Optimising the regulatory review process by evaluating performance and addressing good reliance practices

26-27 March 2019

Singapore

WORKSHOP REPORT

CIRS Centre for Innovation in Regulatory Science

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SECTION 1: EXECUTIVE SUMMARY

Background to the workshop

Regulatory agencies around the world are exploring methods to meet their mission to protect and promote public health and improve patient access to quality medicines. These methods include the convergence of technical and procedural guidelines and an increasing number of agencies are becoming members or observers of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Access to medicines that address unmet medical need is also facilitated through the creation of flexible regulatory pathways and processes such as priority review or conditional approval.

Agencies are also continually evaluating ways to optimise their performance in order to accommodate the increasing number of new medicines, generics and variations that they are being asked to assess in a timely manner. There are two areas that are now being proactively considered by agencies to improve their effectiveness and efficiency.

1. Agencies embed systematic structured approaches to better understand their performance. These approaches use quantitative metrics to identify where time is spent in the process (agency and sponsor) and to identify relevant strategies for improvement.
2. Agencies introduce or evaluate “regulation through reliance” models to ensure that their review is adding value rather than duplicating relevant prior work that might inform its regulatory decision, thereby unnecessarily delaying decisions and the availability of medicines.

Over the last three years, CIRS initiated a practical project called OpERA (Optimising Efficiencies in Regulatory Agencies) to provide the tools and processes for maturing regulatory agencies to proactively use performance metrics as they evaluate their review process. The OpERA initiative currently includes 14 countries and four regional regulatory initiatives, that are either providing information or that are preparing to engage in the programme. Those agencies that have already provided data can now identify or confirm specific areas where time is being spent that may be slowing down the regulatory process. They are also able to engage in discussions of potential ways to focus their improvement efforts by learning how other agencies tackle the same issue.

At the 2017 CIRS Sao Paulo Workshop “Risk-based evaluation of medicines” it became clear that many agencies would like to know when and how they could practically implement a regulation-through-reliance model within their jurisdiction and to also understand when these reliance models could be used. At the 2018 CIRS workshop in Johannesburg, a number of recommendations were made. These included:

- Develop a constructive benchmarking model to assess the elements of interagency trust contained within current systems
- Develop ways to ensure the ability of authorities using reliance-based reviews to continue to make their own informed decisions to protect public health within their jurisdiction
- Conduct a study identifying criteria that agencies use to determine which products should be considered for an abridged review; that is, a review that relies on work products of another trusted agency/ies and what elements of the submission are reviewed
- Determine what reports and data are available from different reference agencies that can be used for reliance-based processes; for example. whether they are redacted or can be “un-redacted” and the timelines for their availability

Following the Workshop in South Africa, CIRS initiated a pilot project to inform the debate and practical implementation of regulation-through-reliance models. At the same time, the need for guidance on good reliance practices as an annex to the WHO Good Review Practices (GRevP) guidance has been

identified by WHO. This is currently in the process of being developed by CIRS in conjunction with CoRE (Centre for Regulatory Excellence) in Singapore, where the principles of good reliance practices and how these can be implemented will be documented.

The purpose of this Workshop was to bring together these initiatives along with an understanding of the elements of trust that need to be established to enable agencies to effectively implement a reliance-based model. The synergies between these activities will enable agencies options to optimise their regulatory performance without sacrificing decision quality or national/regional sovereignty.

Workshop objectives

- Discuss process and practices that enable agencies to optimise and improve their performance without affecting quality or the standards of the review process
- Understand how the use of a systematic, structured approach to agencies measuring the various components of their review process can enable agencies to focus their improvement initiatives, set realistic targets and facilitate future strategic planning and decision making within the review process
- Discuss how the development and introduction of good reliance practices can provide direction and a pathway for agencies to practically embed reliance-based application models within their review process, the benefits of utilising these approaches, and how this can be measured
- Identify the elements of interagency trust contained within current reliance-based systems and how these enable agencies to practically implement a reliance-based application review model
- Recommend how embedded quantitative metrics can be used to optimise review performance and what should constitute good reliance practices that will enable agencies to focus on value-added activities and provide timely regulatory decisions on patient availability to good quality medicines that are safe and effective.

A **reliance-based model** is defined by WHO as “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”.

Key points from presentations

Please note, affiliations are stated as they were at the time of the meeting (26-27 March 2019).

SESSION: EMBEDDING A CULTURE OF MEASUREMENT INTO AN AGENCY AND ADOPTING GOOD RELIANCE PRACTICES - HOW THIS ENABLES AGENCIES TO OPTIMISE PERFORMANCE

Mike Ward, *Coordinator, Regulatory Systems Strengthening Team, Essential Medicines and Health Technologies, World Health Organisation (WHO)*, described the WHO's work to assess regulatory systems including the development and use of the WHO Global Benchmarking Tool (GBT). A WHO survey of International Pharmaceutical Regulators Programme (IPRP) members demonstrated strong support for reliance but also several challenges that need to be addressed, such as bridging decisions from other countries to the local benefit-harm context and the need for secure platforms for exchanging non-public information.

Dr Claus Bolte, *Head of Sector Marketing Authorisation, Swissmedic,* gave an overview of Swissmedic's annual national benchmarking study of new and known active substances and major variations. Through this joint exercise between Swissmedic and sponsors, key indicators were agreed upon in previous years to identify areas for improvement. Integrating these indicators into regulatory practice by monitoring them regularly enabled transparent tracking of process improvement initiatives. Optimising performance appears to be an almost inevitable outcome of this approach, ranging from streamlined processes with shortened review times to a more efficient allocation of precious resources.

Prof John Lim, *Executive Director, Duke-NUS Centre of Regulatory Excellence (CoRE) & Senior Advisor, Ministry of Health Singapore,* spoke about regulatory challenges in the Asia Pacific region and the Singapore Health Authority (HSA)'s experience of implementing risk-based referencing, such as abridged and verification routes. Benefits of regulatory convergence and reliance include better utilisation of limited resources and timely patient access to needed medicines. In the move towards promoting reliance approaches, capacity building, education and training should be maintained, neutral discussion platforms created, political support secured and regulatory 'sandboxes' (testing environments) explored.

SESSION: OPERA – WHAT IS IT AND WHAT IS ITS ROLE IN STRENGTHENING REGULATORY PROCESSES THROUGH QUALITATIVE AND QUANTITATIVE METRICS?

Dr Lawrence Liberti, *Executive Director, CIRS,* gave an overview of the Optimising Efficiencies in Regulatory Agencies (OpERA) programme, an agency-provided metrics programme that has built a culture of measurement to improve timelines and quality of processes. OpERA collaboratively collects and assesses a variety of data that characterise review processes, helping not only regulatory agencies but also Regional Regulatory Initiatives to define and meet their regulatory review performance goals and optimise their review processes.

Dr Ramli Zainal, *Senior Director of Pharmaceutical Services, Pharmaceutical Services Programme, Ministry of Health, Malaysia,* spoke about how the National Pharmaceutical Regulatory Agency (NPRA), Malaysia, has used OpERA methodology to measure key milestones in its approval process and the time spent on each step. This exercise helped to identify areas lacking capacity and informed a number of measures for improvement, including timeline limits for specific processes, staff redeployment and the initiation of a risk-based tiered reliance process.

Andrea Keyter, *Deputy Director, Medical Devices, South Africa Health Products Regulatory Authority (SAHPRA), South Africa,* described how the Medicines and Related Substance Act was revised to allow SAHPRA to replace the Medicines Control Council (MCC) as a separate legal entity outside the

Department of Health. Although SAHPRA is addressing the backlog of marketing authorisation applications it inherited, its approval times remain substantial. There is a need to consider facilitated regulatory pathways and establish a culture of accurate metrics collection and continuous improvement. Key review milestones must be identified and codified into policy and guidelines and appropriate tracking systems and resources put in place.

Ana Carolina Morino, *Advisor for the Directorate of Authorisation and Registration, ANVISA, Brazil,* spoke about how the OpERA programme has helped ANVISA to build a culture of performance measurement and establish strategic plans and objectives. ANVISA is working to improve its IT systems so that data can be easily extracted and made into comparative graphics. These have been useful in evaluating the success of facilitated pathways and in justifying ANVISA's results to Congress and to society.

Dr Charles Preston, *Advisor, Regulatory Systems Strengthening for Medicines and Other Health Technologies, Pan American Health Organisation (PAHO),* unfortunately could not attend the workshop but provided slides giving an overview of the Caribbean Regulatory System (CRS). Although the CRS is faced with challenges related to member state uptake, industry uptake, human resources and sustainability, progress is being made and other small states are looking to CRS as a model regional initiative.

Dr Paul Dearden, *Head of Emerging Markets, Regulatory Policy and Intelligence, AbbVie, UK,* spoke about the benefits of building performance metrics into agencies. For companies, these benefits relate to predictability, early access, innovation and transparency. For example, reporting on performance metrics improves agency transparency, thus giving companies a clearer understanding of regulatory expectations and processes, improved dialogue with agencies, efficient product development and viable decision making.

Dr Murray Lumpkin, *Deputy Director, Integrated Development, Bill and Melinda Gates Foundation,* followed with a funder's perspective on why building in performance metrics into agencies is beneficial. Metrics-related programmes allow funders to evaluate grants and investment possibilities based on data i.e. by showing what is working and where investment might be most impactful. Performance measures and associated goals should be a mutually agreed part of any sustainability 'social contract' with stakeholders who are helping to fund the agency (from the private and public sector).

Dr Songmei Xie, *Deputy Director, Office of Clinical Evaluation II, Center for Drug Evaluation, National Medical Products Administration (NMPA), People's Republic of China,* gave an overview of regulatory reforms implemented by NMPA, including the introduction of priority review and accelerated pathways, establishing Good Review Practice (GRevP) standards and reforming the regulation of clinical trials. As a result of the reforms, there has been a significant reduction in Investigational New Drug (IND) review time and the number of licensing applications waiting for review and approval. Going forward, NMPA will focus its efforts on building a risk and science-based, whole life cycle drug regulation system aligned with international standards and will step up international regulatory exchange and cooperation.

SESSION: GOOD RELIANCE PRINCIPLES AND PRACTICES – WHAT ARE THEY AND HOW ARE THEY BEING USED TO ENABLE AGENCIES TO ENGAGE IN A RISK-BASED APPROACH TO REGULATION?

Dr Mario Alanís, *Independent Consultant, Mexico,* described how reliance in Latin America is either unilateral or negotiated, based on stringent regulatory authorities or Pan American Health Organization (PAHO) regional reference authorities. There is a gradual trend in the region to adopt reliance initiatives and a verification model in Mexico has been successful in increasing access to innovative medicines. Trade or regional initiatives have facilitated discussion of reliance schemes, but more could be done to further advance their use.

Dra. Reri Indriani, *Acting Deputy Chairperson for Drug, Narcotics, Psychotropics, Precursors, and Addictive Substances Control, National Agency of Drug and Food Control (NAFDC), Badan POM (BPOM), Indonesia,* spoke about BPOM's experience of abridged evaluation, which has been successful in facilitating the conduct of efficient and transparent evaluation of global products. However, there have been regulatory challenges related to differences in indication wording and the need to ensure submitted documents are the same as those submitted to reference countries. Industry also reported difficulties in sourcing three full assessment reports from reference agencies. As a result, BPOM has revised this criterion so that only one full assessment report is needed.

Supatra Phongsri, *Pharmacist, Professional Level, Bureau of Drug Control, Thailand Food and Drug Administration,* and **Preeyaporn Natehin**, *Pharmacist, Practitioner Level, Bureau of Drug Control, Thailand Food and Drug Administration,* spoke about the use of abridged review in Thailand. A full assessment report from at least one reference agency must be submitted, as well as all lists of questions and answers during the assessment process and post-approval variations. Benefits of abridged evaluations include shorter review timelines, better management of limited resources and improved quality of review. Challenges include a lack of agency resources and experience in evaluating new chemical entities, differences in requirements between reference agencies and the local agency, and difficulty controlling post-approval variations and pharmacovigilance.

Tariro Makamure Sithole, *Chief Regulatory Officer, Medicines Control Authority, Zimbabwe,* gave an overview of ZAZIBONA, a work-sharing initiative across 13 countries in Southern Africa. For a product to be assessed under ZAZIBONA, the dossier must have been submitted to at least two member countries. Ongoing issues for ZAZIBONA include a lack of centralised submission, submission of different dossiers by some manufacturers and a lack of electronic information systems. Differences in capacity between agencies has also sometimes meant poor implementation of ZAZIBONA recommendations at the country-specific level. Nevertheless, work sharing models like ZAZIBONA bring several benefits including timely patient access, reduced regulatory workload and combined submissions for manufacturers.

Dr Neil McAuslane, *Director, CIRS,* presented results from a CIRS survey carried out with regulatory agencies on their use of abridged reviews. These findings provided some understanding of the selection criteria for reference agencies, the level of detail agencies would like, how the reference agency reports are used and the potential barriers for agencies in undertaking abridged reviews. However, to move forward with the development of an abridged review framework, it is important to gain more clarity from agencies on what is reviewed and to what depth.

Dr Tomas Salmonson, *Partner, Consilium Salmonson & Hemmings, and Former Chair, CHMP, EMA,* spoke about the importance of trust in reliance models. All stakeholders including sponsors must accept responsibility in creating trust and recognise the challenges around complex scientific assessments and subjective conclusions. Furthermore, reliance models should be used frequently to ensure their sustainability. Trust and commitment to a reliance model may not initially be shared throughout a regulatory agency therefore scientific leadership is important as well as a structure to decide and document the level of reliance in individual applications.

Dr Samvel Azatyan, *Group Lead, Regulatory Systems Strengthening Team, WHO, Switzerland,* spoke about the need for global guidance on good reliance practices to increase regulatory capacity and efficiency. WHO is developing a system called Good Regulatory Practices (GRP), which – if implemented - will lead to higher quality regulation, improved decision-making increased efficiency of regulatory systems and better public health outcomes. One element of GRPs will be a guideline on good reliance practices, which is intended to a be a practical instrument promoting strong regulatory cooperation, convergence, harmonisation, work-sharing, reliance and recognition.

Dr Lim Sok Bee, *Senior Associate, the Duke-NUS Centre of Regulatory Excellence (CoRE), Singapore,* described six principles of good reliance practices: 1) uphold the role, responsibilities and authority of the

national regulatory agency (NRA), 2) support regulatory convergence, 3) support evidence-based decision making, 4) communicate efficiently along the entire decision process, 5) apply across the product life cycle and 6) contribute to regulatory system strengthening. The WHO guideline on good reliance practices is under development and feedback from NRAs and industry is continuously being gathered.

Dr David Jefferys, *Senior Vice President, Global Regulatory, Government Relations, Public Affairs and European Product Safety, Eisai Europe Ltd, UK, and Chairman of the IFPMA Regulatory Science Committee,* spoke about pharmacovigilance challenges in low- and middle-income countries (LMICs) and the importance of post-approval support in establishing trust and delivering the benefits of reliance models. The Smart Safety Surveillance initiative was formed as a partnership among manufacturers, cooperative groups, regulators and the Bill and Melinda Gates Foundation to build pharmacovigilance capacity in LMICs and in the long-term, establish end-to-end safety surveillance of products from their clinical development to the post market stages.

Recommendations from across the Roundtables

How can agencies embed a culture of performance measurement and how can the results be used in practical ways to optimise performance?

- Agencies should have a **system** in place to collect data for identified metrics agreed with different stakeholders and integrated into the daily work.
- Agencies should develop a **culture** to incorporate standard processes and metrics, improve processes, analyse resources and encourage a mindset that takes responsibility for patient access to medicines. **People** performance management should include goals, objectives and accountability.
- CIRS, WHO or CoRE should work on the **standardisation** of metrics for the approval process in order to have common framework and language and facilitate benchmarking across agencies and develop relevant metrics based on local country processes.
- Agencies and pharmaceutical companies should ensure **transparency** through tailored regular publication of performance metrics agreed by stakeholders.

Codification of trust – how can we codify trust and how can good reliance practices build on this trust?

- Agency goals should always be to protect the public good and make best use of local resource and capacity. Local decisions supported by reliance model should be defendable to the public.
- Reliance models between agencies should be based on a trust “triangle” that also involves sponsor companies. This has not been made explicit in the discussion to date and so should be considered for inclusion in the good reliance practice guidance document.
- Provision of full documentation is hindered by concerns about future lifecycle activities – further discussion on regulatory strengthening and alignment is required. Return on investment, market access and supply are impacted by lack of common guidance.

Recommendations from across the Roundtables (continued)

The draft good reliance practice guideline – How practical is it? A stakeholder review and discussion

- Use a phased approach with an entry point for implementation of the good reliance practice guideline.
- Use GMP inspection and CMC reports to confirm the quality of the product; this low-hanging fruit supports the implementation of reliance pathways to ministers and politicians.
  - Consider moving toward acceptance of reliance pathways over time.
- Consider requesting from the sponsor a summary of the reference agency's benefit-risk assessment.
  - Module 1
  - 2.5.6 – Benefit/Risk
  - Transparency in terms of findings made by reference agency and motivation by sponsor in support of these concerns
- Perform a formal study to understand what NRAs who have implemented reliance pathways are currently evaluating.

Assessing the implementation of and adherence to good reliance practices – What would informative key performance indicators look like?

- Agencies should ensure a dynamic pathway of reliance for registration for all products throughout the product life cycle. These pathways should be codified in country legislation in all countries where regulatory improvement could occur.
- Agencies and industry share mutual responsibility to successfully implement reliance, including the provision of a transparent mechanism to enable reporting on the use of reliance pathways, such as through annual reports.
- Measurable KPIs are required to assess compliance to and impact of reliance frameworks, including established timelines, measurement of the number or cycles of questions from reliance assessments, the use of reliance to review priority products, and the increase in the number of reviewed products.

Workshop Programme

Day 1: 27 March 2019

KEYNOTE SESSION: EMBEDDING A CULTURE OF MEASUREMENT INTO AN AGENCY AND ADOPTING GOOD RELIANCE PRACTICES: HOW THIS ENABLES AGENCIES TO OPTIMISE PERFORMANCE	
Chair's welcome and introduction	**Prof Hans-Georg Eichler,** *Senior Medical Officer, EMA*
Building, developing and strengthening regulatory systems to meet the needs of patients and healthcare providers over the next decade: What activities are enabling agencies?	**Mike Ward,** *Coordinator, Regulatory Systems Strengthening Team, Essential Medicines and Health Technologies, World Health Organization*
Why a systematic, structured approach to measuring performance and its integration into the regulatory process is key to optimising performance - Mature agency experience	**Dr Claus Bolte**, *Head of Sector Marketing Authorisation, Swissmedic*
Adoption of risk-based approaches to regulation as part of the regulatory process – What is in it for the agencies?	**Prof John Lim,** *Executive Director, Professor of Practice and Senior Advisor, Centre of Regulatory Excellence, Duke-NUS Medical School. Ministry of Health, Singapore*
SESSION: OPERA: OPTIMISING PERFORMANCE THROUGH AN AGENCY-INITIATED METRICS PROCESS– HOW THIS IS BEING USED TO AID INDIVIDUAL AGENCIES AND REGIONAL ALIGNMENT INITIATIVES	
OpERA – What is it and what is its role in strengthening regulatory processes through qualitative and quantitative metrics?	**Dr Lawrence Liberti,** *Executive Director, CIRS*
Four case studies to describe involvement in OpERA, what has been learned and how this is informing change	
Agency 1 - process identification and improvement **Agency 2 - Managing change – identifying policy needs** **Agency 3 - Supporting policy change – delivering policy needs** **Regional initiative – Building a culture of measurement from the start to ensure accountability and efficiency**	**Dr Ramli Zainal,** *Senior Director of Pharmaceutical Services, Pharmaceutical Services Programme, Ministry of Health, Malaysia* **Andrea Keyter,** *Deputy Director, Medical Devices, South Africa Health Products Regulatory Authority (SAHPRA)* **Ana Carolina Marino,** *Advisor for the Directorate of Authorization and Registration, ANVISA, Brazil* *Caribbean Regulatory System (CRS) CARPHA, Trinidad and Tobago* [**Presentation cancelled – summary provided]**
Why key stakeholders benefit when agencies build in performance management metrics and set evidence-based targets	
Company viewpoint **Funder viewpoint**	**Dr Paul Dearden,** *Head of Emerging Markets, Regulatory Policy and Intelligence, AbbVie, UK* **Dr Murray Lumpkin,** *Deputy Director, Integrated Development, Bill and Melinda Gates Foundation, US*

Reforming the Chinese regulatory system: How is the National Medical Products Administration (NMPA) measuring the changes?	**Dr Songmei Xie,** *Deputy Director, Office of Clinical Evaluation II, Center for Drug Evaluation, National Medical Products Administration (NMPA), PRC China*
SESSION: GOOD RELIANCE PRINCIPLES AND PRACTICES: WHAT ARE THEY AND HOW ARE THEY BEING USED TO ENABLE AGENCIES TO ENGAGE IN A RISK-BASED APPROACH TO REGULATION?	
Chair's introduction	**Dr Siu Ping Lam,** *Director, Licensing Division, MHRA, UK*
Four case studies to highlight different approaches to reliance/ verification/equivalence	
Verification/Equivalence	**Dr Mario Alanís**, *Independent Consultant, Mexico*
Abridged review - Indonesia NADFC	**Dra. Reri Indriani,** *Acting Deputy Chairperson for Drug, Narcotics, Psychotropics, Precursors, and Addictive Substances Control, National Agency of Drug and Food Control (NAFDC), BPOM, Indonesia*
Abridged review - Thailand	**Preeyaporn Natehin**, *Pharmacist, Practitioner Level, Bureau of Drug Control, Thailand Food and Drug Administration*
Work sharing - Zazibona	**Tariro Makamure Sithole,** *Chief Regulatory Officer, Medicines Control Authority, Zimbabwe*
Implementing an abridged review: What are the criteria and assessment practices used by agencies?	**Dr Neil McAuslane,** *Scientific Director, CIRS*
Trust is the key to reliance models – How is this being developed across agencies and what are the main elements of a trust paradigm?	**Dr Tomas Salmonson,** *Partner, Consilium Salmonson & Hemmings and Former Chair, CHMP, EMA*
Developing the WHO Good Reliance Practice Guideline	
The need for a global guidance – workplan and objectives	**Dr Samvel Azaytan,** *Group Lead, Regulatory Systems Strengthening Team, WHO, Switzerland*
Components of Good Reliance Practice Guideline and the Identifying Principles of Reliance Practices	**Dr Sok Bee Lim**, *Senior Associate, CoRE*
Post-approval needs and reliance models: The role of Smart Safety Surveillance as a shared responsibility? IFPMA viewpoint	**Dr David Jefferys**, *Senior Vice President, Global Regulatory, Government Relations, Public Affairs and European Product Safety, Eisai Europe Ltd, UK*

Day 2: 28 March 2019

SESSION 4: ROUNDTABLE DISCUSSIONS	
Roundtable A: How can agencies embed a culture of performance measurement and how can the results be used in practical ways to optimise performance?	**Chair: Dr Siu Ping Lam,** *Director, Licensing Division, Medicine and Healthcare products Regulatory Agency (MHRA), UK* **Rapporteurs: Elvira Heyartz,** *Vice President, Regulatory Affairs Asia Pacific, Johnson & Johnson Pte Ltd, Singapore,* and **Kwame Asamoah-Okyere**, *Principal Regulatory Officer, Food and Drugs Authority, Ghana*
Roundtable B: Codification of trust – how can we codify 'trust' and how can good reliance practices build on this trust?	**Chair: Dr Patrick Stewart,** *Director General, Therapeutic Products Directorate, Health Canada* **Rapporteur: Fraser Stodart,** *Senior Director – Head of Emerging Markets (Regulatory), Biogen, UK*
Roundtable C: The draft good reliance practice guideline – how practical is it? A stakeholder review and discussion	**Chair: Asst Prof James Leong,** Head *of Education, CoRE, Singapore* **Rapporteur: Andrea Keyter,** *Deputy Director, Medical Devices, South Africa Health Products Regulatory Authority (SAHPRA)*
Roundtable D: Assessing the implementation and adherence to good reliance practice – what would informative key performance indicators look like?	**Chair: Dr Samvel Azaytan,** *Group Lead, Regulatory Systems Strengthening Team, WHO, Switzerland* **Rapporteur: Ehab Taqieddin**, *Head, Regulatory International Operations, Roche, Singapore*
SESSION 5: FEEDBACK FROM BREAKOUT DISCUSSIONS	
Chair's introduction	**Prof Sir Alasdair Breckenridge**
Feedback by roundtable rapporteurs and discussion	
Reliance review – Reflections on a life cycle approach	
Regulatory viewpoint	**Prof Hans-Georg Eichler,** *Senior Medical Officer, EMA*
Industry viewpoint	**Dr Susan Forda,** *Vice President, Global Regulatory Affairs International, Eli Lilly and Company, UK*
CIRS viewpoint	**Dr Lawrence Liberti**, *Executive Director, CIRS*
Gates viewpoint	**Dr Murray Lumpkin,** *Deputy Director, Integrated Development, Bill and Melinda Gates Foundation*

SECTION 2: PRESENTATIONS

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Strengthening regulatory systems to meet the needs of patients and healthcare providers over the next decade – what activities are enabling agencies?

Mike Ward, *Coordinator, Regulatory Systems Strengthening Team, Essential Medicines and Health Technologies, World Health Organisation (WHO)*

Only 30 percent of national regulatory authorities have the capacity to successfully regulate medicines and vaccines on their markets according to WHO estimates, and this figure is even lower for medical devices. In the face of this reality, the biggest enabler in meeting the demands of patients in most countries is getting the fundamentals right.

The WHO first began assessing regulatory systems in 1997 using a set of indicators designed to evaluate vaccines programmes. In 2014 the World Health Assembly (WHA) recognised the importance of strong, efficient regulatory systems under WHA Resolution 67.20 (Regulatory System Strengthening for Medical Products), with the goal to promote access to quality assured medical products. This led to the development of the WHO Global Benchmarking Tool (GBT), an objective and well-tested methodology for benchmarking regulatory systems, which also establishes an institutional development plan for addressing areas for improvement and for monitoring progress. GBT assesses the maturity of the regulatory system with the aim to bring all regulatory authorities to a stable, well-functioning level. In 2018, 26% of WHO member states were at GBT Maturity Levels 3 and 4 (stable or advanced regulatory systems), 23% at level 2 (an evolving national system that partially performs essential regulatory functions) and 51% at level 1 (some elements of regulatory system exist but no formal approach).

In order to strengthen regulatory systems, authorities need to recognise the importance of good regulatory practices, transparency and accountability, project management, HR development, independence and stability, and advocacy. Addressing country-specific requirements remains a challenge, particularly with the introduction of divergent frameworks for variations, as well as issues around pharmacovigilance, local production and regulatory capture.

Reliance is defined as an act whereby a regulatory authority in one jurisdiction may take into account or give significant weight to work performed by another regulator or other trusted institution in reaching its own decision. It can be used when resources are insufficient to perform all regulatory functions or required functions, or when resources may be sufficient but can be put to better use. This becomes even more important in times of emergency. Reliance is growing in acceptance and is even being used by most resourced agencies to enable smart regulation and investment. The WHO's role in promoting reliance includes the development of international standards, support for convergence, harmonisation and work-sharing through regulatory networks and developing an increasing body of guidance on reliance.

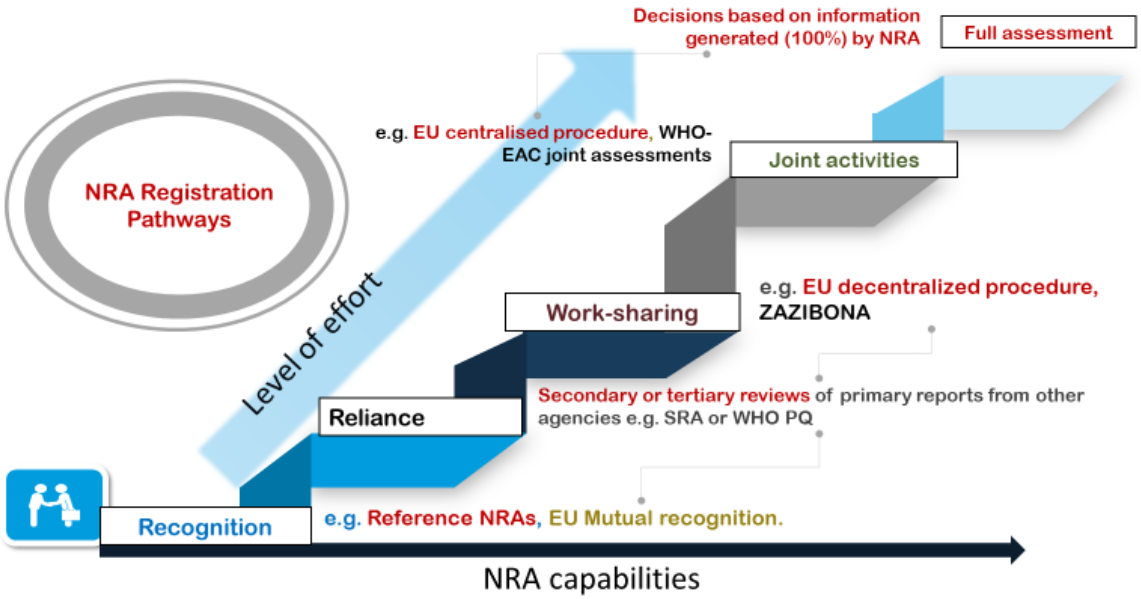
In 2018, the WHO surveyed members of the International Pharmaceutical Regulators Programme (IPRP) on their experiences, challenges, perceived benefits and opportunities of reliance [1]. Perceived benefits included increases in efficiency, effectiveness, capacity, quality and regulatory convergence. However, responses also reflected aspirations, suggesting that evidence to support some of these benefits is limited at present. Reported challenges included differences in report formats, language, technical requirements, regulatory practices and 'risk threshold'; obtaining buy-in from industry and the technical community within authorities; the need to maintain scientific competence and clinical judgement in decision-making and labelling, bridging decisions in other countries to the local benefit-harm context; the

need for secure platforms and procedures for exchanging and managing non-public information; and how to use metrics to measure and document success.

Although the responses were predominantly from higher-income countries with mature regulatory systems, the WHO/IPRP survey highlighted the importance of transparency, which is vital for building trust. With regards to selecting reference agencies, there is a need to establish confidence that the referenced agency has 'similar requirements', or that where differences exist they are known and may be accounted for. In addition, key terms and definitions need to be agreed to ensure common understanding and interpreting guidance.

There are growing concerns with the term 'stringent regulatory authority' (SRA) and the fact that the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) does not have the remit or competence to assess regulatory capacity and is facing expanding membership. In response, WHO expert committees have recommended that the term SRA be replaced by 'WHO listed authority' (WLA). Currently listed SRAs will be regarded as WLAs and the designation of new or additional regulatory authorities will be based on the WHO GBT and completion of a 'confidence-building process'. This will provide a pathway for regulatory authorities to be globally recognised and thereby help guide procurement decisions, provide a robust framework for promoting trust, confidence and reliance, and create an enabling regulatory environment for innovation and local production.

In summary, regulatory systems should be based on science, 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 regulators and institutions for the rest. Although strong support has been expressed for making better use of reliance, its full potential will not be achieved unless challenges are addressed. The regulatory community needs to continuing working with WHO and others to ready itself for transformative change.



References:

[1] WHO (2019) *Reliance – Analysis of responses to WHO questionnaire – an update* [conference presentation]. IPRP Management Committee meeting, 2-3 June 2019, Amsterdam. [Accessed 25 February 2020]. Available at: http://www.iprp.global/news/outcome-who-survey-reliance

Why a systematic, structured approach to measuring performance and its integration into the regulatory process is key to optimising performance?

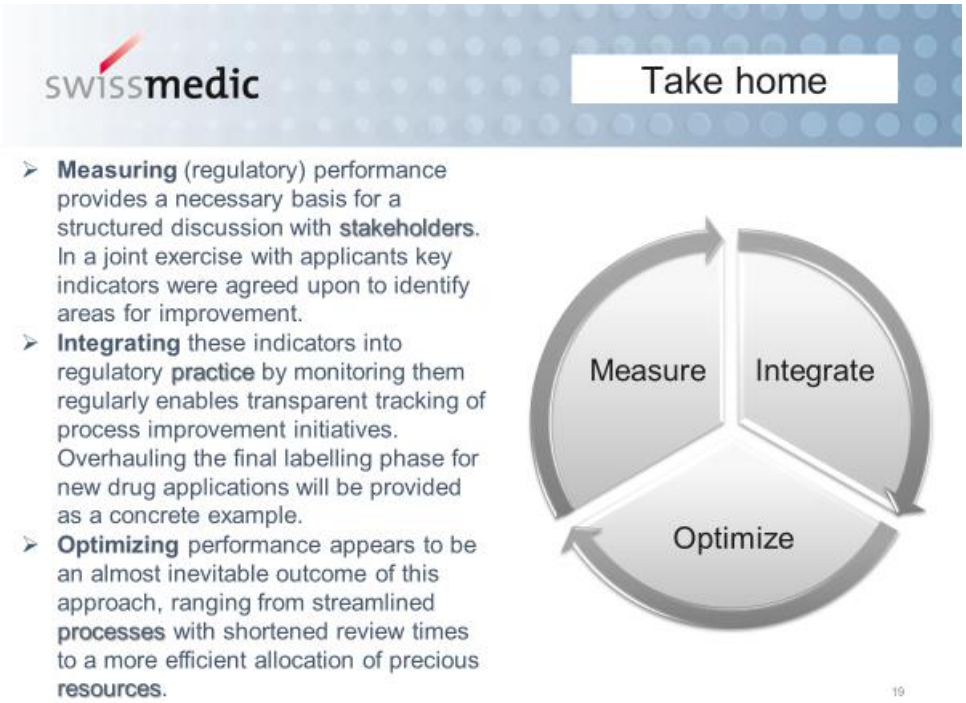
Dr Claus Bolte, *Head of Sector Marketing Authorisation, Swissmedic*

Measuring regulatory performance provides a necessary basis for a structured discussion with stakeholders. A comparison of Swissmedic's marketing authorisation decisions to those of the US Food and Drug Administration (FDA) and European (centralised and decentralised) regulatory agencies (EU) showed that although decisions converged to a high degree among the three agencies, Swissmedic had the lowest average approval rate (84%), followed by FDA (87%) and EU (91%) [1]. Out of 50 applications that had diverging opinions, 15 were rejected by Swissmedic when both FDA and EU approved, suggesting that Swissmedic holds a degree of independence.

Swissmedic undertakes a national benchmarking study of new and known active substances and major variations (excluding vaccines and radiopharmaceuticals) on an annual basis. In addition to internal databases, 70 participating companies provide their own data, which can be benchmarked across key jurisdictions. Through this joint exercise between Swissmedic and sponsors, key indicators were agreed upon in previous years to identify areas for improvement. For example, the time spent on labelling decisions with applicants was highlighted as an issue (this ranged from 64 days to as high as 288 days in 2017).

Integrating these indicators into regulatory practice by monitoring them regularly enables transparent tracking of process improvement initiatives. As a result of Swissmedic's internal benchmarking, amendments were made at an ordinance and guidance level in order to strengthen biomedical research in Switzerland, facilitate market access and increase transparency. Swissmedic undertook a number of measures, including broadening its abridged review pathway, strengthening reliance practices, optimising the labelling phase and amending the procedure with prior notification.

Optimising performance appears to be an almost inevitable outcome of this approach, ranging from streamlined processes with shortened review times to a more efficient allocation of precious resources. An international benchmarking study by CIRS showed that Swissmedic has managed to optimise and reduce its standard review times between 2013-2017 [2]. However, optimisation is not only about resources and timelines, but also the impact of an organisation's operating model i.e. how people are organised. Swissmedic had been very reliant on individual expertise and 'star performers' in the past so subsequently introduced a more collaborative approach with interdisciplinary case teams that can be tailored and deployed depending on incoming applications.



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Adoption of risk-based approaches to regulation as part of the regulatory process – what is in it for the agencies?

Professor John Lim, *Executive Director, Duke-NUS Centre of Regulatory Excellence (CoRE) & Senior Advisor, Ministry of Health Singapore*

Poor regulation of healthcare products is a barrier to access safe, high quality and affordable medicines and medical devices, leading to unmet healthcare needs and lower quality of life. Excellent regulation of healthcare products is a key enabler to address these and related socio-economic issues, and meet expectations of patients, the public and healthcare community. To be smart regulators, we must be relevant, responsive and ready, and balance protecting the public with enabling and facilitating access to medicines.

Key challenges in Asia-Pacific are insufficient regulatory knowledge and capacity, fragmented national regulatory requirements and lack of regulatory science and policy innovation [1]. While these largely describe National Regulatory Authorities (NRAs) and systems, lack of regulatory professional capability and know-how is also an industry issue. Drawing from experience of the Singapore Health Sciences Authority (HSA) [2], potential solutions to implement across the Asia Pacific could be to:

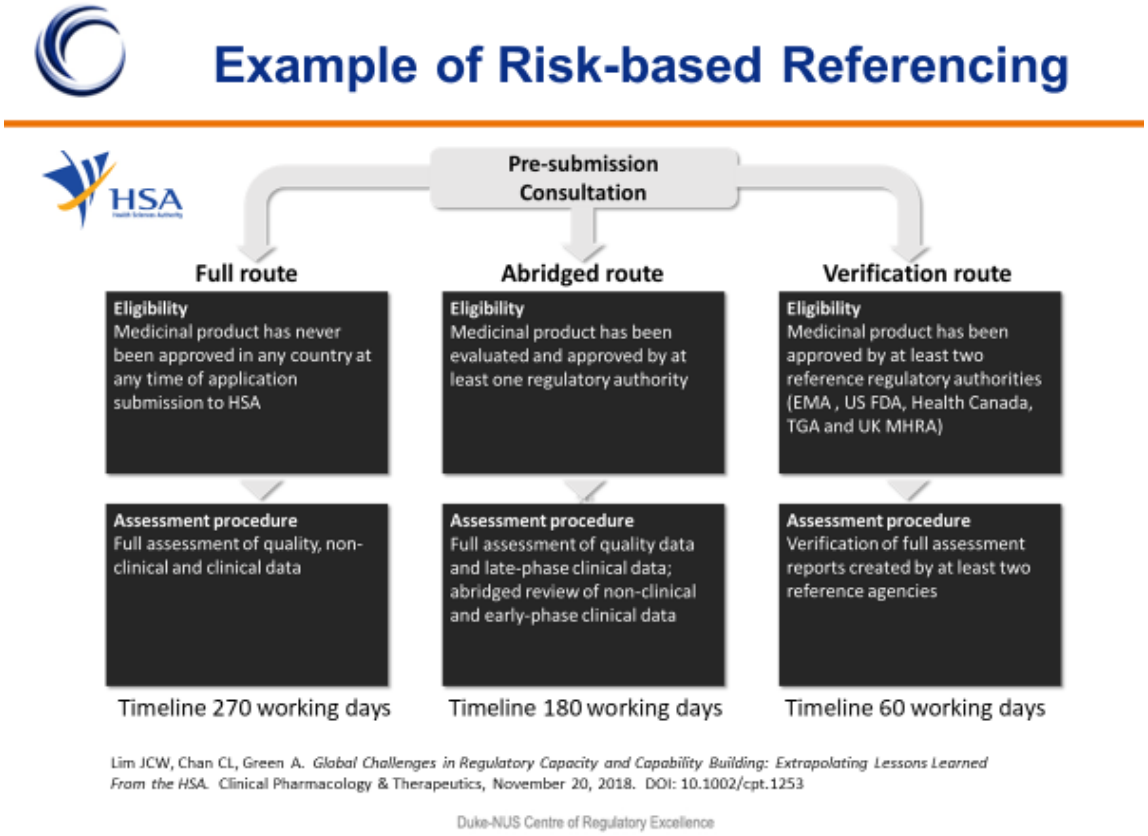
- Adopt risk-based approaches to help overcome resource limitations.
- Promote regulatory cooperation, recognition and reliance to facilitate convergence and harmonisation.
- Develop regional platforms for engagement, collaboration and capacity building.

Most products approved by the HSA go through its abridged (~85%) and verification (~10%) routes (see below), which rely on prior decisions by other trusted NRAs [2]. This risk-based referencing approach streamlines marketing authorisation applications, giving HSA more flexibility in the allocation of resources. The Singapore Health Products Act is an important legislative instrument that allows HSA to make these kinds of decisions and reference other countries.

Regulatory convergence is a voluntary process whereby regulatory requirements across economies become more aligned over time as a result of the gradual adoption of internationally recognised technical guidance documents, standards and scientific principles (harmonisation), and common practices and procedures [3]. It does not represent harmonisation of laws and regulations, which is not necessary to allow for alignment of technical requirements and for greater regulatory cooperation. Benefits of convergence include better utilisation of limited resources, contributing to the quality control and safety of medicines, maintaining sovereignty in decision-making, reducing duplication of efforts, promoting innovation for unmet medical needs, encouraging experience and knowledge sharing, and most importantly, timely patient access for needed medicines. Key Performance Indicators are important for monitoring the progress of regulatory convergence and should be tailored to level of development and capacity of NRAs within economies [4].

Reliance is defined as the act whereby the NRA in one jurisdiction may take into account and give significant weight to evaluations performed by another NRA or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken, as well as local market surveillance, protection of clinical trial subjects within a country and the investigation of adverse event reports. No regulator has all the resources to do everything expected by its government and people, and every regulator has to determine within its jurisdiction the highest risks to public health, what it can address with available resources and how to address other areas by leveraging the work of others. The balance between these two key points informs how risk-based approaches and reliance approaches ought to be applied within a particular jurisdiction or across a region.

In the move towards promoting risk-based approaches, referencing and reliance, it should be ensured that capacity building, education and training are not neglected so that smaller regulators can develop. More neutral platforms need to be created to bring key stakeholders together to learn and discuss issues in a safe setting. In order to secure strong political support, regulators should also be trained in advocacy, making their case in terms that politicians and decision makers can understand. Finally, regulators should explore the feasibility of a 'sandbox' environment, where innovative regulatory approaches can be tested in a way that proves validity, safety and capability, but without having an adverse impact on health, life and wellbeing.



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OpERA – what is it and what is its role in strengthening regulatory processes through qualitative and quantitative metrics?

Dr Lawrence Liberti, *Executive Director, CIRS*

Optimising Efficiencies in Regulatory Agencies (OpERA) is an agency-provided metrics programme to support the information needs of mature and maturing authorities and to build a culture of measurement to improve timelines and quality of processes. OpERA collaboratively collects and assesses a variety of data that characterise review processes, helping not only regulatory agencies but also Regional Regulatory Initiatives (RRI) to define and meet their regulatory review performance goals and optimise their review processes. The formal objectives of OpERA are to:

- encourage the systematic assessment of the processes that occur during the review of a new drug marketing authorisation
- evaluate how the organisational processes used in the review of new drug marketing authorisations compare with peer organisations
- encourage sharing of information on common practices to identify best practices and to improve performance
- provide benchmarking data that can be used by regulatory authorities to define performance targets and focus on ongoing performance improvement initiatives through a culture of ongoing self-assessment.

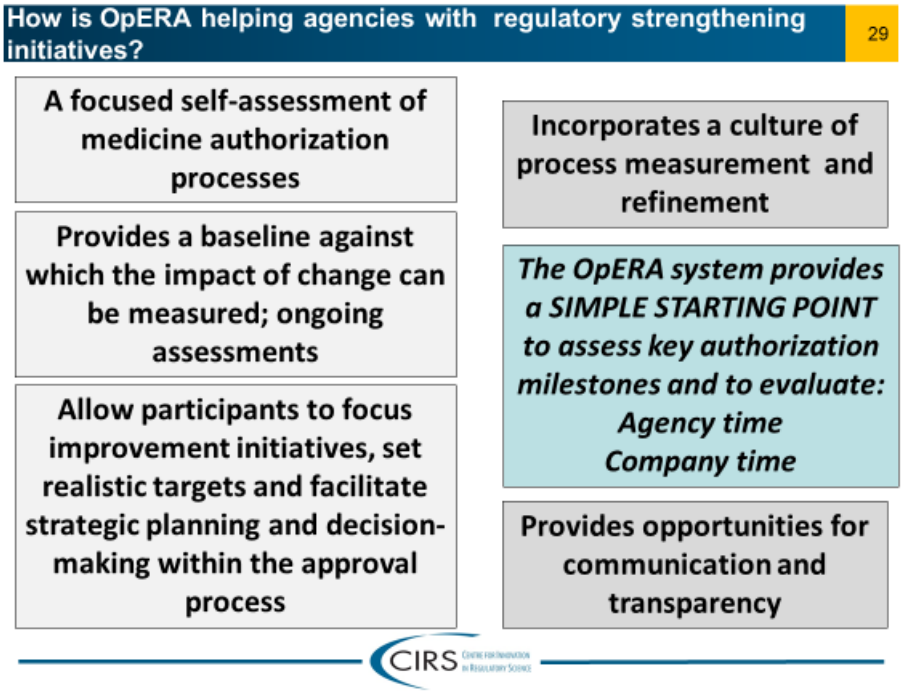
OpERA was initiated by CIRS in 2014 based on regulatory agency requests and following a feasibility study gathering agencies' feedback on relevant milestones to collect. These milestones were further defined and refined, and a methodology was developed and tested in a pilot study of nine emerging regulatory agencies [1]. This validated processes for data collection and country-specific profiling and drew attention to the distinction between the time spent by sponsoring companies and time spent by agencies in the regulatory review process.

There are two key elements to OpERA programme. The first focuses on understanding the regulatory review process at each participating agency through the development of a country-specific report. This outlines the organisation of the agency, types of review models used, key milestones in the review process, and adoption of Good Review Practices (GRevP) and Quality Decision-Making Processes. If agencies are willing to share their reports, global comparisons to similar agencies can be made, which allows for the development of a gap analysis. For several countries this has led to a collaborative peer-review publication with recommendations for agency process improvements, such as the introduction of a risk-based review in Saudi Arabia [2].

The second element of OpERA focuses on evaluating regulatory performance through the collection, interpretation and reporting of metrics. Agencies provide CIRS with specific information about the regulatory milestones (developed by CIRS with agency input) associated with products that go through their regulatory review process. The resulting metrics report helps to identify the major components of the regulatory review and opportunities for optimisation.

With the help of a grant from the Bill and Melinda Gates Foundation, the OpERA programme has expanded to over 20 countries and several regional alignment initiatives across Latin America, Africa, Asia and the Middle East. Although OpERA is aligned with the WHO Global Benchmarking Tool, African Medicines Regulatory Harmonization (AMRH) and New Partnership for Africa's Development (NEPAD) Indicators, Pan American Health Organization (PAHO) Indicators for the assessment of national regulatory systems and APEC Good Review Practices initiatives, it also captures granularity of authorisation activities that are not the focus of other systems.

In summary, OpERA is a focused self-assessment of the medicine authorisation process, helping agencies to obtain a baseline against which the impact of change can be measured. This encourages a culture of process measurement and refinement and allows participating agencies to focus on improvement initiatives.



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Process identification and improvement in Malaysia

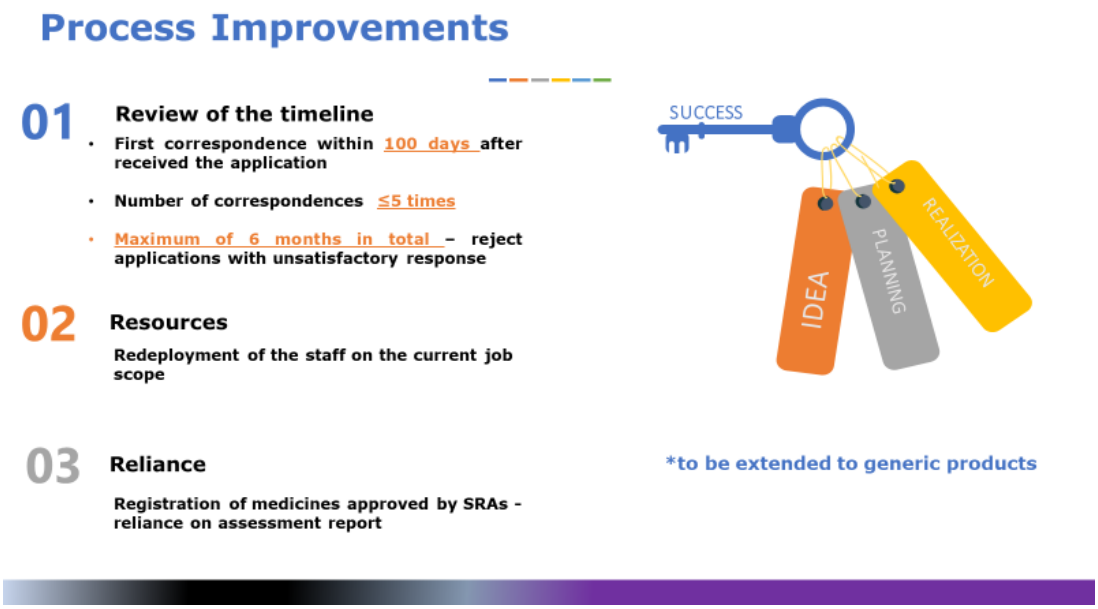
Dr Ramli Zainal, *Senior Director of Pharmaceutical Services, Pharmaceutical Services Programme, Ministry of Health, Malaysia*

The National Pharmaceutical Regulatory Agency (NPRA), Malaysia, has utilised the OpERA methodology to measure key milestones in its approval process and the time spent on each step. In 2017, 26 New Active Substances (NASs) were approved by NPRA in a median approval time of 515 days. The median time spent by the agency on scientific assessment was 166 days and up to six rounds of review were required for approval. NPRA then looked in more detail at its internal processes, which led to the identification of weaknesses such as delays in starting the scientific review, an unlimited number of rounds of correspondence between sponsor and agency, and an unlimited amount of time for sponsors to respond to agency questions.

The OpERA study has helped to inform a number of measures for improvement (see below), including limiting the timeline for specific processes, redefining the categories and requirements, the efficient use of resources through staff redeployment and the initiation of a risk-based tiered reliance process. Emulating what has been done in Singapore, NPRA has proposed a reliance model of Facilitated Registration Pathways, including an Abbreviated Review that takes 120 days and applies to a product approved by at least one reference agency, and a Verification Review that takes 90 days and applies to a product approved by at least two reference agencies. The agency is also in the process of setting up a Normal Registration Pathway for products approved by at least one agency and which would rely on a full dossier.

NPRA has started to observe improvements as a result of some of these changes. By limiting sponsors to up to five rounds of correspondence, median approval times have reduced from 515 days to 480 days. Ensuring that the agency's first correspondence is within 100 days of receiving an application has also brought forward the start of primary scientific assessment from 135 days to 87 days.

Participating in OpERA has helped NPRA to understand its regulatory performance and identify weaknesses and areas lacking capacity. This has allowed process improvements to be implemented, supporting the agency's transitioning towards regulatory excellence.



OpERA case study – Managing change and identifying policy needs in South Africa

Andrea Keyter, *Deputy Director, Medical Devices, South Africa Health Products Regulatory Authority (SAHPRA), South Africa*

The medicines regulatory authority in South Africa was formerly known as the Medicines Control Council (MCC). For many years, MCC resources were overstretched and could not keep up with increasing volumes of marketing authorisation applications, resulting in a significant backlog and extended timelines for product registration. This triggered a drive for improved regulatory systems and a more effective regulatory framework, which ultimately led to the amendment of the Medicines and Related Substance Act in June 2017. SAHPRA then replaced the MCC and became a separate legal entity outside of the Department of Health.

SAHPRA does not currently have targets for overall approval time and key review milestones. Milestones used by National Regulatory Authorities (NRAs) that could be considered include timelines for receipt and validation, queuing for review, scientific assessment, sponsor time and final reporting.

SAPHRA has spent considerable time analysing the backlog of marketing authorisation applications, the majority of which are generic applications. For example, the agency has looked to see how many applications are for the same chemical entity and whether these could be grouped in order to streamline review processes. Learnings from this backlog project could hopefully be implemented into SAPHRA's standard review practice in future.

Although the backlog of marketing authorisation applications is being addressed, there is a need to consider facilitated regulatory pathways to reduce South Africa's substantial approval times. In 2015, the average approval time was 1175 days for 31 New Active Substances (NASs), which increased to 1641 days (for 33 NASs) in 2016. In 2017, the average approval time was 1466 days (for 41 NASs), which suggests some progress is being made.

For South Africa to achieve the full potential of this new regulatory environment, a culture of accurate metrics collection and continuous improvement must be established. Targets must be set for overall approval times and key review milestones in regulatory review must be identified and codified into policy and guidelines. Finally, appropriate systems and resources must be developed to support tracking these elements.

OpERA case study: Supporting policy change and delivering policy needs in Brazil

Ana Carolina Morino, *Advisor for the Directorate of Authorisation and Registration, ANVISA, Brazil*

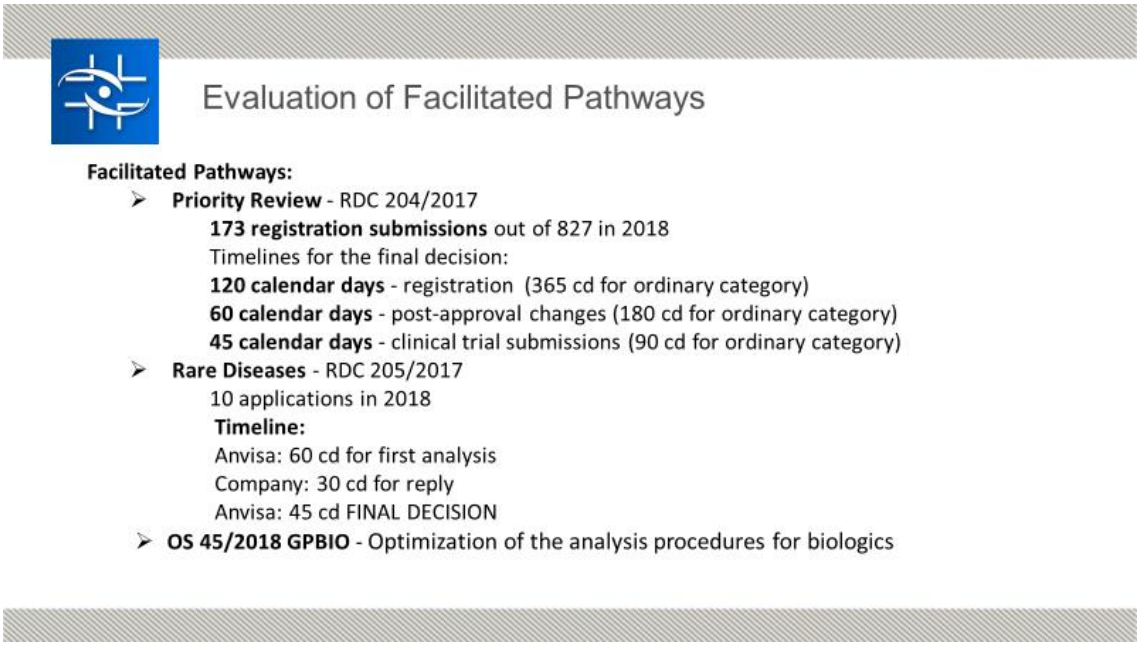
By participating in the OpERA programme, ANVISA is working towards a culture of performance measurement and is currently improving its measurement and reporting tools. The agency's IT system is being made more user-friendly so data can be easily extracted and made into comparative graphics, similar to those used in CIRS R&D Briefings. This information will also be made available in periodic reports on ANVISA's website in order to increase transparency.

Performance indicators are helping ANVISA's management to establish strategic plans and objectives. Some of the questions being addressed are:

- Are we meeting the timeline proposed without compromising the quality of the review?
- Can the timelines be shorter or do they need to be longer?
- Is the review process used adequate?
- Is industry using the available pathways?
- Are submissions using facilitated pathways increasing over the years?

Comparative data have been used to compare timelines with those of other regulatory agencies, considering the review process and agency capacity. Comparative data has also been used to establish strategic plans to improve the timelines of specific types of products and to evaluate the success of facilitated pathways established in 2017 (see below). These data have been valuable in justifying ANVISA's results to Congress and to society, who expect faster access to safe, efficacious and high-quality medicines.

The OpERA programme highlighted to ANVISA that it needed to improve its good review practices. This prompted the agency to evaluate its review template and assessors guide, incorporating some concepts of Universal Methodology for Benefit-Risk Assessment (UMBRA). Industry were given the opportunity to comment and contribute to the review template, which was well received and resulted in useful feedback for the agency. The Safety and Efficacy Review Template is publicly available on ANVISA's website.



OpERA case study: Regional initiative – Carribean Regulatory System progress

Dr Charles Preston, *Adviser, Regulatory System Strengthening in Medicines and other Health Technologies, Pan American Health Organisation (PAHO)*

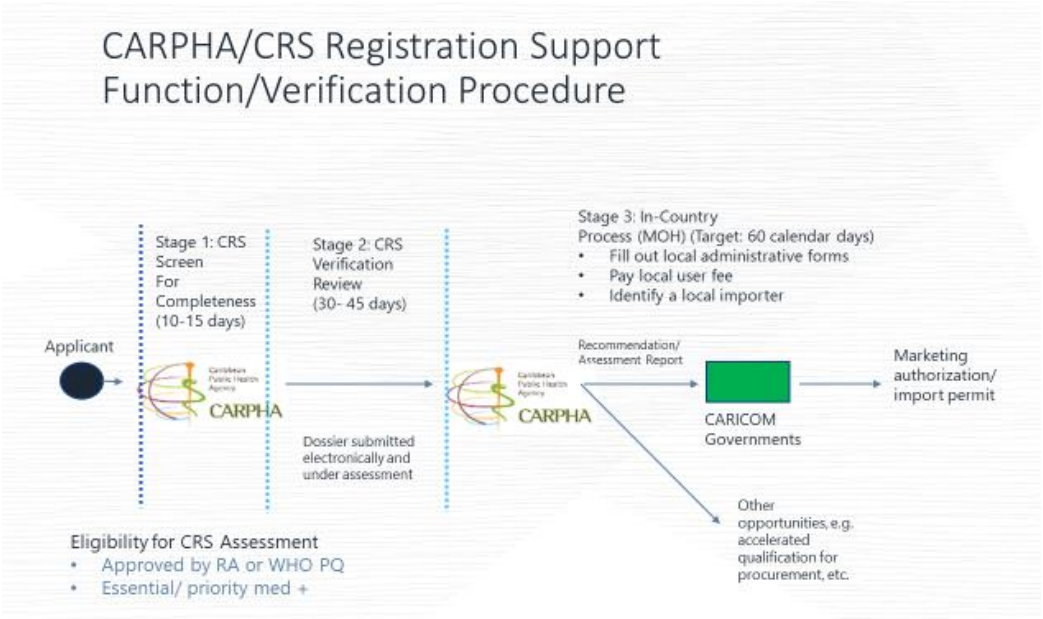
[Unfortunately, Dr Preston was unable to attend the workshop, so this presentation was cancelled. However, this summary is provided for information].

The Caribbean Regulation System (CRS) is a centralised regulatory mechanism intended to speed marketing authorisations/legal sale of quality essential medicines in the Caribbean Community and Common Market (CARICOM). It is a voluntary regional initiative and is not intended to replace national systems. CRS is located within the Caribbean Public Health Agency (CARPHA), with technical support from PAHO/WHO and funding from the Bill and Melinda Gates Foundation.

To be eligible for CRS verification review, a product must be an essential priority medicine approved by a regulatory authority or WHO prequalification (see below). Applications or dossiers can come to CARPHA/CRS either directly or through a Ministry of Health that asks the CARPHA/CRS to review the product as an assessor would. In the latter route, the company signs a waiver to allow the Ministry of Health to release the dossier, which is beneficial if a product has been in backlog and needs timely review. The dossier can be in a variety of formats but needs to contain the CRS submission requirements. The CRS reviews/verifies that the product is the same as approved in the reference authority and if favourable, recommends the product to CARICOM Ministries of Health, who then determine whether to issue a sovereign marketing authorisation.

Since it became operational in 2017, CRS has recommended 37 medicines and issued 47 registrations or tentative registrations, taking on average 8-10 weeks to make decisions on applications. It has been noted that there has been an increase in quality in the applications of local importers. In 2018, 7 CRS recommended products were offered for national tender in Trinidad and Tobago by a local supplier. Of these, 5 out of 7 were 8-25% less expensive in price per unit than the lowest price per unit product in the previous year's tender cycle. This means that CRS-recommended medicines can bring lower cost for patients and governments while at the same time maintaining quality (all were WHO prequalified medicines).

The CRS is faced with challenges related to member state uptake, industry uptake, human resources and sustainability. Despite these challenges, there is a long-term commitment to CRS and other small states are looking to this as a model regional initiative.



Why key stakeholders benefit when agencies build in performance management metrics and set evidence-based targets

Company Viewpoint: Dr Paul Dearden, *Head of Emerging Markets, Regulatory Policy and Intelligence, AbbVie, UK*

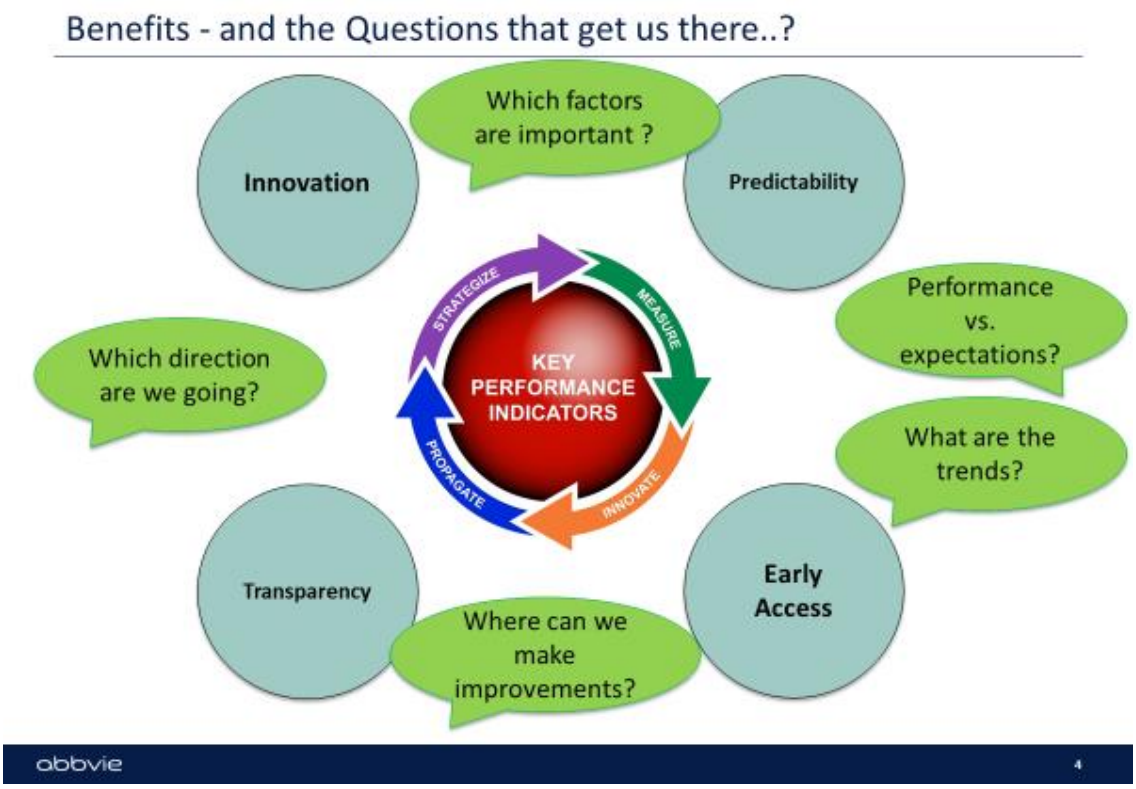
Metrics, targets and key performance indicators (KPIs) facilitate improvement but we need to ask the right questions to get the information we need. Answers to questions such as how is performance relative to expectations? How can we make improvements? Which factors are important? will reveal whether an agency's performance is leading to benefits such as predictability, early access, innovation and transparency.

Predictability is critical in all aspects of drug development and review, particularly as the systems we work in become more complex and complicated. Companies need to be aware of timelines, targets and expectations to be able to manage cross functionally in an effective way and ultimately bring medicines to patients as quickly as possible. For example, the prequalification timeline KPIs developed by the World Health Organisation help to inform companies of the reliability of the prequalification process and what timelines can be expected. Bringing stakeholders together through workshops can also open up valuable and unique discussions on processes, targets and data. For example, the 2016 APEC Good Registration Management Regulatory Science Center of Excellence Pilot Workshop facilitated shared learning and expertise on the specifics of how to do a submission in a good way.

Metrics are key for demonstrating earlier access to medicines, which is improving as regulatory review timelines for agencies across the world continue to converge. Using metrics to benchmark agencies, as CIRS does in its annual R&D briefings, is also helpful when companies are interacting with maturing agencies, in order to demonstrate what is possible in terms of regulatory review timelines and what maturing agencies may be able to work towards.

Reporting on performance metrics improves agencies' transparency, one of the key principles of Good Review Practices. This is beneficial for patients, physicians, companies and other agencies, as it enhances trust, communications and understanding. Specific benefits to companies include clear regulatory processes, improved dialogue with agencies, clear understanding of regulatory expectations, efficient product development and viable decision making.

Finally, the collation of information, metrics and targets is facilitating innovation in regulatory pathways, convergence and regulatory science. Although some areas of activity are still a work in progress, developments in real-world evidence, ICH guideline implementation, reliance and work-sharing are proving to be of global benefit.



Funder viewpoint: Dr Murray Lumpkin, *Deputy Director, Integrated Development, Bill and Melinda Gates Foundation*

The Bill and Melinda Gates Foundation (BMGF) is guided by the belief that every person deserves the chance to live a healthy, productive life. The Foundation forms partnerships (thought partnerships as well as financial partnerships) to discover, develop, and deliver vaccines, drugs, and diagnostics for people suffering from neglected diseases in low- and middle-income countries. BMGF's grant programme is strategy-driven, data-informed, impact-focused and often involves new products and therapies.

All stakeholders (including authorities themselves) want regulatory authorities that are public-health-missioned, politically and conflict-of-interest (including perceptions of or realities of local preferences) independent, scientifically robust, transparent, accountable, predictable, impactful and well-managed. Performance metrics and goals are vehicles for assessing many of these qualities.

Performance measures and any associated goals should be those over which the regulatory authority itself has control. For example, they should be aiming to have a 'complete review' within a certain timeframe, rather than setting the total time to approval, which is not solely dependent on the actions of the regulatory authority. Metrics and goals should be realistic and supported by adequate resources. Agencies should be set up for success and recognise that improvement over time is normal. For example, with a metric to complete reviews in 270 calendar days, the goal might be for 75% of reviews to meet the metric in a certain calendar year, 80% in the next year etc. In addition, performance measures and associated goals should be a mutually agreed part of any sustainability 'social contract' with all stakeholders who are helping to fund the agency (both public and private sector).

Accurate metrics collection allows an agency to defend itself against the inevitable challenges of critics, as well as to benchmark itself against other comparable agencies and continuously improve internal processes. It also facilitates public health improvement and economic development within the sector because the agency becomes predictable and accountable, thus allowing industry, government health systems, funders and others to plan accordingly.

Regulatory and legal reforms, process improvements and collaboration have led to improvements in regulatory performance metrics. For example, the recent shortening of review timing in sub-Saharan Africa national regulatory agencies have allowed those agencies to review their performance against other agencies and against their own past performance (see below).

In summary, making use of performance metrics allows an agency to benchmark itself against its peers and against its previous performance and fosters a data-driven discussion about performance rather than one based on bias and perception. The OpERA programme and other CIRS metrics-related initiatives are helpful to agencies and the wider community in driving continuous improvement, independence and agency credibility. Metrics-related programmes allow funders to evaluate grants and investment possibilities based on data i.e. by showing what is working and where investment might be most impactful.

IMPROVEMENTS IN PRODUCT REGISTRATION TIMELINES (2013 -> 2018)

	Registration pathway	Median Times (months) 1st regulatory authority (RA) approval time	PQ approval time	Gap from 1st RA approval to 1st SSA NRA submission	Spread from 1st SSA NRA submission to last SSA NRA submission	Sub-Saharan Africa (SSA) NRA approval time	Total
2013	Drug – Novel, SRA first	10	4	9	52	11	30-82 [1st – last SSA NRA]
	Drug – Generic, NRA first	~12	27	~3-6	~24	~18	39-60 [1st – last SSA NRA]
	Vaccine – SRA first	15	16	5	78	16	36-114 [1st – last SSA NRA]
	Vaccine – NRA first	~12	16	~3-6	N/A	N/A	N/A
Reliance Re-engineering Regionalization							
2018	Drug – Novel, SRA first	10	3.3 (WHO target) 1.6 (WHO actual) 2.9 (company actual)	Theoretically 0 (depends on company)	Theoretically 0 (if company submits simultaneously to all CRP countries)	3 (target) 2.8 (actual)	16.3 (target) 17.5 (actual) [1st or multiple]
	Drug – Generic, NRA first	~12	9 (WHO target) 8.3 (WHO actual) 15.2 (company actual)	Theoretically 0 (depends on company)	Theoretically 0 (if company submits simultaneously to all CRP countries)	3 (target) 2.8 (actual)	24 (target) 38.5 (actual) [1st or multiple]
	Vaccine – SRA first	15	3.3 (WHO target) 4.9 (WHO actual) 2.7 (company actual)	Theoretically 0 (depends on company)	Theoretically 0 (if company submits simultaneously to all CRP countries)	3 (target) 6 (actual)	21.3 (target) 28.1 (actual) [1st or multiple]
	Vaccine – NRA first	~12	9 (WHO target) 8.0 (WHO actual) 8.4 (company actual)	Theoretically 0 (depends on company)	Theoretically 0 (if company submits simultaneously to all CRP countries)	3 (target) 6 (actual)	24 (target) 34.4 (actual) [1st or multiple]

- For products accessing a procurement market and requiring three rounds of registration: 1st approval, prequalification, receiving country registration
- 2013 data from: Ahonkhai V, Martins SF, Portet A, Lumpkin M, Hartman D. Speeding Access to Vaccines and Medicines in Low- and Middle-Income Countries. **PLoS One**. Nov 16, 2016
- 2018 data developed based on PQ and CRP performance metrics received from WHO RHT, Jan 2019

Reforming the Chinese regulatory system: How is the National Medical Products Administration (NMPA) measuring the changes?

Dr Songmei Xie, *Deputy Director, Office of Clinical Evaluation II, Center for Drug Evaluation, National Medical Products Administration (NMPA), People's Republic of China*

Between 2010-2015, the regulatory system in China was unable to meet the needs of an evolving industry and faced an increasing backlog of marketing authorisation applications. This growing problem was attributed to policy barriers e.g. multicentre trials were only allowed for drugs that were in phase II studies abroad, a lack of risk-based scientific regulatory processes, lower standards for registration, lower quality submissions, severe shortage of human resources, lack of transparency and ineffective internal and external communication.

Over the past several years, NMPA has instituted a number of initiatives to overcome these barriers to develop innovative drugs and high-quality generics and to provide timely access to medicine for the people of China. The regulation of clinical trials was reformed, in order to make the processes of acceptance, review and approval more integrated and precise, and to strengthen communication with sponsors (see below). To help clear the backlog of applications, two new review pathways were launched: a priority review pathway for clinically valuable new drugs and urgently needed generics, and an accelerated pathway for new drugs for rare or life-threatening diseases that show significant clinical advantages and have been already licensed in the US, EU or Japan.

In order to address the quality gaps of existing products in the market and improve the performance of the entire Chinese pharmaceutical industry, NMPA has rolled out consistency evaluation on generic products and refined, developed or translated over 150 technical guidelines, including a series of bioequivalence guidelines. In 2018, NMPA announced that it would apply five secondary guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

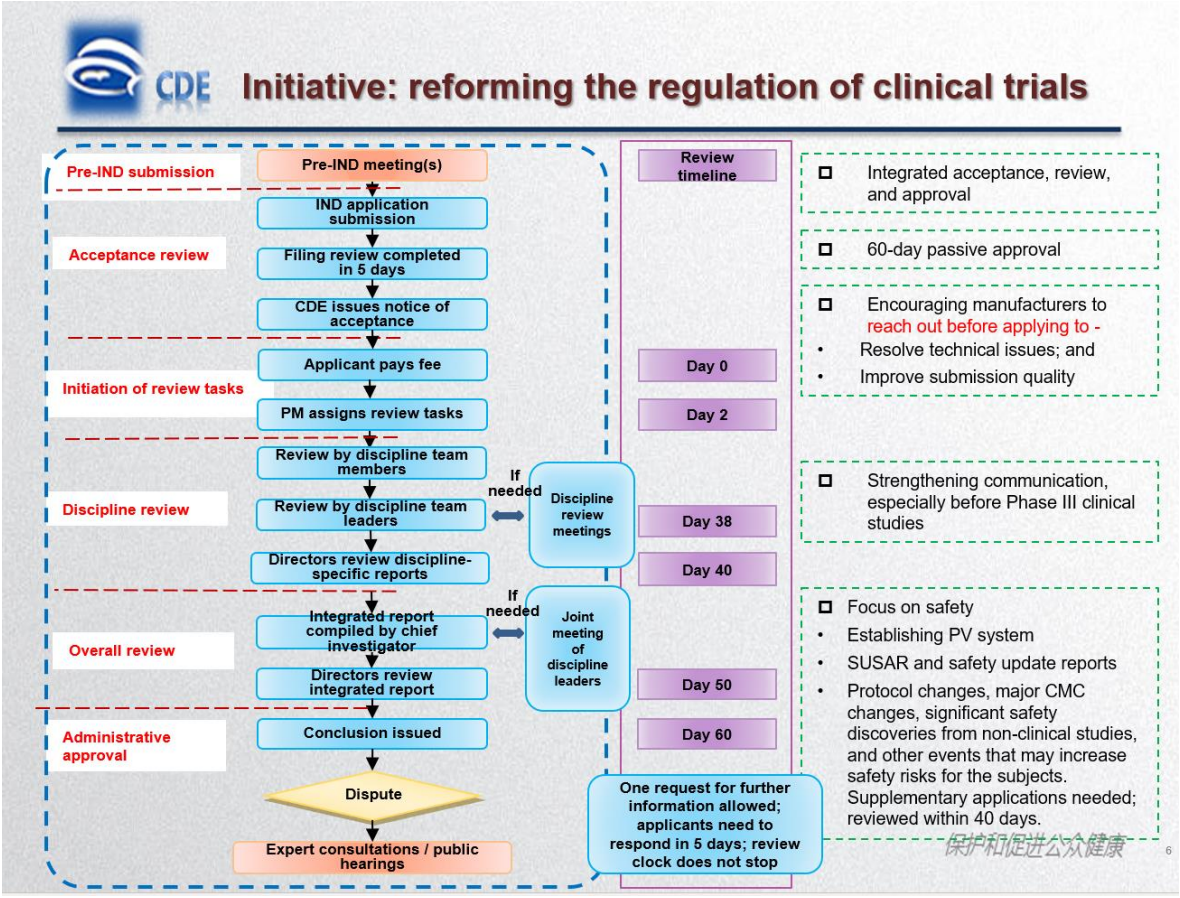
NMPA has optimised its review and approval process by integrating acceptance, review and approval processes for Investigational New Drugs (INDs) and by integrating acceptance and review for New Drug Applications (NDAs). Review, inspection and testing are now carried out simultaneously, which has improved internal communications. NMPA has also optimised and expanded its organization and workforce by adding several new divisions including for clinical trial management, compliance and data management, as well as creating indication-based and project management teams. In addition, internal training schemes have been put in place and international exchange and collaboration efforts have been increased.

To help build a more robust review quality management system and reduce review time, NMPA has established Good Review Practice (GRevP) standards, evaluated the quality of technical review reports and improved its review time management. The agency has also improved its transparency by disclosing review processes and progress to applicants and publishing review reports and instructions for new drug marketing applications.

The reforms implemented by NMPA have already resulted in measurable impact. IND review time has been significantly reduced and the number of licensing applications waiting for review and approval dropped from 22,000 to 3,440 during 2014-2018. 133 products with significant clinical value were approved for marketing via the expedited priority channel between 2016-2018, playing an effective role in addressing clinical needs, reducing drug-related expenses, and promoting public health. There has also been a dramatic increase in requests for communication and consultation and a steady increase of INDs and NDAs approved.

Going forward, NMPA will focus its efforts on building a risk and science-based, whole life cycle drug regulation system aligned with international standards. The agency will step up international regulatory

exchange and cooperation and will continue developing good quality management and strengthen training to enable comprehensive improvements in regulatory capacity. These efforts will help to make China a welcoming ecosystem for drug R&D and evaluation, and ultimately to better protect and promote public health.



Reliance in Latin America: key characteristics and experience in the region

Dr Mario Alanís, *Independent Consultant, Mexico*

Reliance in Latin America is either unilateral or negotiated, based on stringent regulatory authorities (SRAs) or Pan American Health Organization (PAHO) regional reference authorities. Unilateral reliance, such as that of the Caribbean Regulatory System, concentrates on WHO essential medicines and is a verification centralised review based on PAHO reference / SRA approvals. Negotiated bilateral reliance agreements can be initiated in PAHO Level IV reference NRAs (Argentina, Brazil, Chile, Colombia, Cuba, Mexico) and the implementation process is performed by each pair of countries.

Within the Central America Integration System (SICA), there is a mutual recognition procedure where medical products manufactured in one country can receive a marketing authorisation in another. SICA members using this recognition mechanism include El Salvador, Honduras, Costa Rica, Guatemala and Nicaragua (Panama is currently setting this up).

Mercosur is a South American trade zone made up of Argentina, Brazil, Paraguay and Uruguay. Within Mercosur, GMPs are harmonised so that inspection reports can be exchanged between member countries and GMP certificates from manufacturing countries can be adopted and published by the importing country. GMPs are similarly harmonised in the Pacific Alliance, which is made up of Chile, Colombia, Mexico and Peru.

The verification model in Mexico is a unilateral instrument that employs a simplified review process of a full dossier and is based on previous review by FDA, EMA, PMDA, Swissmedic, Heath Canada or TGA. The model applies to innovative chemical entities and the legal time of response is 60 working days, half the time for a normal procedure. The verification model has been very successful in Mexico and is helping to increase access to innovative medicines. In addition, Mexico GMP reliance on Pharmaceutical Inspection Co-operation Scheme (PIC/S) countries has facilitated access, reduced costs for companies and allowed the regulatory agency to better assign resources.

In summary, reliance is a necessary requirement to facilitate regulatory convergence and harmonisation and there is a gradual trend in Latin America to adopt reliance initiatives. Trade or regional integration negotiations have facilitated discussion of reliance schemes but more could be done to further advance their use.

Indonesia's experience on abridged evaluation

Dra. Reri Indriani, *Acting Deputy Chairperson for Drug, Narcotics, Psychotropics, Precursors, and Addictive Substances Control, National Agency of Drug and Food Control (NAFDC), Badan POM (BPOM), Indonesia*

The medicine regulatory system in Indonesia faces challenges related to the country's large geographical area, drug crime, ineffective law enforcement, lack of resources, universal health coverage and product competitiveness and innovation. Indonesia is strengthening its regulatory system through strategic policies, developing risk-based review, strengthening institutional capacity and maintaining regional and international collaboration through WHO, ASEAN and APEC.

Prior to 2017, assessment for marketing authorisation in Indonesia was conducted based on a full evaluation of non-clinical, clinical and quality data. However, it became increasing difficult for BPOM to fulfil timelines of evaluation due to limited quantities of evaluators. Therefore, in 2017, BPOM implemented a risk-based approach to simplify the registration process and reduce the timeline of full evaluation from 300 to 120 working days. The main criteria for this reliance mechanism are that the product must be approved by at least three mature agencies and the applicant needs to provide three full assessment reports. All aspects of the product's quality, including but not limited to the formulation, manufacturing site(s), release and shelf life specifications and primary packaging, are identical as currently approved by reference agencies. The product does not need a more stringent assessment as a result of differences in local disease patterns and/or medical practices e.g. some anti-infection drugs, antivirus (Hep C, HIV), anti-malaria drug, TB drug.

In 2018, 10 new medical products were evaluated using this abridged review system, though not without any challenges. Regulatory challenges included differences in indication wording and the need to ensure that the documents submitted to BPOM are exactly the same as those submitted to reference countries. Industry also reported finding it very difficult to obtain three full assessment reports from SRAs. In response to these challenges, BPOM is revising its reliance mechanism. Changes will be made to the following criteria:

- The number of countries that must have approved the medicine will be reduced from three mature agencies to a minimum of one
- Biological products will be included
- Reference agencies must have good evaluation systems and publish Assessment Reports (in English). Reference countries will be specified as EU, USA, Australia, Canada, UK and Japan.

In summary, reliance is a key strategy for BPOM to overcome timeline gaps and resource limitations in its marketing authorisation process. Although the agency's abridged review process needs further refinement, it is facilitating the conduct of efficient and transparent evaluation of global products in Indonesia and timely patient access to good quality medicines that are safe and effective.

Conclusion

- Reliance mechanism is a breakthrough:
  - to conduct efficient and tranparant evaluation of the same global products, and
  - to provide timely patient availability to good quality medicines that are safe and effective.
  - To prevent duplication evaluation proces during pre-market
  - Implementing Agency should have established Regulatory System inline with GRP , industry should also GSP (Good Submission Practices) to expedite registration approval

Thailand's experience of abridged review

Supatra Phongsri, *Pharmacist, Professional Level, Bureau of Drug Control, Thailand Food and Drug Administration*

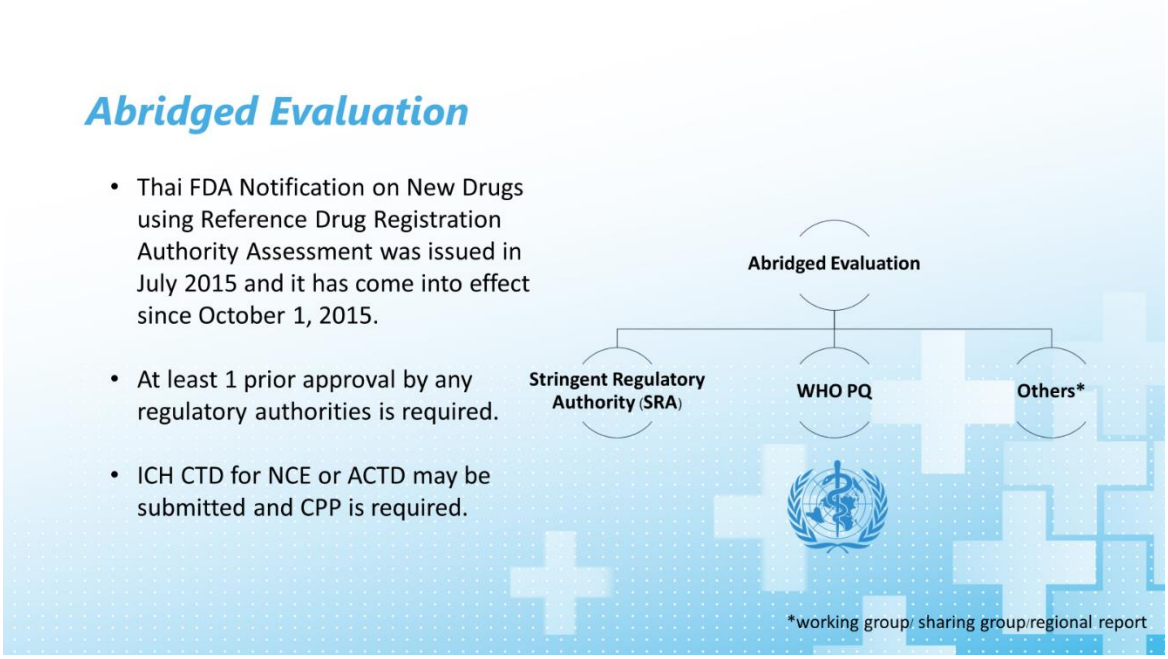
Preeyaporn Natehin, *Pharmacist, Practitioner Level, Bureau of Drug Control, Thailand Food and Drug Administration*

In Thailand, the channels for drug evaluation are full review, priority review and abridged review. While full reviews are conducted for medicines with no prior approval worldwide, priority reviews can be used to fast-track products with R&D based in Thailand, first generic medicines, medicines for life-threatening conditions or medicines addressing urgent public health problems.

Abridged evaluations came into effect in October 2015 following the issue of the Thai FDA Notification on New Drugs using Reference Drug Registration Authority Assessment. They require prior approval by at least one reference agency, within two years from the original approval date. Proposed indications, dosage regimens, patient groups and/or directions for use must be the same as those approved by the reference agency. The full assessment report of the reference agency must be submitted, as well as all lists of questions and answers during the assessment process and post-approval variations and related documents. These are generally reviewed by experts and internal reviewers. A proposal is made to the New Drug Subcommittee for consideration if expert opinions are not unanimous, the drug is not approved, the drug may cause social or other problems or may have high potential for misuse/abuse, or in the case of a pending phase III clinical trial.

Abridged evaluations shorten standard review timelines from 280 to 200 working days and priority review timelines from 220 to 150 working days. Other benefits include better management of limited resources, improved quality of review and provision of a learning experience for new reviewers.

Challenges of abridged evaluations include the need for full assessment reports, a lack of agency resources and experience in evaluating new chemical entities, differences in requirements between reference agencies and the local agency, and difficulty controlling post-approval variations and pharmacovigilance. For example, the applicant may submit the registration dossier and post-approval variations at the same time worldwide for some pharmaceutical products, which means that the reviewer cannot review the dossier by using the assessment report.



ZAZIBONA Collaborative Medicines Registration Procedure

Tariro Makamure Sithole, *Chief Regulatory Officer, Medicines Control Authority, Zimbabwe*

The South African Development Community (SADC) is a regional economic group made up of 16 member states, of which 11 actively issue marketing authorisations. In 2013, four SADC members (Zambia, Zimbabwe, Botswana, Namibia) founded a work-sharing initiative called ZAZIBONA to allow their national regulatory authorities to jointly assess medicines for registration purposes. It was hoped that this would address common challenges such as significant backlogs of applications, long registration times, high staff turnover, limited capacity to assess certain types of products and inadequate financial resources.

As of March 2019, there are 13 SADC member states participating in ZAZIBONA (Botswana, Democratic Republic of Congo, Namibia, South Africa, Zambia, Zimbabwe, Mozambique, Tanzania, Malawi, Angola, Seychelles, Swaziland, Madagascar). Participation is voluntary and active member or observer status is granted based on capacity to do assessments and GMP inspections. The objectives of ZAZIBONA are to:

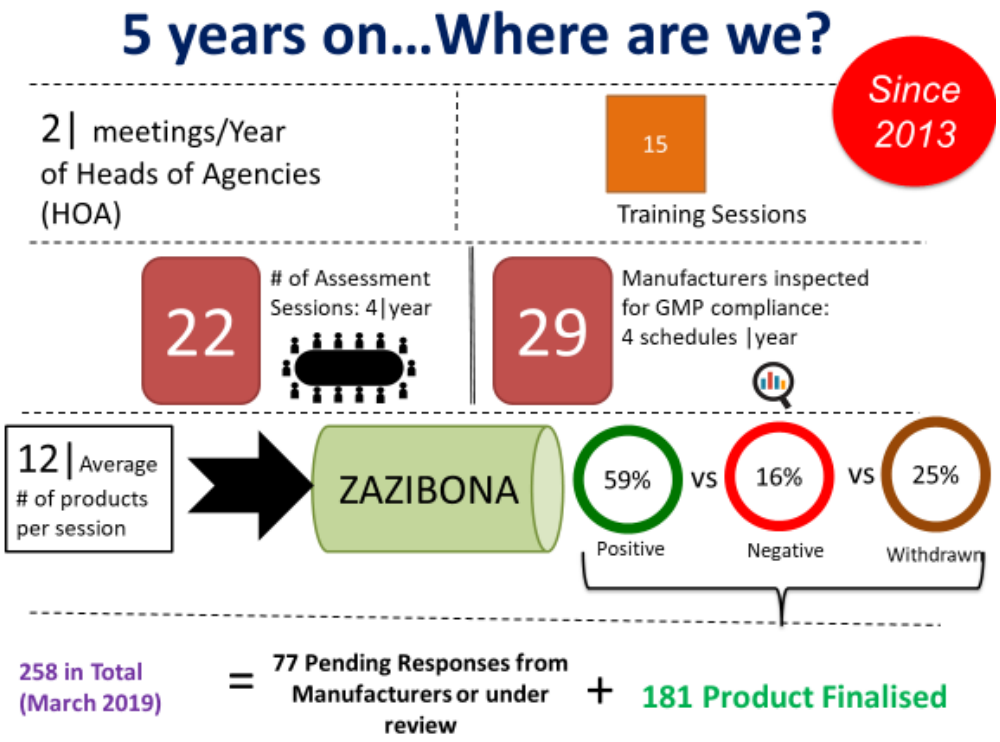
- Reduce regulatory workload
- Develop mutual trust and confidence in regulatory collaboration
- Test the mechanism of co-operation among regulatory authorities
- Provide a platform for training and capacity building
- Ultimately facilitate harmonisation of regulatory requirements in the region.

For a product to be assessed under ZAZIBONA, the manufacturer must have submitted the dossier to at least two countries, paid the fees to all countries it wants to market in and consented to the work-sharing agreement. One country (rapporteur) will conduct the first review and then the second country (co-rapporteur) will conduct the second review. The final quality assurance check is carried out by WHO. All countries have access to the reports and can make comments, though the formal assessment is carried out by the rapporteur and the co-rapporteur. At the end of the assessment process, ZAZIBONA makes a recommendation for registration that is then passed onto the decision-makers within each country.

Over the last five years, 181 products have been assessed by ZAZIBONA review and 77 are pending reviews (see below). Most of these products are generics because individual countries can conduct abridged review of SRA-approved products. The median time for ZAZIBONA review is 330 days, which includes the manufacturer's time to respond to questions.

Work sharing can be challenging, as it requires an ongoing building of trust and confidence amongst regulators and inevitably means more work for mature agencies, whilst capacity is built elsewhere. Ongoing issues for ZAZIBONA include a lack of centralised submission, submission of different dossiers by some manufacturers, country-specific requirements e.g. labelling, different comparators and a lack of electronic information systems. Differences in capacity and inadequate human resources within agencies has also sometimes meant poor or no implementation of ZAZIBONA recommendations at the country-specific level.

Nevertheless, work-sharing models like ZAZIBONA bring several benefits to patients, regulators and manufacturers. For patients, they help to improve timely access to quality-assured medicines. Benefits to regulators include reduced workload, capacity building, improved effectiveness of the medicine registration process, efficient use of limited resources and regulatory intelligence through improved information sharing and networking. Manufacturers also benefit from enlarged market access (approximately 350 million people reside in ZAZIBONA countries), reduced regulatory workload (through combined submissions and joint GMP inspections), and a shorter time to registration.



Implementing an Abridged Review: What are the criteria and assessment practices used by agencies?

Dr Neil McAuslane, *Scientific Director, CIRS*

During a CIRS workshop on reliance models in March 2018, a roundtable discussion highlighted some areas where more information would be of value to aid those considering or implementing abridged reviews [1]. For example, what elements constitute an abridged application, what are the requirements for documentation from reference agencies, which part of the dossier should be focused on, and how to manage the change of moving from a full review to an abridged review.

To gain a better insight into abridged review practices, CIRS ran a survey with agencies that had either recently instigated or had experience in undertaking an abridged review. The aim was to identify the criteria used to determine which products should be considered for an abridged review and to determine what elements of the submission are reviewed and the level of detail considered. Six agencies responded to the survey: Australia, Brazil, Israel, Health Canada, Gulf Cooperation Council (GCC), and Thailand.

When asked about the criteria used for abridged study, all six agencies indicated that the application should be identical to that approved by or submitted to the reference agency in terms of dosage form, strength formulation, and manufacturing. Three agencies also indicated that the proposed indication of the medicine would need to be based on a broadly similar population, demographics, disease profiles, and expectations regarding public health outcomes between the jurisdiction and the reference agency itself. While some agencies did not specify a timeframe for submission, the majority indicated that this should be within one or two years of approval from the reference agency.

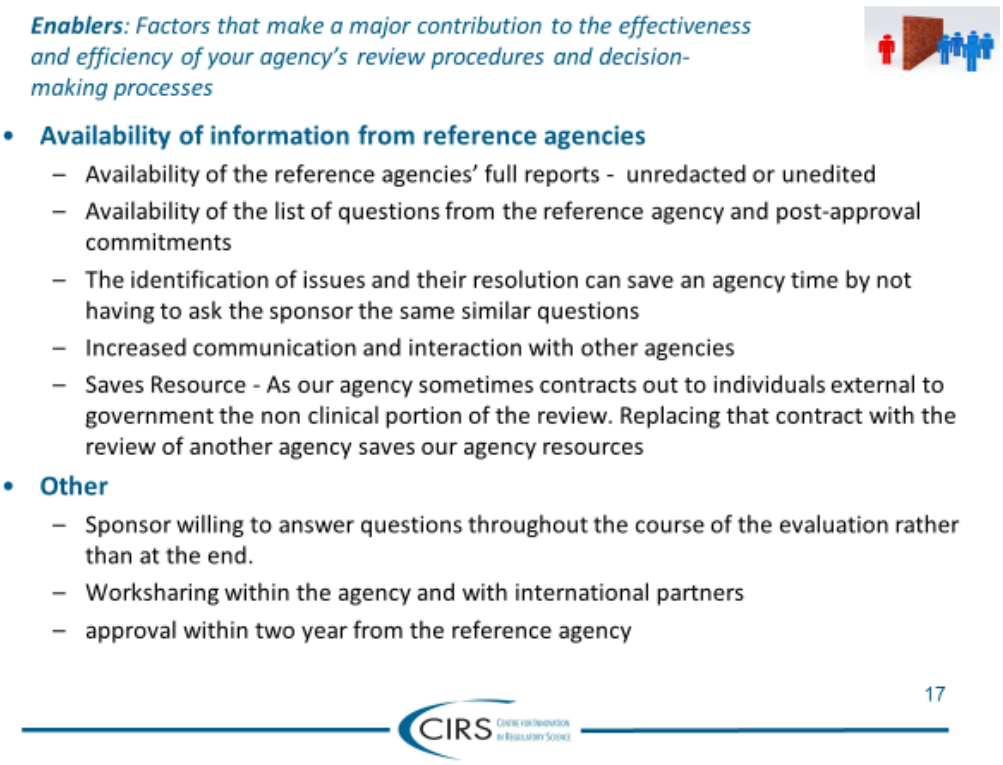
The most used reference agencies were the US Food and Drug Administration (FDA) (listed by 100% of responding agencies), European Medicines Agency (EMA) (100%), Swissmedic (67%) and the Medicines and Healthcare products Regulatory Agency (MHRA) (67%). Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada and Therapeutic Goods Administration (TGA) were also indicated by half of respondents. When selecting a reference agency, all responding agencies considered the utility and compliance to global standards and technical guidelines, and the availability of the reference agency assessment report to be most important.

Most agencies required one reference agency's unredacted assessment report as well as the full list of questions asked by the reference agency and the company's responses, the deliberations by the advisory bodies, and post-marketing experience and commitments. In terms of the depth of review, the reference agency assessment reports were reviewed in detail by most agencies but the use of the submitted dossier seemed to vary. In addition, five out of six agencies required a full ICH/ASEAN Common Technical Document and four agencies required the Certification of Pharmaceutical Product (CPP) from the reference agency.

The survey highlighted that the availability of information from reference agencies was a key enabler to performing abridged reviews (see below). Barriers included resistance from reviewers and companies to accept this type of assessment, differences in regulatory requirements between the jurisdiction and the reference agency, difficulty in obtaining an unredacted assessment report, inadequate transparency of the reference agency decision making process, and concerns that the risk-benefit assessed in an overseas review is marginal or not clearly generalisable to the local population.

In summary, this pilot study identified similarities and differences in how agencies have implemented and are utilising abridged reviews. It has provided some understanding of the selection criteria for reference agencies, the level of detail agencies would like, how the reference agency reports are used and how these are seen to enable the review, and the potential barriers for agencies in undertaking abridged reviews. Although this research is a valuable first step, to move forward with the development of an

abridged review framework it is important to gain more clarity from agencies on what is reviewed and to what depth.



References:

[1] CIRS workshop (2018) Practical implementation of reliance models: what are the barriers and facilitators to the successful application of these models for innovative medicines, generics and variations? South Africa, 7-8 March 2018.

Trust is the key to reliance models – how is this being developed across agencies and what are the main elements of a trust paradigm?

Dr Tomas Salmonson, *Partner, Consilium Salmonson & Hemmings and Former Chair, CHMP, EMA*

Trust can be defined as reliance on the character, ability, strength or truth of someone or something; if you trust someone, you believe that they are honest and sincere and will not deliberately do anything to harm you. The regulatory agency delivering the assessment report, the sponsor and the regulatory agency relying on the assessment report, all have a responsibility for building trust.

Reliance models are in the interest of public health and safety and trust in the initial assessment is essential for reliance to function properly. The agency that carried out the initial assessment has a responsibility to explain its legislation, procedures, public health role, scientific standards including adherence to guidelines and use of expert working groups, structure of internal assessment teams, decision making process and benefit-risk structure. Transparency is essential and can be facilitated by providing a comprehensive assessment report, being open about subjective judgements and giving relying agencies opportunities to ask questions or to follow an individual application through the assessment process.

The sponsor should have a prospective approach to reliance e.g. by allowing the relying agency to follow the initial review of a selected application. The entire final assessment report (and earlier versions) should be made available as well as any updates made to the application and details of scientific advice, paediatric development plans, orphan status or conditional marketing authorisations.

The receiving agency has a responsibility to invest in the reliance model and obtain internal buy-in. Scientific leadership is important as well as a structure to decide and document the level of reliance in individual applications. Training and scientific support should be provided to assessors, who may be uncertain about how to conduct the review due to questions about the initial assessment or the degree of review required. Reliance models should be used frequently to ensure internal commitment and sustainability.

In summary, trust is essential for reliance and once it is established, it must be maintained. To move forward with reliance models, all stakeholders must accept responsibility in creating trust and recognise the challenges around complex scientific assessments and subjective conclusions.

All involved have responsibility for building trust

The agency initially reviewing the application	Applicant	The receiving agency
Legislation and procedures. Public health role and responsibilities.	Allow a "prospective" approach	Invest in the reliance model – expect internal resistance
General scientific standards	The entire final assessment report plus earlier versions made available	Training, including why we rely on the work of other agencies?
Assessment teams and quality assurance	Updates made to the application	Scientific support to the assessors
Decision making process	Scientific Advice	Frequent use of the reliance model
B/R structure, policies e.g. wording of the indication	Paediatric development plans, orphan status, Conditional Marketing Authorisation	Maintenance of trust
Transparency		

Developing the WHO Good Reliance Practice Guideline

The need for a global guidance – workplan and objectives

Dr Samvel Azatyan, *Group Lead, Regulatory Systems Strengthening Team, WHO, Switzerland*

Globally, 30% of National Regulatory Authorities for Medical Products (NRAs) have limited capacity to perform core regulatory functions. There is a regulatory capacity gap between low- and high-income countries in terms of human and financial resources, regulatory functions effectively performed, expertise available for fulfilling regulatory functions, availability of proper systematic training for regulators and applying quality management principles. For example, a WHO study of 26 African regulatory systems demonstrated that guidelines and assessment procedures are not up to international standards and are often of an administrative rather than technical nature [1]. Despite resource constraints, only few countries relied on decisions made by more stringent regulators or by WHO, and some countries even had restrictive regulations not allowing reliance.

Although NRAs are mandated in their jurisdictions to ensure timely access to safe, effective and quality medical products in line with international standards, there is no clear vision or policy about how to set up regulatory systems in times when it is unrealistic to manage all functions in one national setting for most regulators. This is especially challenging as new products become more complex and sophisticated. Several International Conferences of Drug Regulatory Authorities (ICDRA) meetings have highlighted that desired public health goals can only be achieved through collective efforts of regulatory and other stakeholders.

A regulatory framework made up of a system of laws, regulations and guidelines is essential for protecting and promoting public health, though the degree to which it is implemented and fulfils policy objectives is equally as important. For this reason, the WHO is developing a system called Good Regulatory Practices (GRP), which – if implemented - will lead to higher quality regulation, improved decision-making increased efficiency of regulatory systems and better public health outcomes. One element of GRPs will be a guideline on good reliance practices, which is intended to a be a practical instrument promoting strong regulatory cooperation, convergence, harmonisation, work-sharing, reliance and recognition. This will facilitate regulatory authorities to move up the regulatory cooperation hierarchy.

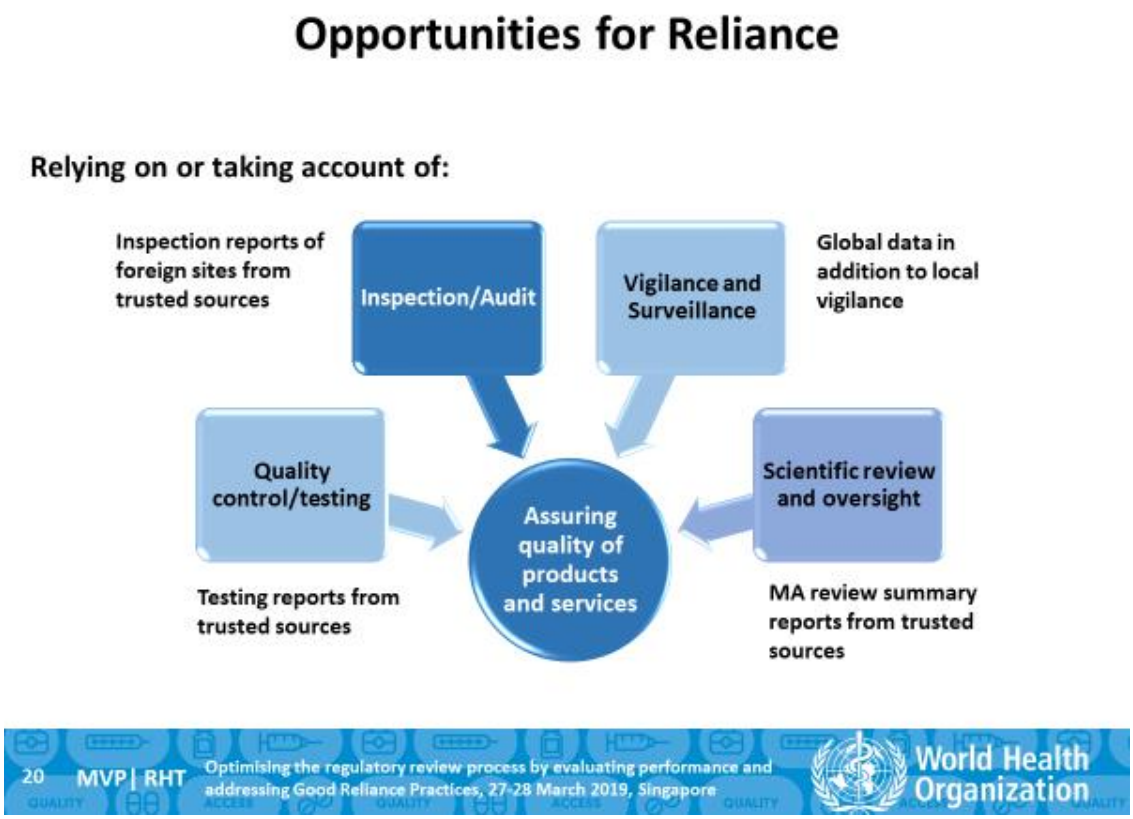
There are several key principles that should be followed for information and work sharing models:

- Outcome orientation: efforts should lead to measurable public health gains.
- Operational flexibility: one approach may not be appropriate for all situations.
- Pragmatism: employing a stepwise approach that builds on successes and lessons learned.
- Utilising best international practices: importance of common requirements and approaches based on international best practices and standards, such as the Common Technical Document (CTD), in achieving optimal outcomes.
- Accountability: the work needs to be planned and staffed appropriately and the outputs need to be implemented consistently, predictably, and transparently.

Reliance and recognition are frequently used terms that sometimes lack formal definition. Reliance is defined as the act whereby a regulatory authority in one jurisdiction may take into account and give significant weight to evaluations performed by another NRA or other trusted institution for reaching its own decision. Recognition is the routine acceptance by the NRA in one jurisdiction of the regulatory decision of another NRA or trusted institution. While reliance models are about streamlining or reducing internal workload, recognition is an operational replacement, where internal work is replaced with that done by someone else. However, in both cases, the sovereignty of decisions remains in the hands of national regulators.

Some elements of regulatory oversight can be shared through reliance, such as evaluations of quality, efficacy and safety, inspections and testing. For example, inspection reports of foreign sites from trusted sources could be relied on for inspection/audit purposes. However other elements must be local, including licensing decisions, local manufacturing oversight, pharmacovigilance, appropriate distribution controls and product security.

In summary, we are faced with a changing regulatory paradigm, where regulators are starting to operate more as a functional network rather than individual players focusing on where they can give the best added value. Since it is becoming increasingly difficult for a single regulator to fulfil all regulatory work alone, the future of medical products regulation must be in convergence/harmonisation, collaboration and networking based on reliance.



References:

[1] WHO (2010) *Assessment of medicines regulatory systems in sub-Saharan African countries: an overview of findings from 26 assessment reports*. [Accessed 25 February 2020]. Available at: http://apps.who.int/medicinedocs/en/m/abstract/Js17577en/

Developing the WHO Good Reliance Practice Guideline

Components of the Good Reliance Practice guideline and the identifying principles of reliance practices

Dr Lim Sok Bee, *Senior Associate, the Duke-NUS Centre of Regulatory Excellence (CoRE), Singapore*

The purpose of the WHO Good Reliance Practices (GRelP) guideline is to facilitate the implementation of a systematic and optimised framework where reliance approaches can be effectively and consistently applied by NRAs to minimise duplication of effort, improve efficiency and achieve intended goals with reasonable time, effort and cost. The GRelP will be incorporated as an annex to the WHO Good Regulatory Practices guideline and its scope will cover pharmaceuticals, including small molecules, biologics and vaccines, clinical trial applications, product applications and post-approval activities.

There are six principles of GRelP (see below), the first being to uphold the role, responsibilities and authority of the NRA. The NRA should be transparent, efficient and accountable for ensuring that the approved medical product is of the required minimum safety, efficacy and quality standards. However, it should also maintain the flexibility to request additional information to reach a locally relevant benefit-risk decision.

The second principle of GRelP is to support regulatory convergence. Technical regulatory requirements of NRAs need to be similar or aligned before reliance on each other's regulatory assessment/decision can be confidently undertaken. The adoption of internally recognised technical guidance, standards, terminology and registration formats will facilitate alignment and also promote better communication between NRAs.

Evidence-based decision-making is the third principle of GRelP. Reliance models support evidence-based decision making because the relying agency is either partially or totally relying on the scientific risk-based assessment that has been performed by the reference NRA. This aids the development of a scientifically justified decision by the relying NRA that is impartial and avoids conflict of interest.

Consistent communication along the entire decision-making process is the fourth principle of GRelP. The reliance model adopted should be applied consistently throughout the entire regulatory decision-making process by the relying NRA, who needs to have a proper understanding of the concerns and limitations of the source report. Factors contributing towards the final decision of the reference NRA should not be taken out of context to suit the needs of the relying NRA.

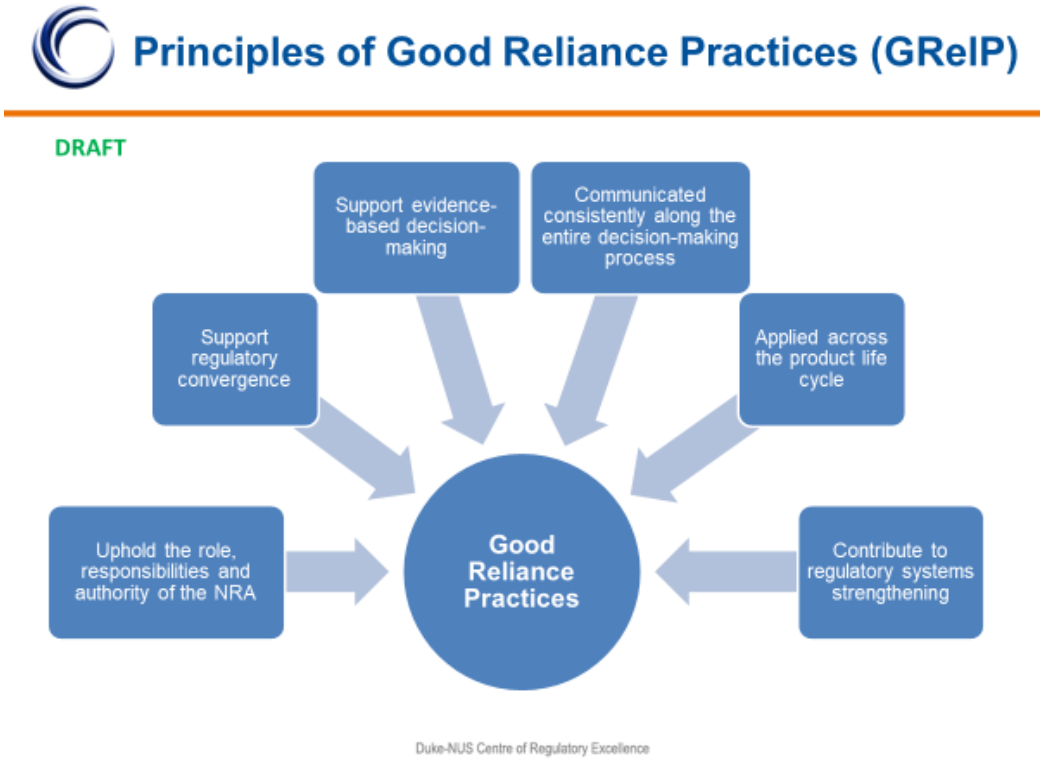
The fifth principle of GRelP is to apply reliance approaches across the product lifecycle. This will support post-approval functions required to mitigate the risks associated with a reliance approach and monitor the robustness of the initial marketing approval decision with respect to the local population. For example, post-marketing pharmacovigilance signals that have been picked up by the source reference country may be required to complement the pre-market decision that was referenced upon.

The final principal of GRelP is to contribute to regulatory system strengthening. Reliance practices are a tool to develop the regulatory capabilities of an NRA and provide opportunities for NRAs to review their local technical assessment capabilities to that of reference NRAs. However, NRAs are still required to develop and maintain their technical regulatory capabilities in the various reliance models, to check for conformity, and to adapt to local circumstances and idiosyncrasies when necessary.

In addition to the six principles, the GRelP guideline will include information on models of reliance and infrastructure for their implementation. Possible models will include mutual recognition, referencing decisions using unredacted assessment reports of other NRAs, work sharing and joint assessments.

Supportive infrastructure will cover legal and regulatory frameworks, communication with stakeholders, capacity building and existing platforms and partnerships.

The GRelP guideline is in the first stage of development and feedback from NRAs and industry is continuously being gathered. The next step will be to revise and release the draft guideline for public consultation. Milestones for implementation are yet to be confirmed, but proposed milestones include communication with stakeholders, gap analysis of infrastructure required for implementation of GRelP by an NRA, development of curriculum and training materials, identification of trainers and training organisations, and training of NRAs (with some activities being conducted in parallel).



Post approval needs and reliance models: the role of Smart Safety Surveillance as a shared responsibility?

International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) viewpoint

Dr David Jefferys, *Senior Vice President, Global Regulatory, Government Relations, Public Affairs and European Product Safety, Eisai Europe Ltd, UK, and Chairman of the IFPMA Regulatory Science Committee*

Post approval support is fundamental to establishing trust and delivering the benefits of reliance models. Global and regional initiatives such as the ICH implementation training programme and WHO Global Benchmarking Tool are a key part of reliance building. Industry also have a role in this area and should consider complementing the IFPMA Good Regulatory Submission Practice document with something on reliance.

While most low- and middle-income countries (LMICs) have an established national pharmacovigilance centre for data collection, which feeds into the WHO Safety Database, there is often limited reporting and a low local capacity/capability to analyse the data collected. Furthermore, only a small number of national regulatory authority have the capacity/capability to act on alert signals received (3 in 55 countries according to a 2008 survey by WHO).

These existing pharmacovigilance challenges in LMICs are being exacerbated by an evolving product landscape. New vaccines, drugs and diagnostics are increasingly being specifically developed for LMICs, meaning that these countries can no longer rely on safety surveillance of developed economies. Moreover, safety data packages for developed economies may not be relevant for LMICs due to differences in benefit-risk profiles, concomitant diseases and medications. This has significant implications for patient risk, product risk, delaying access to market, reputational/ethical risk, and systemic risk to global health.

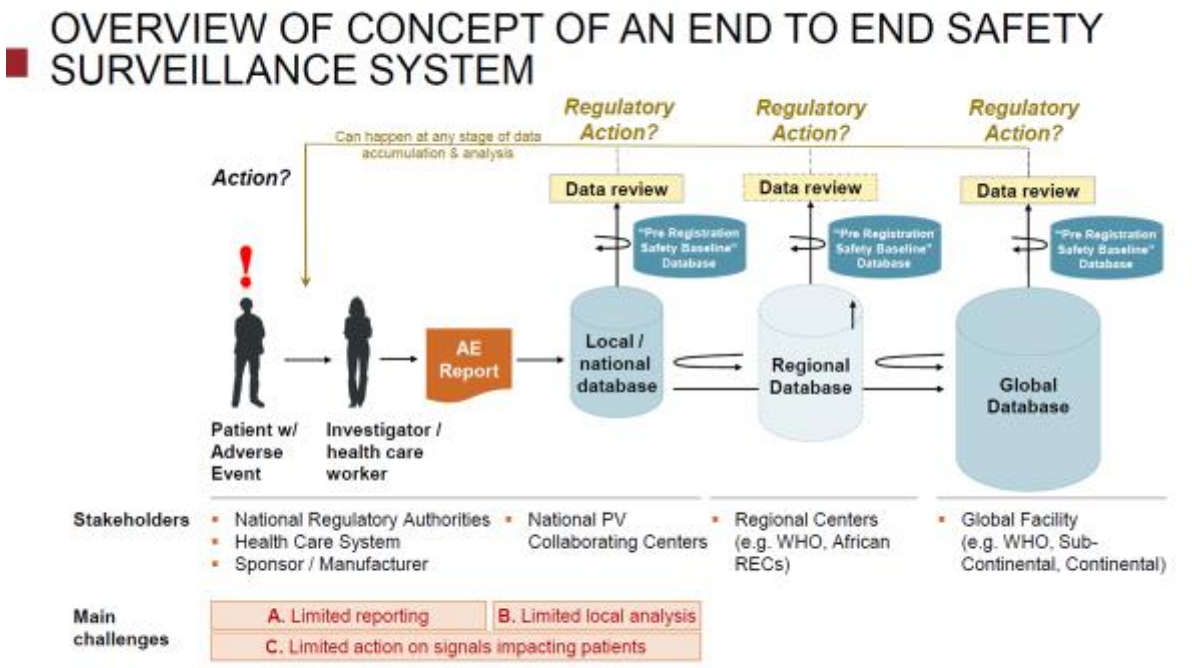
The Smart Safety Surveillance (3S) initiative is part of a Bill and Melinda Gates Foundation approach to build pharmacovigilance capacity in LMICs and in the long-term, establish end-to-end safety surveillance of products from their clinical development to the post market stages. 3S was formed as a partnership among manufacturers, cooperative groups and regulators. The vision of 3S is to ensure real-time and adequate reporting, review and action on adverse events in LMICs where priority global health products will be introduced. One of its key principles is to support strategic capacity building through convergence and mutual reliance of resources where pertinent. Although 3S focuses on LMICs, its learnings should be relevant to all countries' post-marketing surveillance systems, which all have their own issues.

The WEB-RADR app is an example of a project to move pharmacovigilance forward in Africa. The app enables patients, caregivers and healthcare professionals to report adverse drug reactions and receive up-to-date information and news alerts. A generic multi-country version of the app, called Med Safety, is now available for wider adoption.

Delayed post marketing changes are burdensome for both industry and LMICs and contribute to drug shortages. For example, for some vaccines, companies may have to cover or carry forward dozens of different inventories because of the delays in some countries in processing post-approval changes that have occurred. This is costly to industry and damaging to public health, as the latest products are not available in these countries. Industry play a part in these extra demands/costs by making numerous post-approval changes in terms of Chemistry, Manufacturing and Controls (CMC), and so should carefully consider whether all of these changes are necessary.

In summary, we need to be making innovative drugs available earlier to LMICs and delivering programmes for universal health coverage by addressing regulatory capacity issues and drug shortages.

However, reliance models cannot be fully accepted until post marketing concerns - both in terms of pharmacovigilance and post-authorisation changes – are addressed.



Panel discussion: Reliance review – reflections on a life cycle approach

Regulatory Viewpoint - Prof Hans-Georg Eichler, *Senior Medical Officer, EMA*

Industry Viewpoint – Dr Susan Forda, *Vice President, Global Regulatory Affairs International, Eli Lilly and Company, UK*

CIRS Viewpoint – Dr Lawrence Liberti, *Executive Director, CIRS*

Gates Viewpoint – Dr Murray Lumpkin, *Deputy Director, Integrated Development, Bill and Melinda Gates Foundation, USA*

Summary of key points:

- Learning about a product does not end of on the day of licensing so we must plan proactively.
- A life cycle approach is mostly about developments in clinical information, though quality aspects are also important.
- The shift to post licensing activities will increase workload for regulators, which in turn will drive reliance in all countries (not just LMICs).
- Real world data is context dependent so will require extrapolation and more transparency from source agencies regarding how the drug was used in their country.
- Reference agencies do not necessarily have a legal or moral obligation to enable reliance, but every regulator should be so transparent that anyone else can reproduce and understand what was done and decided.
- Chemistry, Manufacturing and Controls (CMC) aspects should be part of a life cycle approach.
- Complexities in supply chains can create significant time lags between first and last approvals.
- There is a need for more convergence in terms of CMC to help get medicines to more patients quicker.
- Ratings using the WHO Global Benchmarking Tool are a baseline measure of comparable capabilities, which is one characteristic of trust but also requires 'softer' metrics related to relationships.
- Trust is about describing processes through a culture of performance measurement as well as being able to assess the judgement mechanism and decision-making practices used by an agency.
- Reliance occurs when there is an asymmetry of capacity and capability, whereas recognition is based on outsourcing a decision, where the balance is equal. As maturity levels increase across agencies, the balance could shift and use of recognition increase.
- Reliance enhanced life cycle management (RELM) brings together clinical variations, CMC, pharmacovigilance, post approval commitments and real-world evidence. This concept could be developed further by CIRS as part of its focus on facilitated regulatory pathways.
- Reliance is not a new concept – the Certification of Pharmaceutical Product (CPP) was one of the earliest forms of reliance. There are concerns around whether the CPP is still fit-for-purpose and these should be investigated further by speaking to different countries.
- Reliance exists in several forms, including work sharing and joint assessments. These can operate across the life cycle e.g. the joint assessment of clinical trial applications in Africa, the WHO prequalification collaborative process.
- We must be realistic about what real world data could achieve in LMICs and in the case of longstanding products, we must maintain focus on the issue of product quality. However, for new innovative products that are being developed specifically for LMICs, real world data could be an opportunity to address the lack of pharmacovigilance infrastructure – how could we create an active surveillance programme where information gathering is incorporated into rollouts?

SECTION 3: ROUNDTABLE DISCUSSIONS

Roundtable Discussion A

How can agencies embed a culture of performance measurement and how can the results be used in practical ways to optimise performance?	
Chair	**Dr Siu Ping Lam,** *Director, Licensing Division, Medicine and Healthcare products Regulatory Agency (MHRA), UK*
Rapporteurs	**Kwame Asamoah-Okyere**, *Principal Regulatory Officer, Food and Drugs Authority, Ghana* **Dr Elvira Heyartz,** *Vice President, Regulatory Affairs Asia Pacific, Johnson & Johnson Pte Ltd, Singapore*

Background

To meet their mission to protect and promote public health, regulatory agencies around the world are exploring ways to improve patient access to quality medicines, particularly access to innovative medicines that address unmet medical needs. In large part, this access is being expedited through the convergence of technical and procedural guidelines and through the creation of flexible regulatory pathways and reliance-based reviews.

Agencies are also proactively striving to improve their effectiveness and efficiency by embedding the use of systematic structured approaches with quantitative metrics to better understand their performance and to identify where sponsor and agency time is spent in the regulatory process. These approaches allow agencies to identify relevant strategies for internal improvement as well as to provide them with factual information that can:

- encourage adherence to processes that support the mandates of the agency
- enable process improvements and opportunities for work optimisation without compromising product safety, efficacy or quality
- allow the setting of realistic and attainable targets
- monitor improvement initiatives
- help to better convey an agency's mission and needs to internal staff, policy makers and external stakeholders including patients, healthcare providers and companies.

Monitoring performance requires agencies to have a clear understanding of their processes and identifiable and trackable milestones within those processes and to conduct ongoing, systematic assessments of the processes on a continual basis. Therefore, agencies need to embed a culture in which performance measurement is at its core, requiring changes to internal mindsets and practices.

As agencies look to embed a culture of performance measurement there needs also to be alignment around at least three other considerations: 1) a **strategy** must be agreed for measuring and improving performance that is aligned to agency mission and objectives and that is relatable and relevant for staff; 2) **people** within the organisation must demonstrate a commitment and accountability to performance measurement through their behaviours; and 3) **processes** must be in place that are fit for purpose to understand, measure and manage agency performance. The question and focus for this Roundtable is how can agencies embed a culture of performance measurement and how can the results be used practically to optimise performance?

Questions for consideration

1. Why is it important to embed a culture into agencies in which the approval process is continually measured? What is in it for the agency and for other stakeholders, such as policy makers, companies and patients?
2. What would a successful culture for measuring the approval process look like; that is, what processes and mechanisms should be in place?
3. What strategy, people and processes needs to be in place at an agency to embed a culture of performance measurement for the approval process?
4. What are the potential barriers to building a performance measurement culture within agencies and how can these be best overcome?
5. Do companies have embedded cultures for measuring performance and if so, are there any lessons for agencies?
6. What are the practical ways in which an agency can use an embedded performance culture to optimise their performance?
7. What training is required for regulators to change internal mindsets in order to build a culture of performance measurement? What would be important components that any training programme would need to consider?

Discussion results

It is essential to have a data-driven culture that collects and uses metrics so that actions can be taken to improve processes and performance. Developing such a culture requires an inclusive and positive approach, focusing on incentives rather than penalties. Change management can be challenging but training should help to change mindsets and engage people on the importance of measurement and the impact it has on patient access to treatments.

Key Performance Indicators (KPIs) are important for maintaining accountability and transparency and should be impactful and fit-for-purpose. Collaborations with external stakeholders will help to determine KPIs but potential ones could focus on quality and timelines.

For reliable metrics collection, it is important to have a quality management review system. Internal audits are required to check and verify the data that is being collected and analysed.

Other critical issues identified related to training, capacity building and resources. Technical training is important for understanding processes, innovation and regulatory science but other types of training are also needed to improve competencies and embed a new culture where regulation is about patient access to medicines, in addition to the quality and efficacy of medicines. Taking advantage of ongoing initiatives, such as with WHO and CIRS, will aid development and build capacity. However, agency resources, budget and independency in terms of decision making, could be significant barriers to growth.

Recommendations

- Agencies should have a **system** in place to collect data for identified metrics agreed with different stakeholders and integrated in the daily work.
- Agencies should develop a **culture** to incorporate standard processes and metrics, improve processes, analyse resources and encourage a mindset that takes responsibility for patient access to medicines. **People** performance management should include goals, objectives and accountability.

- CIRS, WHO or CoRE should work on the **standardisation** of metrics for the approval process in order to have common framework and language and facilitate benchmarking across agencies and develop relevant metrics based on local country processes.
- Agencies and pharmaceutical companies should ensure **transparency** through tailored regular publication on performance metrics as agreed by stakeholders.

Roundtable Discussion B

Codification of trust – how can we codify trust and how can good reliance practices build on this trust?	
Chair	**Dr Patrick Stewart,** Director General, Therapeutic Products Directorate, Health Canada
Rapporteur	**Fraser Stodart,** Senior Director – Head of Emerging Markets (Regulatory), Biogen, UK

Background

A reliance model is defined by WHO as *"*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." A number of reliance models have been established such as the WHO prequalification process, regional and consortium work sharing and individual agencies' regulatory verification and abridged review pathways. These processes vary, depending on whether the medicines have already been reviewed by one or more comparable or reference agencies. The key to reliance is trust between agencies and access to trusted reports from reliable sources. However, there are still potential barriers to reliance for agencies to overcome including the lack of a legal framework, secure IT platform or the national/regional political will.

At the CIRS workshop on the practical implementation of reliance models in South Africa in 2018, Syndicate discussion participants agreed on the following points:

- Although trust is built through relationships, government policies should also reinforce trust building.
- Trust building should also be regarded as an institutional goal with defined criteria that acknowledge and codify trust building as a long-term learning process that entails an acceptance of failure risk.
- Dialogue, communication and transparency within and across agencies are key to successful trust building and trust must be built among all stakeholders.
- Industry and agencies can build trust through early dialogue in which the parameters of compliance and liability and a secured environment for information sharing are established.
- Regulatory authorities can build trust with each other through the convergence of regulatory requirements and the use of common approaches (e.g., good review practices).
- A fair balance should be established between trust givers and accepters and reciprocity in active or passive roles should not be a condition of the development of trust among stakeholders.

Finally, the group in South Africa questioned the criteria or areas that need to be aligned that will help build trust between agencies and made a recommendation that constructive benchmarking could be established to measure the elements of trust in current systems.

Trust is defined as the firm belief in the reliability, truth or ability of another. The definition of trust and the identification of trusted parties in the context of reliance models could be based on the answers to questions in three main areas: 1) **competency;** that is, do the reference agencies have the skills, knowledge, and experience? 2) **reliability**; that is, is the reference agency consistent in its approach and decision making? 3) **alignment**; that is, are the reference agency's mission and objectives aligned with the agency using the reliance model? What can and should be codified and documented in these three

areas to provide clarity to patients, healthcare providers and policy makers regarding the context in which agencies establish reliance mechanisms for review? Therefore, the question and focus for this Roundtable is can there be a codification of trust and how can good reliance practices build on this trust?

Questions for consideration

1. As agency-to-agency and agency- to-sponsor trust is the foundation of any reliance model, should trust be codified and what are the implications if it is not?
2. What are the main advantages and disadvantages for the codification of trust as it pertains to leveraging another agency's approval?
3. What are as the main domain areas that can be formally codified for an agency to rely on or have trust in another agency? Please consider areas such as risk tolerance, similarities in objectives and goals, alignment of standards and technical guidelines, capability is comparable or higher, predictability in review process and integrity of decision making, transparency in communication regarding processes and decision making.
4. What are the main domain areas that can be formally codified for an agency to rely on or have trust in a sponsor's submission?
5. How does the use of independent agency assessment such as WHO GBT help inform confidence in a peer or other comparable agency?
6. What are the potential barriers to building agency-to-agency and agency-to-sponsor trust and how can these be best overcome?
7. Should a one-size-fits-all reliance model be used or should there be a set of different criteria depending agency maturity level or resource constraints? If yes what might this look like?
8. How can good reliance practices build on the codification of trust? What needs to be put in place within companies and agencies to enable utilisation of reliance models?

Discussion results

While it is possible to codify trust, there are likely to be some subjective elements to consider, for example, how do we define good judgement? Codifying trust is unlikely to be 'black and white' and there will be nuances to consider, which could make it difficult to document. In addition, trust is not absolute and continuously evolves (for good or bad), so would need constant monitoring.

Establishing trust takes place on two levels, which can be developed in parallel. One level is based on the knowledge of how each agency works, including 'hard' elements like infrastructure, legislation, process/quality systems, capability and capacity. The other is based on 'softer' elements such as the relationships between agencies and how they work together outside their infrastructures. Cross cultural considerations are also important in building trust.

WHO guidance and benchmarking tools help to install confidence between agencies, but there also needs to be an understanding of how WHO assessed and came to these recommendations. This needs to be widely shared and endorsed by governments and recipient agencies.

Although trust is dependent on agencies' capacity and expertise/experience, it is not logical to 'shop' for individual components of assessment e.g. toxicology, clinical, non-clinical. Reliance should depend on the output/outcome of only one agency.

Sponsor companies have an important role in reliance models and there has to be trust that the agency providing the assessment report has assessed the same dossier as the receiving agency. Agencies should have discretion on the level of trust placed in the sponsor company. While companies must

commit to full transparency and provision of full documentation, they also need to be given the confidence that confidentiality is maintained by agencies, as IP is inevitably a concern.

Recommendations

- Agency goals should always be to protect the public good and make best use of local resource and capacity. Local decisions supported by reliance model should be defendable to the public.
- Reliance models between agencies should be based on a trust “triangle” that also involves sponsor companies. This has not been explicit in the discussion to date and so should be considered for inclusion in the good reliance practice guidance document.
- Provision of full documentation is hindered by concerns about future lifecycle activities – further discussion on regulatory strengthening and alignment is required. Return on investment, market access and supply are impacted by lack of common guidance.

Roundtable Discussion C

The draft good reliance practice guideline – How practical is it? A stakeholder review and discussion	
Chair	**Asst Prof James Leong**, *Head of Pharmaceutical Regulatory Science Programme, Centre of Regulatory Excellence, Duke-NUS Medical School*
Rapporteur	**Andrea Keyter**, *Deputy Director, Medical Devices, South Africa Health Products Regulatory Authority (SAHPRA)*

Background

A reliance model is defined by WHO as *"*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.*"* A number of reliance models have been established such as the WHO prequalification process, regional and consortium work sharing and individual agencies' regulatory verification and abridged review pathways. These processes vary, depending on whether the medicines have already been reviewed by one or more comparable or reference agencies. Reliance is gaining recognition as a regulatory pathway and for many agencies it is no longer a question of if they should use reliance models as part of their investment in smart regulation, but when and how. The movement toward regulatory reliance has also resulted in highlighting the need for stronger post-market activities at the local level.

As more agencies consider reliance pathways, good reliance practices, defined as *"practices that facilitate the implementation of a systematic and optimised framework by national regulatory agencies where reliance approaches can be effectively incorporated and consistently applied to minimise duplication of work"* are in the process of being developed. As the regulatory reliance practices would be considered new or require incorporation into an existing regulatory framework, successful adoption of reliance models should address practical concerns from the relevant stakeholders.

This group sought input from regulatory authorities and companies and focus on a discussion of practical considerations to assist authorities in the successful implementation of good reliance practices and related processes into their organisations.

Questions and issues for consideration

Priorities and processes to consider for implementation of regulatory reliance models

1. To establish reliance practices in a regulatory authority, what processes in regulatory decision-making should be considered as entry points to implement such models?
2. Relating to the product life cycle, should the initial implementation of reliance practices focus on:
   a. market approvals/pre-market activities OR other phases of the life cycle (please specify)
   b. new medicines/innovations OR generics

   Please provide reasons supporting your choices
3. Discuss the advantages and disadvantages of initiating reliance practices for market approvals/pre-market activities

Practical challenges and solutions in implementing reliance practices

4. Specific to market approvals of new medicines and new clinical uses, identify key operational or process-related challenges to utilising any reliance models
5. Propose pragmatic solutions to address the challenges identified in C4, including the consideration of time to achieve observable outputs
6. If training is required, specify what topics should be considered as priority subjects

Strategies to initiate practical steps

7. For the solutions in issue 5, list the resources (including any potential partners) required.
8. Discuss to whom and how the needs and solutions should be communicated, to ensure suitable follow-ups

Discussion results

The underlying principles of good reliance practice are to uphold the role, responsibilities and authority of the regulator, support regulatory convergence, support evidence-based decision making, communicate consistently along the entire decision-making process, apply across the product life cycle and contribute to regulatory system strengthening. There needs to be infrastructure for implementation such as a legal and regulatory framework, consistent communication with stakeholders, capacity building, and existing platforms and partnerships.

In order to assess the practical challenges and solutions in implementing reliance practices, we need to have a clear understanding of why and how National Regulatory Authorities (NRAs) are using reliance. It could be an attempt to free up resources when there are capacity constraints, or it could be due to a lack of expertise to evaluate a certain type of product. Qualifiers for reliance are that the full dossier and unredacted assessment report must be made available by the reference agency, and that the product must be identical to that in the reference country. Drawing on the experience of NRAs who have implemented reliance pathways is crucial; so far this has revealed that only a small number of submissions qualify, as there are often difficulties in obtaining the full unredacted assessment report. It is also important to have an understanding of what relying NRAs are currently evaluating e.g. are there parts of the reference agency's assessment report that are ignored or considered important? Are there differences in the way NRAs apply reliance in the evaluation of different types of products e.g. generics, New Chemical Entities (NCEs), biologics?

When considering the implementation of reliance, it's important to recognise that the regulatory decision is always country specific. Therefore, the relying NRA must have the in-country infrastructure to support the registration of the product, which in the case of accelerated or conditional approvals, may include post approval commitments made by the sponsor. However additional resources gained through reliance activities could be used to support strengthening of post marketing activities and surveillance.

Another challenge in implementing reliance is resistance from local manufacturers, who often believe that preference is given to multinational companies. Maintaining a dialogue with local manufacturers is key to demonstrating that reliance will help to free up NRA resources, which could then be focused on local products.

Practical next steps for implementing good reliance practices should be to develop a communication strategy to assist with internal and external stakeholder engagement and ensure transparency. It is critical to have buy-in from all parties and to communicate what the criteria will be for a qualifying product and what the evaluation criteria will be when applying the reliance pathway. Developing a checklist of evaluation criteria for reliance could also be a useful way to support transparent communication with sponsors.

Quality management system development would also be useful as it provides a framework for transparency and accountability by supporting consistent, predictable decision making. English proficiency should not be assumed within agencies so it is important to consider potential language barriers and whether translations may be required.

Recommendations

- Use a phased approach with an entry point for implementation of the good reliance practice guideline.
    - Use GMP inspection and CMC reports to confirm the quality of the product; this low-hanging fruit supports the implementation of reliance pathways to ministers and politicians.
    - Consider moving toward acceptance of reliance pathways over time.
- Consider requesting from the sponsor a summary of the reference agency's benefit-risk assessment.
    - Module 1
    - 2.5.6 – Benefit/Risk
    - Transparency in terms of findings made by reference agency and motivation by sponsor in support of these concerns
- Perform a formal study to understand what NRAs who have implemented reliance pathways are currently evaluating.

Roundtable Discussion D

Assessing the implementation of and adherence to good reliance practices – What would informative key performance indicators look like?	
Chair	**Dr Samvel Azatyan,** *Group Lead, Regulatory Systems* Strengthening Team, WHO, *Switzerland*
Rapporteur	**Ehab Taqiedden,** *Head, Regulatory International Operations, Roche, Singapore*

Background

A reliance model is defined by WHO as *"*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*."* A number of reliance models have been established such as the WHO prequalification process, regional and consortium work sharing and individual agencies' regulatory verification and abridged review pathways. These processes vary, depending on whether the medicines have already been reviewed by one or more comparable or reference agencies. Reliance is gaining recognition as a regulatory pathway and for many agencies it is no longer a question of if they should use reliance models as part of their investment in smart regulation, but when and how. The movement toward regulatory reliance has also resulted in highlighting the need for stronger post-market activities at the local level.

As more agencies consider reliance pathways, good reliance practices (GRelP), defined as *"practices that facilitate the implementation of a systematic and optimised framework by national regulatory agencies where reliance approaches can be effectively incorporated and consistently applied to minimise duplication of work"* are in the process of being developed. In parallel to the development of GRelP, it is important to consider measures or key performance indicators, defined as *"*quantifiable measures used to evaluate the success of an organisation in meeting the objectives*."* In this case, the objectives would be the implementation of and adherence to GRelP.

The development of the GRelP is the subject for Table 3, Group C, whilst this group should focus on discussing key performance indicators that will assess an agency's implementation of and adherence to GRelP as well as establishing baseline indicators that will enable a periodic assessment after implementation of reliance-based models to assess effectiveness.

Questions for consideration

1. What are the areas of **implementation of** GRelP that would be amenable to being measured; that is, the areas that should be considered for monitoring the progress of the **incorporation of** reliance processes or practices into the existing regulatory framework or decision-making procedures? Please consider both qualitative and quantitative measures.
2. What are the areas of **adherence to** GRelP that would be amenable to being measured; that is, the areas that should be considered for monitoring or assessing **compliance with** reliance processes or practices into the existing regulatory framework or decision-making procedures? Please consider both qualitative and quantitative measures.
3. Which of the above measures should be considered as key performance indicators by the agency and other stakeholders such as patients, policy makers and sponsors for implementation and adherence?

4. Should there be a one-size-fits-all approach or should there be a set of fit-for-purpose key performance indicators, depending on the type of reliance model, agency maturity level or resource constraints? If yes, what are the considerations in selecting the most appropriate set of key performance indicators?
5. What roles do companies play in enabling the implementation and adherence to GRelP? Are there any key performance indicators that should be utilised to measure a company's role and should these align to good regulatory management practice guidelines?
6. What processes and mechanisms should be in place by agencies or other stakeholders to both measure and communicate the implementation and adherence to GRelP?
7. What are the potential barriers for agencies to implementing KPI and how can these best be overcome?
8. What training is required for regulators to implement KPI? What would be important components that any training programme would need to consider?
9. Please discuss and identify potential measures that could be used after implementation of a reliance-based model to assess effectiveness of model being used.

Discussion results

Before measuring the implementation of GRelP, we must first investigate which agencies are providing a reliance pathway and whether it is codified. We must also find out the reasons why some agencies do not have a reliance pathway, for example is there legislation prohibiting it.

GRelP should apply to all countries and to all products throughout their life cycle. Both regulators and industry have a mutual responsibility to successfully implement reliance. There should be a transparent mechanism to inform stakeholders of how reliance pathways are being used and report on some of the metrics and KPIs. This could be through annual reports, for example.

It is essential to have measurable KPIs that assess compliance and adherence to the reliance framework. Timelines associated with the reliance framework should be established and then adherence to those timelines measured. For industry, the number of questions, number of cycles of questions, or quality of the questions from agencies would be a good indicator of the impact of GRelP. It will also be important to measure the approval of priority products using a reliance pathway versus a standard pathway, to see if reliance is being used to facilitate access to highly needed medicines. In addition, the total number of products approved by reliance pathways should be measured, which would give an indication of whether efficiency is increasing i.e. is there an increase in the number of products approved with same resource pool?

Recommendations

- Agencies should ensure a dynamic pathway of reliance for registration for all products throughout the product life cycle. These pathways should be codified in country legislation in all countries where regulatory improvement could occur.
- Agencies and industry share mutual responsibility to successfully implement reliance, including the provision of a transparent mechanism to enable reporting on the use of reliance pathways, such as through annual reports.
- Measurable KPIs are required to assess compliance to and impact of reliance frameworks, including established timelines, measurement of the number or cycles of questions from reliance assessments, the use of reliance to review priority products, and the increase in the number of reviewed products.

APPENDIX: WORKSHOP ATTENDEES

Regulatory agencies and independent consultants		
Dr Denize Ainbinder	*Head of Drug Registration Department*	*Ministry of Health, Israel*
Dr Mario Alanis	*Independent Consultant*	*Mexico*
Dr. Dra. Rizka Andalucia	*Director for Drug Registration*	*National Agency of Drug and Food Control (NADFC), BPOM, Indonesia*
Kwame Asamoah-Okyere	*Principal Regulatory Officer*	*Food and Drugs Authority, Ghana*
Dr Claus Bolte	*Head of Sector Marketing Authorisation*	*Swissmedic*
Prof Sir Alasdair Breckenridge	*Former Chair*	*MHRA, UK*
Agnes Chan	*Director, Therapeutic Products Branch*	*HSA Singapore*
Dr Ming-Hsiao Chan	*Director, Division of New Drugs*	*Center for Drug Evaluation, Chinese Taipei*
Ke-Hsin Chen	*Senior Specialist, Division of Medicinal Products*	*Taiwan Food and Drug Administration, Chinese Taipei*
Prof Hans-Georg Eichler	*Senior Medical Officer*	*European Medicines Agency*
Dr Paul Huleatt	*Program Management Unit Director, Indo-Pacific Regulatory Strengthening Program*	*TGA, Australia*
Dra. Reri Indriani	*Act. Deputy Chairperson for Drug, Narcotics, Psychotropics, Precursors, and Addictive Substances Control*	*National Agency of Drug and Food Control (NADFC), BPOM, Indonesia*
Andrea Keyter	*Deputy Director, Medical Devices*	*South African Health Products Regulatory Authority (SAHPRA)*
Dr Siu Ping Lam	*Director, Licensing Division*	*MHRA, UK*
Dr Penny Lukito	*Head*	*National Agency of Drug and Food Control (NADFC), BPOM, Indonesia*
Tariro Makamure-Sithole	*Chief Regulatory Officer – Human Medicines*	*Medicines Control Authority, Zimbabwe*
Ana Carolina Marino	*Deputy Manager of the Office of Inspections and Monitoring of Medical Devices*	*ANVISA, Brazil*
Preeyaporn Natehin	*Pharmacist, Practitioner level, Bureau of Drug Control*	*Food and Drug Administration, Thailand*
Tuan Anh Nguyen	*Officer of Drug Registration Division*	*Drug Administration of Vietnam – Ministry of Health, Vietnam*

Supatra Phongsri	*Pharmacist, Professional level, Bureau of Drug Control*	*Food and Drug Administration, Thailand*
Pia Angelique Priagola	*Food Drug Regulation Officer III, Center for Drug Regulation and Research*	*Food and Drug Administration, the Philippines*
Dr Tomas Salmonson	*Former Chair* *Partner*	*CHMP, EMA* *Consilium Salmonson & Hemmings, Sweden*
Renata de Lima Soares	*Advisor for the Second Directorate*	*ANVISA, Brazil*
Dr Patrick Stewart	*Director General*	*Therapeutic Products Directorate, Health Canada*
Diana Sutikno	*Head of Bureau, International Cooperation*	*National Agency of Drug and Food Control (NADFC), BPOM, Indonesia*
Dr Songmei Xie	*Deputy Director, Office of Clinical Evaluation II, Center for Drug Evaluation*	*National Medical Products Administration (NMPA), PRC China*
Dr Ramli Zainal	*Senior Director of Pharmaceutical Services*	*Pharmaceutical Services Programme, Ministry of Health Malaysia*
Pharmaceutical companies		
Mary Ann Coronel	*Director, Regional Regulatory Strategist*	*Pfizer, Singapore*
Dr Paul Dearden	*Head, International Regulatory Policy*	*AbbVie, UK*
Mei Ding	*JAPAC Regional Lead, RPI*	*AbbVie, Singapore*
Dr Susan Forda	*Vice President, Global Regulatory Affairs International*	*Eli Lilly and Company, UK*
Tarn Yeong Goh	*Regulatory Affairs Director*	*MSD, Singapore*
Maylis Guyot-Sionnest	*Regulatory Affairs Officer*	*Ipsen, Singapore*
Vicky Han	*Senior Director, Head of regulatory policy for Asia Pacific*	*Janssen Singapore*
Dr Elvira Heyartz	*Vice President, Regulatory Affairs Asia Pacific*	*Johnson & Johnson Singapore*
Dr David Jefferys	*Senior Vice President, Global Regulatory, Government Relations, Public Affairs and European Product Safety*	*Eisai Europe Ltd, UK*
Dr Tse Siang Kang	*Head of Regulatory Affairs West ASEAN/ Head of Regulatory Affairs, Singapore*	*Pfizer, Singapore*

Alexandra Kitashova	*Vice President, Emerging Market Regulatory*	*GlaxoSmithKline, Singapore*
Siew Hong Lek	*Regulatory Affairs*	*Merck Pte Ltd, Singapore*
Dr Sandra Lim	*Head of Regulatory Affairs-Asia Pacific, Pharmaceuticals*	*Bayer, Singapore*
Dr Atsuko Shibata	*Executive Director, Regulatory Affairs*	*Amgen Inc, USA*
Fraser Stodart	*Senior Director – Head of Emerging Markets (Regulatory)*	*Biogen, UK*
Ehab Taqieddin	*Head, Regulatory International Operations*	*Roche, Singapore*
Jing Ting Teo	*RA Manager, Asia*	*Sanofi, Singapore*
Akira Toyoshima	*Regulatory Affairs Lead, South East and South Asia*	*Astellas Singapore*
Sau Wei Wong	*Asia Area Regulatory Lead/ Singapore Regulatory Affairs Director*	*AstraZeneca, Singapore*
Non-profit organisations and academic institutions		
Dr Samvel Azatyan	*Group Lead, Technologies, Standards and Norms Team*	*World Health Organisation*
Yuan Chen	*Senior Program Officer*	*Bill and Melinda Gates Foundation, PRC China*
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Asst Prof James Leong	*Head of Education*	*CoRE, Duke-NUS Medical School, Singapore*
Prof John Lim	*Executive Director, Centre of Regulatory Excellence, Duke-NUS Medical School and Policy Lead, Singapore Duke-NUS Global Health Institute*	*Duke-NUS Medical School, Singapore*
Dr Sok Bee Lim	*Senior Associate*	*CoRE, Duke-NUS Medical School, Singapore*
Dr Murray Lumpkin	*Deputy Director Integrated Delivery / Regulatory Affairs - Lead for Global Regulatory Systems Initiatives*	*Bill and Melinda Gates Foundation, USA*
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Dr Neil McAuslane	*Director*
Dr Jamie Munro	*Strategy Director*
Prisha Patel	*Manager, Global Development Programme*
Professor Stuart Walker	*Founder*
Tina Wang	*Manager, HTA Programme*