaluation of quality, efficacy and safety and inspections. Other elements of regulatory oversight must be local such as licencing decisions, local manufacturing oversight, pharmacovigilance, appropriate distribution controls and product security.

It is no longer a question as to whether *reliance,* a risk-based approach to meeting regulatory challenges, will be in use, but when and how.

It is no longer a question as to whether *reliance,* a risk-based approach to meeting regulatory challenges, will be in use, but when and how. Reliance, which is promoted by WHO through various mechanisms, informs an agency's decisions, flows from principles of good regulatory practices and is about smart regulation and investment. Reliance depends on the importance of transparency and of trust in processes and systems of regulatory decisions and outputs of rationale for decisions. Reliance is taking place even amongst most resourced and mature regulatory agencies. As detailed in a March 2017 US FDA news release, US and EU regulators agreed to be able to utilise each other's good manufacturing practice inspections of pharmaceutical manufacturing facilities, allowing "the FDA and EU to *avoid the duplication of drug inspections, lower inspection costs and enable regulators to devote more resources to other parts of the world where there may be greater risk."*

Reliance allows the NRAs with limited staff in low-income countries of millions of people to more efficiently authorise quality medicines, 98.5% of which are imported, for patients faster and more efficiently through a reduction in duplication of effort. Reliance is increasingly important in helping to fulfil regulatory mandates and implies an acknowledgement that a regulator may be considered 'functional' even if relying on others for certain regulatory functions. WHO guidance and tools can assist member states in promoting a pragmatic and transparent approach to reliance.

Regulators must consider, however, when reliance is possible and appropriate, whether reliance will be bilateral, network or unilateral, whether it will be by design or default and how it should be established, measured and documented. In addition, it should be determined if the definition of *stringent regulatory authority* needs to be revisited and what relationship that definition will have to the maturity of an agency (Figure 1)

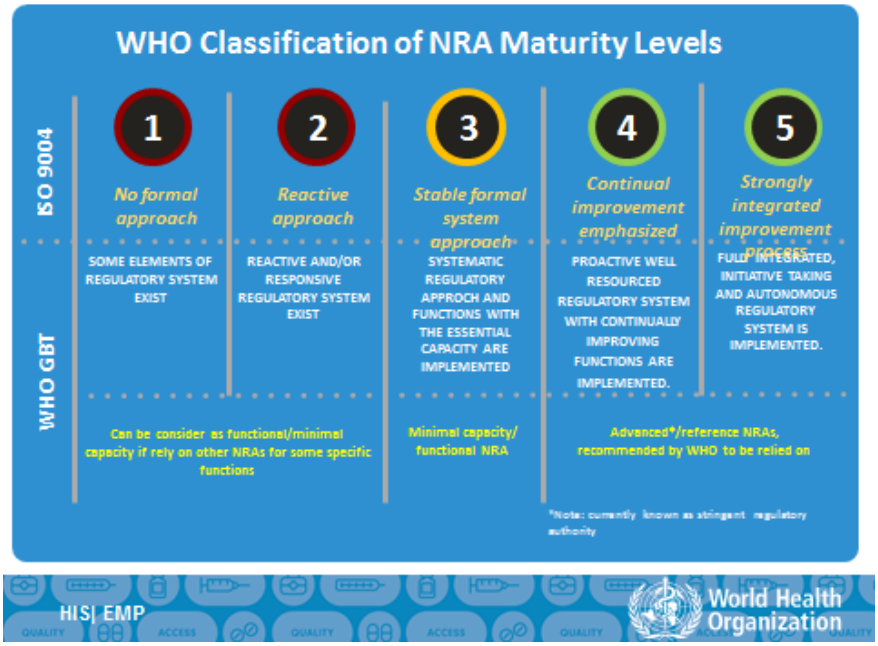

Figure 1. National regulatory authorities must determine if reliance on prior evaluations will be based on the maturity level of the predicate agency.

Since 2013, 189 products have been approved through the use of WHO collaborative procedures, which are voluntary for manufacturers and NRAs and do not interfere with national decision-making processes (Figure 2). Interested NRAs sign a confidentiality undertaking, commit to follow principles of the process and strive to register the product in 90 days. Product and registration dossier in countries are the same as those approved through the WHO PQP. WHO shares detailed outcomes of its assessment and inspections with interested regulators to support decision making in exchange for an accelerated registration process. The harmonised product status is monitored and maintained by WHO.

New developments to the WHO collaborative procedure include an extension of the process to vaccines and plans to further extend to in vitro diagnostics and to harmonise/optimise procedures for diagnostics. A similar model of the procedure that is applicable for innovator products and generics was constructed in collaboration with associations of industry, relevant SRAs and companies and piloted to facilitate registrations of medicines approved by SRAs.

The risked-based audit programme for devices used by NRAs in Australia, Brazil, Canada, Japan and US, in which the quality management system is audited against international standards, may be the model for medicines for the future. In this system, regulatory resources are pooled to develop a framework for recognition and oversight of third-party auditing organisations and the results of audits are shared. This

programme may be expandable for other aspects of regulatory oversight as all regulators must consider how they can leverage the resources of other authorities and institutions while focussing on what they must do in their own country or region.

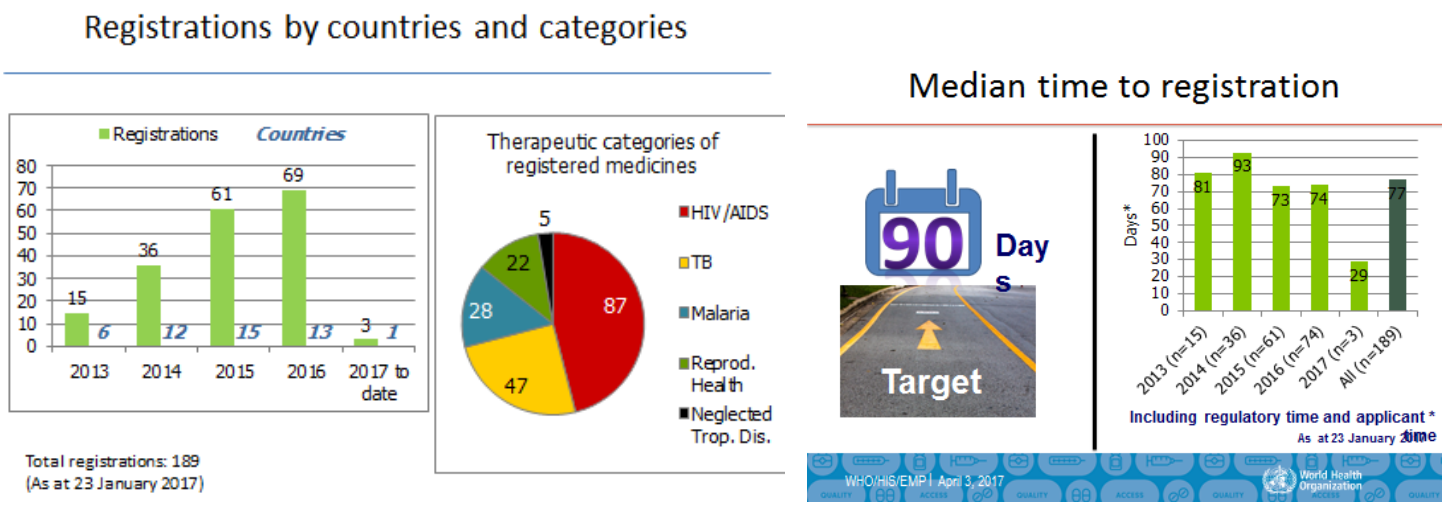

Figure 2. Number, type of product and median time to registration for products reviewed under the WHO collaborative procedure.

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3. Kernaghan K. Partnership and public administration: conceptual and practical considerations. Can Public Adm 36:57–76 (1993).

What are the different risk-based evaluation models/approaches that agencies can consider or adopt? What are their main advantages and possible barriers?

Lawrence Liberti, *Executive Director, Centre for Innovation in Regulatory Science*

Equitable access to medicines is a right of all patients and speedy regulatory authorisations should not be limited to jurisdictions where initial assessments benefit from an accelerated pathway. For products where safety and efficacy have been confirmed, patients in other jurisdictions should expect timely access facilitated by the regulatory process. Therefore, there is a need for a framework that describes the use of flexible systems that offer the benefits of timely assessments of safe and effective medicines while protecting the public health in all jurisdictions.

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Primary facilitated regulatory pathways

Ideally, the regulation of medicines should provide review paths to expedite the review process under specific conditions. Primary facilitated regulatory pathways (FRPs) such as Accelerated Approval/Assessment, Priority Review, Breakthrough Therapy designation, Conditional Marketing Authorisation, Marketing Authorisation under Exceptional Circumstances and Sakigake, are the first to assess a product, speed the development, review and approval of a product and are typically implemented by a stringent regulatory authority,.

Primary FRPs have effectively reduced the time to patient access for certain medicines. From 2006 through 2015, there was a continuation of the convergence and general decrease in the approval times amongst six major regulatory authorities, the EMA, the US FDA, the Japanese PMDA, Health Canada, Swissmedic and the Australian TGA. There was a further reduction among five of those agencies for products using expedited review. For 2015, the overall median approval time across the six agencies for standard review was 407 days, compared to 265 days for expedited review. The sixth agency, TGA, is in the process of rolling out a program for expedited review.

Secondary facilitated regulatory pathways

Secondary FRPs are used by national regulatory authorities or regional regulatory initiatives wherein their decisions can be expedited by the reliance on or recognition of prior reviews. These include Verification or Abridged reviews, “Pro-forma” registration and the use of pathways such as the World Health Organization Prequalification of Medicines Programme/Collaborative Registration process and the reliance and/or recognition of the work of another trusted regulatory authority, as detailed by Mr Ward at this Workshop.

Determining the most appropriate pathway

In 2016, Mr Liberti and colleagues published the results of a descriptive study to assess characteristics and common elements of currently implemented FRPs in national regulatory authorities in jurisdictions with emerging pharmaceutical markets.[1] The objective of this study was to understand the diversity and similarities of these FRPs, to identify common processes, to help with the ongoing assessment and development of

efficient processes in national regulatory systems and to provide evidence for international organisations to help focus strategies for increasing regulatory capacity at these emerging regulatory authorities. The study found that several characteristics were consistent across FRPs in these markets, including the requirement to conduct some kind of post-authorisation study, which is one way to manage uncertainty around a product approved on the basis of authorisation by a recognised authority. Based on this and other ongoing research in this area, Mr Liberti proposed a four-step framework to determine the most suitable use of FRPs (Figure 3).

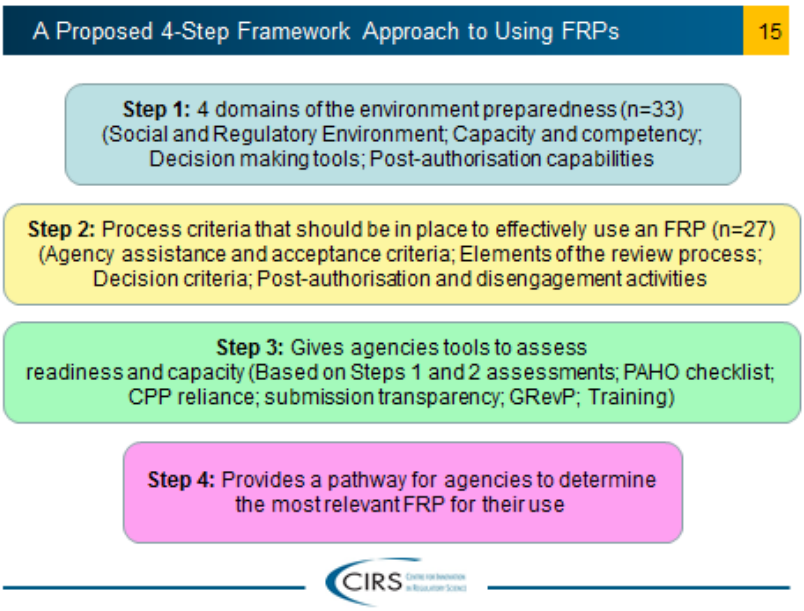

Figure 3. Assessing agencies' environments, capabilities and capacities can help to determine the appropriate FRP for their use.

The first step in the approach is to understand the environmental preparedness of the agency, based on 33 domains that describe an agency's political will, governmental structures, capacity, competency, available decision-making tools and post-authorisation capability. In the second step, the status within the agency of 27 process criteria such as dossier acceptance requirements, review elements, decision criteria and post-authorisation abilities are examined. Step 3 gives agencies tools to assess all of the items in steps 1 and 2. As a result of that assessment, a tier-based approach can be used to categorise the agencies based on their readiness to implement an FRP process, with tier 1 being *ready to implement primary or secondary FRPs*; tier 2 *having the capacity to implement some FRPs*; and tier 3 *not having the capacity to implement FRPs*. Finally, step 4 provides a pathway for agencies to determine the most relevant FRP for their use (Figure 4).

There are limitations to the use of FRPs. A single FRP cannot address the accelerated review of all medicines nor is one pathway applicable to every jurisdiction. An agile approach is needed; no guidelines or international best practices describe elements of/ and conditions needed to implement an FRP. Primary and secondary FRPs can provide good options to efficiently apply regulatory resources to potentially expedite review times. The proposed four-step framework can help to assess agencies' environment, capabilities and capacities to determine the most appropriate FRP.

			Secondary FRPs	
Class	Full (Standard)	Full (expedited) **Primary FRPs**	Abridged	Verification
Tier 1. Prepared to Implement FRPs				
A (Mature)	YES	YES	YES	YES
B (Maturing)	YES	POSSIBLY	YES	YES
Tier 2: Have the capacity to implement some FRPs				
C (Realising)	POSSIBLY	POSSIBLY	YES	YES
D(Evolving)	NA	NA	YES	YES
E (Foundational)	NA	NA	POSSIBLY	YES
Tier 3: Do not have the capacity to benefit from an FRP				
F (Ill-Equipped)*	NA	NA	NA	NA
Regional Regulatory Initiatives				
RRIs	POSSIBLY	POSSIBLY	YES	YES

Figure 4. Assessing agencies according to the four-step process helps determine which FRPs are most relevant to the country.

Reference

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Risk-based evaluation: Singapore's perspective and experience

Agnes Chan, *Director of Therapeutic Products Branch, Health Sciences Authority, Singapore*

Implemented in 1987, the drug registration system of the Health Sciences Authority (HSA) in Singapore was first implemented under the Medicines Act and transferred to the Health Products Act in November 2016. The legislation laid down the key criteria for regulatory approval that all therapeutic products must demonstrate quality, safety and efficacy and must not be contrary to public interest. There are three evaluation routes, each with different requirements and turnaround times allowing the sponsor flexibility and choice. HSA maintains in-house capabilities complemented by external experts and advisory committees' accepted reference agencies are the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), the UK Medicines and Healthcare products Regulatory Agency (MHRA), the Australia Therapeutic Goods Administration (TGA) and Health Canada.

The depth of HSA evaluation is calibrated according to prior approvals of the reviewed product. The first HSA evaluation route introduced in 1987 was the abridged route, a pragmatic approach in accordance with the agency's limited resources, which requires prior approval by one regulatory agency, an abbreviated review of the clinical data and a full review of quality data by HSA and which has a target timeline of 180 working days. By 1998, the agency had developed the necessary capabilities to perform full reviews, which include quality, nonclinical and clinical evaluations and which have a timeline of 270 working days. To further increase efficiencies and avoid duplicative work, HSA introduced the verification route in 2004, which requires product approval by two or more reference agencies and HSA verifies the benefit-risk based on the assessment report of the selected reference agency. This route has a short timeline of 60 working days. HSA conducts ongoing fine-tuning and re-calibration of these procedures, guided by risk assessment, national policies and international environments.

The full evaluation route has a low rate of utilisation at HSA, as industry often places Singapore in the second tier in their marketing strategy and 95% of new drugs have already obtained an approval from a major market such as US or EU when they reach Singapore. Nonetheless, HSA recognises the strategic importance of retaining capability for first-in-the-world evaluations. For the past 10 years, the abridged route remains the most preferred evaluation route by industry despite the fact that approximately 80% of products reviewed through abridged applications have already obtained approval from more than one reference agency, thereby potentially qualifying these products for use of the verification route at HSA (Figure 5). The popularity of this route could be attributed to the flexibility it confers to industry to seek approval for clinical indications or quality specifications that may not be the same as those approved by reference agencies. Verification evaluations depend on the availability of the assessment report from the reference agencies and the clinical indication and quality specifications must be the same as those approved by the agencies. However, industry considers these requirements to be potentially restrictive and hence uptake of this route remains low. HSA maintains a

fine balance between reduced evaluation and sufficient safeguard measures that ensure robustness in regulatory decisions.

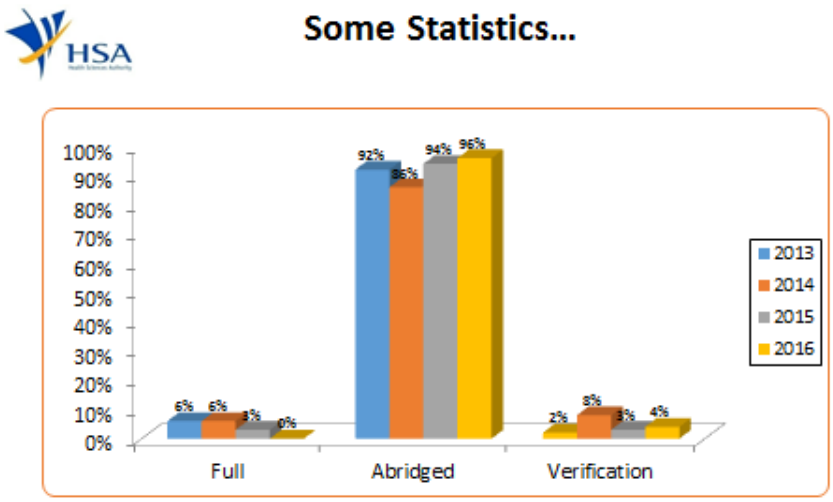


Figure 5. The abridged route of review at HSA has been overwhelmingly favoured by industry over the past 10 years.

There are practical challenges to making regulatory decisions based entirely on the assessment by reference agencies, as the regulatory threshold and decisions may vary among reference agencies. Benefit-risk considerations may also differ due to local factors such as disease epidemiology, demographics and clinical practice. Other non-scientific factors such as policies and stakeholder lobbying may have influence. In addition, a company's filing strategies may involve differing clinical indications, chemistry, manufacturing and controls data and quality specifications for different markets. Typically, filing strategy prioritises the US, EU, Japan and then "rest of the world." Finally, there are potential knowledge gaps in the evaluation of post-approval variations throughout a product life cycle.

For HSA, a small agency with a combined staff of 30 evaluators for clinical and quality evaluation, it would be impractical and impossible to reproduce the depth of evaluation by major agencies such as FDA and EMA. By recognising agency limitations, identifying elements in the benefit-risk assessment that are critical in the local context and bridging reference agency assessments to the Singapore population, HSA is able to leverage the work of larger agencies while ensuring the benefit-risk assessments are applicable to the people of Singapore. Only approximately 1% to 2% of applications with reference agencies approval receive a negative decision from the agency.

Thus, relatively objective elements such as pre-clinical and early phase clinical study evaluations can to a large extent, can leverage on the work done by reference agencies, as can CMC evaluations except for region-specific data, if quality specifications are the same. The benefit-risk assessment focuses primarily on

phase II and III data and the key is to identify differences (if any) in patient population, disease profile, epidemiology, clinical setting and demographics that may be pertinent to the local context.

Observations from past experience include the fact that efficacy endpoints considered in other regions may not be relevant to Singapore's population because of the nature or prevalence of the disease, rendering the observed clinical efficacy irrelevant in local context. Differences in demographics between Singapore and other regions such as race and body weight, may increase the incidence of adverse effects and render the benefit-risk balance negative in the Singapore population. In addition, there are differences in clinical practice and regulatory thresholds, for example, for evidence based on surrogate endpoints and there are diseases of local public health importance and unmet medical needs that need to be considered (Figure 6).

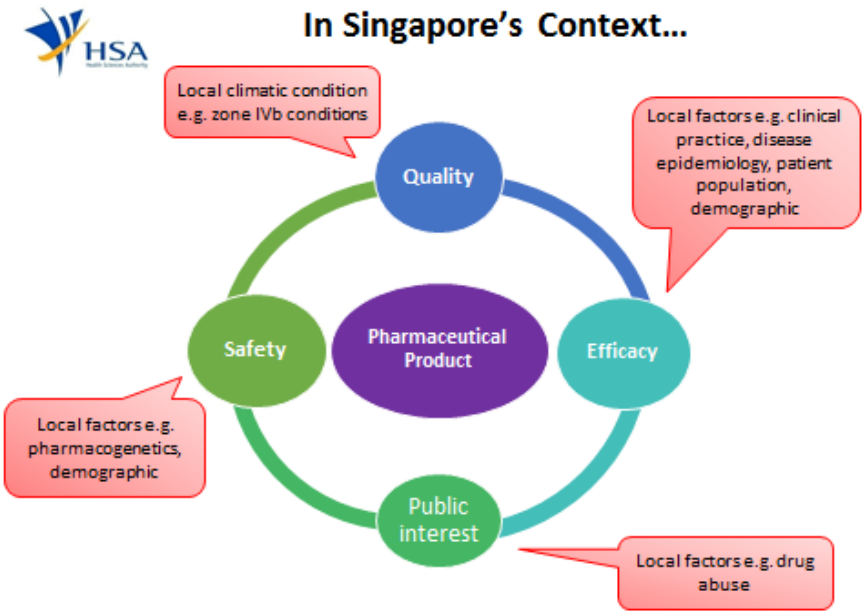


Figure 6. HSA bridges product assessments by reference agencies to the local Singapore context.

Singapore has designed a regulatory system based on its risk threshold, regulatory capabilities, national policies and international developments in regulatory convergence. Risk-based evaluation remains the most pragmatic approach that enables HSA to optimise limited resources effectively while ensuring robustness in its decisions. It has been key for the agency to identify gaps and retain regulatory capability in order to bridge benefit-risk assessments done by reference agencies to the local Singapore context. Capabilities to perform independent evaluations remains strategically critical and support must be ensured for regional biomedical research and development growth.

Risk-based evaluation remains the most pragmatic approach that enables HSA to optimise limited resources effectively while ensuring robustness in its decisions.

Work-sharing vs information sharing in the evaluation of medicines – Some practical considerations

Adj Prof John Skerritt, *Deputy Secretary for Health Products Regulation, Department of Health, Australia*

Pharmaceutical regulatory *work sharing* can be defined as two regulators sharing the workload by evaluating different parts of a dossier such as clinical, quality or toxicology. This is a possibility when the applications are received by the two regulators at the same time. *Information sharing*, on the other hand, can be defined as the use of the evaluation report of another regulator to assess the Common Technical Document content when one regulator has already granted market authorisation to the product.

International regulatory cooperation in Australia

Australia is the only known country where international regulatory cooperation is government policy enunciated at the highest (Prime Ministerial) level.. In late 2014, the then Australian Prime Minister said *"... if a system, service or product has been approved under a trusted international standard or risk assessment, then our regulators should not impose any additional requirements for approval in Australia, unless it can be demonstrated that there is a good reason to do so."* This was further emphasised in decisions contained in the 2014-16 *Review of Medicines and Device Regulation* which stated that for the evaluation of new prescription medicines, TGA will "develop and apply transparent criteria for identifying comparable overseas regulators [and evaluate medicines upon] submission of a complete dossier for de novo assessment . . . [either] undertaken in full by TGA, or via work-sharing between TGA and a comparable overseas regulator . . . submission of an un-redacted evaluation report . . . along with a copy of the dossier and an Australian-specific Module 1."

Some criteria were proposed by the TGA Review Panel: to define "comparable overseas regulators" These regulators should

- Regulate for a demographic that is broadly representative of the Australian population and has similar health outcomes AND
- Adopt ICH guidelines AND
- Have a credible and consistent track record of approving safe and effective medicines AND
- Conduct de novo evaluations of dossiers for all medicine types AND
- Require peer/ independent assessment of evaluations AND
- Employ evaluators with the necessary technical and clinical expertise AND
- Have access to un-redacted evaluation reports and where applicable, individual patient data AND
- Communicate and prepare evaluation reports in English

It was contemplated whether membership in particular international organisations could confer the status of "comparable regulator." However, the number of regulatory agencies that have joined – or been accredited to - these organisations is highly variable: 7 in the *International Council on Harmonisation* of Technical

Requirements for Registration of Pharmaceuticals for Human Use (ICH), 49 in the Pharmaceutical Inspection Convention/Co-operation Scheme (PIC/S) and 23 in the International Coalition of Medicines *Regulatory* Authorities (*ICMRA*). Therefore this seemingly attractive approach is not feasible in practice.

Practical challenges around the identification and acceptance of comparable regulators might be met through the publication of lists of "acceptable" regulatory agencies to ensure transparency and increase the likelihood of applicants proposing a work-sharing or information-sharing pathway and by identifying specific issues around a particular submission that must be considered at the time of submission. Also requiring sponsors to provide the full data package and international evaluations on the medicine would enable the basis of decisions on indications to be better understood and potential risks managed and would enable the local regulator to respond very quickly if major problems emerge and to check the medicine against local experience.

. . . requiring sponsors to provide the full data package and international evaluations on the medicine would enable the basis of decisions on indications to be understood and potential risks to be managed . . .

The Review Panel also proposed criteria for product similarity for regulatory work or information sharing with TGA. The products reviewed by both regulators should be identical in dosage form, strength, formulation and indications and manufactured at a plant that has received good manufacturing process certification or clearance from TGA under identical processes and there should be no specific issues regarding applicability of the submitted data to the Australian context. But if there are differences, TGA must assess the extent to which the differences have the potential to impact the quality, safety or efficacy of the product.

Current models for work- or information-sharing include the EMA evaluation model, which is not really work sharing but rather the formation of rapporteur and co-rapporteur teams from two regulatory agencies, who separate evaluate products. Others are the EU centralised and decentralised procedures on evaluation of generic drug applications, the International Generic Drug Regulator's Programme (IGDRP), which represents the convergence of technical requirements and for which a work-sharing trial is underway and the Australia, Canada, Singapore and Switzerland (ACSS) regulatory cooperation coalition, which explored benefit-risk assessment methodologies and tools for purposes of work sharing.

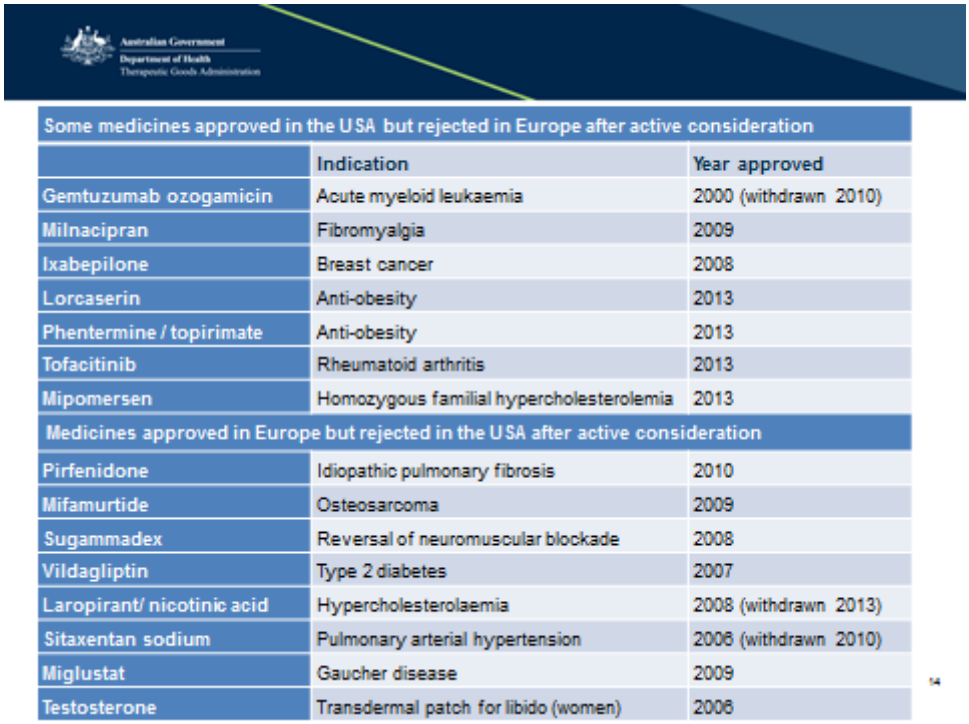
According to a 2016 TGA survey of the Australian pharmaceutical industry, work-sharing is felt feasible in principle because larger companies increasingly submit applications simultaneously to multiple regulators but is of limited interest to industry stakeholders unless it reduced regulatory timeframes or fees. Survey respondents also indicated that differences in evaluation timeframes or milestones between agencies may add complexity and delay approvals and that there would be a need to monitor transaction costs associated with communications. There was also a concern that if a drug has "challenges" in one country, its review may potentially struggle in several countries and that the process would be less likely to be used for generic drugs, as patent expiration dates differ significantly between countries.

While the promise of work sharing in regulatory review should not be ignored, information sharing; that is, the reliance on the use of a completed evaluation report, may be feasible in more situations than work sharing. Information sharing is already being used for example by Singapore, Mexico, New Zealand, Taiwan and several other small and medium-sized regulators. As reported by Dr Chan at this Workshop, there are three evaluation pathways for new medicines in Singapore. Full evaluations have a target of 270 working days and abridged evaluations have a target of 180 working days and require previous approval of the product by one other agency and full assessment by HSA of the quality and pivotal clinical data but only the summaries of other parts. The verification route at HSA has a target time of 60 working days, requires previous approval of the product by two other reference agencies and HSA review of summaries and evaluations, however this is not used widely. Countries using information sharing may have to accept a submission lag of a year or potentially somewhat more while waiting for the appropriate documentation. For agencies without a submission lag, information sharing may be useful for encouraging local market authorisation of "older" medicines that are currently only available through compassionate access schemes.

But there are challenges to information sharing including the fact that it can be difficult to obtain un-redacted evaluation reports from some regulators, only a few regulators publish a compiled evaluation report and here are often differences between the indications approved in reference countries. Most critically significant cultural change may be required if evaluation staff are not used to using external reports. In addition, it is not uncommon for different regulators to reach different conclusions on overall market authorisation or on particular indications based on the same data (Figure 7).

Confidence building and changing internal culture in regulatory agencies are critical. Many agencies currently have informal processes for using reports. For example, within TGA there is routine use of external reports by manufacturing quality and toxicology teams but at present there is more limited use by pharmaceutical chemistry and clinical teams. It is necessary too for peers and senior management to provide reassurance in this regard and to build standard operating procedures for the use of reports into the regulatory review process.

Until recently, regulatory submissions by industry to "second-tier" regulatory agencies were often subject to a lag but that is currently changing. Several actions could integrate this change and other global developments into work- and information-sharing including a stronger focus on real-world data, parallel regulatory and health technology assessment or payer scientific advice and the expanded aligned use of priority review and provisional/adaptive/conditional licensing pathways. In addition, increased emphasis on transparency is required for information or work sharing but there may be very different approaches between countries; for example, approaches vary regarding publication of information on new medicines that are currently under review, information on positive and negative decisions for medicines, access to (patient de-identified) clinical trials data, good manufacturing practice (GMP) inspection information and reports and enforcement information.



Some medicines approved in the USA but rejected in Europe after active consideration		
	Indication	Year approved
Gemtuzumab ozogamicin	Acute myeloid leukaemia	2000 (withdrawn 2010)
Milnacipran	Fibromyalgia	2009
Ixabepilone	Breast cancer	2008
Lorcaserin	Anti-obesity	2013
Phentermine / topirimate	Anti-obesity	2013
Tofacitinib	Rheumatoid arthritis	2013
Mipomersen	Homozygous familial hypercholesterolemia	2013
Medicines approved in Europe but rejected in the USA after active consideration		
Pirfenidone	Idiopathic pulmonary fibrosis	2010
Mifamurtide	Osteosarcoma	2009
Sugammadex	Reversal of neuromuscular blockade	2008
Vildagliptin	Type 2 diabetes	2007
Laropirant/ nicotinic acid	Hypercholesterolaemia	2008 (withdrawn 2013)
Sitaxentan sodium	Pulmonary arterial hypertension	2006 (withdrawn 2010)
Miglustat	Gaucher disease	2009
Testosterone	Transdermal patch for libido (women)	2006

Figure 7. Different regulatory agencies often come to differing conclusions regarding the same data.

There are multiple constraints on international collaboration, including the fact that regulatory processes are codified nationally in legal frameworks. In addition, there are differing financial models and resources for the agencies to work under, variable timing for receipt of applications, the types of reports obtained, confidentiality issues with sponsors, incompatibility of IT systems and different languages. There is often also an initial increase in cost and work before work sharing can become “business as usual” and staff may be concerned regarding a perceived loss of control in data evaluation. But it can be done. Originating in 1970, PIC/S comprises 49 regulatory authorities that developed and maintains harmonised GMP standards and quality systems for medicines inspectorates. The use of GMP “clearances” based on reports from recent inspection by other regulators reduces the number of TGA overseas inspections required by 90%.

Greater cooperation among regulatory agencies could mean more consistent submission requirements and GMP inspection processes across countries. Only country-specific requirements would be assessed, for example, product information, consumer medicine information, national clinical guidelines/ context of use, risk management plans, medicine’s classification and local labelling requirements. If reports are shared or obtained in a timely manner it could potentially provide faster evaluation times and earlier availability of medicines.

Integration of collaboration between regulators will take time and more effort at first but in time, there will be benefits for industry, regulators and patients including faster market access and lower costs, reduced workload, less duplication and earlier access to medicines.

Stakeholder perspectives: Why should agencies establish risk-based approaches and how could stakeholders enable the process? NGO perspective

Dr Shyam Bhaskaran, *Program Officer, Regulatory Affairs, Bill & Melinda Gates Foundation, USA*

The vision of the Regulatory Affairs Team at the Bill and Melinda Gates Foundation is to accelerate access to quality products in target countries by supporting the regulatory aspects of the development, approval and lifecycle management of global health vaccines, drugs, diagnostics and other global health technologies.

In 2013, the Foundation commissioned research to determine the extent and nature of the gap between the availability of medicines in their country of origin and low- and middle-income countries. To introduce a vaccine or drug in many low- or middle-income countries, the product generally needs a first registration, usually in the country of origin, or a recognised stringent regulatory authority, often also requiring a Certificate of Pharmaceutical Product. Next, to help ensure suitability for these regions and to meet the quality requirements of donors and procurers, the product typically needs World Health Organization Prequalification (WHO-PQ) and finally, the product must be registered with the target country's national regulatory authority (Figure 8).

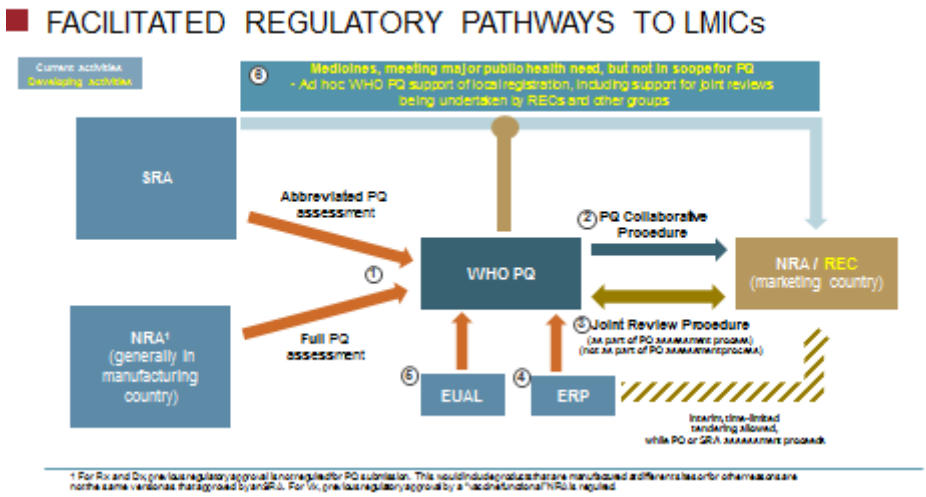


Figure 8. The interrelated steps toward the availability of medicines in lower- and middle-income countries.

Research showed that added to the time required for these steps, there is frequently a significant gap between a product sponsor's submission to the first regulatory authority and its submission to regulatory agencies in low- and middle-income countries, resulting in a total delay in access to medicines that can amount to four to seven years (Figure 9).

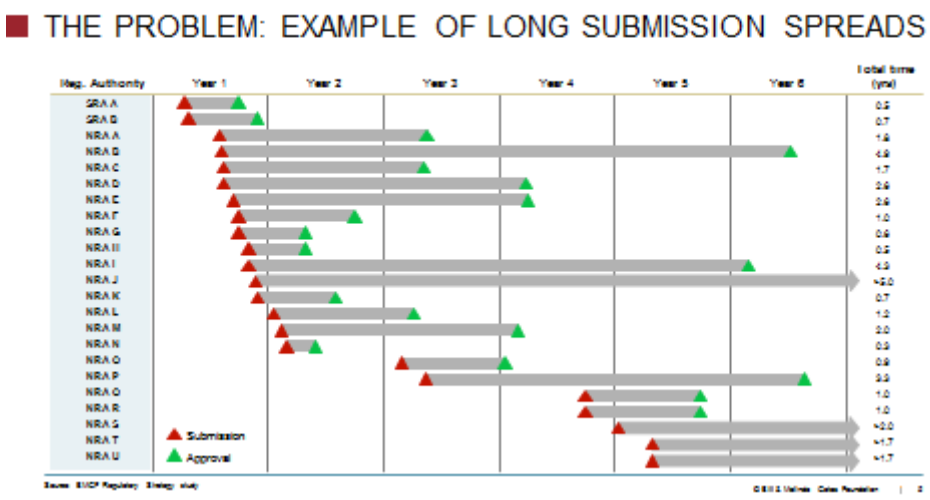


Figure 9. Delays in submission to regulatory authorities in low- and middle-income countries can greatly exacerbate delays in access to medicines.

Having determined the significance of this gap in access, the Foundation seeks to develop strategies to accelerate the availability of medicines through two key axes. First, the organisation works to promote "horizontal" integration, through a focus on value-added activities that maximise reliance, minimise redundancy and encourage work through regionalization. Second, it strives to promote "vertical" efficiency through a concentration on process improvements, project management, prequalification standards in manufacturing countries and the increase of regulatory capacity and capability.

Building on principles of reliance, re-engineering and regionalisation, the major focus of the programme to date has been on registration, optimising the prequalification process to be predictable, accountable and transparent, expanding the prequalification collaborative procedure and supporting regulatory regionalisation through such groups as African Medicines Regulatory Harmonisation (AMRH), Caribbean Community (CARICOM) and the Association of Southeast Asian Nations (ASEAN).

Building on principles of reliance, re-engineering and regionalisation, the major focus of the programme to date has been on registration

Other regulatory efforts have centred on monitoring national regulatory authority and regional economic community metrics, strengthening national regulatory authority value-added capacity in targeted countries, developing WHO Guidance on Good Reliance Practices and global regulatory communication, training and sharing of best practices. Expansion is ongoing into the clinical development area with regional approaches to clinical trial and ethics committee authorisation such as AVAREF (African Vaccine Regulatory Forum). Delivery and surveillance activities will include improving safety and surveillance activities in low- and middle-income countries, strengthening the regulatory components of supply chain integrity and regulatory oversight of vaccine variations.

The Foundation recognises that to improve efficiency and timelines, the development and regulation of medicine should be regarded as an ecosystem, with each element affecting the outcome in an interrelated way. It also understands that its interactions with national regulatory authorities are dependent on that agency's capabilities, goals and legal mandates. Rather than a strict dependence on mature regulatory agencies, reliance can be based on regional group cooperation and global regulators have demonstrated a keen interest and willingness to develop activities and alliances that will ultimately expedite access to needed medicines for all patients.

Country approaches to risk-based evaluation – Prioritisation based on reference agency approval: Opportunities and challenges – Indonesia viewpoint

Togi Junice Hutadjulu, *Director of Drugs and Biological Product Evaluation, NADFC*

The existing procedure for the review of new drug applications in Indonesia was stipulated in the decree of the head of the National Agency of Drug and Food Control (NADFC) in 2011. This procedure, however, is currently being revised owing to stakeholder demand for process acceleration. In general, the drug evaluation procedures consists of six steps, 1)submission; 2) scientific evidence-based dossier screening; 3) review for efficacy, safety and quality, including quality control of product and production process; 4) decision making, based on a benefit-risk evaluation; 5) labelling and licencing and 6) any post-approval changes.

In the risk-based review of medicines in Indonesia the timeline encompasses two steps. In step 1, which takes 40 working days, the registration category, evaluation path/timeline and registration fee are determined. In step 2, the dossier is evaluated according to the registration category. In step 2, life-saving or orphan drugs or drugs for a national programme are reviewed in 100 working days, drugs that have been reviewed by mature agencies are reviewed in 150 working days and drugs that are not included in the 100- or 150-day category are reviewed within 300 working days.

Multiple factors drive efforts to revise this process including a backlog of drug applications, particularly of new products requiring extensive evaluation in the face of resources limitations. In addition, industry has questioned decisions that are divergent from those of other agencies and it is understood that the reliance on other agencies' work may result in a faster decision-making process. Ineffective and efficient drug evaluation system that avoids duplicative work will result in wise use of limited resources for critical drug registrations. Finally, there is a demand by stakeholders to expedite the registration process and avoid delays to patient access to needed drugs

. . . reliance on other agencies's work may result on a faster decision-making process and effective and efficient drug evaluation system that avoids duplicative work . . .

There are challenges to overcome for reform efforts. Currently, a full, nonclinical, clinical and quality assessment is performed for all evaluation paths. To prioritise the review of needed products such as those that fulfil unmet medical need, orphan drugs or drugs for national programmes, a strategy is proposed that includes reducing the shortened queuing time and closed monitoring review time. In addition, the number of regulatory reviewers has decreased from 82 to 75, whilst the number of applications has increased (Figure 10). Whilst this challenge might be met by an increase on the reliance of the work of other regulatory agencies, there are also barriers to that strategy, including the necessity to build trust in other regulatory agencies' decisions. In addition, an appropriate decision-making process must be established, including the criteria and procedures for reliance and the need to determine if dossiers and quality-assurance documentation is the same for both agencies and the conditions of reliance when relabeling for differing indications is required.

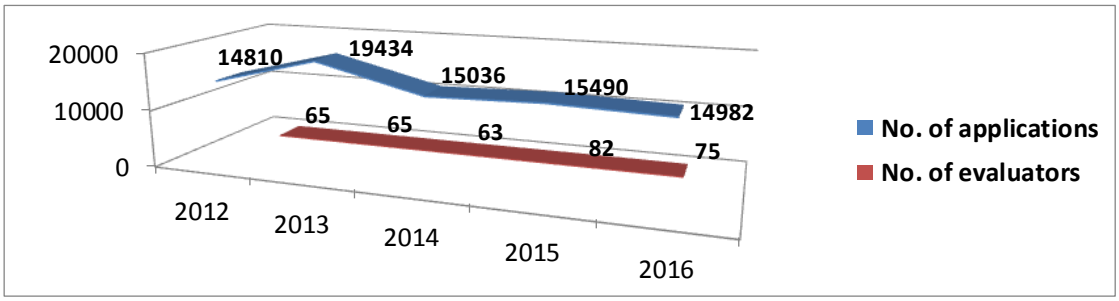


Figure 10. The amount of new drug applications has increased in Indonesia and the number of reviewers has decreased.

With these needs in mind, a simplification of the evaluation process for new drug applications for new drugs that have been approved by mature agencies (the 150-working day category), except for some products that are currently in the 100-working day category, is underway using reliance mechanisms; this is expected to reduce the timelines to 100 working days. The criteria of the reliance mechanism include medicinal products with similar indications and dosing regimens that have been approved by at least three mature agencies with published assessment reports from these three agencies. All aspects of the products' quality, including but not limited to the formulation, manufacturing sites, release and shelf-life specifications and primary packaging must be identical to that currently approved by the reference agencies. In addition, the product must not need a more stringent assessment as a result of differences in local disease patterns and/or medical practices; for example, for some anti-infection, anti-virus, anti-malaria or tuberculosis drugs. By applying these reliance mechanisms, evaluations will focus on country-specific requirements for certain excipients, stability studies and product information and labelling.

In addition, a paperless *online* system for NDA submission will be initiated in mid-2017 which is expected to enhance the expediency and transparency of the evaluation process and provide a tracking mechanism for product sponsors.

In conclusion, issues related to the long registration process in Indonesia have driven the regulatory agency to build an effective and efficient system for prioritised risk-based decision-making, including the possibility of using the application of a reference system that will expedite regulatory review and decision making through reliance. Ultimately, the aim of these reforms is to accelerate patient access to good-quality medicines that are safe and effective.

Regional approaches to risk-based evaluation: Caribbean Community (CARICOM) regulatory efforts

Dr Charlie Preston, *Advisor for Regulatory Systems Strengthening for Medicines and Other Health Technologies, PAHO/WHO, Trinidad*

The Caribbean Community (CARICOM) comprises a diverse group of 11 countries with a combined population of 17 million people. Unfortunately, regulatory capacity among these countries is limited. Using the basic indicators for regulatory capacity specified by the Pan American Health Organization (PAHO), with 39% capacity, the non-Latin Caribbean is severely lagging behind other sub-regions in the Americas (Figure 11).

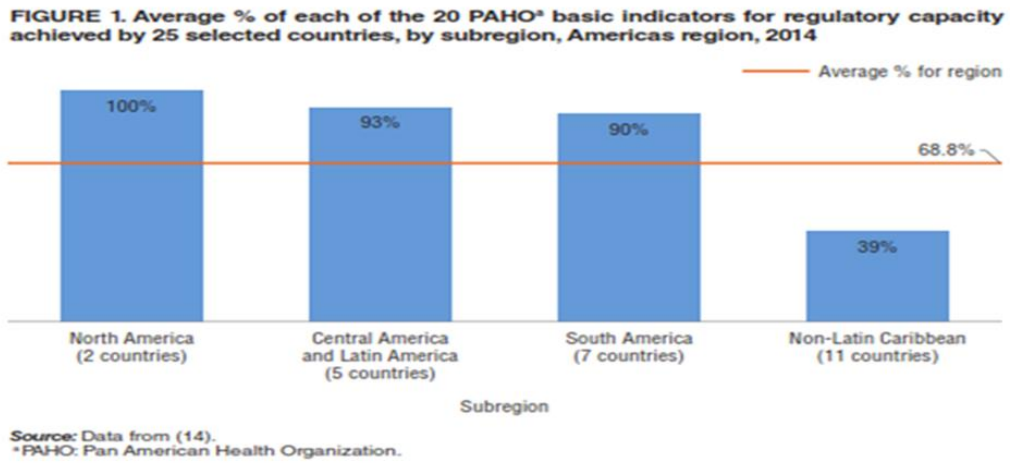


Figure 11. Countries in the Caribbean Community do not have currently the needed regulatory capacity.

Limited capacity in these small states is complicated by registration backlogs, difficulties with laboratory testing, a general lack of target timelines with limited accountability to the public in terms of performance metrics, no or limited pharmacovigilance and post-market surveillance, the wide availability of substandard and falsified medicines and no robust regulatory activity among the Organization of Eastern Caribbean States (OECS). However, efforts are ongoing to strengthen regulatory capacity. A regional approach has been years in the making and there is political support from CARICOM Ministers of Health and financing from the Bill and Melinda Gates Foundation to meet this goal.

The regional regulatory unit of the Caribbean Regulatory System is housed in and managed by the CARICOM Regional Public Health Agency (CARPHA). Dedicated staff there carry out assessment activities for eligible products and perform pharmacovigilance or post-market surveillance. Sustainability through user fees is the goal for the system.

Applications or dossiers can come to CARPHA/CRS in two ways - directly or through a Ministry of Health (MOH), which asks the CARPHA/CRS to review the product as an assessor, after the company signs a waiver to allow the MOH to release the dossier (Figure 12). This is a good option for companies with products whose review is slowed by backlog or for the efficient expansion of registration to other markets in CARICOM. The CARPHA/CRS team then looks for the verification elements and requests any additional required documentation.

Companies submitting directly to the CRS can use the Common Technical Document format or the format typically submitted to the MOH, provided it contains all information needed to conduct the verification, thereby relieving them of the necessity to organise dossiers into new formats. If CRS verification is favourable, the product is recommended to all CARICOM Member and Associate Member States. Basic product information, including the name, dose, formulation and manufacturer is then posted publicly on the CARPHA/CRS website for all stakeholders, creating a list of available regulatory-assured products. Following the CRS recommendation, individual countries are asked to provide their own recommendation in 60 days.

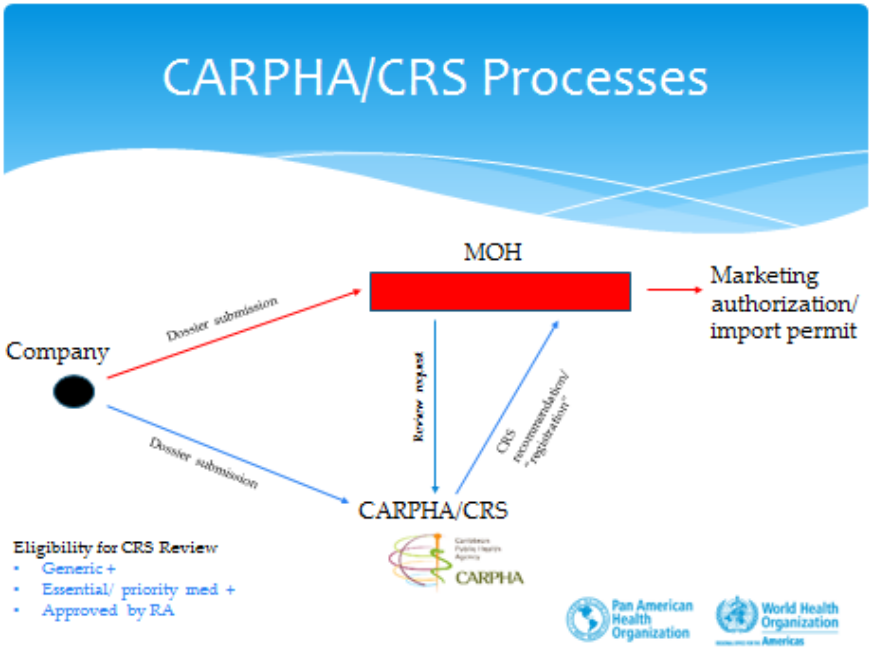


Figure 12. Applications can be submitted to the CARICOM Regional Public Health Agency via two routes.

CARICOM reliance on reference authorities allows the abbreviated review of already approved products and verification procedures based on the World Health Organization Prequalification (WHO PQ) process. Agencies can then focus on the highest priority regulatory needs such as essential generic medicines, which may be less complex in terms of regulatory science and freeing the agencies to allocate more time on pharmacovigilance or post-market surveillance.

CARICOM states have the political foundation for participation and CRS is working to ensure that Memoranda of Understanding (MOUs) are in place with governments to enable the sharing information and timelines for these assessments. CARPHA/CRS also signs MOUs with procurers to recognise recommended products

CARPHA/CRS regulatory review can be of benefit to patients. Having a single portal of entry to all markets with vastly improved review timelines (180 for the CRS review followed by 60 days for the local jurisdictional review) improves patient access and facilitates increased competition, often decreasing prices. There are also incentives for industry participation including easier access to a 17-million-person market, simpler, harmonised procedures with faster timelines and linkage to procurement.

Having a single portal of entry to all markets with vastly improved review timelines improves patient access and facilitates increased competition

Although companies and ministries of health have been somewhat slow to submit dossiers, focal points have already been appointed in many countries and CARPHA/CRS is ready for regulatory work. MOUs have been signed with Guyana, the Organization of Eastern Caribbean States / Pharmaceutical Procurement Service and Suriname. In April 2017, a workshop will be conducted for the review of live dossiers using the WHO PQ collaborative procedure.

SADC Collaborative Medicines Registration Initiative: Zambia, Zimbabwe, Botswana and Namibia, (*ZaZiBoNa)*

Gugu Mahlangu, *Director-General, Medicines Control Authority, Zimbabwe*

SADC and ZaZiBoNa

The South African Development Community (SADC) is a regional economic group with 15 Member States (MS). There are varying regulatory capacities in the region and 11 MS actively issue marketing authorisations. A directive issued by the SADC Ministers of Health in 1999 began efforts to harmonise the registration of medicines in the area and to date, this work has focused on the development of more than 22 technical guidelines. The regional policy documents guiding the harmonisation work include the SADC Protocol on Health 1999 as well as the SADC Pharmaceutical Business Plan of 2015–2019. This harmonisation supports the SADC regional industrialisation strategy, which in turn is supported by a regional manufacturing strategy for essential medicines and health commodities.

The collaborative process

The SADC Collaborative Medicines Registration Initiative (ZaZiBoNa) was endorsed by SADC Ministers of Health and Ministers Responsible for HIV & AIDS in January 2015. The objectives of the collaborative are to cooperate in the assessment and inspections for medicines registrations with the goal of reducing workloads, shortening timelines to registrations, developing mutual trust and confidence in regulatory collaboration and developing a platform for training and collaboration in other regulatory fields. Since its inception, the collaborative has expanded and there are currently five active participating MS:*,* Zambia and Zimbabwe. Botswana, Namibia and South Africa *(joined June 2016).* Swaziland, which joined Nov 2016, is a non-active participating MS.

Any medicine meeting the essential medicine criteria is invited to be considered for registration via the ZaZiBoNa collaborative process. However, priority is given to the 10 priority disease conditions identified by SADC plus reproductive health products as well as products included in the List of UN Commission for Life-Saving Commodities for Women and Children. Any other medicines that are important from a public health perspective may be considered on a case-by-case basis. Participation is voluntary and requires the written consent of the manufacturer. The application must have been lodged with at least half of the participating countries and submissions are made in the SADC CTD format using the same technical dossier and product information as is submitted to the countries.

A product is assigned a rapporteur who performs the primary assessment, which is then circulated to participating countries for comments. Inspections are performed by two inspectors from two countries and the inspection reports are also circulated to the participating countries. Consensus on the assessment and inspection reports is reached through meetings facilitated by WHO, with consolidated reports and a

consolidated list of questions from assessment and inspections sent to the applicant, allowing sponsors the opportunity to provide one response to all the participating countries.

The WHO provides technical assistance and quality assurance for the assessment reports. This approach helps in sharing the workload among the regulators without duplication of work. The ZaZiBoNa scheme provides for 210 regulatory and 90 applicant days for registration. The assessment and inspection reports could also be shared with other interested SADC regulators to facilitate their own decision making for the same products; facilitating, for example, procurement decisions for those countries that do not yet register medicines but need a reliable source of information on the acceptability of the products.

The heads of agencies, who provide direction and oversight, meet twice a year and the assessors meet four times a year on a rotational basis among the participating countries. One assessors' meeting is scheduled each quarter, during which an average of 12 new products are considered. From 2013 to 2016, a total of 13 sessions have been convened. In addition, four GMP inspections are scheduled per year and 13 manufacturers have been inspected to date. The ZaZiBoNa approach also provides an opportunity for capacity building of assessors and inspectors and 10 training sessions have been held concurrently with the assessment meetings or during the GMP inspections so far. This training, which is facilitated by the WHO, helps to enhance the technical skills and capacity of the participating regulators.

Results

In just 3.5 years of operation, evaluation through the ZaZiBoNa process has been finalised for 85 products, with 59% receiving a positive opinion with recommendation of registration to the countries, while 29% received negative recommendations. For 69 products responses from manufacturers are pending; that is, they have undergone reviews and manufacturers have to respond to some outstanding issues before a final recommendation is made (Figure 13).No initiative that is similar to this cost-effective collaboration has delivered these kinds of results in a relatively short period. The median time to recommendation has been 9 months, including regulators' and applicants' time to respond to queries, which corresponds to the target time for the process. The mean number of review cycles was 2.5 per product, which slightly exceeds the target of 2 cycles but the average response time to questions for manufacturers fell within the three-month target and the median time for final approval at the national level after the ZaZiBoNa process was 1.5 months, shorter than the target of 2 months, although this is based on data from two countries.

ZaZiBoNa is not a replacement for the national regulatory agencies, as it only focuses on the review and inspection processes and actual registration is still performed at the national level and requires submission of product applications to the countries following applicable national requirements. There is no central single

submission yet but the same dossier is submitted to all the ZaZiBoNa countries based on the SADC common technical document and registration guidelines.

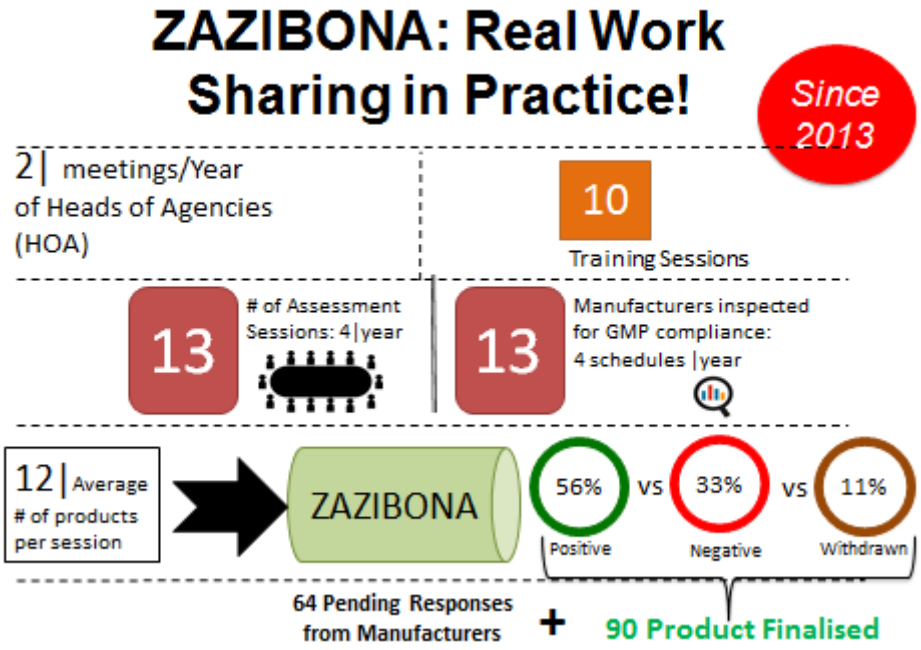


Figure 13. Results of the ZaZiBoNa collaborative process to date.

ZaZiBoNa success factors

Certain factors have been key to the success of this initiative including participation of partners who select the level of their participation and who maintain a balanced relationship, with a rotation of coordination and hosting of meetings. Mutual respect and trust enables decision making by consensus, with the WHO functioning as a neutral moderator and facilitator. Because products considered need to be of interest to at least 50% of participating MS, there are shared common goals. Relationship support from the WHO for assessments and inspections is critical, as relationship building takes time and effort.

ZaZiBoNa has exerted a demonstrably positive effect in terms of group efficiency, reducing the resource burden, shortening timelines and enhancing the quality of work and the technical capacity of regulators and inspectors . . .

ZaZiBoNa has exerted a demonstrably positive effect in terms of group efficiency, reducing the resource burden, shortening timelines and enhancing the quality of work and the technical capacity of regulators and inspectors and cost sharing by the WHO and MS partners has produced a lean cost structure. The right leadership and management and the political support of the SADC the Ministers of Health as well as the ownerships of activities, decisions and the organisation of meetings by MS has been of critical importance as has communication through a secure online platform for information

sharing. Effective governance has been established through twice-yearly meetings of decision makers to set targets and approve work plans and budgets and formalisation of the collaboration has been set through an established legal and operations framework.

Conclusions

ZaZiBoNa represents a potential mechanism for improving the regulatory systems in low- and middle-income countries. This efficient, effective and sustainable collaboration is cost effective, producing good value for cost. The average cost of this process is USD$4,500 per product. (This cost solely represents ZaZiBoNa meetings and excludes national regulatory agency and GMP costs). Meetings are organised and hosted by MS and this transparent, risk-based approach also enhances regulatory capacity.

Advantages and barriers to regional alignment of review models

Dr David Jefferys, *Senior Vice President, Eisai*

Co-Chair, International Federation of Pharmaceutical Manufacturers (IFPMA)

The International Federation of Pharmaceutical Manufacturers Association (IFPMA) approaches regional alignment of regulatory review in multiple ways. The Association supports appropriate regulatory capacity building and training, while recognising that this support might be best developed through trusted third partners such as the Gates Foundation or the Regulatory Affairs Professional Society. As a standing member of the International Council on Harmonisation of Technical Requirements for Registration of *Pharmaceuticals* for Human Use *(*ICH*),* IFPMA supports ongoing regulatory convergence and harmonisation, which is being facilitated by the expansion of ICH beyond its three founding members.

Activities that IFPMA regards as being key in this area include the development of the *Good regulatory review practices: guidelines for national and regional regulatory authorities* through a partnership between the Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC) and the World Health Organization (WHO). In addition, to fulfil a complementary need, the Good Regulatory Submission Practice work stream was launched at the 8th Asia Regulatory Conference in Taipei in 2016.

IFPMA has recently focussed on two regions relevant to the geographic interests of its members: Asia Pacific and Africa. In the Asia Pacific, IFPMA has participated in the work and accomplishments of the Asia Partnership Conference of Pharmaceutical Associations (APAC) over the past several years as they seek to achieve regulatory convergence in Asia. In Africa, IFPMA participated in the pre-meeting event at the International Conference of Drug Regulatory Authorities (ICDRA) in Cape Town in 2016. Other important work in Africa in which industry can share and support is being performed by the Africa Regulatory Network African Medicines Regulatory Harmonisation Programme (AMRH) and the New Partnership for Africa's Development *(*NEPAD*).* IFPMA shares the vision of African union – to unify 54 countries to 5 regions to 1 continent and to use the AMRH as a foundation for the formation of the African Medicines Association (AMA).

Industry also supports the efforts toward regional alignment that have been facilitated by stringent regulatory authorities through reliance on such programmes as EMA Article 58, in which the EMA evaluates the quality, efficacy and safety of medicines or vaccines intended primarily for use outside of the EU, reserving the licencing decisions for regulators in the countries where the medicines will be used. Industry and IFPMA also stand ready to assist with other programmes cited by speakers at this Workshop including the WHO Prequalification Procedure, the use of the Certificate of Pharmaceutical Product (CPP) and regional work sharing. These programmes may benefit from assistance in further enhancement such the provision of digital on line “self-service” options for the CPP and streamlining of the Prequalification Procedure.

Industry has played and will continue to play a part in these efforts to align regional regulatory review. However, current concerns centre largely on the life cycle management of medicines, including pharmacovigilance and safety reporting. In fact, as the number of conditional approvals increases, new trials are required and the majority of industry resources are now focussed on lifecycle management rather than on filing for new medicines. In addition, maintaining older products through variations that vary across jurisdictions adds to costs, drains resources and ultimately affects patients' access to medicines. The European Federation of Pharmaceutical Industries and Associations *(*EFPIA*)* recently developed a draft of a publication *Management for Timely Access to Medicines Worldwide* on this important topic and the WHO is currently drafting *Concepts Note on Variations Management.*

A risk-based approach to medicines' regulation would reduce duplication, decrease resource use and diminish drug shortages. In this multi-lateral risk-based partnership, a "red flag" approach could be used, where products with a potentially critical impact on public health would be identified and prioritised for review and manufacture.

A risk-based approach to medicines' regulation would reduce duplication, decrease resource use and diminish drug shortages.

Utilization of a systematic structured benefit-risk or decision-making framework to enable consistency within and across agencies

Dr Neil McAuslane, *Director, Centre for Innovation in Regulatory Science*

The importance of a benefit-risk framework for agencies

Determining the benefit-risk balance of a medicine is one of the most important steps in its review. There is a general agreement that there is a need for a structured, standardised, systematic approach to the benefit-risk assessment of medicines using a framework that should ideally be feasible and practical within the regulatory review process. A *framework* is a set of principles, guidelines and tools to guide decision makers in selecting, organising, understanding, summarising and communicating the evidence relevant to benefit-risk decisions. The rationale for using a framework for benefit-risk decision making is that it enables a more transparent, predictable and consistent review of medicines, which may be of considerable value to agencies in communicating their views and decisions and is also in line with the *Good Review Practices for Regulatory Authorities* developed by the World Health Organization. The use of a framework could also facilitate agreement in benefit-risk assessment, which is necessary for regulatory authorities that wish to work together and collaborate within a region in joint and shared reviews and provide value to agencies conducting both abridged and verification reviews where there is reliance to some degree on the assessment by reference agencies.

Benefit-risk frameworks that are currently used include the US FDA benefit-risk framework and EMA PrOACT-URL (problems, objective, alternatives, consequences, trade-offs, uncertainties, risk perception and links) model with its Effects Table and the model developed by Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team (PhRMA BRAT), which was transferred to CIRS in 2011. It was the consensus of participants at CIRS Workshops that these methodologies could be mapped to the CIRS eight-step Universal Methodology for Benefit-Risk Assessment (UMBRA) framework, an overarching framework that provides a platform for the coordinated development of benefit-risk assessment methodologies.[1]

Benefit-risk frameworks, risk stratification and quality decision making

. . . agencies utilising the reviews of reference agencies in verification and abridged reviews must understand the reference agency benefit-risk decisions. This understanding can be facilitated through use of tools such as the UMBRA framework

In addition to undertaking an assessment of a medicine's benefit-risk for their population and building quality into the their decision making, agencies utilising the reviews of reference agencies in verification and abridged reviews must understand the reference agency benefit-risk decisions. This understanding can be facilitated through transparency provided through the use of tools such as the UMBRA framework (Figure 14)

iSABRE

A documentation system was developed in support of UMBRA and the Summary portion of this system, which consists of a simplified Benefit-Risk Template and User Manual, has recently been evaluated in the CIRS

International Summary Approach to Benefit Risk Evaluation (iSABRE) feasibility and pilot studies by regulatory agencies in China, Indonesia, Malaysia, Philippines and Chinese Taipei to determine the applicability of the use of the Electronic Benefit-Risk Summary Template by agencies in the emerging markets as an appropriate mechanism for documenting benefit-risk decisions.

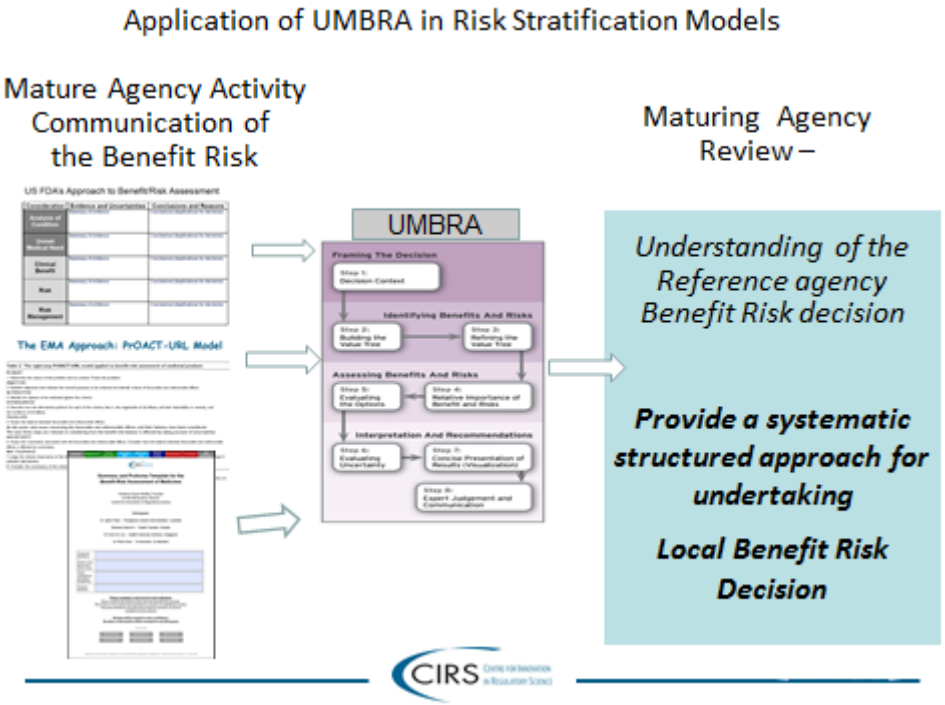


Figure 14. The UMBRA framework can assist agencies performing verification or abridged review in an understanding of reference agency benefit-risk decisions.

All agencies participating in these studies saw that a systematic structured approach to documenting benefit-risk had value within their agency as it included items within clinical assessment template, provided structure for expert clinical consultant reports and facilitated the discussion of difficult cases internally and with the sponsor. Study participants also agreed to convene a two-day training workshop on the topic of benefit-risk assessment for regulators in the Asia Pacific region, *The value of using a systematic standardised approach to the review of medicines,* which was scheduled to be held in May 2017 at Duke-NUS in Singapore. The objectives of this workshop were to:

- Provide an understanding of the approaches for benefit-risk assessment of medicines both by major international agencies and locally within Asia Pacific
- Discuss benefit-risk as one of the cornerstones of good review practices and how utilisation of a benefit- risk framework builds quality into the decision-making process
- Evaluate the UMBRA eight-step qualitative framework in order to review its applicability within the agencies in the maturing markets
- Discuss quality of decision-making practices as a component of good review practices

Workshops on the use of the benefit-risk summary template also have been scheduled to take place in Israel and Saudi Arabia and interest in the programme has also been expressed by regulators in Jordan, Brazil and South Africa.

CIRS quality decision-making programme

The CIRS programme in quality decision making represents a natural evolution of CIRS work in performance metrics, good review practices and benefit-risk assessment. As part of this programme, CIRS conducted a study among 17 pharmaceutical companies and 10 regulatory agencies in 2015 to identify current decision-making practices used by companies' in their decision to submit and by agencies' in their decision to approve a new drug application. It also looked to ascertain how they measure the quality of the decision-making process and the challenges and solutions. The results of this study were published by CIRS Senior Research Analyst Magda Bujar and associates in *Therapeutic Innovation and Regulatory Science* in 2016.[2]

Hurdles to quality decision making reported by companies included overconfidence, a poor assessment of uncertainty/strength of evidence, internal misalignment from competing interests, biases arising from previous experience, lack of data or information availability and time pressure. Agencies meanwhile cited barriers such as a lack of knowledge with regard to decision-making concepts, a reluctance to discuss uncertainties or value judgements, inconsistent review or evaluation practices, internal and external biases, lack of availability of data or information and resource constraints and time pressure. Some solutions, however, were suggested to these barriers: establish or implement a structured decision-making framework or method that requires values, preferences and uncertainty be made explicit; conduct a more formal review of process and outcomes; provide education on decision-making concepts and theory; create an environment that encourage dissenting opinions and challenging ideas; ensure transparency and information access; have a robust system that focuses on evidence and facts; and include all stakeholders, especially patients.

In another study to investigate issues that influence quality decision making, interviews were conducted with 29 key opinion leaders from regulatory agencies and pharmaceutical companies.[3] One result of this research was the identification of the 10 Quality Decision-Making Practices that support quality process and that were considered relevant by pharmaceutical companies and regulatory agencies. The 10 practices are organised into four areas, *Structure* and *Approach*, *Evaluation*, *Impact* and *Transparency and Communication,*[4] and can be mapped against the key frameworks used during medicines' development, particularly in the area of benefit-risk assessment as well as in decision making, including the CIRS Benefit-Risk Summary template.

Dr McAuslane concluded his presentation by quoting Dr Robert M. Califf in his discussion of benefit-risk assessments and their role in decision making at the US Food and Drug Administration:

> "A harmonized [BR] framework would foster consistent consideration across the spectrum of products and provide a rational basis for deciding when the benefit-risk balance is acceptable—and for assessing

changes in that balance as evidence accumulates. Importantly, a shared understanding of the framework would reduce variability in decision making while promoting principled, transparent regulatory flexibility."[5]

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What tools and agency activities can be put in place to facilitate risk-based evaluation-based approaches

Mario Alanís Garza, *Director General de Asuntos Internacionales COFEPRIS*

Global pharmaceutical regulation and harmonisation

Regulatory issues abound for pharmaceutical markets, including globalised manufacturing of active ingredients and finished medicines, increasing numbers of global clinical trials, growing interactions among international counterpart agencies, the need for overseas inspections and the risk of falsified, substandard and counterfeit medicines. Meanwhile, challenges faced by medicines' regulatory agencies and governments comprise limited resources, the need to develop synergies for more effective use of resources, demands for increasing access, the provision of quick and efficient information and the growing use of risk-based approaches.

Despite these challenges, there are numerous global harmonisation initiatives including those supported by the World Health Organization (WHO), The *International Council on Harmonisation* of Technical Requirements for Registration of Pharmaceuticals for Human Use (*ICH*), the International Medical Device Regulators Forum (IMDRF), the International Pharmaceutical Regulators Forum (IPRF), the International Generic Drug Regulators Programme (IGDRP) and the International Coalition of Medicines Regulatory Authorities (ICMRA).

Regional efforts include the European Medicines Agency (EMA), the Pan American Network for Drug Regulatory Harmonization (PANDRH), Asia-Pacific Economic Cooperation (APEC), Association of Southeast Asian Nations (ASEAN), Gulf Cooperation Council (GCC) and the New Partnership for Africa's Development (NEPAD).

One of the goals of these initiatives is improved access to new medicines through cooperation and reliance. Regulatory *reliance* can be defined as "Considering the results, processes or tasks performed and documented by another system or institution (domestic or foreign) to determine or issue a formal decision that will become part of the formal regulatory process". Its main characteristics are sovereign decision, full or selected functionality, unilateral or mutual dependence and its main benefits are increased access, conservation of resources, avoidance of duplication and risk-based regulation.

COFEPRIS

Pharmaceutical regulation evolved significantly in Mexico after the Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS) was created in 2001. Since that time after the passage of several important reforms including the National Health Law Reform on renewal of Sanitary Registrations in 2010, in 2012 PAHO recognised COFEPRIS as an NRA of Regional Reference and in 2014, the World Health Organization declared COFEPRIS a functional national regulatory agency.

The main objectives of COFEPRIS' policies are to improve population access to a well-supplied drug market that offers innovative and generic medicines at the best prices. This objective is based on principles in ethics, technical proficiency, efficiency, competitiveness and global presence.

In the COFEPRIS reliance model, authorised third parties support the health agency in risk mitigation while facilitating review processes. This support is voluntary, clearly defined, normed and regulated and COFEPRIS is responsible for making final regulatory decisions. Work by third parties includes assistance with dossier preparation, bioequivalence evaluation, clinical protocol revisions and laboratory work. The "pre-dictamination" (a pre-evaluation to COFEPRIS' assessment) by third parties allows significant reduction of review time by COFEPRIS for submissions. For new registrations, this reduction is approximately 2 years.

Beginning in 2011, COFEPRIS unilaterally accepted good manufacturing process certifications issued by FDA (USA), ANVISA (Brazil), Health Canada, PMDA (Japan), TGA (Australia), MFDS (South Korea), SwissMedic and EMA, independent of the country of manufacture. Equivalence agreements were also recognized for new drugs with the US, Canada, Australia, Switzerland and the European Union, shortening the number of days required to grant registration for innovative medicines from 360 to 60 days (Figure 15). New guidelines for the COFEPRIS New Molecules Committee (CMN) classified submissions according to categories and developed a checklist of requirements for those categories. The guidelines also provided for both face-to-face and remote meetings of the CMN, resulting in faster access to medicines. As a result of these new policies, COFEPRIS issued 213 new marketing authorisations for innovative medicines from 2012 to 2016, decreasing opportunity costs by 40 million dollars (500 million pesos) and reducing regulatory burden by 82% (Figure 16). COFEPRIS also recognises medical device registrations issued by the US FDA, Health Canada and Japan and will issue the corresponding registration in a maximum period of 30 working days; 3,693 medical device applications have been approved by this scheme

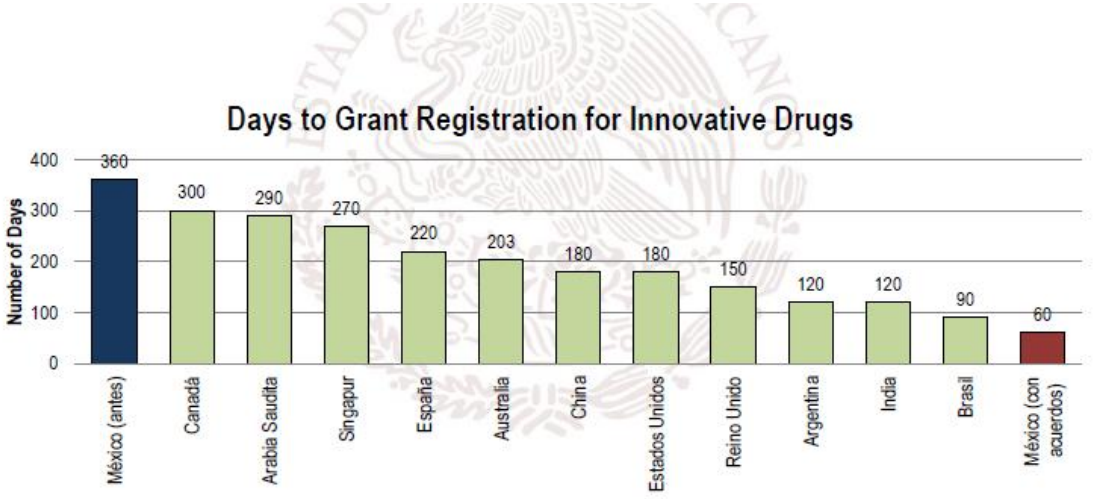

Figure 15. COFEPRIS equivalence agreements for new drugs have significantly reduced the time until approval of innovative new medicines.

According to the new COFEPRIS scheme for renewal of market authorisation extensions, the sponsor submits an application for the extension at the same time it presents the application for the modification of a market approval, reducing the time of resolution by 150 days. The new plan for research protocols establishes parallel stages in the process, reducing approval times to 45 days, similar to timing in the United States, Canada and South Korea and increasing the number of protocols submitted in Mexico.

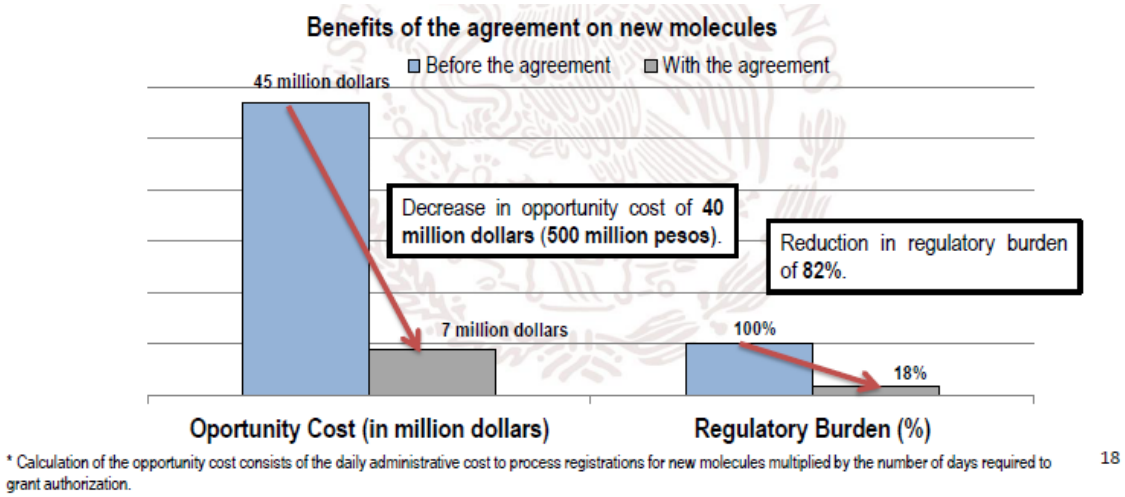

Figure 16. As a result of its new policies, COFEPRIS has realised significant reductions in opportunity cost and regulatory burden.

Instituto Mexicano del Seguro Social (IMSS) and the Ministry of Health recently signed a framework agreement for the promotion of clinical research in Mexico and agreements are being negotiated between Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE) and the National Institutes of Health and High Specialty Regional Hospitals Coordinating Commission (CCINSHAE). These agreements would dramatically increase Mexican resources for clinical research.

Bilateral agreements have been reached or are being developed between COFEPRIS and multiple agencies in Latin America, North America, Europe and Asia and fast-track processes are being established for national regulatory agencies in Ecuador, El Salvador, Paraguay, the Dominican Republic, Peru and the Caribbean Regulatory System. COFEPRIS works with technical groups on best international practices and harmonisation of regulations, participating in Alianza del Pacífico, specifically in the sub-group for Technical Barriers to Trade, integrated by COFEPRIS, INVIMA in Colombia, ISPCH in Chile and DIGEMID in Peru.

To develop COFEPRIS as a regulatory Center of Excellence, the agency established collaborations with regulatory agencies, industry and academic institutions for the research and development of new knowledge through the CONACYT project. COFEPRIS also created an electronic platform for the dissemination of information and the development of a network of areas of excellence, ensuring free access to health information, obtained the recognition of WHO, documented and published good regulatory practices for COFEPRIS as well as for research, industry and academic centres and developed a national and international network of partners interested in supporting the Centre of Excellence and its activities.

As an international reference regulatory agency recognised by WHO, COFEPRIS is committed to strengthening excellence in the control, monitoring and prevention of health risks, to promoting collaboration with other agencies and industry worldwide and reducing the knowledge gap in health through research, publications, seminars and the provision of access to information. In addition, COFEPRIS has had the first pilot training programme within the region recognised by APEC. COFEPRIS, patients and sponsors has benefited from its programmes of reliance in terms of cost, time, resources, industry productivity and access to medicines and believes that further discussion and agreement on generally accepted reliance concepts and modalities would add to those benefits.

COFEPRIS has benefited from its programmes of reliance in terms of cost, time, resources, industry productivity and access to medicines

Good registration management as critical components to enabling agencies to undertake a risk-based review process

Chao-Yi (Joyce) Wang, *Director, Division of Medicinal Products, Taiwan Food and Drug Administration*

Promotion of Good Registration Management in APEC

Good registration management (GRM) facilitates the efficient registration of medical products through the promotion of good review and good submission practice (GRevP; GSubP). GRevP strengthens the performance, predictability and transparency of regulatory agencies through the implementation or enhancement of quality measures and GSubP enriches the quality and efficiency of the medical product registration process by improving the quality of submission as well as its management.

The Good Registration Roadmap was initiated in 2011 when GRevP was endorsed as a priority work area by the Asia Pacific Economic Cooperation Life Science Innovation Forum Regulatory Harmonization Steering Committee (APEC LSIF-RHSC) and Chinese Taipei was named as its champion. The goals of this project are to promote the concept of GRM and to enhance the mutual trust needed for regulatory convergence among the APEC member economies by 2020. The first action toward the envisioned completion of the Roadmap in 2020 was the conduct of a gap analysis survey of APEC members. Following the survey, *Good review practices: Guidelines for national and regional regulatory authorities* was adopted and published by the World Health Organization in 2015 (Figure 17). In 2016, *Good Submission Practice Guidelines for Applicants* was endorsed by the APEC LSIF-RHSC and in 2017, the Taiwan Food and Drug Administration (TFDA), in partnership with the Regulatory Affairs Professionals Society Taiwan Chapter was endorsed as a formal APEC GRM Centre of Excellence (CoE) by the LSIF-RHSC.

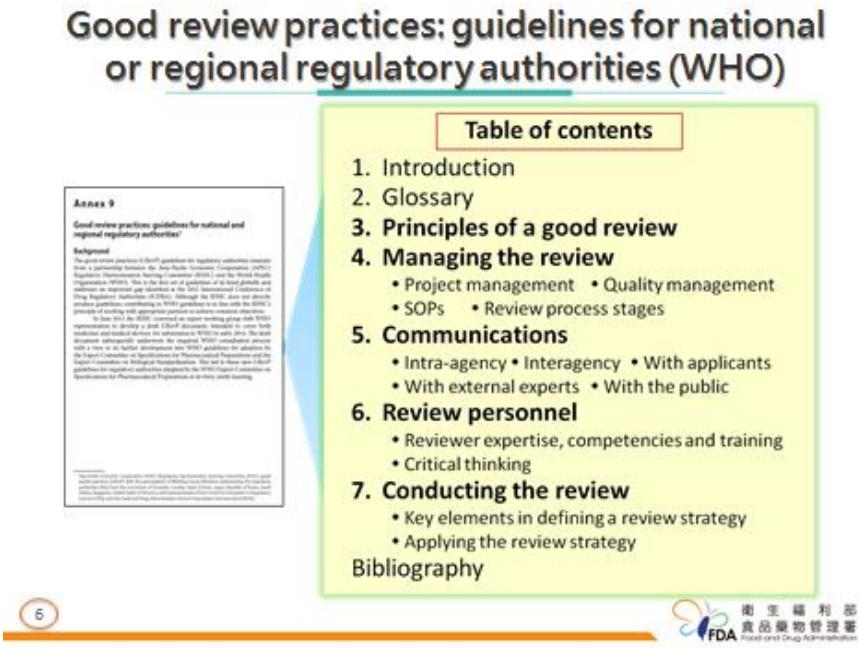

Figure 17. The World Health Organization published *Good review practices: guidelines for national or regional authorities* in 2015.

APEC CoEs are sustainable platforms for promoting regulatory convergence, capacity and cooperation in the development and regulation of medical products with a scientific and best-practice focus. In the concept model for APEC Training Centres of Excellence for Regulatory Science, the centres are topic focussed and hosted by academic institutions or organisations with appropriate expertise. With the oversight and expertise of the APEC RHSC and champion economies and the coordination efforts of the APEC harmonisation centres, academia, regulators and industry form partnerships to deliver and maintain educational programmes, yielding benefits to all.

2016 APEC GRM Regulatory Science Center of Excellence Pilot Workshop

Fifty-six trainees, 32 speakers and 3 facilitators from Asia Partnership Conference of Pharmaceutical Associations (APAC), TFDA, Japanese PMDA and the Chinese Centre for Drug Evaluation (CDE) participated in the 2016 APEC GRM Regulatory Science Center of Excellence Pilot Workshop, which took place November 2016 in Chinese Taipei. Learning objectives for this workshop included principles of GRevP and GSubP and the requirements for a good review and a good application; the curriculum was developed based on GRevP and GSubP guidelines (Figure 18). Attendees of the meeting generally rated the workshop as above average in quality, although the organisers experienced several challenges including:

- highly variable backgrounds, levels of regulatory experience and points of review focus among reviewer participants from different APEC member economies
- the provision of a curriculum that met the needs of all individual trainees with varying backgrounds,
- case studies for industry (especially from well-resourced companies) focusing on the registration of new drugs and
- the need to provide more opportunities for regulator and industry interaction.

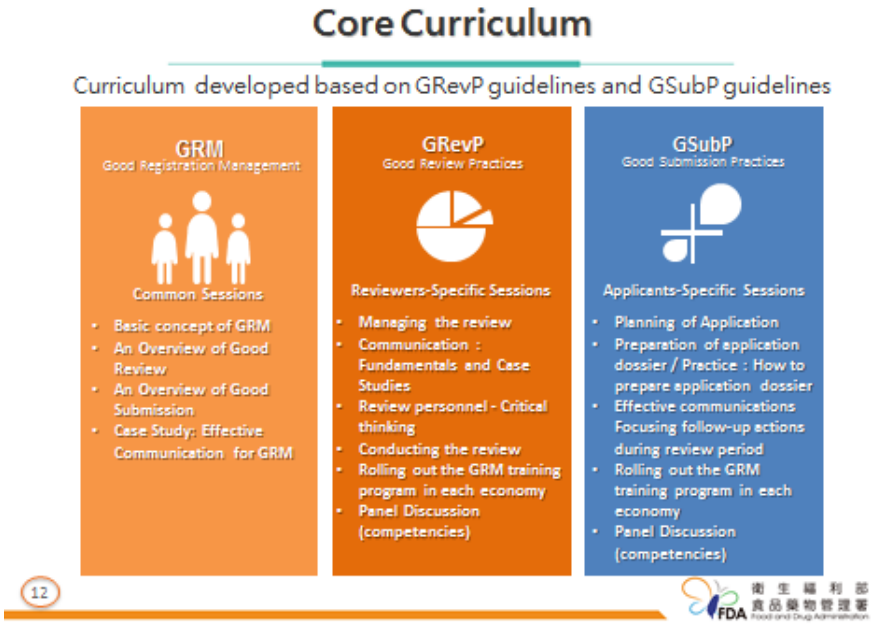

Figure 18. Curriculum for the 2016 APEC GRM Regulatory Science Center of Excellence Pilot Workshop.

Organisers regarded the workshop as a well-rated opportunity for good partnership and collaboration with significant interactive elements, such as discussions and case studies and practices. It is expected that future training programmes will contain more collaborative interactive sessions between industry and regulators with more case studies and interactive discussions and greater emphasis on topics of communication and critical thinking.

Conclusions and future directions

GRM (GRevP and GSubP) could serve as critical components in enabling agencies to undertake a risk-based review process.

GRM (GRevP and GSubP) could serve as critical components in enabling agencies to undertake a risk-based review process. GSubP enables applicants to understand the principles of a good submission, strengthens their core competency in understanding the nature of the benefits and risks of products and benefit-risk analyses when preparing for submission. GRevP enables regulators to understand the principles of a good review, strengthens their knowledge and skills for risk-based analysis in reviewing a medical product application, enhances their competency in critical thinking, facilitates the determination as to whether an application permits a conclusion about benefits and risks and allows the application of a review strategy to understand benefit-risk profiles.

After being formally endorsed by the APEC LSIF-RHSC as a GRM CoE in February 2017, the Taiwan FDA expects to host annual training events for APEC member economies. In turn, “Train the Trainer” participants are expected to develop and deliver local training in their respective APEC member economies. Ultimately, it is foreseen that the dissemination of GRM will promote efficient registration processes for medical products and regulatory convergence in APEC.

Prioritisation: Balancing the evidence available within the submission and local jurisdictional requirements – What are the practical/scientific issues that agencies face?

Claudiosvam Martins Alves de Sousa, *Manager, Office of Safety and Efficacy Assessment of Synthetic Drugs, ANVISA, Brazil*

In Brazil, a new drug must be registered through the National Health Surveillance Agency, Agência Nacional de Vigilância Sanitáriaregistration (ANVISA) and this registration must be renewed every five years. Categories of drugs registered through ANVISA include “new” drugs, synthetic and semi-synthetic drugs, biologicals including biosimilars, herbal medicines, synthetic and semi-synthetic drug “copies”, generic drugs and branded generics. Each drug category is covered by specific legislation and requirements.

The objective of the review of drugs at ANVISA is to assess their safety, quality and efficacy. In their assessment of new medicines’ benefit-risk profiles, ANVISA evaluates non-clinical and clinical data for safety and efficacy. Complete chemistry and manufacturing data are assessed from the drug master file, production report, quality control report, analytical method validation, stability studies of pilot batches, company authorization and good manufacturing practice certification. Labelling is evaluated through a brand name and prescriber and patient insert analyses. Other elements of a new drug dossier that may be assessed include biopharmaceutics, biostatistics and any risk management plans.

The review process at ANVISA consists of a pre-submission meeting with the sponsor followed by the electronic submission of the dossier, internal ANVISA review of the dossier, external expert evaluation, submission of a list of questions or notice of deficiency to the sponsor to which applicants should respond within a specified time period and finalisation of the evaluation and the issuance of a final opinion and decision letter (Figure 19).

Figure 19. The path for review of new drugs at ANVISA.

ANVISA does not yet employ an accelerated or conditional approval approach but for medicines with ongoing phase III trials that are developed to treat serious and life-threatening disease and unmet clinical need, registration can be approved based on promising phase II clinical trial evidence. Also, discussions are ongoing for a new pathway for regulatory review at ANVISA that will facilitate earlier access to medicines that address rare disease within a reduced timeframe. ANVISA expects to implement this pathway in mid-2017 after the criteria for compliance are defined and period of public consultation takes place.

According to Law 13411/2016 approved by the National Congress at the end of 2016 and to be implemented as of March 2017, the deadlines established for the final decision in the registration and post-registration modifications for new medicines will take into account technical complexity and clinical, economic and social benefits of the use of the product. Based on these criteria applications will be classified as *priority* applications, with a deadline for marketing authorisation decision of 4 months from submission, or *common* applications, with a deadline for marketing authorisation of 1 year from submission. For drugs assigned a *priority review* designation, the target deadline by which ANVISA should provide either a notice of deficiency or review conclusion is 75 days. Drugs designated as "priority" must be targeted to fulfil unmet medical needs or serve the interest of public health. This designation, however, does not alter the scientific or medical standards for approval or the quality of evidence required. However, in this conventional approach to ANVISA review, there is no benefit from the recognition of the evaluations from other authorities.

There are challenges to the implementation of a risk-based prioritisation approach in Brazil, such as legal issues. According to RDC 60/2014: …"a full set of nonclinical and clinical data (full study reports) and risk management plans (RMPs) and pharmacovigilance plans" must be submitted for registration of a new drug. However the Law 6360/1976 is general: "…the product, through scientific evidence and analysis, be recognized as safe and effective for the intended use and possess the necessary identity, activity, quality, purity and innocuity.";

As a former observer and current standing member of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Brazil endorses the ICH vision of reducing unnecessary duplication and facilitating faster access to new products, including implementation of the common technical document for medicines registration and others ICH Guidelines. It is envisioned that CIRS will be a partner to ANVISA in its efforts to improve its review process through structured systematic standardised approaches to the benefit-risk assessment of medicines, a stepwise implementation of good review practices and the better use of available resources, especially reliance on existing international tools, decisions and strategies, which can be adapted for the Brazilian environment to improve the review process for drug registration.

Brazil endorses the ICH vision of reducing unnecessary duplication and facilitating faster access to new products. , , and the better use of available resources, especially existing international tools and strategies, which can be adapted for the Brazilian environment to improve the review process for drug registration.

Managing safety post-approval: What do agencies using risk-based approaches need to consider?

Dr Lembit Rägo, *Secretary-General, Council for International Organizations of Medical Sciences, Switzerland*

Knowledge about new medicines is typically incomplete at the time of their evaluation by regulators. However, as Sir Austin Bradford Hill said, “All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.[1]

When considering the regulatory activities related to new medicines or vaccines that can bring “added value” after the first full-scale review, it must be recognised that some elements of regulatory oversight such evaluation of quality, efficacy and safety can be based on shared activities, whilst other elements such as licensing decisions, local manufacturing and clinical trial oversight, pharmacovigilance, product information considering local specificities and product security such as protection against counterfeiting and adulteration and distribution chain decisions should remain local. A regulatory framework should also provide for the expedited review or waiving of registration in the case of emergencies or other important public health situations.[2]

Managing post-approval safety

Not a single effective new medicine is completely safe – the emergence of unknown risks during real world use that were not detected during development is an unpleasant but realistic possibility. There are some key questions to answer in this regard. Is this setting where the new medicine is to be launched different from that where it was tested or first approved? What are the differences and might those differences indicate a need to be prepared for a different response? In an example of the need for preparedness, the fixed dose combination drug for malaria amodiaquine plus artesunate was prequalified for use by the World Health Organization (WHO), was approved in several countries based on this assessment and rapidly taken up in the anti-malaria programmes of many countries. Both the manufacturer and regulatory authorities where the product was in use were actively engaged in safety monitoring, which in many cases consisted of obtaining spontaneous safety reports. Through collaborative monitoring, ten cases of amodiaquine-induced dystonic reactions were reported in Ghana according to a publication by Akpalu and colleagues, highlighting the importance of increased safety monitoring of amodiaquine in combination with artesunate as first-line treatment for uncomplicated malaria in Ghana.[3]

CIOMS Working Group reports

The Council for International Organizations of Medical Sciences (CIOMS) CIOMS Working Group VIII was formed to provide a systematic and holistic strategy to better manage the entire life cycle of a drug safety signal. Their publication, *Practical aspects of signal detection in pharmacovigilance* was published in 2010.

In 2014, **the CIOMS Working Group IX** published *Practical approaches to risk minimization for medicinal products*, which provides pragmatic principles for the identification and application of risk minimisation tools as well as examples.

The CIOMS Working Group X was formed to develop a consensus on scientific and methodologic criteria for the application of good meta-analysis practices to clinical safety data within the biopharmaceutical regulatory process, to be used by both industry and regulators. Their report, *Evidence synthesis and meta-analysis for drug safety,* was published in 2016.

Standardised Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) have been developed over the past decade by senior scientists from many countries. **CIOMS, in conjunction with the ICH MedDRA Management Board, the MedDRA Maintenance and Support Services Organization (MSSO), the Japanese MedDRA Maintenance Organization (JMO) and other stakeholders** published *Development and rational use of standardised MedDRA queries (SMQs): Retrieving adverse drug reactions with MedDRA* in 2016. Prior to publication by the MSSO and JMO, the CIOMS Working Group had extensively tested each SMQ for fit-for-purpose functionality with real-world data in both health authority and company product databases.

The first CIOMS/WHO Working Group on Vaccine Pharmacovigilance, which was initiated in 2005 to support global surveillance of vaccine safety and the evolving need for a harmonised terminology and case definitions, published *Definition and Application of Terms for Vaccine Pharmacovigilance* in 2012. Created to continue to address unmet needs in the area of vaccine pharmacovigilance in 2013, the new CIOMS Working Group on Vaccine Safety published *CIOMS Guide to Active Vaccine Safety Surveillance* in 2017.[4] This Working Group will also produce an addendum regarding vaccine safety communication.

According to the *CIOMS Guide to Active Vaccine Safety Surveillance,* knowledge gaps may occur in risk-based approaches to the evaluation and approval of new vaccines. The term *knowledge gap* refers to lack of available or easily accessible information on vaccines in countries that need the respective information in contexts such as vaccine introduction, new safety issues, changes in the nature of vaccination programmes or inadequate passive surveillance systems. This lack of information signifies a research gap or an unanswered question of some aspect of vaccines safety that has not been answered sufficiently; for example, maternal immunisation. If the knowledge gap has the potential to negatively influence the benefit-risk profile of the vaccine to such a degree that it could significantly affect the safety of those receiving vaccinations, it can be described as a significant knowledge gap (SKG). An SKG may be specific to a particular country, region or population subset such as the elderly, pregnant women or indigenous people. A six-step algorithm has been

proposed for determining the need for active vaccine safety surveillance. The steps should be followed to identify outstanding informational needs and to formulate an appropriate strategy to obtain them.

CIOMS Guide to Active Vaccine Safety Surveillance (AVSS) provides a structured approach to identifying and analysing specific vaccines safety knowledge gaps, while considering all available sources of information, in order to determine whether AVSS is an appropriate solution. If AVSS is confirmed as being the appropriate tool, the Guide provides additional essential information on AVSS, a detailed overview of common types of AVSS and practical implementation considerations. It also provides a framework for a well-constructed and informative AVSS when needed, thus aiming to ensure the best possible safety of immunisation under new circumstances.[4]

Conclusions

Effective collaboration between authorities in the area of safety and pharmacovigilance at the global, regional and sub-regional levels has become increasingly important. Because regulatory authorities have responsibility for their populations - all jurisdictions should have at least minimal pharmacovigilance capacity when approving new complex medicines and vaccines. Each national jurisdiction must carefully study and understand the risk minimisation activities of reference authorities and appreciate the adjustments that may be needed in those activities for their national setting.

Each national jurisdiction must carefully study and understand the risk minimisation activities of reference authorities and appreciate the adjustments that may be needed in those activities for their national setting.

References

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Section 3: Roundtable Discussions

Roundtable A

What are the main criteria utilised in defining "risk based" and what need to be the key considerations?
Chair: Catherine Parker, Director General, Biologics and Genetic Therapies Directorate, Health Canada
Rapporteur: Jorge Azar, Area Regulatory Director LA, AstraZeneca, USA

Background

As countries develop their regulatory capabilities, it is being suggested that their regulatory agencies consider a risk-based evaluation approach. Agencies developing their skill sets need to identify how to balance the complexities of requirements necessary to ensure they address scientific, legal and health promotion and protection mandates while facilitating patient's access to medicines.

Risk-based approaches to medicines' regulation can help agencies find the appropriate balance based on resources and needs. This approach can take many forms within agencies and be utilised across a range of regulatory activities. Indeed, the development of prioritised risk-based approaches to decision making is increasing in well-resourced or mature agencies. Risk-based decision making can address both compliance and product risks and can be implemented across the life cycle of new medicines from preclinical development, through the oversight of clinical trials, the manufacturing process and inspections, marketing authorisation and post-marketing compliance and review of variations.

Agencies may employ different models of reliance, recognition and regionalisation in the review of new medicines. Each of these models have different considerations and agencies may wish to consider a mix of different risk-based approaches depending on types of products reviewed and available agency resources, maturity level and priorities. The focus for this Roundtable Discussion Group was to determine the main criteria that agencies should utilise in defining risk-based stratification and the potential advantages for agencies in adopting a risk-based approach to the assessment of new medicines.

Definitions

A risk-based approach to medicine's regulatory review includes the use of a systematised decision-making framework and procedures to prioritise regulatory activities and deploy resources appropriately, principally relating to inspection and enforcement, based on an assessment of the risks that regulated firms or products pose to the regulator's objectives (adapted from *OECD Reviews of Regulatory Reform: Risk and Regulatory Policy*)

Reliance is an act whereby a regulatory authority in one jurisdiction may take into account/give significant weight to work performed by another regulator or other trusted institution in reaching its own decision. (*M. Ward, presentation Utrecht University – Jan 2017)*

Recognition is the routine acceptance of the regulatory decision of another regulator or other trusted institution. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B. *(M. Ward, presentation Utrecht University – Jan 2017)*

Questions for consideration

- What do *risk-based approaches to the registration of medicine* mean to the participants of the group? If the group does not agree with the above definition, how should it be reworded?
- What are the main criteria agencies should utilise in defining *risk based* and can these be used across all agencies?
- Should all agencies have an underlying philosophy or principle of considering a risk-based approach to registration of medicines as standard practice unless there are good scientific reasons for not adopting this approach?
- Should there be a one-size-fits-all approach or should there be a set of different models which, depending on type of product, agency maturity level or resource constraints, could be used? If yes, what might this look like?
- What does the group perceive as the key opportunities for agencies and their stakeholders in adopting risk-based approaches to medicines' registration? Are there specific types of products that should go through different approaches?
- What would a guideline on good reliance practice need to address in terms of supporting risk-based reviews?
- For what other activities should agencies consider risk based approaches?

Discussion results

Critical issues

By deleting reference to the relationship of a risk-based approach to inspection and enforcement, this Roundtable group slightly revised the definition of this model to "the use of systematised decision- making frameworks and procedures to prioritise regulatory activities and deploy resources appropriately, based on an assessment of the benefits-risks balance that regulated firms or products pose to the regulator's objectives."

Issues relevant to the development of risk-based approaches that were identified by the group included limited regulatory resources and the need to incorporate patient needs into decision making. It was also agreed that it

is important to evaluate both industry and agency strengths and weaknesses and agency priority criteria, standard operating procedures, review practices and guidelines, which may not be transparent but which must be transparently and clearly communicated. In addition there may be a lack of adoption or a partial adoption of international guidelines such as those of ICH, WHO or PIC/s to facilitate risk-based approaches to product review. Finally, information from other regulators can be challenging to access in a timely manner.

Recommendations

- Consider the criteria categories of *products, facilities, evaluation processes* and *an evaluation of strengths and weaknesses* in developing a risk-based regulatory review:
    - Products should be new chemical entities or first in class, with a market history in another country. Other considerations in this category are the target treatment population, knowledge regarding the product's benefit-risk profile and unmet medical need.
    - Facilities of manufacture should have a good history of good manufacturing processes compliance as well as a history of inspection by PIC/s members.
    - Evaluation processes within the agency should include clear standard operating procedures and guidelines, being able to obtain usable foreign regulatory reports in a timely manner and establishing partnerships with mature agencies. Criteria for defining a "priority review" must be clearly defined for a risk-based product evaluation. There needs to be the ability to meet country-specific requirements.
    - Evaluated strengths should include whether adequate resource and expertise are efficiently used and the ability to integrate other agencies' evaluation processes.
- Communicate key drivers for the adoption of a risk-based regulatory review, which include high-quality and timely decision making, faster access, best use of resources and the development of a better environment between regulators.
- Communicate key opportunities for the adoption of a risk-based regulatory review, which include the prospect to enhance knowledge and expertise from other agencies the ability to respond to emergency situations, accountability by agencies and companies to establish clear commitments, the identification of the relevant aspects of product evaluation that should be strengthened in a particular country.

- Ensure that any guidelines or best practice guide for risk-based regulatory review include: agreed timelines, types of products eligible for assessment, acceptable certifications from good reference agencies, reliance on good review practices, clear information regarding roles and responsibilities for compliance, transparency from regulators regarding protection of intellectual property, identification of regulatory activities suitable for reliance practice such as product testing and good manufacturing practice audits and the strengthening of post-approval safety.

Roundtable Discussion B

What are the main internal considerations, policy challenges and opportunities for individual agencies to incorporate a risk stratification-based decision-making approach to the review of new medicines?
Chair: Adj Prof John Skerritt, *Deputy Secretary for Health Products Regulation, Department of Health, Australia*
Rapporteur: **Dr Catherine Burgess,** Senior Director, Head of Emerging Markets Regulatory Affairs – Pipeline, Takeda, USA

The *Background, Definitions* and *Questions for Discussion* for this Roundtable group were the same as those supplied for Roundtable Discussion A. However, the focus for this group was the main internal considerations, policy challenges and opportunities needed for individual agencies to incorporate a risk stratification-based decision-making approach to the review of new medicines. The group was asked to centre the discussion primarily around the practical applicability of incorporating risk-based approaches in the registration process for medicines.

Discussion results

Critical issues

Reliance was defined by this group as "leveraging the work of other regulatory authorities as part of a regulatory review." The mechanisms of this reliance could be the mutual review by consortiums, such as the benefit-risk consortium formed by Australia, Canada, Singapore, Switzerland (ACSS), or the regulatory collaborative initiatives of Zambia, Zimbabwe, Botswana and Namibia (ZaZiBoNa) or the East Africa Community (EAC) or by direct contact as is currently occurring in the pilot programme between regulators in the Japanese PMDA and the Taiwan FDA. Reliance could also take place through the use of assessment reports by reference agencies or approval letters, certificates of pharmaceutical product (CPP) or good manufacturing process (GMP) certification.

The group asked certain key questions about the topic:

- How much risk is a country prepared to accept?
- How much reliance on other agency decisions will be practiced?
- Will the risk of reliance take place regarding a product's CMC, safety or efficacy?
- How will the risk be managed internally?
- What internal cultural changes have to take place?
- Are changes to legislation or policy required?

Positive aspects to a risk-based approach include the fact that large agencies tend to be very comprehensive in their review. An agency can review individual assessments by a reference country and assess if that evaluation is relevant to the local jurisdiction. Risk-based reviews allow agencies to focus their review on areas of jurisdictional concerns, which may be in areas such as CMC, clinical safety or benefit-risk evaluation, which are often influenced by local experience or standard of care. Risk-based review also facilitates the avoidance of duplication.

Negative aspects to risk-based approaches include potential delay in patient access. Many countries incorrectly think they have the resources for a full review and fear that reliance on outside regulatory review may result in missing a detail that potentially impacts local population, local patients and local medical practices. There may be a lack of trust in a reference country or no access to reference country reviews. Many countries do not have a mechanism or path for an abridged review or there may be a lack of support within the regulatory agency or by the government, which may have legislated a specific type of regulatory review. Finally, there may be a preference for conducting a full independent review within a subset of the culture of the agency.

There is variability in the information needed to support uptake of a risk-approach, which can include evidence of reference country approval through the use of the CPP or GMP inspection certificates. For example, in Argentina approval in two reference countries is needed to support immediate approval. In Chinese Taipei, CPPs can help address local requirements. The use of assessment reports supports faster review but may not eliminate review altogether. For some countries it can be problematic to use the US as a reference country as the availability of FDA reports can be delayed relative to approval and public documents can be heavily redacted. Full dossier submission is still required by many countries, even when using a facilitated risk-based review pathway.

Steps suggested to implement a risk-based review approach included obtaining management support, conduct pilot studies for information sharing to build trust, gather data on timelines and local impact, consider legislative changes to alter the ability to share data among and rely on other agencies, policy changes that incorporate details on how to conduct review and cultural changes to facilitate buy-in at all levels.

Recommendations

- CIRS should assemble a list of assessment templates used by different countries utilising reference country assessment reports.
- The performance of reliance models should not just be measured by speed of review; CIRS should assess whether abbreviated reviews have resulted in subsequent safety or quality issues.
- CIRS should highlight the need for reform relative to CPP availability from reference countries, including electronic availability and the subsequent acceptance by regulatory agencies.

Roundtable Discussion C

What are the main internal considerations, policy challenges and opportunities that agencies need to address in order to take a regional approach to the joint/shared review of new medicines?
Chairman: Lahouari Belgharbi, *Director General, Center of Excellence, for Regulatory Sciences (RS), Good Regulatory Practices (GRP) and Good Regulatory Management (GRM),* COFEPRIS*, Mexico*
Rapporteur: Gugu N. Mahlangu, *Director-General, Medicines Control Authority, Zimbabwe*

Background

Even well-resourced regulatory agencies are seeking opportunities to improve the efficiency and effectiveness of their review processes. Also, many emerging national regulatory agencies (NRAs), especially those in low- and middle-income countries, do not have a robust complement of systems, skills and capabilities in place to provide effective and efficient regulatory support.

One approach to improving regulatory effectiveness is based on the concepts of reliance and recognition. *Reliance* is an act whereby a regulatory authority in one jurisdiction may take into account/give significant weight to work performed by another regulator or other trusted institution in reaching its own decision *Recognition* of another agency's decisions is a more complex and advanced cooperative arrangement. It indicates that conformity with the other country's regulatory requirements is sufficient to meet its own regulatory requirements. Recognition may be unilateral or multilateral and an NRA or regional alignment initiative (RAI) may recognise the approved marketing authorisation of another agency without additional assessment other than to confirm, for example, that the medical product in question is the same as that in the reference country.

RAIs that focus on work sharing for joint assessments of marketing applications could be considered to be practicing a form of reliance in which the assessments of the components assigned to each party are combined into a single assessment report. By addressing reliance and recognition in the context of verification, abridged and full review options, agencies can work towards the efficient use of resources while addressing their legal mandates to ensure quality, safe and effective medicines in a timely manner for their constituents.

In order to implement a regional approach to joint reviews or to reliance on decisions made by other agencies, appropriate policies and structures need to be in place for their success. To address these topics, the focus for this Roundtable Discussion was on the main internal considerations, policy challenges and opportunities for agencies associated with taking a regional approach to the joint or shared review of new medicines.

Questions for consideration

- What forms the basis for RAIs? Can these be based on regional economic blocs or are there other criteria for determining the most relevant groupings of countries?
- Trust is the foundation of an RAI. What processes and mechanisms should be in place to build mutual confidence to allow reliance, recognition and work sharing? What role do companies play in participating in this trust?
- What formal or informal agreements should be in place for RAIs to be successful? Do recognition or reliance agreements need to be bilateral?
- Not all agencies within an RAI will have similar capabilities and depth of expertise. How can this be addressed?
- There is no single right approach to the process an RAI uses. What are the various approaches for RAI operation? The Roundtable should illustrate 2 or 3 possible models.
- What types of medicines should RAIs address? (e.g., generics, WHO PQP medicines, Essential Medicines, new actives substances)
- What are the key challenges to ensuring that an RAI functions according to its mandate? The Roundtable should make recommendations on how to address/overcome these based on real-world experience.

Discussion results

Critical issues

This Roundtable Group developed an historical timeline illustrating the robust history of global and regional alignment initiatives (RAIs), coalitions of common interest with provisions for recognition and sharing information.

Global initiatives

1948: The Organisation for Economic Development and Cooperation (OECD) – health division
1949: Council for International Organisation of Medical Sciences (CIOMS) -- 49 members
1970: Pharmaceutical Inspection Co-operation Scheme (PIC/S) (1995) – Focus on mutual recognition of regulatory inspections, Harmonisation of inspection and exchange of information – 49 countries
1980: Asia Pacific Economic Cooperation Life Science Innovation Forum Regulatory Harmonization Steering Committee (APEC LSIF-RHSC) -- 21 countries
1980: World Health Organisation (WHO)
1990: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) --7 founding member but expanded to new members since 2016.
2000: International Pharmaceutical Regulators Forum (IPRF) – 38 countries + 6 networks
2007: International Regulators Consortium Initiative (IRCI)

2012: International Coalition of Medicines Regulatory Authorities (ICMRA) -- 19 members (plus 28 countries in EMA)
2012: International Generic Drug Regulator's Programme (IGDRP)

Alignment initiatives with a regional or sub-regional focus

1981: Middle East – Gulf Cooperation Council (GCC) – 6 countries
1990: Asia – Association of Southeast Asian Nations Pharmaceutical Product Working Group (ASEAN PPWG) – 10 countries
1995: Europe – European Medicines Agency (EMA) – 28 countries
1999: Americas – Pan American Network for Drug Regulatory Harmonization (PANDRH)
1999: Africa – African Medical Regulatory Harmonisation East African East Africa Community (AMRH – EAC) (2012) – 15 initial countries to be expanded to 8 regional economic communities in 52 countries
2007: Australia, Canada, Swissmedic, Singapore (ACSS) Consortium
2009: DCVRN – Developing countries Vaccine Regulatory Network - WHO
2012: Africa – World Health Organization African Vaccines Regulatory Network (AVAREF) – WHO
2012: Australia – New Zealand – 2 countries
2014: Caribbean– Caribbean Public Health Agency – Caribbean Community (CARPHA-CARICOM) – 20 countries
2015: Africa – Zambia, Zimbabwe, Botswana and Namibia, **(**ZaZiBoNa) – 5 countries active participating and 1 country non-active participating
2015: Eastern Europe – 5 countries

Bases for RAIs that were agreed by the group included economic blocs developed through existing political treaties that encourage collaboration, addressing common public health problems such as yellow fever in Panama and counterfeit and substandard medicines in Africa, solidarity among like-minded organisations, cultural ties, desires to expand social services to the community and the desire to maximise the benefits of joint or pooled procurement processes.

Processes and mechanisms to build mutual confidence to allow reliance included reliance through benchmarking of performance such as is practiced for example by PAHO reference national regulatory authorities and the use of the WHO global assessment tool. Mechanisms to facilitate recognition include having transparent published summary basis of approval resources that encourage work sharing are common guidelines and templates. For their part, sponsors can assist in capacity building to disseminate scientific knowledge and strengthen regulatory systems.

Agreements that can facilitate the success of RAIs include treaties and or common protocols, memoranda of understanding and confidentiality agreements. There may be a common legislative basis for the agreement such as the Model Medical Products Law in Africa and agreements can be unilateral or bilateral in nature.

Disparities in capacity, capabilities and depth of expertise among agencies within RAIs can be addressed by documenting the knowledge gaps and delivering the needed training; training can occur for example, during

work-sharing sessions such as good manufacturing process inspections, performing quality assurance checks of processes using external specialist such as is implemented in the ZaZiBoNa initiative or by offering peer technical support, as has been done through WHO PAHO national regulatory authority assessments.

Various successful approaches for RAIs were listed by this Roundtable Group including PAHO(which incorporates a national regulatory authority reference approach), CARICOM (which uses a centralised verification of dossier by domestic consultants), ZaZiBoNa (which employs joint dossier review and inspection by the active participants), the EAC (which uses a common funded secretariat to manage and monitor the process with assessments conducted by country experts), the EMA (which employs a rapporteur system) and the GCC (which has implemented a centralised committee for drug registration).

The group did not feel that there should be a limitation regarding the type of medicines that should be addressed by RAIs. Dependent on the development phase of the RAI it could review essential medicines, medicines that treat unmet medical needs or priority disease areas.

Multiple challenges must be met to ensure that an RAI functions according to its mandate, including building trust in the decision-making process used by each member state. A buy-in period for the concept may be required and there will be a need for advocates with a long-term vision for success. Decision-making sovereignty issues could be problematic if countries do not accept joint recommendations; importantly, stakeholder expectations will need to be managed. The potential for increased resources requires commitment among partners and raises the possible need for user fees to manage the associated expenses. Other problematic issues include language barriers, the need to establish a business case for RAIs to convince stakeholders of the merits of RAIs, a lack of strong guidance by the leadership, expertise or knowledge gaps and lagging capacity development and the need for effective governance with clear structure and role definition. For some RAIs, there has been limited consultation and input from key stakeholders and industry. Consequently, in some cases, to move these initiatives forward while waiting for the implementation of formal or legal agreements, regulators have been proceeding to the extent possible within their existing mandates and legal frameworks.

Recommendations

- Document the processes being used in the current models of RAIs.
- Establish clarity regarding the long-term expectations for RAIs.
- Develop model instruments and tools to guide the establishment and conduct of RAIs,
- Address regulatory knowledge gaps through capacity-building and training programmes.
- Donors should invest in the creation and support of RAIs and the support of their associated capacity-building and training programmes.

Roundtable Discussion D

What are companies looking for in agencies or regions that might use a risk evaluation-based approach – what would a successful system look like?
Chair: Dr Janet Vessotskie, *Head of Americas, Regulatory Policy and Intelligence, UCB, USA*
Rapporteur: Cammilla Horta Gomes, *Health Regulations Expert, ANVISA, Brazil*

Background

As countries develop regulatory capacity, it is important that regulatory systems be science based, respect international standards and best practices and adopt an approach that focuses on what can be done by a national regulatory agency (NRA) while leveraging the work of other trusted agencies and regulatory networks for the rest. Therefore, when considering the review of an application, be it for a generic medicine or new molecular entity, the agency must clearly define how its activity adds value, especially when prior reviews have been conducted with positive recommendations by stringent regulatory authorities or reference agencies. This value may be a local jurisdictional confirmation that the new product meets the required standards or that the safety profile is appropriate for the local population.

One procedure that builds on reliance on prior regulatory decisions to inform a local recommendation is the use of a risk-stratification process. In one approach, this can based on the types of prior approvals and enables an agency to allocate constrained resources more efficiently. A risk-stratification approach that is gaining acceptance among a growing number of NRAs is the process formally codified and implemented by Singapore in which a three-tier review strategy is used to stratify reviews. Commonly referred to as *verification*, *abridged* and *full review* options, this approach can rely on prior decisions, provides regulatory flexibility, the ability to allocate resources to key dossier reviews, the jurisdictional sovereignty to reach a locally relevant benefit-risk decision and the ability to speed the review of important new medicines. The characteristics of this model are illustrated in figure 21.

As no single review system will work for every agency, flexible review options are needed. The focus for this Roundtable Discussion group was what companies look for from individual agencies or regional alignment initiatives (RAIs) that might use a risk evaluation-based approach and what successful systems look like.

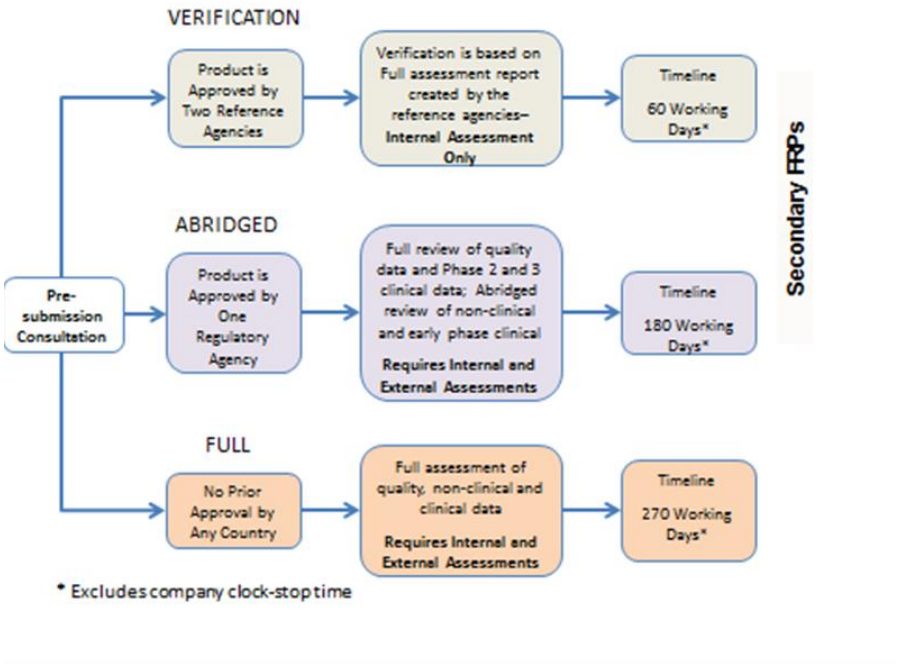

Figure 21. Verification, abridged and full regulatory reviews.

Questions for consideration

- What types of products are best addressed by risk-based evaluation options; for example, generics, WHO prequalified medicines, essential medicines or new actives substances
- Is the “Singapore Model” an appropriate approach to make reviews efficient for companies and agencies? What are the strengths and weaknesses of this approach? How can weaknesses be overcome?
- What would the submission package that a company provides to an agency look like for verification, abridged or full review? What content do companies need to ensure is consistent across submissions?
- Can realistic timelines be set for the various components of risk-based reviews? What would agency and company response timelines look like in ideal scenarios for verification, abridged and full reviews? What are the causes of extended timelines from the agency and company perspective?
- How can an agency ensure that questions it raises add value to the review and could not have been addressed by responses to questions raised by other agencies that have done prior reviews of the product? How can the company most efficiently address questions that are not seen as adding value to the review?
- What metrics should be used to determine the effectiveness of risk-based review strategies? What are the measures of agency and company activity that should be evaluated? What quality measures beyond timelines should be assessed?
- Post-authorisation commitments are often key to risk-based stratified approvals. How can these be aligned regionally or globally, ensuring a lack of duplication while meeting the scientific goals of the relevant questions?

Recommendations might have arisen from the above topics or could relate to whether refinements or improvements could be made to the "Singapore" model, timelines that could be recommended for the various pathways, for both companies and agencies, efficiencies that could be built into the timelines and methods for the alignment of post-authorisation commitments across countries.

Discussion results

Critical issues

This Roundtable Discussion Group agreed that the standards for decision making using a risk-based evaluation does not vary based on the route followed, but is rather related to agencies` capabilities and local market requirements. It was further concluded that there is a window of opportunity for agencies to provide added value in their review of innovative products by building on other agencies' previous reviews. Participants disagreed, however, that the risk-based evaluation process for generic products is less complex, as it could require a detailed review based on quality issues. It was felt that whilst the concepts in the Singapore model are useful, their application would vary depending on the jurisdiction.

National, regional or independent guidance documents are needed to describe objective criteria that might be considered by regulatory agencies for each review pathway and the technical data requirements for industry for each pathway. These documents should include a list of meaningful, value-added local requirements for regulatory authorities adopting abridged or verification pathways, descriptions of the means to expedite each review pathway, the criteria for establishing a list of reference agencies and the principles for independent and consistent decision making in the context of reliance approaches.

Review pathways and submission packages

- A full review should require a complete submission package, ideally in the common technical document format ensuring that relevant local needs are addressed.

- Use of a complete submission package, ideally in the common technical document format plus local requirements, for an abridged review would depend on the ability of the authority to host the information in case they agency wished to seek more details. In addition, the authority would have to transparently communicate what is assessed in the review and what information is relied upon and from whom.

- Use of a complete submission package for a verification review would also depend on the ability of the authority to review and host all the information. Ideally, in its simplest form, the submission would be a summary (module II common technical document format) plus assessment report(s) from reference agency(ies) in addition to information as mandated by local requirements.

Local requirements should not exceed international standards and should add value to the review. Therefore, when building risk-based regulatory pathways based on reliance it is important to introduce flexibilities in legislation and provide training to change processes resulting from the evolution of organisational culture.

Recommendations

- Develop national, regional or independent guidance documents to describe objective criteria that might be considered by regulatory agencies for each review pathway and the technical data requirements for industry for each pathway.
- Conduct a mapping exercise research project of existing timelines for each pathway to establish suggested target timelines for agencies.
- Apply reliance approaches for post-approval changes. It would be useful to have a survey or mapping of models or experiences describing mechanisms in place for implementing risk-based approaches for post-approval changes based on reliance or other efficiencies.

Roundtable Discussion E

Managing risk post-approval: What are the roles and responsibilities of companies, agencies and other stakeholders?
Chair: **Prof Hans-Georg Eichler,** *Senior Medical Officer, European Medicines Agency*
Rapporteur: **Maria Cristina Mota,** *Director – Scientific Regulatory Policy and Intelligence- Latin America, AbbVie, USA*

Background

Utilisation of risk-based approaches for the registration and licensing of new medicines is currently being advocated and agencies are looking at different models of reliance, recognition and regionalisation. Each of these models has different considerations with regard to local review and levels of local benefit-risk decision making. Agencies should consider a mix of different risk-based approaches and depth of local review depending on types of products, resources available, maturity level and priorities.

As countries adopt risk-based approaches for the registration of medicines, the post-registration period is also critically important, as medicines are then being utilised by the population for which the agency has responsibility to ensure the safe use of effective medicines. Determination of the benefit-risk balance of medicines should be an ongoing activity throughout a product's life cycle and as new information becomes available, regulatory decisions can be qualified or even reversed. These decisions should be based on analysis of available safety and efficacy information. However, how can agencies with different resources and capacities ensure fit-for-purpose ways to manage the post-approval risk of medicines within a country that are aligned to the risk-based approach used for registration of the medicine?

There are several factors that can affect a medicine's risks within countries including the available infrastructure to monitor utilisation, to learn about quality, safety and efficacy profiles and to act on potential adverse effects. Some countries also may face issues related to supply security and counterfeiting and the potential inflow of substandard medicines. The two main agency tools for managing post-approval risk agencies are the proactive risk management plan agreed and in place by medicines' sponsors at the time of licensing and the infrastructure and active mechanisms to support pharmacovigilance through local and international monitoring.

The focus for this Roundtable Discussion Group was the roles and responsibilities of the company, agency and other stakeholders in managing post-approval risk. The group was requested to focus the discussion primarily around the strategic and practical applicability of managing risk post-approval for agencies that are incorporating risk-based approaches for the registration of medicines, discussing what needs to be in place to provide both agencies and patients confidence in managing safety based on the type of regulatory assessment made by the agency.

For the purpose of this discussion group *risk-based approach* refer to overarching utilisation of reliance recognition, prequalification or regionalisation approaches as well as the specific review process that maybe used such as, verification, abridged and full review (with or without requirement for a reference agency approval)

Questions for consideration

- Managing risk post-approval: What should be the main objectives and what are the main regulatory tools that can be used by mature and maturing national regulatory agencies?
- As agencies have differing infrastructure and resources, should they consider a risk-based approach to manage the post-approval phase? What would be a risk-based approach(es) and what tools, such as risk management plans should be considered?
- Should the activities and processes differ depending on the type of risk-based approach or evaluation that has been used for the registration of the medicine? What does this group believe are the critical activities or processes that should be put in place at the time of registration? Will these need to be modified if used by regional alignment initiatives?
- What are the responsibilities of the differing stakeholders, such as the regulatory agency, World Health Organization, the company, the healthcare provider, the pharmacist and the patient?
- Is post-market monitoring an area where working with other agencies can improve the efficiency of the regulatory system? Should this involve active participation in work sharing or should activities centre on information sharing and regulatory convergence to ensure quality and supply chain?
- Post-authorisation commitments are often key to risk-based stratified approvals. How can these be aligned regionally or globally, ensuring a lack of duplication while meeting the scientific goals of the relevant research questions?
- What kind of metrics or indicators could an agency put in place to measure the effectiveness of its process?

Recommendation may arise from the above topics and/or could relate to the main objectives for agencies managing risk post-approval, the risk-based approaches and tools for agencies using risk based registration processes, the main responsibilities of the different stakeholders or the metrics or indicators an agency could put in place.

Discussion results

This Roundtable Discussion Group discussed the development of criteria to prioritise products that might require extra post-approval surveillance. These criteria included whether the product, like vaccines for dengue, was targeted to emerging regions, where clinical use might be the only opportunity to develop more knowledge about a drug. Post-approval surveillance might also be required if the practice of medicine or the target population is different from those tested in clinical trials or the benefit-risk of product is context

dependent if the product has been conditionally approved. There must be tools to address a product's potential benefits and harms as well as the uncertainty which may surround those parameters.

It should be determined if jurisdictions relying on reference agency decisions for new product registrations, could continue this reliance for follow-on decision. Regional centres should be developed so that pharmacovigilance data can be shared for decision making and mutual pre-notifications of on-market activities can occur.

Recommendations

- Regulators should avoid the historic mistake of solely focussing on post-approval safety and consider how best to evaluate the balance between safety and effectiveness. They should additionally focus on better communication with patients as one of the key stakeholders in medicine, potentially through social media or other avenues of education.
- Electronic healthcare records should be built in such a way that this essential real-world data for efficacy and safety can be collected for use in decision making.
- Regional centres should be developed so that pharmacovigilance data can be shared for decision making and mutual pre-notifications of post-licensing activities can occur.

APPENDIX: WORKSHOP ATTENDEES

Regulatory agencies		
Marisse Ang	Food and Drug Regulation Officer III	**Food and Drug Administration, Philippines**
Ana Carolina Moreira Marino Araújo	Health Regulation Expert	**ANVISA, Brazil**
Lahouari Belgharbi	Director General, Center of Excellence, for Regulatory Sciences, Good Regulatory Practices and Good Regulatory Management	**COFEPRIS, Mexico**
Luiza Novaes Borges	Health Regulation Expert	**ANVISA, Brazil**
Prof Sir Alasdair Breckenridge	Former Chair	**MHRA, UK**
Eugenia Cabrera	Chemist and Pharmacist, Drug Registration Evaluator	**Health Public Institute, Chile**
Dr Agnes Chan	Director, Therapeutic Products Branch	**Health Sciences Authority, Singapore**
Lien-Cheng (Eric) Chang	Associate Researcher, Division of Medicinal Products	**Food and Drug Administration, Chinese Taipei**
Dr Petra Dörr	Head of Communication & Networking, Deputy Director	**Swissmedic**
Prof Hans-Georg Eichler	Senior Medical Officer	**European Medicines Agency, UK**
Dr Ana Gabriela Silva Flor	Executive Director of Pharmaceutical Products	**Ministry of Health, DIGEMID, Peru**
Dr Mario Alanís Garza	Director General de Asuntos Internacionales	**COFEPRIS, Mexico**
Dr Churn-Shiouh Gau	Chief Executive Director	**Center for Drug Evaluation, Chinese Taipei**
Cammilla Horta Gomes	Health Regulations Expert	**ANVISA Brazil**
Dr Javier Guzman	Director General	**INVIMA, Colombia**
Togi Junice Hutadjulu	Director of Drugs and Biological Product Evaluation,	**NADFC, Indonesia**
Andrea Keyter	Medicines Control Officer	**Medicines Control Council, South Africa**
Dr Roberto Lede	Sub-Administrator	**ANMAT, Argentina**
Gugu Mahlangu	Director-General	**Medicines Control Authority, Zimbabwe**
Ellen Nogueira	Health Regulation Expert	**ANVISA, Brazil**
Lisette Pérez Ojeda	Head of International Affairs Office	**Centre for State Control of Drug and Medical Devices, Cuba**
Balbiana Verazes Sampaio Oliveira	Advisor to the Director	**ANVISA, Brazil**
Catherine Parker	Director General, Biologics and Genetic Therapies Directorate	**Health Canada**
Renato Alencar Porto	Director	**ANVISA, Brazil**
Dr Tomas Salmonson	Chair	**CHMP, EMA**
Eliza Sison	Food and Drug Regulation Officer III	**Food and Drug Administration, Philippines**

Adj Prof Dr John Skerritt	Deputy Secretary for Health Products Regulation	**Department of Health, Australia**
Claudiosvam Martins Alves de Sousa	Manager, Office of Safety and Efficacy Assessment of Synthetic Drugs	**ANVISA, Brazil**
Nanik Sundari	Senior Evaluator for New Drug Evaluation.	**NADFC, Indonesia**
Patrícia Oliveira Pereira Tagliari	Head of International Affairs Office	**ANVISA, Brazil**
Chao-Yi (Joyce) Wang	Director, Division of Medicinal Products	**Food and Drug Administration, Ministry of Health and Welfare, Taiwan, R.O.C.**
Pharmaceutical companies		
Aparecida Veríssimo Alves	RA Manager LATAM	**Novo Nordisk Latin America, Brazil**
Regina Araki	Director of Regulatory Affairs Brazil	**Bayer S/A, Brazil**
Jorge Azar	Area Regulatory Director LA	**AstraZeneca, USA**
Erika Esteves Balestero	Regulatory Affairs Manager	**Eli Lilly, Brazil**
Dr Catherine Burgess	Senior Director, Head of Emerging Markets Regulatory Affairs - Pipeline	**Takeda Pharmaceuticals, USA**
Anabelle Castro	LATAM Regulatory Policy Lead	**Roche Servicios S.A, Costa Rica**
Paula Cavallieri	Regulatory Affairs Associate Director	**Vertex Pharmaceuticals, Brazil**
Renata Bessa de Siqueira Corrêa	Regulatory Affairs Manager	**AstraZeneca do Brasil Ltda, Brazil**
Paula Ribas Da Costa	Regulatory Affairs Director	**GlaxoSmithKline, Brazil**
Renata Dias	Latam Regulatory Director	**Takeda Pharma, Brazil**
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Débora Germano	Regulatory Affairs Director	**Pfizer, Brazil**
Renata Seixas Gonçalves	Regulatory Affairs Manager	**Sanofi, Brazil**
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Erika Machado	Executive Director, Regulatory Affairs	**MSD, Brazil**
Vilma Lourenço de Carvalho Mello	LATAM Regulatory Affairs Head EP	**Sanofi, Brazil**
Marcos Paulo Moreira	Executive Director, Regulatory Affairs, LATAM Lead	**MSD, Brazil**
Maria Cristina Mota	Director- Regulatory Policy and Intelligence Latin America	**AbbVie, USA**
Gabriel Zen Obata	Manager, Regulatory Affairs	**Celgene Corporation, Brazil**

Jaime Cesar de Moura Oliveira	LatAm Regulatory Policy and Intelligence Director	**Bayer S/A, Brazil**
Gabriela de Paula Pereira	Regulatory Affairs Coordinator	**Merck S/A, Brazil**
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Karina de Souza Silva	Regulatory Affairs Manager	**Sanofi, Brazil**
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Jacob Swarnaraj	Director – Asia Pacific, Regional Liaison	**MSD Pharmaceuticals Pvt. Ltd, India**
Fabiana Yumi Teramoto	Regulatory Affairs Supervisor	**Shire Farmacêutica Brasil Ltda, Brazil**
Carlos Eduardo Thomazini	Regulatory Affairs & Quality Director	**AbbVie Farmacêutica Ltda, Brazil**
Janet Vessotskie	Head of Americas, Regulatory Policy and Intelligence	**UCB, USA**
Sonia Viejobueno	Latin America Lead, Global Regulatory Policy and Intelligence	**Janssen Cilag Farmacéutica SA, Argentina**
Ding Xu	Registration and Certification Manager	**Produtos Roche QFSA, Brazil**
Non-profit organisations		
Dr Shyam Bhaskaran	Program Officer, Regulatory Affairs	**Bill and Melinda Gates Foundation, USA**
Dr Charlie Preston	Advisor, Regulatory Systems Strengthening for Medicines and Other Health Technologies	**PAHO/WHO, Trinidad**
Dr Lembit Rägo	Secretary-General	**Council for International Organizations of Medical Sciences (CIOMS), Switzerland**
Mike Ward	Coordinator, Regulatory Systems Strengthening, Essential Medicines and Health Products	**World Health Organization**
Centre for Innovation in Regulatory Science		
Magda Bujar	Research Analyst	
Patricia Connelly	Manager, Communications	
Lawrence Liberti	Executive Director	
Dr Neil McAuslane	Director	
Sandi McIntyre	Project Coordinator	
Prisha Patel	Manager, Global Development Programme	
Prof Stuart Walker	Founder	