Effectiveness of the regulatory approval process – moving from measuring performance to operational excellence

15-16 September 2020

Virtual meeting

WORKSHOP REPORT

CIRS Centre for Innovation in Regulatory Science

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The Centre for Innovation in Regulatory Science is a neutral, independent UK-based subsidiary of Clarivate plc. Its mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and Health Technology Assessment policies and processes. CIRS provides an international forum for industry, regulators, HTA bodies and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. It is governed and operated by Clarivate for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities and grants.

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Report date: 6 January 2021

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Section 1: Executive Summary

Background to the workshop

Regulatory authorities are already being evaluated quantitatively, from the point of view of measuring the overall time spent on the approval of new medicines, and qualitatively to assess the quality of the regulatory review process as defined by Good Review Practices. Indeed, agencies are challenged to improve the approval process and to ensure they "Say what they do, do what they say, prove it and Improve it". This in turn requires operational measures to be put in place.

CIRS through the OpERA programme is enabling agencies to embed a performance driven culture to measure where time is spent in the approval process, both their time and company time. Agencies are very focused on ensuring that the review is done in a timely manner, thereby balancing the effort vs. resource vs. cost or "doing the thing right" which relates to the efficiency of the process. However, the question for agencies when identifying areas that need improvement is how we go beyond efficiency and ensure that they are also effective (doing the right thing) focusing on the right aspects of the review and utilising the correct pathways/tools so that they are adding value to the process and the quality of the review is not being compromised. Therefore, it is important that agencies also have measures of effectiveness. This is becoming more important as agencies look to conserve resources and change review process by adding new pathways such as facilitated regulatory pathways and reliance models.

Improving agencies' performance needs a clear understanding of systems and processes in place. These could include system indicators which look at input (e.g. number of applications received), output (e.g. number of applications reviewed), performance (e.g. % approvals completed within the timeframe, resource per output (e.g. time to undertake the clinical/CMC/ safety review) and quality of the process. However, regarding an agencies effectiveness this can be perceived differently by stakeholders ie a patient perspective will differ from that of a company to that of a reviewer on what makes up an effective regulatory approval process. Indeed, the Australian government has developed a framework to measure the performance of regulators – articulating the government's expectations with overarching key performance indicators (KPIs) [1]. A company has recently published what it perceived as the 10 Hallmarks of Strong Regulatory Review Systems [2]. The question is, is there alignment and can these be of value as measures of an agency's effectiveness?

Australian Government expectations regulatory performance [1]	**Company expectations of regulatory performance [2]**
• Regulators do not unnecessarily impede the efficient operation of regulated entities. • Communication with regulated entities is clear, targeted and effective. • Actions undertaken by regulators are proportionate to the regulatory risk being managed. • Compliance and monitoring approaches are streamlined and coordinated.	• Strong support for regulatory convergence, guideline development and review • Clear structure, organisation and decision making • Effective application screening and review tracking mechanisms • Commitment to prioritisation and transparent metrics • Mechanisms for applicant-authority dialogue across the product lifecycle should be in place • Transparency on marketing authorisation review decisions

• Regulators are open and transparent in their dealings with regulated entities. • Regulators actively contribute to the continuous improvement of regulatory frameworks.	• Commitment to work-sharing, training, recognition, and reliance • Supportive Information Technology (IT) infrastructure and human resourcing • Commitment to advancing regulatory science • Support for innovation via regulatory data protection

This CIRS 2020 global development workshop brought together agencies and companies to discuss how to identify the most relevant and universal indicators of effectiveness as well as how to manage change and mindsets within agencies.

Venue

The workshop was held virtually over two days; attendees situated in Asia, Africa and the Middle East participated on 15 September 2020 while those situated across the Americas participated on 16 September 2020. This report provides an account of presentations and breakouts from both days.

Workshop objectives

- Discuss what is required beyond measuring just time to understand a regulatory authorities' performance and how this can be utilised by agencies to improve their effectiveness.
- Identify comparative measures of effectiveness that could allow for cross agency learning.
- Make recommendations on a common set of key indicators across authorities that could be used as a measure of effectiveness.

References

[1] Australian Government Regulatory Performance Framework. https://www.tga.gov.au/regulator-performance-framework-self-assessment-report-july-2016-june-2017

[2] O'Brien, J., Lumsden, R. S., Diehl, D. H., & Macdonald, J. C. (2019). Building a Better Approach for the Benefit of Patients: 10 Pillars to Strengthen Regulatory Review Systems Globally. *Therapeutic Innovation & Regulatory Science*. https://doi.org/10.1177/2168479019834529

Key points from presentations

Session 1: What is being utilised currently as effectiveness measures of the regulatory approval process?

Dr Tomas Salmonson, *Former Chair, CHMP, EMA*, described the role of a 'modern' regulator today and elements that enhance effectiveness and efficiency such as clear roles and responsibilities, internal leadership and education, adherence to timelines, rewards for good performance and ensuring that public health is always the key focus. No regulator can manage its workload alone, highlighting the growing importance of collaboration, reliance and recognition models.

Dr Junko Sato, *Office Director, Office of International Program, Pharmaceuticals and Medical Devices Agency (PMDA), Japan,* gave an overview of PMDA's full review processes for New Active Substances and emphasised the importance of predictability, transparency, fairness and good stakeholder communication in regulatory review. Regulators must ensure that they are effective, in that their view is based on good science, while also being efficient by using the minimum amount of necessary data.

Dr John Patrick Stewart, *Director General, Therapeutic Products Directorate, Health Canada,* spoke about how regulatory agencies can optimise their effectiveness, such as through good communication with sponsors, consistent internal processes, leveraging information from other regulators and supportive technology systems. In order to identify opportunities to improve efficiency and effectiveness, agencies must be relevant, transparent, monitor their performance and create an internal culture of continuous improvement.

Nancy Ngum, *Programme Assistant, African Union Development Agency New Partnership for Africa's Development (AUDA-NEPAD)* gave an overview of the African Medicines Regulatory Harmonisation (AMRH) initiative, which aims to promote harmonisation of medicines regulation in Africa. Improved work-sharing through shared knowledge and skills among agencies in the East African Community has resulted in faster regulatory approvals and improved availability of safe, efficacious, and quality medicines.

Dr Rian Marie Extavour, *Technical Coordinator, Caribbean Regulatory System (CRS), Trinidad and Tobago,* described how the CRS reviews medicines using reliance and verification procedures and issues recommendations for marketing authorisation to members of the Caribbean Community (CARICOM). The CRS uses the Optimising Efficiencies in Regulatory Agencies (OpERA) tool to monitor key timelines and identify possible inefficiencies and delays as well as an internal database to track and document reviews. A key challenge for CRS is the limited ability to confirm market registration or import at the national level to complete tracking steps.

Elkiane Macedo Rama, *Biological Products Office, ANVISA, Brazil,* spoke about ANVISA's Reliance Pilot Project, which was introduced in 2018 as an alternative review pathway for the assessment of biologics for marketing authorisations and variations. While there have been challenges regarding uptake by companies and obtaining approval reports, the Reliance Pilot Project has been an effective strategy to speed up application reviews and avoid duplication of effort. ANVISA is now reviewing the conditions of this pathway with the aim to encourage companies to submit more applications by this procedure.

Torkil Fredborg, *Senior Director, GRA International, Eli Lilly and Company,* and **Dr Rebecca Lumsden,** *Director - Regulatory Policy, Global Regulatory Policy & Intelligence, Pfizer,* gave company perspectives on what an effective regulatory approval process should look like. While both industry and regulars aim to deliver safe, efficacious and quality medicines to patients in a timely manner, there can be differences in what each stakeholder views as the 'right' outcome, label and timing. From an industry point of view, key features of an effective regulatory approval process are transparency, open dialogue, predictability, convergence with international standards and commitment to risk-based review approaches.

Session 2: Moving from performance measurement to operational excellence – what activities can improve the effectiveness of the approval process?

Prisha Patel, *Manager, Global Regulatory Policy and Intelligence, CIRS,* gave an overview of OpERA, an agency-provided metrics programme that has built a culture of measurement and refinement within participating regulatory agencies. The OpERA methodology focuses not only on the speed and efficiency of review, but also about having the 'right', most effective review process in place.

Andrea Keyter, *Senior Manager, Medical Devices and Radiation Control, South Africa Health Products Regulatory Authority (SAHPRA),* described several tools that agencies can use to improve their efficiency and effectiveness, including the WHO Global Benchmarking Tool, CIRS OpERA tool and the Universal Methodology for Benefit-Risk Assessment (UMBRA) template. A proposed review model for SAHPRA, which could also be a blueprint for other agencies, focuses on benefit-risk assessment, quality decision making, risk-stratification strategies, strengthened reliance networks, reinforced good regulatory practices and enhanced transparency.

Dr Hasenah Ali, *Director, National Pharmaceutical Regulatory Agency (NPRA), Malaysia,* spoke about how participating in the OpERA programme has helped NPRA to understand its regulatory performance and identify weaknesses and areas lacking capacity. This has allowed process improvements and reliance pathways to be implemented, supporting the agency's transitioning towards regulatory excellence.

Pahola Pulgarin, *Advisor to the General Director and Coordinator of the Clinical Research Group, INVIMA, Colombia,* spoke about strategies that INVIMA has implemented to reduce its average protocol assessment time, such as online protocols and pre-presentation of protocols before they are submitted to the ethics committee. In addition, INVIMA is piloting the online VigiFlow platform for reporting adverse events of research products/medicines.

Heriberto Garcia, *Director, Institute of Public Health (ISP/ANAMED), Chile,* spoke about how reliance mechanisms contribute to the assessment of regulatory submissions among reference agencies in Latin America. Legal frameworks are essential to be able to recognise and utilise the decisions of other agencies; for example the Inter-institutional Cooperation Agreement of the Pacific Alliance allows the recognition of inspection proceedings/reports for the certification of Good Manufacturing Practices between INVIMA (Colombia), COFEPRIS (Mexico) and ISP (Chile).

Cammilla Horta Gomes, *Latam Regulatory Policy Lead, Roche, Brazil,* described how industry can work with agencies to enhance effectiveness of the review process. For example, industry should provide feedback on agencies' performance and support them in advocating externally about the importance of a robust framework for regulatory activity. The greatest enabler for successfully improving the effectiveness of the review process is to have the patient at the heart of activities.

Dr Juliana Leite-Schnell, *Global Regulatory Strategy Director, Abbvie, USA,* spoke about good communication practice between industry and regulators, which is based on transparency, appropriate timing, collaboration, a common objective and trust. Open dialogue is becoming increasingly important considering scientific innovation and new development pathways and companies should look for opportunities to move beyond traditional agency interactions.

Dr Churn-Shiouh Gau, *Adjunct Professor, School of Pharmacy, National Taiwan University, and Former CEO of Centre for Drug Evaluation, Taiwan,* gave an overview of Good Submission Practices and how they were developed through a series of workshops in the Asia-Pacific Economic Cooperation (APEC) region. Good Submission Practices and Good Review Practices are complementary, so it is necessary to

promote both concomitantly to enhance overall quality and efficiency of the medical product registration process.

Dr Neil McAuslane, *Director, CIRS,* presented the results of a CIRS survey that gathered company and agency perspectives on the measures and influences of regulatory efficiency and effectiveness. The survey showed that most agencies have formalised measures of effectiveness and identified several activities that can have a major influence on an agency's effectiveness, both within the agency and by sponsors. Key challenges that agencies reported in improving their effectiveness were around the need for more well-trained assessors, an IT infrastructure that is fit for purpose and evolving as the regulatory landscape changes.

Session 3: Breakout discussions and future thinking

Breakout A was asked to discuss the activities agencies should implement to inform on and improve the effectiveness of review. Specific activities that came out of the discussion included harmonising requirements to support the use of reliance, internal training to align reviewers and implementing quality measures and monitoring. The breakout group also highlighted agencies' challenges with such activities, for example, changing mindsets at the individual and agency level.

Breakout B examined what KPIs agencies should consider in order to provide feedback on the effectiveness of their regulatory approval process. The breakout group concluded that KPIs may be needed for several aspects of medicine approval, such as the review process and timelines, capacity, competency and turnover of staff and information and quality management systems. Suggested effectiveness KPIs included % products processed within published timelines, quality of reviewer questions/assessment, % applications in Common Technical Document (CTD) format and compliance with Good Review Practices.

Breakout C were asked to discuss how the actions of sponsors could be improved to enable agencies to improve their review effectiveness. Activities related to dossier quality, transparency, engagement and responding efficiently to agency questions were identified as key areas for sponsors to focus on. Similarly, engagement and transparency were areas that agencies have a role in to support sponsors, in addition to implementing good review practices and using digital tools to aid communication.

Breakout D examined what agencies using abridged review need from reference agencies and sponsors to improve effectiveness and efficiency of their reliance route. Unredacted assessment reports, Question and Answer (Q&A) documents and Certificate of Pharmaceutical Product (CPP) were some examples of the documents that should be provided by reference agencies, whereas sponsors should ideally provide the full dossier, any additional Q&As available, proof that the product is identical, the Common Technical Document and for post-approval changes, designation of the classification of changes.

Dr Thomas Kühler, *Head of Global Regulatory Science and Policy EU/AMEE, Sanofi, France,* and **Dr Felipe Dolz,** *Head, Global Regulatory Science & Policy, Sanofi, USA,* closed the workshop with presentations on the potential for Cloud-based approaches to improve the effectiveness of submission and review. Although there are still issues to be addressed, multinational companies have signalled that they are ready to partner to accelerate adoption of Cloud-based strategies and regulatory authorities have expressed an interest in a continued dialogue. A coordinated strategy between industry and regulators will be essential for taking this vision of a dynamic assessment model forward.

Workshop Programme

15 September 2020 (Asia, Africa and the Middle East)

Session 1: What is being utilised currently as effectiveness measures of the regulatory approval process?	
CIRS welcome and introduction	**Dr Jamie Munro,** *Executive Director, CIRS*
Session Chair – objectives of session and introductory words	**Adj Prof John Skerritt,** *Deputy Secretary for Health, Products Regulation, Department of Health, Australia*
What is the role of the 'modern' regulatory today and why is it important to go beyond just efficiency to have an effective regulatory approval process?	**Dr Tomas Salmonson,** *Partner, Consilium Salmonson & Hemmings and Former Chair, CHMP, EMA*
Measuring the effectiveness of different regulatory approval processes – what key performance indicators for effectiveness need to be considered?	
Full review processes for New Active Substances	**Dr Junko Sato**, *Office Director, Office of International Program, Pharmaceuticals and Medical Devices Agency (PMDA), Japan*
Regional Regulatory Initiatives	**Nancy Ngum,** *Programme Assistant, African Union Development Agency New Partnership for Africa's Development (AUDA-NEPAD)*
What does an effective regulatory approval process look like and what would be good measures of effectiveness?	**Torkil Fredborg,** *Senior Director, GRA-International, Eli Lilly and Company, UK*
Session 2: Moving from performance measurement to operational excellence – what activities can improve the effectiveness of the approval process?	
How can agencies utilise OpERA to go beyond measuring time spent in the approval process to identifying activities which can improve an agency's effectiveness?	**Prisha Patel,** *Manager, Global Regulatory Policy and Intelligence, CIRS*
Performance measurement - Enabling an effective review through understanding where time is spent in conjunction with process, procedures and practices Two Case Studies: 10 minutes each to describe practical activities that can be undertaken during the review which can improve an agency's effectiveness for different activities	
Agency 1 – Essential tools for an agency to become more efficient and effective	**Dr Andrea Keyter,** *Senior Manager, Medical Devices and Radiation Control, South Africa Health Products Regulatory Authority (SAHPRA)*
Agency 2 – Implementation of changes to improve the approval process and cycle times	**Dr Hasenah Ali,** *Director, NPRA, Malaysia*
The development of good submission practices – how is this being achieved?	**Dr Churn-Shiouh Gau**, *Former Executive Director, Center for Drug Evaluation, Chinese Taipei*

Session 3: Breakout Discussions	
Results of a CIRS survey of companies and regulators on measures and influences of effectiveness	**Dr Neil McAuslane,** *Director, CIRS*
Roundtable A: What activities should agencies consider implementing that inform on and improve the effectiveness of the review at both the organisation and individual level - how can these 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: Dorte Strobel,** *Senior Manager, Head of Global Regulatory Intelligence, LEO Pharma, Denmark*
Roundtable B: What would be the key performance indicators that an agency should consider that would provide feedback to the agency and other stakeholders on the effectiveness of their regulatory approval process?	**Chair: Dr Alireza Khadem**, *Scientist, WHO, Switzerland* **Rapporteur: Dr Sannie Chong,** *Asia Pacific Technical Regulatory Policy, Roche, Singapore*
Roundtable C: How could the actions/activities of applicants/sponsors be improved to enable agencies to improve their review effectiveness?	**Chair: Virginia Acha,** *Associate VP, Global Regulatory Policy, MSD, UK* **Rapporteur: Dr Vivien Woodworth,** *Regulatory Science Specialist, Lundbeck A/S, Denmark*
Roundtable D: Focus on the utilisation of an abridged reliance review process - What does an agency need from their reference agencies and from the applicant that can improve the effectiveness and efficiency of their reliance route?	**Chair: Dr William Wekwete,** *Head, Evaluations and Registration, Medicines Control Authority, Zimbabwe* **Rapporteur: Dr Bettina Doepner**, *Global Lead Regulatory Intelligence and Policy, Director, CSL Behring, Germany*
Future thinking - Improving the effectiveness of the submission and review using Cloud-based approaches – are we ready? What are the opportunities and barriers?	**Dr Thomas Kühler,** *Head, Regulatory Science & Policy, EU/AMESA, Sanofi, France*

16 September 2020 (Americas)

Session 1: What is being utilised currently as effectiveness measures of the regulatory approval process?	
CIRS welcome and introduction	**Dr Jamie Munro,** *Executive Director, CIRS*
Session Chair – objectives of session and introductory words	**Katherine Serrano,** *Director, Latin America Office, Office of Global Operations, US FDA*
What is the role of the 'modern' regulatory today and why is it important to go beyond just efficiency to have an effective regulatory approval process?	**Dr Tomas Salmonson,** *Partner, Consilium Salmonson & Hemmings and Former Chair, CHMP, EMA*
Measuring the effectiveness of different regulatory approval processes – what key performance indicators for effectiveness need to be considered?	
Full review processes for New Active Substances	**Dr J Patrick Stewart**, *Director General, Therapeutic Products Directorate, Health Canada*
Reliance/abridged reviews of processes for biological products	**Elkiane Macedo Rama,** *Biological Products Office, ANVISA, Brazil*
Regional Regulatory Initiatives	**Dr Rian Extavour,** *Technical Coordinator, Caribbean Regulatory System, Trinidad and Tobago*
What does an effective regulatory approval process look like and what would be good measures of effectiveness?	**Rebecca Lumsden,** *Director, Global Regulatory Policy & Intelligence, Pfizer, UK*
Session 2: Moving from performance measurement to operational excellence – what activities can improve the effectiveness of the approval process?	
How can agencies utilise OpERA to go beyond measuring time spent in the approval process to identifying activities which can improve an agency's effectiveness?	**Prisha Patel,** *Manager, Global Regulatory Policy and Intelligence, CIRS*
Performance measurement - Enabling an effective review through understanding where time is spent in conjunction with process, procedures and practices Two Case Studies: 10 minutes each to describe practical activities that can be undertaken during the review which can improve an agency's effectiveness for different activities	
Agency 1 – How reliance contributes to the assessment of regulatory submissions among regional reference agencies (PAHO level IV)	**Heriberto Garcia,** *Director, Institute of Public Health (ISP/ANAMED), Chile*
Agency 2 – Using performance measurement to build a science-based regulatory agency	**Pahola Pulgarin,** *Advisor to the General Director and Coordinator of the Clinical Research Group, INVIMA, Colombia*
Working with an agency to enhance the effectiveness of the review process	**Cammilla Horta Gomes,** *Latam Regulatory Policy Lead, Roche, Brazil*

The development of good submission practices – what does this look like and how can this improve the effectiveness of the review process?	**Dr Juliana Leite-Schnell,** *Global Regulatory Strategy Director, AbbVie, USA*
Session 3: Breakout Discussions	
Results of a CIRS survey of companies and regulators on measures and influences of effectiveness	**Dr Neil McAuslane,** *Director, CIRS*
Roundtable A: What activities should agencies consider implementing that inform on and improve the effectiveness of the review at both the organisation and individual level - how can these be used in practical ways to optimise performance?	**Chair: Dr J Patrick Stewart,** *Director General, Therapeutic Products Directorate, Health Canada* **Rapporteurs: Jorge Azar,** *Senior Area Regulatory Director Latin America, AstraZeneca, USA*
Roundtable B: What would be the key performance indicators that an agency should consider that would provide feedback to the agency and other stakeholders on the effectiveness of their regulatory approval process?	**Chair: Dr Jude Nwokike,** *Vice-President & Director, US Pharmacopeia, USA* **Rapporteur: Leonardo Semprun,** *Global Regulatory Policy Director – LatAm, MSD, Panama*
Roundtable C: How could the actions/activities of applicants/sponsors be improved to enable agencies to improve their review effectiveness?	**Chair: Ginny Beakes-Read,** *Executive Director GRR&D Policy, Amgen, USA* **Rapporteur: Raul Stucchi,** *Director, Regulatory Affairs, Latin America, Eli Lilly and Company, Peru*
Roundtable D: Focus on the utilisation of an abridged reliance review process - What does an agency need from their reference agencies and from the applicant that can improve the effectiveness and efficiency of their reliance route?	**Chair: Sebastian Duarte,** *Director of Institutional Relations and Regulation, ANMAT, Argentina* **Rapporteur: Michael Cunha,** *Senior Director, Regulatory Policy and Intelligence, Bayer, USA*
Future thinking - Improving the effectiveness of the submission and review using Cloud-based approaches – are we ready? What are the opportunities and barriers?	**Dr Felipe Dolz,** *Head, Global Regulatory Science & Policy, Sanofi, USA*

Section 2: Presentations

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What is the role of a 'modern' regulator today and why is it important to go beyond efficiency to have an effective regulatory approval process?

Dr Tomas Salmonson, *Former Chair, CHMP*

The role of the regulator is to represent society in the handling of medicinal products and have a positive impact on public health. Although the details of this role may differ slightly by country or region, there are several features that are important to all regulators. There must be a specific, transparent approval process that sponsors can understand in order to respond to challenges or questions, and that fellow regulators can trust when utilising reliance or recognition models. It is also important for regulators to clearly communicate approval decisions, timelines, indication, pharmacovigilance, drug utilisation, post-licensing evidence generation (PLEG) and risk minimisation activities. Finally, regulators have an important role in providing information to other stakeholders, including the healthcare system, HTA bodies, payers and patients.

Most regulators have a capacity problem and weaknesses in important areas such as a shortage of methodologists/statisticians. Rather than just recruiting more people, a more effective solution may be to improve scientific leadership, have clear priorities and responsibilities, and to collaborate with other regulatory agencies. Internal leadership and education are critical as some reviewers may be too ambitious/committed, which reduces efficiency, while others may not like being challenged, which risks having a negative impact on transparency. It is important that regulators look out for negative behaviours internally such as reluctance to trust other agencies, discuss the outcome of an assessment or to take decisions, as well as long lists of 'nice to know' questions.

Elements for success include clear roles and responsibilities, adherence to timelines (by monitoring performance metrics), rewards for good performance, collaboration between regulatory agencies and ensuring that public health is always the key focus (see below). At the start of a review, it is important to identify priorities and understand to what extent reliance can be used. During review, support should be given to less-experienced assessors and more responsibility placed on those who are more senior.

Regulatory systems in the EU have very clear timelines, benefit-risk structures, pharmacovigilance and PLEG guidance and provide information to healthcare systems, HTA bodies and payers through the European Public Assessment Report (EPAR) and Summary of Product Characteristics (SmPC). However, improvements could be made to the level of transparency during review as well as in how information is provided to patients.

No regulator can manage its workload alone, highlighting the growing importance of collaboration, reliance and recognition models. Effective regulators view transparency as a strength, rather than a threat, and ensure that there are clear responsibilities and scientific leadership within their agency.

RECIPE FOR SUCCESS (?)

- Clear roles and responsibilities – decision makers vs assessment teams
  - Start of review - identify priorities. To what extent can we rely on other agencies?
  - Support during review
  - Decision making. Who takes responsibility?
- Adherence to timelines – performance metrics
  - Eternal question – what to measure? Being able to explain assessments?
- Reward good performance…
- Stimulate collaboration between regulatory agencies
- Always public heath in focus

Measuring the effectiveness of different regulatory approval processes:

Full review processes for New Active Substances in Japan

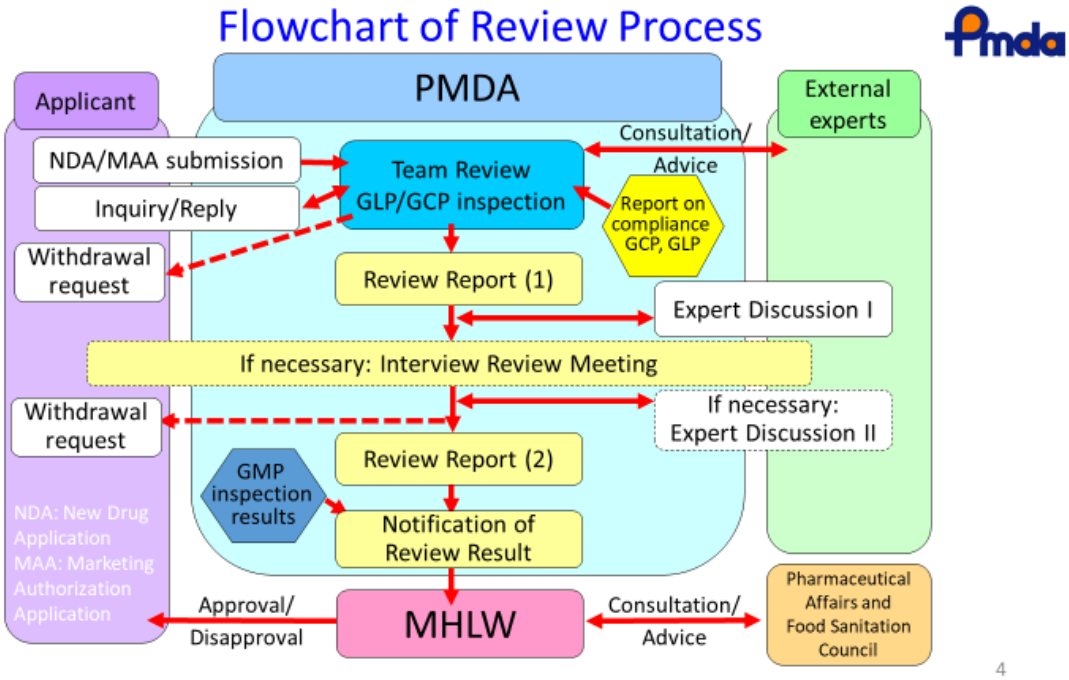
Dr Junko Sato, *Office Director, Office of International Program, Pharmaceuticals and Medical Devices Agency (PMDA), Japan*

In Japan there are two health regulatory authorities: the Pharmaceutical Safety and Environmental Health Bureau (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA). While the PMDA's main responsibilities are scientific review for drugs and medical devices, Good Clinical Practice (GCP), Good Manufacturing Practice (GMP) inspections and clinical trial consultation, the MHLW has other responsibilities such as the final authorisation of medical products, publishing guidelines and supervising PMDA activities.

Stakeholder engagement is key to the regular review process in Japan (see full process outlined below). When the PMDA receives a New Drug Application (NDA) or Marketing Authorisation Application (MAA), there is a 'team review' where further information may be gathered from the sponsor and the first review report is prepared. Next there is a consultation period with external experts, who comment on the review report and help to decide whether an Interview Review Meeting is needed (most products skip this step). A second review report is prepared based on the discussion with external experts and is submitted to MHLW. The Pharmaceutical Affairs and Food Sanitation Council advises the MHLW on whether the product should be approved or not.

Providing detailed review milestones and timelines supports agency predictability. The PMDA has reduced its median approval time over the last decade and consistently achieves its 12-month target for standard reviews and 9-month target for priority reviews. The agency also publishes review reports on its website in Japanese and English to facilitate transparency.

In summary, predictability, transparency, fairness and good stakeholder communication are essential in regulatory review. Regulators must ensure that they are effective, in that their view is based on good science, while also being efficient by using the minimum amount of necessary data.



Measuring the effectiveness of different regulatory approval processes:

Effective review of New Active Substances in Canada

Dr John Patrick Stewart, *Director General, Therapeutic Products Directorate, Health Canada*

Health Canada regulates, evaluates and monitors the safety, efficacy and quality of therapeutic products as mandated by the Food and Drugs Act. When the Act was created 50 years ago, the focus of drug regulations was around pre-market safety, but now the world has shifted to a lifecycle approach that includes post-market safety as well as other post-market commitments for early-access products. Health Canada continues to review and modernise the Food and Drugs Act to ensure it stays relevant and enables Health Canada to be efficient and effective.

The Therapeutic Product Directorate of Health Canada is divided into several offices/bureaus that focus on specific areas e.g. clinical trial oversight, disease groups, classes of drugs. This subdivision helps to ensure effectiveness as each bureau develops a degree of clinical expertise and knowledge as to where innovation is going, as well as competencies in reviewing particular trials or drugs.

Information sharing and discussion with the sponsor prior to receipt of the full submission is instrumental to the success of an efficient path through the review process. This includes guidance documents, which must be kept up-to-date, and pre-submission meetings, which are important opportunities to provide advice, answer the sponsor's questions and address issues before the submission comes in. It can also be useful to engage with industry associations to identify gaps and challenges in regulatory, science and policy, as well as to engage directly with industry through company-based pipeline meetings.

Another component to ensuring effectiveness is consistent internal processes; review staff must have reliable approaches to the review of scientific data and documenting decisions. This can be achieved by implementing Good Review Practices, review plans and milestones, internal quality audits and a quality management system. The Therapeutic Product Directorate's Office of Planning, Performance & Review Services is responsible for training and monitoring performance and has a good review practice office as well as a quality management system programme.

Monitoring performance is essential for discussing issues, identifying submissions at risk and developing mitigation strategies. Health Canada uses performance dashboards to present monthly workloads and performance data for discussion with senior management. These include action plans to build review capacity as well as cost recovery information.

Collaboration is another key success factor to optimising effectiveness. Internal teams should be open to exchanging ideas in a mutually respectful, professional environment and recognise the importance of documenting issues. International collaboration and work-sharing also greatly contribute to efficient review. For example, Health Canada is a member of Project Orbis, a US Food and Drug Administration (FDA) initiative that brings together regulators to review cancer submissions, and the ACSS Consortium that facilitates work-sharing between Australia's Therapeutic Goods Administration, Health Canada, Singapore's Health Sciences Authority and Swissmedic*.

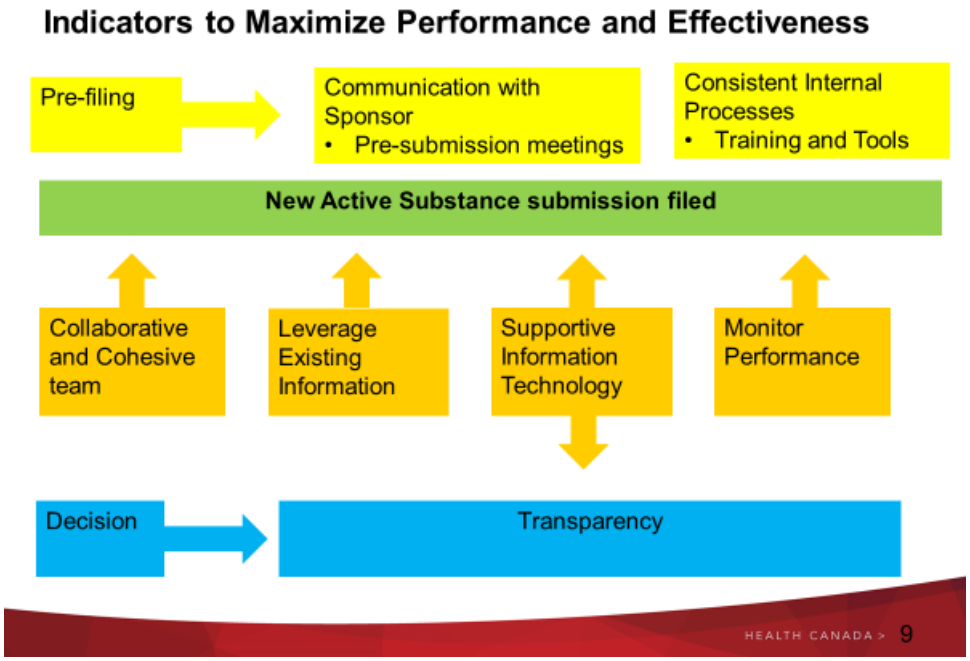
Given that every regulator has resource constraints, leveraging information from other regulators, such as Questions and Answers, Executive Summaries and Review Decision reports, is greatly beneficial. Not only does this approach supplement reviews, but it avoids duplication of efforts and reduces burden on

* The UK Medicines and Health products Regulatory Authority (MHRA) will also join the Consortium from 1 January 2021: https://www.gov.uk/government/news/uk-medicines-regulator-joins-up-with-australia-canada-singapore-and-switzerland-regulators

industry. While some review staff may be cautious or reluctant to utilise foreign regulatory information, a more accepting culture can be encouraged by sending staff to attend international submission meetings.

Supportive Information Technology (IT) systems are also important for optimising effectiveness. Health Canada utilises docuBridge, a submission and document management system that streamlines assignment of workload and internal approval processes. This is connected to a secure gateway with the FDA, allowing officers from both agencies to view documents, update their review status and assign workloads.

In order to identify opportunities to improve efficiency and effectiveness, regulatory agencies must be relevant, transparent, monitor their performance and create an internal culture of continuous improvement. Agencies should ensure a clear division of responsibilities and accountabilities internally and seek international alignment and collaboration where possible.



Measuring the effectiveness of different regulatory approval processes:

African Medicines Regulatory Harmonisation Initiative

Nancy Ngum, *Programme Assistant, African Union Development Agency New Partnership for Africa's Development (AUDA-NEPAD)*

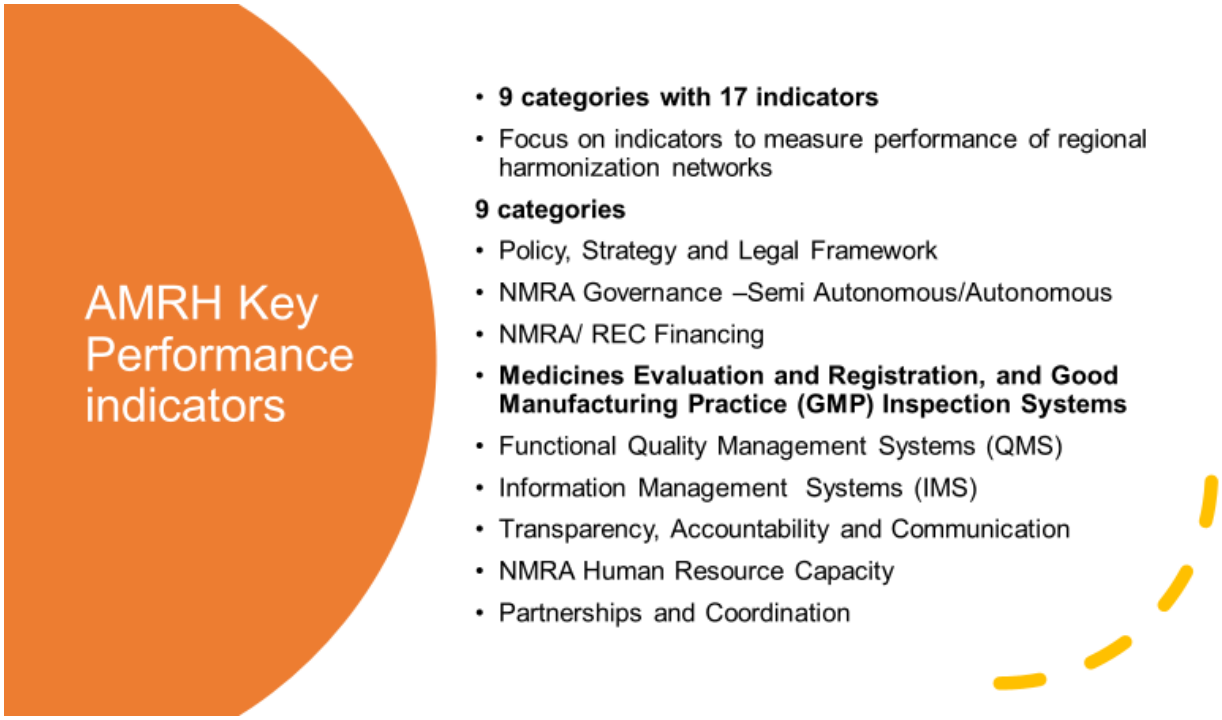
There are 55 National Medicine Regulatory Authorities (NMRAs) that govern medicines regulation across Africa, each with varying degrees of capacity, different requirements and formats, a lack of clear guidelines, minimal transparency and no clear timelines. In addition, there are NMRAs that have reference evaluations that are being underleveraged. The vision of the African Medicines Regulatory Harmonisation (AMRH) initiative is to bring these NMRAs together under 5-7 regional economic communities that enable faster registration, resource pooling and information sharing, transparent regulatory processes with clear timelines and guidelines, a single set of requirements per region and stronger institutionalised regulatory capacity and systems strengthening programmes.

17 Key Performance Indicators (KPIs) across nine categories were developed to measure the performance of regional harmonisation networks (see below). For example, KPIs for GMP inspection take into consideration assessments made using the WHO Global Benchmarking Tool, use of harmonised guidelines, number of manufacturing site inspections (joint and by individual NMRAs) and number of GMP inspection decisions made based on document review/inspection report.

Through the AMRH initiative, countries in the East African Community (EAC) and the Southern African Development Community (SADC) have recorded significant improvements in registration timelines from the average 2-7 years to a median of 7 months [1]. There has also been significant improvement in the level of autonomy of the NMRAs and in registration systems, as some NMRAs now have a legal mandate to register medicines and have a system to manage applications from receipt to the issuance of marketing authorisation. In addition, reliance mechanisms have been enhanced and the use of harmonised guidelines for registration and standard operating procedures for joint review of dossiers has increased. Although all NMRAs participate in the joint review of dossiers, the time taken to register a product based on the outcome of the joint review still varies from country to country.

QMS and IMS are necessary tools for improving efficiency of regulatory processes. Since the initiation of the AMRH initiative, IMS have improved for the EAC Member States and most countries that had no QMS during baseline studies are now initiating the International Organisation for Standardisation (ISO) certification process, while others are already ISO certified.

Evaluation of the AMRH initiative has demonstrated that policy and legal frameworks provide a foundation for effective regulation and reliance and cooperation are key factors for building trust and capacity among NMRAs. Improved work-sharing through shared knowledge and skills among NMRAs has resulted in faster regulatory approvals and improved availability of safe, efficacious, and quality medicines to the people of the EAC.



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Measuring the effectiveness of different regulatory approval processes:

Caribbean Regulatory System

Dr Rian Marie Extavour, *Technical Coordinator, Caribbean Regulatory System, Trinidad and Tobago*

The Caribbean Regulatory System (CRS) was established by the Caribbean Community (CARICOM) in 2016 to support the regulation of medicines in terms of market authorisation, pharmacovigilance and post-marketing surveillance. Located within the Caribbean Public Health Agency (CARPHA), CRS receives technical support from the Pan-American Health Organisation (PAHO) and funding from the Bill and Melinda Gates Foundation.

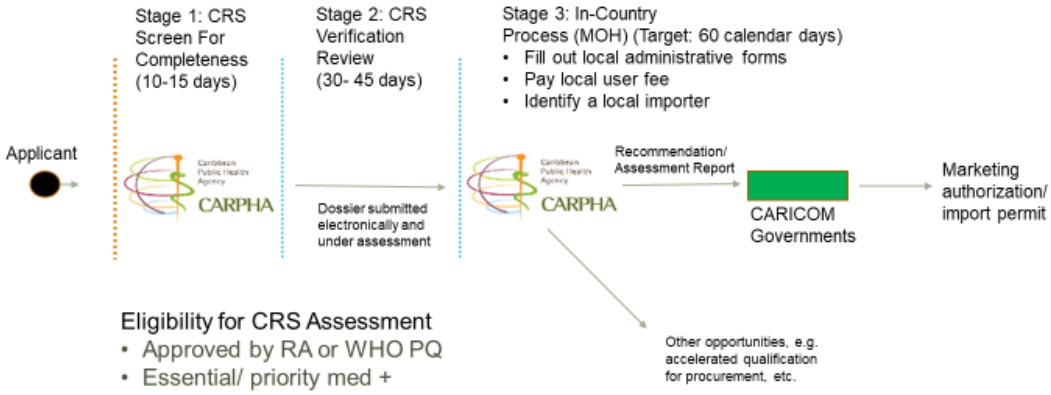
CRS is a centralised assessment unit that reviews medicines using reliance and verification procedures, and issues recommendations for marketing authorisation (CRS does not have the authorisation to register products in each CARICOM state). Eligible products must be on the WHO Model List of Essential Medicines or approved by CARICOM Expanded Technical Advisory Committee for Pharmaceutical Policy (TECHPHARM) and must have been assessed and approved for market by an authority of reference e.g. US FDA, ANVISA, EMA, Health Canada or WHO PreQualification program. Once products have been screened for eligibility, CRS verifies the marketing authorisation status and checks documentation related to the quality of manufacturing, product stability and consistency of product information (as per the marketing authorisation).

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 (see below). 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, or an import permit.

Internally, CRS uses a spreadsheet to document the verification review e.g. when the application was received, its validity, notice of eligibility, final decision, total time in queue etc. Since its inception in April 2017, this database has collected information on 149 dossiers, most of which are for generic products. In terms of therapeutic classes, most products are anti-infectives (51%) or anti-cancer/immunomodulators (18.8%). The majority of approvals required 1-2 review cycles (63.6%) and there were very few that needed a fourth review cycle (2%). Collecting this information helps the CRS to understand its review performance and availability of support personnel, as well as whether there are gaps or issues in guidance. CRS also uses the CIRS Optimising Efficiencies in Regulatory Authorities (OpERA) tool, which helps to track key timelines, identify possible inefficiencies or delays and plan for improvement through training and communication.

A key challenge for CRS is the limited ability to confirm market registration or import at the national level to complete tracking steps. Although CRS requests this information from National Regulatory Authorities (NRAs), there are various country-specific issues that prevent or delay this getting to CRS. In addition, uptake of CRS recommendations is voluntary for local NRAs and use of the CRS is voluntary for market authorisation holders.

CARPHA/CRS Registration Support Function/Verification Procedure



Measuring the effectiveness of different regulatory approval processes:

Reliance/abridged reviews of processes for biological products

Elkiane Macedo Rama, *Biological Products Office, ANIVSA, Brazil*

ANVISA's Biological Products Office is responsible for marketing authorisation and post-approval change applications, such as Chemistry Manufacturing and Controls (CMC), pre-clinical and clinical studies. This covers a wide range of products including biotechnological products, vaccines, hyperimmune sera, blood products, medicines obtained from biological fluids or animal-originated tissue, medicines containing live, attenuated or dead microorganisms, probiotics and allergens.

In response to an increased backlog of applications, in 2016 the National Congress of Brazil passed Law n.13411/2016, which established shorter deadlines for the conclusion of applications. The target timelines for ordinary and priority marketing authorisations are 365 days and 120 days, respectively, while the target timelines for ordinary and priority post-approval changes are 180 days and 60 days, respectively. These timelines were achieved in most cases for biologics with the help of new assessment strategies.

One such strategy was the Reliance Pilot Project initiated by the Biological Products Office in 2018 (Orientation of Service n.45). This established an alternative review pathway for the assessment of biologics for marketing authorisations and variations. If the sponsor selects this pathway, ANVISA performs an optimised review focusing on the evaluation of critical documents and an assessment of the decision made by US FDA and/or EMA. The reference authority decisions are used to help with the evaluation of the product, rather than for mutual recognition; ANVISA still makes its own decision based on the evidence presented and knowledge of the local population. To be eligible for the marketing authorisation reliance pathway, a product must be approved in the US and Europe with the same indication, posology and precautions, and approval reports must be provided by the sponsor.

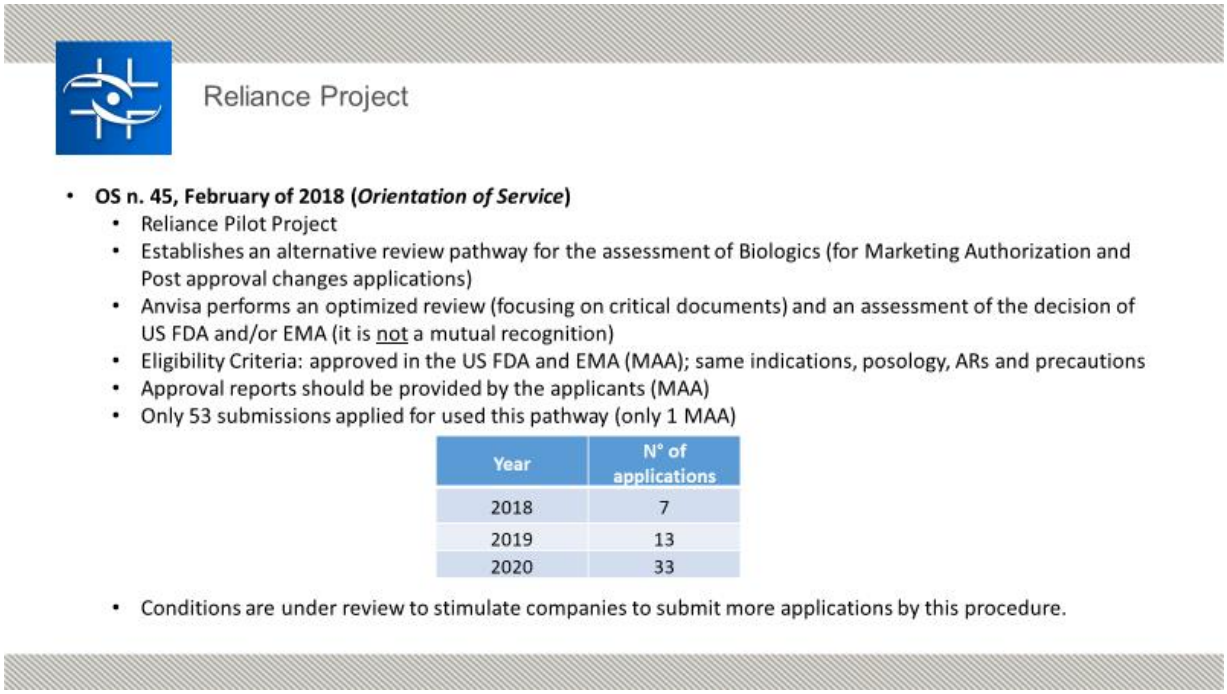
Since 2018, the number of applications using this reliance pathway has increased year-on-year but remains a small number (see slide below). ANVISA is maintaining an open dialogue with companies to better understand the reasons for not choosing to use this pathway. In addition, the conditions to use the reliance pathway are currently under review with the view to stimulate companies to submit more applications by this procedure.

Of the 36 applications that have been concluded for CMC variations, all of them were approved. For the majority of these CMC variations, ANVISA did not need to send a list of questions to the company, as it was recommended that companies send the list of questions from the reference authorities as well as the answers that were provided. However, most applications for efficacy and safety variations did require ANVISA to send a list of questions to the company, as there were often queries about labelling, problems regarding the presentation of the information/documents or doubts that were not elucidated by the approval report.

ANVISA has experienced several challenges with the Reliance Pilot Project. Since Brazil is often in the first wave of submissions, FDA and/or EMA have not concluded their evaluations at the time of submission in Brazil, so the reliance pathway cannot be used. Another problem is that the approval report is not always easily available from the reference agency; companies should therefore request the approval report in advance as it can take time to receive it. There have also been difficulties in identifying the exact change that was approved by the reference authorities, particularly for CMC variations, which do not usually have a detailed approval report. In addition, as the reliance pathway is a new procedure for many companies, there have been problems with documents not being submitted properly.

In summary, the Reliance Pilot Project is an effective strategy to speed up application reviews and avoid duplication of effort, especially considering reduced workforce scenarios. Some difficulties, such as the

absence of the approval report, are considered critical for the accomplishment of target timelines as well as to identify the exact change that was approved by the reference authority. ANVISA is now reviewing the conditions of this pathway with the aim to encourage companies to submit more applications by this procedure.



What does an effective regulatory approval process look like and what would be good measures of effectiveness? A company perspective

Torkil Fredborg, *Senior Director, GRA International, Eli Lilly and Company*

Dr Rebecca Lumsden, *Director - Regulatory Policy, Global Regulatory Policy & Intelligence, Pfizer Ltd*

Please note – these speakers gave separate presentations[†] but this summary amalgamates key points from both.

An effective regulatory approval process should deliver safe, efficacious and quality innovative medicines to patients in a timely manner. This is a common objective for both industry and regulators, though there can be differences in what each stakeholder views as the 'right' outcome, label and timing. From an industry point of view, key features of an effective regulatory approval process are transparency, open dialogue, predictability, convergence with international standards and commitment to risk-based review approaches.

Transparency

Transparency is a key component of an effective review process. Guidelines and timelines must be easily accessible on agency websites and applicants should be able to track the progress of their application and have awareness of who is reviewing it. Agencies must be transparent about the basis of their marketing authorisation decisions and publish public assessment reports if possible. This may be a good Key Performance Indicator (KPI) for effectiveness as it demonstrates that the authority has applied consistent review standards. In addition, there should be transparency in how the label was derived.

As well as transparency in the review process, there must also be transparency in prioritisation mechanisms. For example, does an agency look at the health needs of its population and offer different ways of prioritising product review? Are safety updates or manufacturing changes prioritised if there is a potential threat to patients or supply chains, respectively? Having an understanding of agency prioritisation mechanisms can help companies to plan and make strategic decisions.

Dialogue

An effective review process should be based on open dialogue, where the expertise of the applicant is acknowledged and there are opportunities to engage before, as part of and after the review. Collecting feedback from companies and agencies after the review may be a good indicator of the effectiveness of both stakeholders. As well as the review process itself, companies should also have the opportunity to comment on draft agency guidelines and regulations.

Predictability

Agencies must have clear regulatory guidance and requirements that are scientifically driven and based on international standards, so that companies are able to predict likely outcomes. Each pathway and review model must be clearly defined and have consistent review metrics. There should also be a tracking system so companies can check the progress of a dossier and know when a decision is likely to be made.

[†] Mr Fredborg spoke at the Asia meeting on 15 September and Dr Lumsden spoke at the Americas meeting on 16 September.

Convergence

Convergence with international standards and best practices is a key feature of an effective regulatory approval process. Harmonisation to technical standards or convergence with international best practices could be considered, not only for new product submissions but for lifecycle management as well. A potential KPI could be whether agencies are taking part in regional convergence or harmonisation with other agencies, and the level of international harmonisation can be measured by The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) implementation survey. With the emergence of advanced therapies, real-world evidence, innovative trial designs and novel manufacturing methods, agencies should commit to advancing regulatory science and look to other agencies that have experience with these novel regulatory models and have developed relevant guidance.

While some divergence in labelling may be appropriate due to local medical environments or differing regulatory review, significant divergence can sometimes occur, even between major agencies. Reference labels - where an agency relies on other agencies' labelling reviews – could help to eliminate redundant discussion and encourage convergence in labelling.

Risk-based review approach

Commitment to risk-based review approaches, such as reliance, recognition and work-sharing initiatives, could be a good measure of effectiveness. Underpinned by regulatory convergence, these initiatives help to ensure that agencies are not 'reinventing the wheel' and that the review is being carried out by subject matter experts. In addition, it allows agencies with limited resources to focus on other essential aspects of review and post market surveillance that cannot be done through reliance.

As not every agency may be ready to carry out risk-based review approaches, it is also important to consider participation in information-sharing initiatives or training, such as through CIRS or the Asia-Pacific Economic Cooperation (APEC). In addition, participation in other collaborative regulatory initiatives such as Project Orbis – an FDA initiative to provide a framework for concurrent submission and review of oncology products among international partners – could be a good indicator of effectiveness, as could the use of reliance tools to reduce the duplication of effort e.g. the use of a Stringent Regulatory Authority's public assessment reports.

Supporting slides from each presentation

Conclusion: Proposed Measures of an Effective Regulatory Approval Process

PREDICTABILITY	TRANSPARENCY	DIALOGUE	CONVERGENCE
Are regulatory processes well-defined? • Procedure for each pathway and review model • Tracking system to check progress of the review • Consistent review metrics within each pathway and for NAS vs Generics	Is relevant information publicly available? • Regulatory guidelines, pathways and review models • Redacted Assessment rpts • Reviewers and their qualifications	Open communication with applicants? • Consultation on draft guidelines and regulations • Interactions with Agency before and during review • Applicant feedback after approval	Global standards and optimal use of reliance models? • Reliance and work-sharing initiatives • ICH implementation survey • Regional convergence or harmonization with other major agencies

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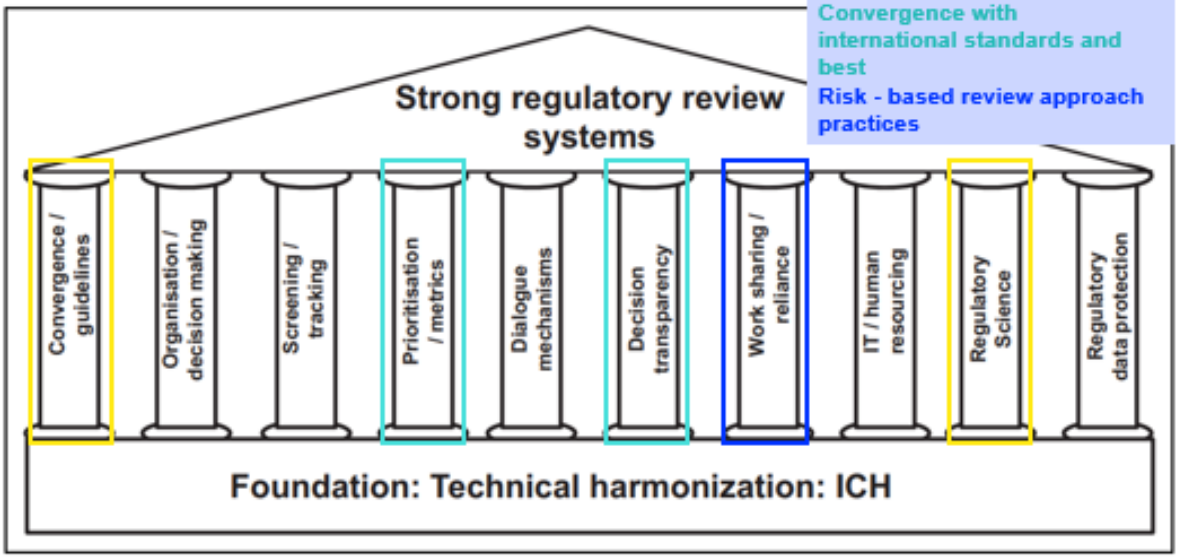
10 Pillars to Strengthen Regulatory Review Systems Globally



O'Brien, J., Lumsden, R. S., Diehl, D. H., & Macdonald, J. C. (2019). Building a Better Approach for the Benefit of Patients: 10 Pillars to Strengthen Regulatory Review Systems Globally. *Therapeutic Innovation & Regulatory Science*. https://doi.org/10.1177/2168479019834529

Breakthroughs that change patients' lives 2 Pfizer GLOBAL PRODUCT DEVELOPMENT Global Regulatory Affairs

How can agencies utilise OpERA to go beyond measuring time spent in the approval process to identifying activities which can improve an agency's effectiveness?

Prisha Patel, *Manager, Global Regulatory Policy and Intelligence, CIRS*

The Optimising Efficiencies in Regulatory Agencies (OpERA) programme was initiated by CIRS in 2013, building on previous work carried out with regulators in terms of benchmarking and monitoring performance. The programme has been designed to support the information needs of developing national regulatory authorities and collaboratively collects and assesses a variety of data that characterise the regulatory processes within participating agencies. The objectives of the OpERA programme are to:

- Encourage systematic measuring of processes
- Provide a simple process to collect benchmarking data specific to the regulatory review and assessment process
- Compare accurately the processes used in the review of new drug marketing authorisations
- Promote a systematic approach to self-monitoring and continuous improvement.

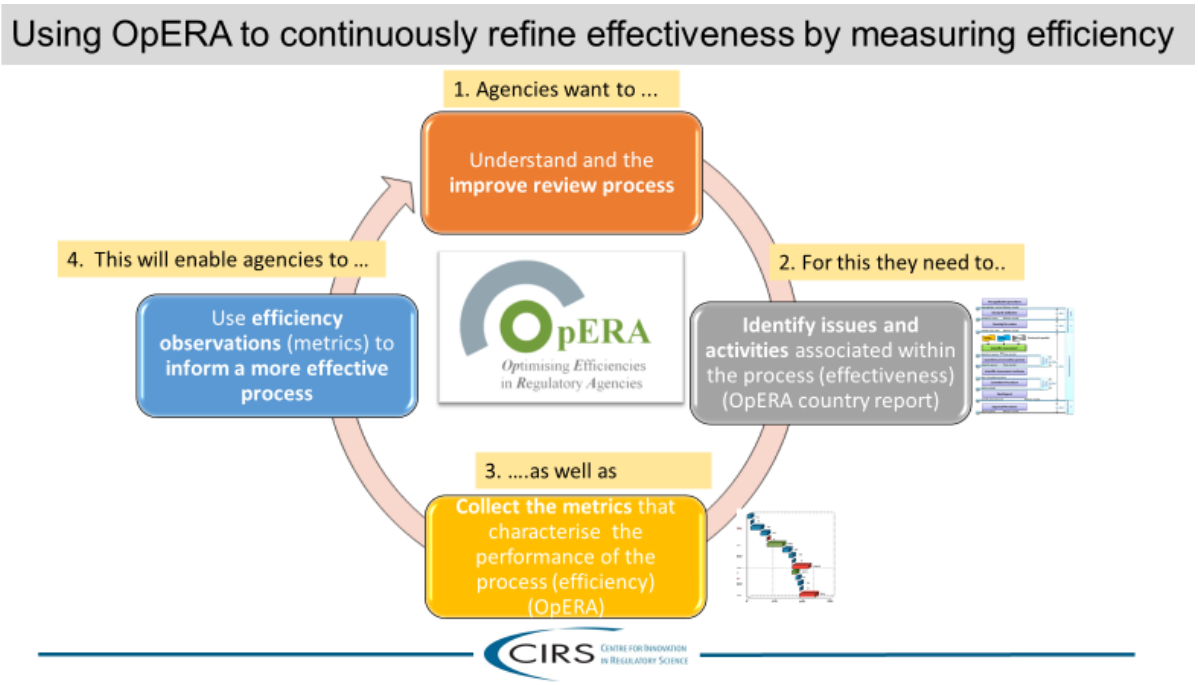
There are two key elements to the OpERA programme. The first focuses on understanding the regulatory review process at each participating agency through the development of a country-specific report. This outlines the organisation of the agency, types of review models used, key milestones in the review process, adoption of Good Review Practices (GRevP) and use of 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 and recommendations for improvement.

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 associated with products that go through their regulatory review process. The resulting metrics report helps agencies to identify where time is being spent as well as opportunities to improve the effectiveness of their process.

These two elements go hand-hand, as to be able to identify measures of effectiveness, an agency must first break down its review process and identify efficiency measures. For example, the Country Report may identify issues within submission and validation steps such as a lack of timeline for requesting further information, long queue time and an inadequate tracking system. Relevant efficiency measures that could therefore be implemented are timelines for company response, screening for quality of submission as well as quality of guidelines and their interpretation and the use of project managers. Collecting such efficiency measures will then characterise the performance of the process and inform a more effective process (see slide below).

Brazilian agency, ANVISA, is a longstanding participant in the OpERA programme and has collected metrics on its review timelines from 2013 to 2016 [1]. This dataset is now being used as a baseline to assess the impact of process improvement initiatives, such as the implementation of risk assessment models for generics to improve use of resource. In addition, ANVISA has tried to reduce review backlogs by offering companies a one-time opportunity to advance selected products to an earlier position in the review queue.

In summary, the OpERA programme has successfully built a culture of measurement and refinement within participating regulatory agencies, helping them to define their review performance goals and optimise their processes. It is important to remember that optimisation is not only about doing things quicker and more efficiently, but also about doing them effectively and in the right way.



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Case studies from OpERA participants:

Essential tools for an agency to become more efficient and effective

Dr Andrea Keyter, *Senior Manager, Medical Devices and Radiation Control, South Africa Health Products Regulatory Authority (SAHPRA)*

All agencies strive to be patient-focused, evidence-based, risk-orientated, transparent, effective and flexible. However, there is global mounting pressure for agencies to deal with larger volumes of marketing authorisation applications, more complex submissions and increased categories of medicines. Agencies of all sizes and maturity levels are responding to the challenges of this new regulatory environment by revising legacy systems and re-engineering processes.

As well as participating in international benchmarking and implementing pragmatic solutions to address regulatory inefficiencies, agencies can utilise the WHO Global Benchmarking Tool (GBT) to make an evidence-based assessment of their strengths and weaknesses. The WHO GBT evaluates nine component functions of the regulatory system against a series of sub-indicators; during the assessment, agencies are required to provide evidence supporting the implementation of each of the sub-indicators. This will help to formulate an effective and workable institutional development plan and implement an improved regulatory model based on WHO Good Review Practices. In addition to the WHO GBT, there are several other tools available that have been developed and validated by CIRS and have been used by a number of regulators:

- **Quality of Decision-Making Orientation Scheme (QoDoS)** - a questionnaire that can assess what the decision-making qualities and practices look like in an organisation and identify differences in decision-making across individuals and within an organisation [1].
- **Abridged review questionnaire** – used to determine the criteria and current practices for implementing an abridged review process [2].
- **Review process questionnaire** – used to better understand what an agency's review process looks like and areas for improvement.
- **ICH questionnaire** – used to evaluate conformity to phase I and phase II ICH guidelines.
- **OpERA tool** – an online tool that is effective for tracking, measuring and monitoring regulatory processes and performance.
- **Universal Methodology for Benefit-Risk Assessment (UMBRA) template** – provides a systematic approach to benefit-risk decision making [3].

A series of studies have resulted in recommendations for an improved regulatory review model in South Africa [4]. Since these recommendations are underpinned by WHO Good Review Practices and link to the WHO GBT sub-indicators, they are relevant to any regulator and could therefore be a 'blueprint' for regulatory efficiency and effectiveness.

Quality measures

Regulators should have a dedicated quality management unit and formally implement a quality management system (QMS), which could be supported by certification against ISO 9001 and the WHO guideline on QMS. In addition, quality policies, Standard Operating Procedures (SOPs), guidelines and assessment templates should be codified and institutionalised and quality decision-making practice implemented.

Monitoring and evaluating review times

Regulators must identify key milestones in their review process, formalise the target timeline for review and record and measure the timelines for each of the milestones. Timelines for each of the milestones should be continuously monitored and target timelines should be embedded in performance contracts. An electronic document management system is key to ensuring applications can be accurately tracked and performance metrics collected.

Application of a risk-based approach

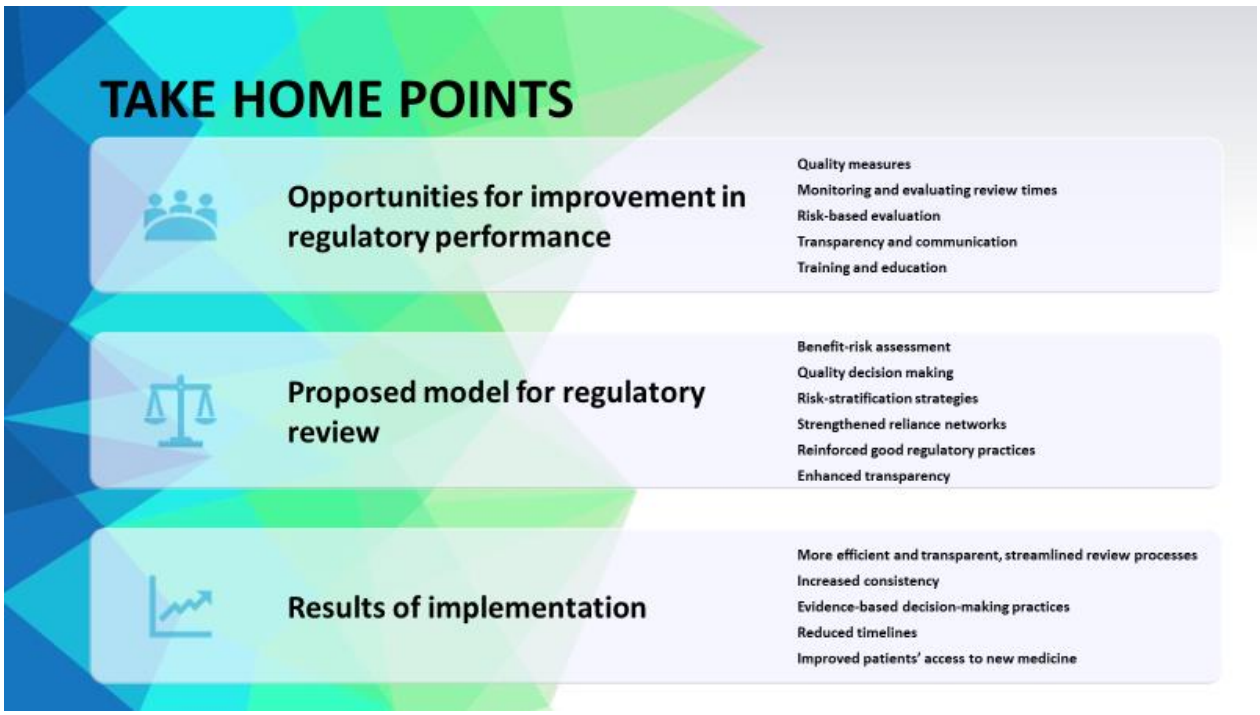
To apply a risk-based approach to review, regulators must have the right policies, SOPs, target timelines, templates, milestones and evaluation criteria in place. Facilitated Regulatory Pathways (FRPs) should be formalised and alternatives to the full review process should be considered, such as abridged review, verification review and relying or recognising other agencies' assessment reports or decisions. Strengthening collaborations and initiatives for joint reviews or work-sharing is also recommended.

Transparency and communication

Regulators can enhance stakeholder relationships by improving transparency and communication. It is important to publish updated lists of licence holders and medicines registrations as well as Public Assessment Reports that outline the basis of decisions. Transparency in decision-making can be demonstrated by using the QoDoS tool and UMBRA assessment template (for benefit-risk decisions).

Training and education

Regulators must ensure they have formalised training programmes, with priority being placed on the professional development of internal and external assessors. Ongoing skills development may be maintained through the initiation of mentorship programmes and a mechanism must be developed to evaluate and demonstrate the effectiveness of training.



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Case studies from OpERA participants:

Implementation of changes to improve the approval process and cycle times

Dr Hasenah Ali, *Director, National Pharmaceutical Regulatory Agency (NPRA), Malaysia*

NPRA 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 (NAS) were approved by NPRA in a median approval time of 515 days [1]. The median time between dossier receipt and the start of scientific assessment was 135 days and up to six cycles of review were required for approval. While NPRA spent a median of 166 days on scientific assessment, applicants took a median of 131 days to respond to questions.

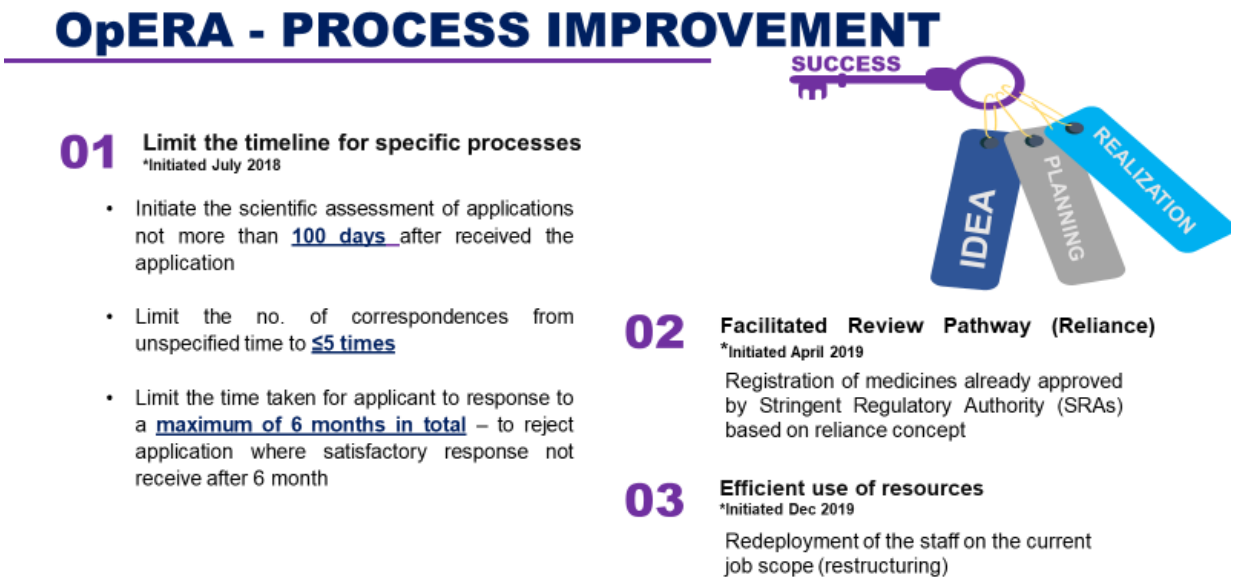
As part of the OpERA study, NPRA also examined its review process in detail and identified areas of weakness. This revealed that there were often delays in starting the scientific assessment, unlimited rounds of correspondence between the applicant and NPRA, and the applicants took a long time to respond to questions.

In response to these observations, NPRA carried out the following process improvements in July 2018: the scientific assessment must start no later than 100 days after the application is received; the number of correspondence cycles is limited to no more than five; and the applicants have a maximum of six months to respond to questions (the application is rejected if no satisfactory response is received after six months). Preliminary analysis suggests that these changes have reduced median approval times (515 days in 2017, 480 days in 2018, 445 days in 2019) and the time taken to initiate scientific assessment (135 days in 2017, 87 days in 2018, 79 days in 2019). However, the data from 2019 is still being collected and therefore needs to be verified.

In addition to improving its review process, NPRA implemented a facilitated registration pathway based on reliance in April 2019. This includes an Abbreviated Review, which takes 120 days and requires an approval from at least one reference agency, and a Verification Review, which takes 90 days and requires an approval from at least two reference agencies.

NPRA also underwent major restructuring in December 2019 to streamline and align its work processes and improve internal communication. Staff were redeployed to three new units: Centre of Regulatory Strategic Planning and Coordination, which is responsible for policies and training; Centre of Product and Cosmetic Evaluation, which combines all evaluation activities under one unit, including lab evaluation and clinical trial applications; and the Centre of Compliance and Quality Control, which is responsible for all inspection activities as well as quality control and post-marketing activities.

In summary, participating in the OpERA programme has helped NPRA to understand its regulatory performance and identify weaknesses and areas lacking capacity. This has allowed process improvements and reliance pathways to be implemented, supporting the agency's transitioning towards regulatory excellence. NPRA will continue to monitor its review performance and see whether its process and policies can be further refined.



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Effectiveness of the regulatory approval process – moving from measuring performance to operational excellence

Pahola Pulgarin, *Advisor to the General Director and Coordinator of the Clinical Research Group, INVIMA, Colombia*

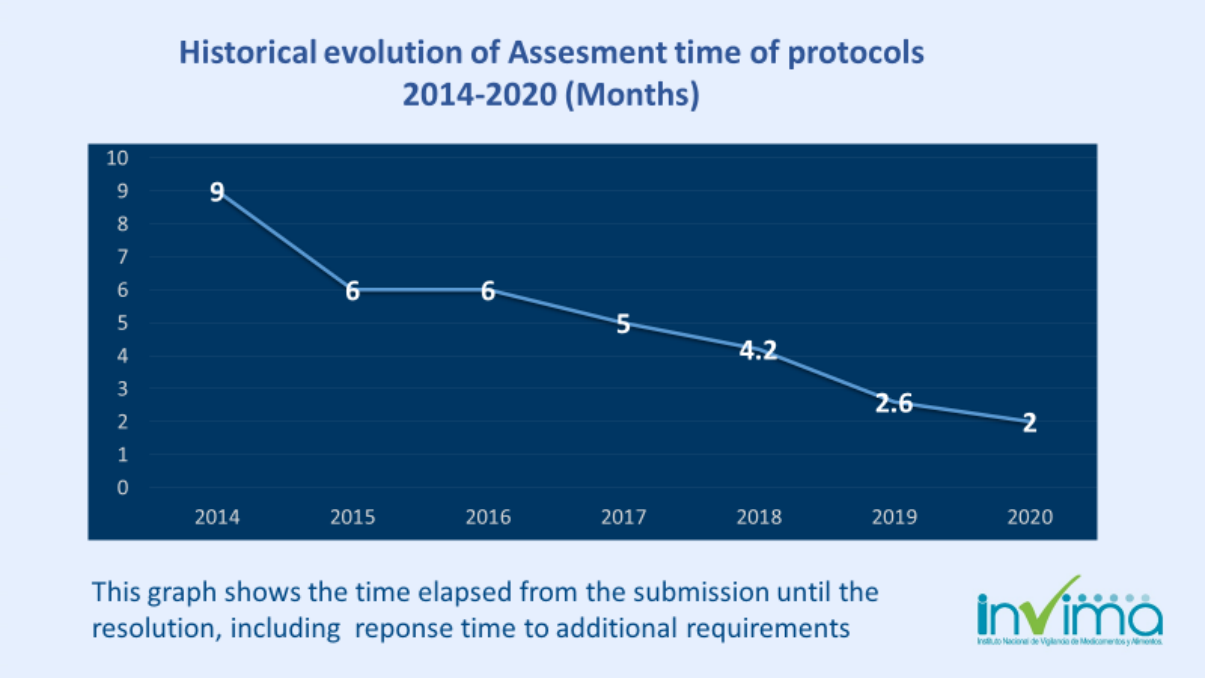
The Group of Clinical Research (GIC) is one of 12 groups that make up the Directorate of Medicines and Biologic Products of INVIMA. The group is made up of 13 professionals including medical doctors, chemical pharmacists, bacteriologists and specialised technical administrators.

In Colombia there are 123 research centres certified in Good Clinical Practice. During the period 2014-16 the assessments of initial protocols were accomplished jointly between the Specialised Group of Medicines and Biologic Products (of the Revisory Commission) and the GIC. Starting in 2016 with the objective to strengthen clinical research in Colombia, it was decided that the assessment of protocols would be performed only by the GIC. As a result of this decision, assessment time (which includes response time to additional requirements) has fallen year-on-year, from an average of six months in 2016 to 2.6 months in 2019 (see below).

INVIMA's average assessment time for initial protocols is 30 days. From December 2020, INVIMA will implement strategies to assess protocols more quickly, such as introducing online protocols and reducing requests for additional requirements by piloting the pre-presentation of protocols before they are submitted to the ethics committee. Online protocols and pre-presentation of protocols are already available for COVID-19 trials; the maximum time for protocol revision is five days, including parallel evaluations of the ethics committee and INVIMA. The average assessment time for COVID-19 initial protocols is four days.

To ensure clinical studies were not disrupted during the COVID-19 pandemic, INVIMA revised Resolutions 2378 of 2008 and 8430 of 1993. The agency also produced guidance on how sponsors/Contract Research Organisations should carry out monitoring and informed consent processes [1].

As part of its ongoing digital transformation initiative, INVIMA is piloting the VigiFlow platform to strengthen pharmacovigilance in Colombia. VigiFlow is an online management system maintained by Uppsala Monitoring Centre, Sweden, which supports the collection, processing and sharing of individual case safety reports (ICSRs) from national pharmacovigilance centres worldwide. If the pilot is successful, Colombia will use VigiFlow for reporting adverse events of research products/medicines.



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[1] INVIMA (2020) Exceptional measures and actions applicable to the development of clinical trials during the validity of the COVID-19 emergency [press release, 29 July 2020]. Accessed on 28 October 2020 at: https://www.invima.gov.co/medidas-y-acciones-excepcionales-aplicables-al-desarrollo-de-ensayos-clinicos-durante-la-vigencia-de-la-emergencia-por-covid-19

How reliance contributes to the assessment of regulatory submissions among regional reference agencies (Pan-American Health Organisation Level IV)

Heriberto Garcia, *Director, Institute of Public Health (ISP/ANAMED), Chile*

Reliance is defined by the World Health Organisation (WHO) as the act whereby a National Regulatory Authority (NRA) in one jurisdiction may consider and give significant weight to assessments performed by another NRA or trusted institution in reaching its own decision [1]. This includes work-sharing and abridged pathways, whereby NRAs leverage the work of other competent or trusted authorities to reduce workload and inform independent final decision-making. As the level of reliance increases, more trust is built amongst NRAs and regional reliance mechanisms may be utilised e.g. centralised evaluation conducted for a group of countries. Recognition is the acceptance of the regulatory decision of another NRA or trusted institution and may be unilateral or mutual, the latter of which may be based on treaties or agreements.

Legal frameworks and/or international treaties and/or procedures are essential to be able to recognise and utilise the decisions taken by other NRAs. The Inter-institutional Cooperation Agreement of the Pacific Alliance allows the recognition of inspection proceedings/reports for the certification of Good Manufacturing Practices between INVIMA (Colombia), COFEPRIS (Mexico) and ISP (Chile). ISP also recognises certificates of validation of production procedures to accredit bioequivalence of products from reference NRAs and WHO pre-qualified products. In addition, the agency has a process of sanitary registration of biotechnological products that uses EMA guidelines as a reference.

Confidentiality agreements facilitate the exchange of information between NRAs e.g. amongst PAHO Level IV NRAs, between FDA and PAHO Level IV NRAs etc. ISP has a bilateral agreement with FDA, where FDA is authorised to provide non-public information to ISP in relation to regulated products as part of cooperative efforts to enforce law or usual activities of cooperation. ISP also has a Memorandum of Understanding with PAHO in relation to the Regulatory Information Secure Exchange (RISE) module. This is a module within the Regulatory Exchange Platform that allows participating NRAs to benefit from a protected space to exchange non-public regulatory information. Such exchange helps to promote reliance practices in the region, improve process efficiency and increase regulatory convergence.

The objectives of Decree 54 in Chile are to reduce registration time by utilising reliance among regulatory agencies and increase availability of safe and effective medicines. Medicines already registered by 'high vigilance' regulatory agencies are eligible for the accelerated procedure of registration. The applicant choosing the accelerated registration procedure must present ISP with the same background information presented to the regulatory agency that granted the registration, together with the Certificate of Pharmaceutical Product (CPP). Sanitary registration under this procedure will only be granted if the product has not been denied by other vigilant agencies.

In summary, implementing good reliance practices can improve the effectiveness of collaboration amongst regulatory agencies and build trust in the work of other NRAs as well as facilitate the exchange and availability of information. This helps to enforce commitment between interested parties and promote regulatory convergence and harmonisation of requirements.

References:

[1] WHO (2020) Good reliance practices in regulatory decision-making: high-level principles and recommendations. Working document QAS/20.851 June 2020. Accessed on 28 October 2020 from: https://www.who.int/medicines/areas/quality_safety/quality_assurance/QAS20_851_good_reliance_practices.pdf?ua=1

Working with an agency to enhance the effectiveness of the review process – a company perspective

Cammilla Horta Gomes, *Latam Regulatory Policy Lead, Roche, Brazil*

There is a key role for industry in improving the effectiveness of review processes. To support regulators in their daily activities, companies must be proactive in understand and shaping the regulatory environment, and they should do this by giving input on draft regulations and guidelines, as well as engaging in activities that promote the exchange of knowledge and expertise. Industry should also advocate for, promote and engage in opportunities for information sharing with agencies before and during the review processes, ensuring that submissions are of good quality and consistent with international guidelines and making use of different regulatory pathways to promote their sustainability and improvement. Moreover, industry should provide feedback on regulators' performance and support them in advocating externally about the importance of a robust framework for regulatory activity.

Industry can go even further to enhance the effectiveness of the review process. As a basis, industry must understand that working with an agency requires an understanding of how the regulator perceives their task for a given process. The following case study focused on the use of a reliance pathway to meet the submission strategy of a company in a Latin American country.

When planning the submission strategy, the company understood that, in the case of a reliance pathway, the regulator's goals are to have sufficient information to allow understanding of the rationale for the approval by the reference agency and to achieve the same regulatory outcomes with fewer resources when compared to the standard submission pathway. Therefore, for reaching success in this strategy, the company decided to engage in early dialogue with the agency before submission, which enabled the identification of potential concerns and alignment of expectations. The company also used the same information submitted to the reference agency, while respecting local regulatory requirements, and voluntarily shared the Q&A document from the reference agency for an analysis by the relying agency. This strategy resulted in the minimisation of questions from the regulator, leading to shorter approval timelines and earlier access for patients.

In summary, being effective "requires an understanding of where you are going". To get there, agencies and industry must work together to achieve clear and transparent requirements and processes and promote convergence with international guidelines and standards, which will enable submissions with greater quality. They should also work together to support the use of different assessment or prioritisation pathways, and to build trust in the work of reference authorities for reliance pathways. Openness to dialogue is another important enabler of greater effectiveness, which includes the receptivity of the regulator and a good reputation from industry. The greatest enabler for successfully improving the effectiveness of the review process is to have the patient at the heart of activities.

There is a key role for industry in improving the effectiveness of review processes

Engage in activities that promote the exchange of knowledge and expertise

Advocate for, promote and engage in opportunities for **information sharing** with the agency before / during the review process

Send **feedback to agencies** on their performance

Present **input to draft regulations and guidelines**

Make **use different regulatory pathways** to promote their sustainability and improvement

Ensure **quality submissions** that consistent with requirements in **international guidelines**

Support agencies in **advocating externally** about the importance of a robust framework for regulatory activity

The development of good communication practice - what does this look like and how can this improve the effectiveness of the review process?

Dr Juliana Leite-Schnell, *Global Regulatory Strategy Director, Abbvie, USA*

Good communication practices between industry and regulators are based on transparency, appropriate timing, collaboration, a common objective and trust. It is important that transparency "goes both ways" and that interactions are started early and are maintained throughout the life cycle of a product. There must be a willingness to collaborate in a respectful, equal manner, and a recognition that both parties share a common objective in making a difference for patients. Trust links all of these elements, as without trust, it is difficult to be transparent, collaborative and appreciative of a common goal.

Regulatory interactions vary across jurisdictions; while some agencies have well-established processes and formal interaction policies, others are in the process of developing these. Therefore, industry should focus advocacy efforts towards establishing a common dialogue with these agencies that adds value to both parties.

Industry should seek close communication with regulators throughout the development process as well as throughout regulatory review. AbbVie prepares for interactions with agencies by looking at its clinical programmes with a global mindset and then customising this view to meet local expectations. Close collaboration between internal global and area teams is key to ensuring submission packages contain relevant scientific information alongside tailored content and messages to address the needs of each regulatory agency.

It is important to consider how industry and regulators can move beyond traditional pre-submission interactions, particularly when there are novel or complex concepts involved e.g. modelling and simulation, paediatric indications based on extrapolation, adaptive study designs or submissions based on early results for diseases with high unmet medical need. For example, Abbvie had a face-to-face pre-submission meeting with Brazilian agency ANVISA, where the Clinical Pharmacology team had the opportunity on present on pharmacokinetic modelling and simulation. After the presentation, ANVISA's feedback was collected and used to further supplement the modelling information in the submission package. This led to a successful application and was the first time the agency had approved an indication based on this type of novel package.

In summary, sharing a common goal centred around patients is fundamental for transparent and collaborative communication between companies and agencies. Open dialogue is becoming increasingly important considering scientific innovation and new drug development pathways and companies should look for opportunities to move beyond traditional agency interactions. If interaction policies are not in place, formal procedures should be established to discuss early development phases and/or pre-submission meetings.

abbvie

Final thoughts and how to move forward together

- Share a common goal is fundamental for transparent and collaborative communication
- There are opportunities for innovation on Sponsor and Health Authorities communicate, as well as within Health Authorities
- Increasing importance of open dialogue considering scientific innovation and new drug development pathways
- If interaction policies are not in place yet, highly recommend the establishment of formal procedures to discuss early development phases and/or presubmission meetings
- Discuss potential to expand interactions for topics typically not covered via established mechanisms (e.g., Q&A during regulatory reviews, COVID-19 pandemic; etc.)

abbvie

The development of Good Submission Practies – how is this being achieved?

Dr Churn-Shiouh Gau, *Adjunct Professor, School of Pharmacy, National Taiwan University, and Former CEO of Centre for Drug Evaluation, Taiwan*

As Good Review Practices (GRevP) were being developed in the Asia-Pacific Economic Cooperation (APEC) region from 2011-2015, it became clear that the quality of submission was an issue for regulatory agencies. This prompted the concept of Good Registration Management, a collaborative effort between agencies and industry to bring together GRevP and Good Submission Practices (GSubP). This was proposed to the APEC Regulatory Harmonisation Steering Committee in 2015 and subsequently adopted by its members. The roadmap for GRevP in the APEC region was then revised to promote Good Registration Management i.e. GRevP and GSubP in parallel. A series of APEC workshops between 2015-2019 helped to enhance discussion on Good Registration Management and improve understanding between regulatory agencies and industry.

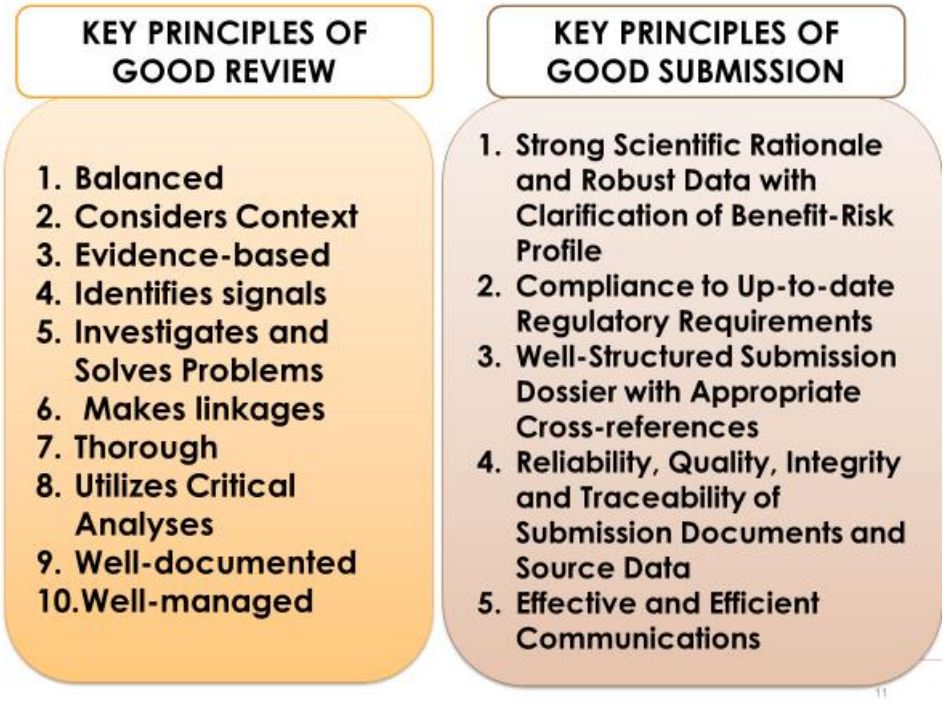
While GRevP aim to strengthen the performance, predictability and transparency of agencies, the objective of GSubP is to improve the quality of regulatory submission as well as its management. GSubP is an industry practice for any aspect related to the process, format, contents and management of submission for registration of medical products. To promote continuous improvement, all aspects of GSubP should be evaluated and updated on an ongoing basis.

GRevP and GSubP are complementary so it is necessary to promote both concomitantly to enhance overall quality and efficiency of the medical product registration process. GRevP and GSubP guidelines have a similar structure in that both focus on key principles of good review/submission (see below), management of review/submission, communications and competency and training.

A good regulatory submission should be based on a strong scientific rationale and clear benefit-risk profile, be well-structured and compliant with current requirements, contain reliable documents/sources and provide efficient and effective communications. Good management of submissions includes planning using checklists, templates, glossary, timeline tables etc, preparation and submission of the application dossier and quality checks. Good communications must apply within an applicant's organisation as well as with the review authorities.

Agencies can help to improve submission quality through regulations, communications and training. For example, the Taiwan Food and Drug Administration (TFDA) and Centre for Drug Evaluation (CDE) have held stakeholder meetings, consultations and educational workshops for industry as well as a preview service for generic applications from local pharmaceutical companies. The CDE also encourages reviewers to design training courses aimed at technical personnel within companies. So far over 425 people have attended these training courses covering a range of topics from data preparation of cell, manufacturing and control for early cell therapy trials to economic evaluation and budget impact analysis in Health Technology Assessment (HTA).

To achieve excellence in registration management, regulatory agencies and industry should collaborate and build mutual conversation that promotes better understanding of one another. GRevP and GSubP must be promoted in parallel to enhance overall quality and efficiency of the medical product registration process.



Measures of and influences on efficiency and effectiveness of the regulatory approval process – agency and company perspective

Dr Neil McAuslane, *Director, CIRS*

While efficiency is about making the best possible use of resources, such as the time taken to approve a new medicine, effectiveness relates to getting the right things done, for example, the number of approved medicines within the target timelines, which are good quality, safe and effective. When regulatory agencies are looking to identify areas for improvement, it is important that they consider how to go beyond efficiency and ensure that they are also effective. Nevertheless, efficiency and effectiveness are coupled together, so the overarching aim should be to achieve agency goals with high productivity and no waste of resource.

To get a better understanding of the measures and influences of regulatory efficiency and effectiveness, CIRS carried out a survey of companies and agencies. The objectives of the study were to:

- Identify criteria that agencies use to determine the efficiency and/or effectiveness of the regulatory approval process and what is measured
- Determine what measures, influences and activities within the approval process can enable an efficient and effective review process
- Develop a framework with the OpERA programme based on current criteria and activities to enable agencies to evaluate their process and implement efficiency and effectiveness measures.

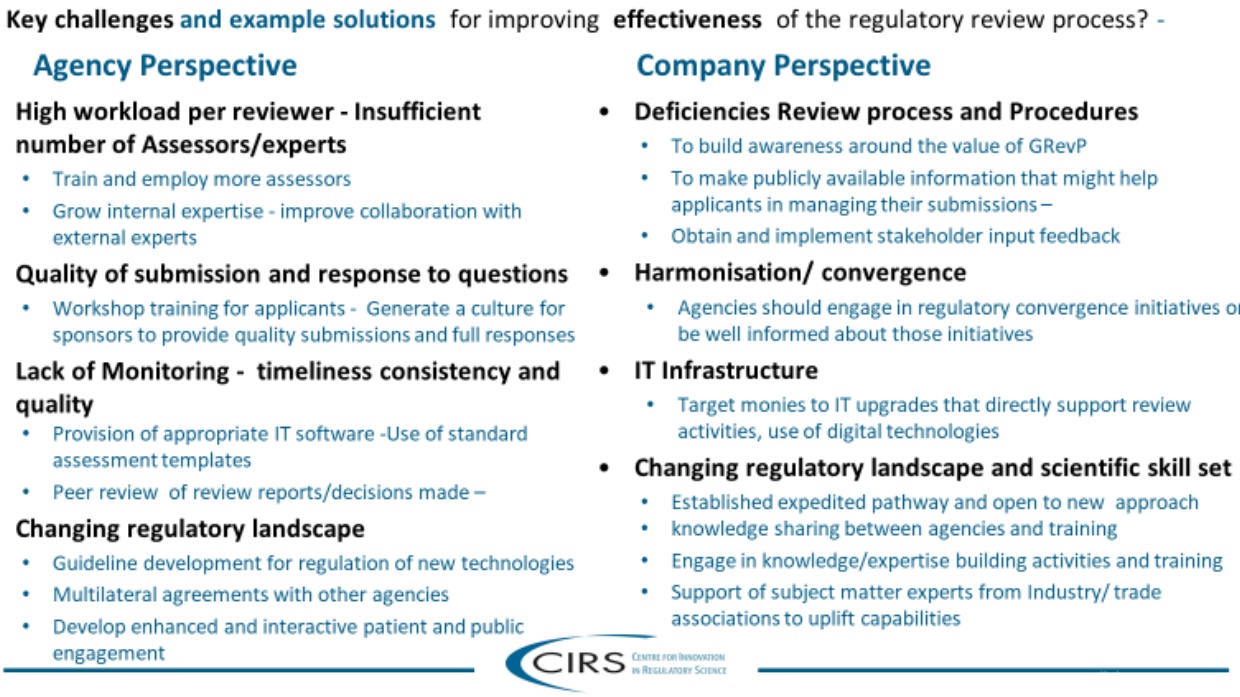
A total of nine companies and 10 agencies from various jurisdictions responded to the survey. When asked about the measures they have in place to measure the effectiveness of the review process, 80% agencies reported having formal measures, which included outcome measures, such as the percentage of applications processed/approved/rejected/withdrawn within the target time, and routine assessments or audit reports, such as management and quality control indicators. Company respondents were in agreement that agencies should have outcome measures in place, though they also highlighted the importance of measures of transparency, consistency, quality, engagement and alignment.

Agencies and companies were also asked to rate 40 activities in terms of their influence on review effectiveness so that their responses could be compared. Both stakeholders agreed that regulatory convergence and adoption of international standards, formal and regular in-house seminars and training workshops, and quality of the submission were major influences on review effectiveness. Other activities rated highly by companies but less so by agencies were transparency and clarity of review process, pre-submission meetings, complete answers to agency questions, commitment to reliance practices and company transparency.

From an agency perspective, key challenges for improving effectiveness of the review process were high workload per reviewer, quality of submission and response to questions, lack of monitoring (including IT infrastructure) and the changing regulatory landscape (see below). While companies also recognised the challenge of IT infrastructure and the changing regulatory landscape, they also highlighted deficiencies in review process and procedures and harmonisation/convergence as key challenges.

Finally, the survey investigated what actions applicants could take to help agencies improve their effectiveness. Company and agency respondents agreed that applicants should ensure quality of submission and response as well as engaging in effective dialogue with agencies. Agency respondents also highlighted that applicants should be transparent in their interactions and help agencies to reduce waste of resource by requesting the use of reliance models and being well informed of regulatory requirements. Similarly, company respondents indicated that applicants should ensure training of staff and support convergence/harmonisation by advocating for international standards and adoption of reliance models.

In summary, the survey showed that most agencies have formalised measures of effectiveness and identified several activities that can have a major influence on an agency's effectiveness, both within the agency and by sponsors. These included regulatory convergence and adoption of international standards, formal and regular in-house seminars and training workshops for reviewers, and quality of the submission. Key challenges that agencies reported in improving their effectiveness were around the need for more well-trained assessors, an IT infrastructure that is fit for purpose and evolving as the regulatory landscape changes. The survey results have been used to provide information for this workshop's breakout sessions and in future will be integrated into an R&D Briefing and used alongside the workshop outcomes to facilitate regulatory strengthening through the OpERA programme.



Section 3: Breakout discussions

Breakout A

What activities should agencies consider implementing that inform on and improve the effectiveness of the review at the organisational and individual level? How can these be used in practical ways to optimise performance?		
15th September (Asia meeting)	**Chair**	**Dr Siu Ping Lam,** *Director, Licensing Division, MHRA, UK*
	Rapporteur	**Dorte Strobel,** *Senior Manager, Head of Global Regulatory Intelligence, LEO Pharma, Denmark*
16th September (Americas meeting)	**Chair**	**Dr J Patrick Stewart,** *Director General, Therapeutic Products Directorate, Health Canada*
	Rapporteur	**Jorge Azar,** *Senior Area Regulatory Director Latin America, AstraZeneca, USA*

Please note: the breakout groups on both days were asked to examine the same three questions, so the results presented here are an amalgamation of the key discussion points from both groups.

Background

Regulatory authorities are already being evaluated quantitatively, measuring the overall time spent on the approval of new medicines, and qualitatively to assess the quality of the regulatory review process as defined by Good Review Practices.

Improving agencies' performance needs a clear understanding of systems and processes in place. This requires operational measures to be put in place.

The question for agencies when identifying areas that need improvement is how to go beyond efficiency and ensure that they are also effective (doing the right thing - goals) focusing on the right aspects of the review and utilising the correct pathways/tools so that they are adding value to the process and the quality of the review is not being compromised. It is therefore important that agencies also have measures of effectiveness but ensure that these are balanced with an efficient process.

One measure of an agency's effectiveness could be whether they are meeting the objective of ensuring availability of safe, efficacious and quality medicines to patients in a timely manner. However, to achieve this, agencies need to build into the review system both effective and efficient (doing the process in a timely, correct manner) processes and activities as well as implementing how these will be measured.

This is becoming more important as agencies look to conserve resources and change review process by adding new pathways such as facilitated regulatory pathways and reliance models. However, regarding an agency's effectiveness, this can be perceived differently by stakeholders i.e. a company perspective will differ from that of the reviewer on what makes up an effective regulatory approval process.

The key considerations for discussion from this breakout are:

- Why should agencies implement activities that improve effectiveness – what is in it for the agency?
- How can these be used to optimise an agency's performance?

- What are the key challenges for the agency to implement or improve the effectiveness of the regulatory review process?

Discussion results

What are the main drivers or incentives for an agency to implement activities or measures that inform on or improve the effectiveness of the review process at either the organisational or individual level?

What specific activities could an agency consider taking, which would improve its effectiveness and help optimise its performance with respect to authorisation reviews?

- Harmonise requirements to support the use of reliance
- Learn from other agencies e.g. measures taken or expertise available
- Provide internal training to align reviewers e.g. distinguish between 'need to know' and 'nice to know' questions
- Adhere to timelines in order to manage expectations and strengthen the focus during review
- Implement quality measures and monitoring
- Implement new pathways, reliance and other initiatives in order to share learnings with other agencies
- Translate guidelines/publications and allow enough time for consultation with industry
- Improve clarity of guidance documents and implement SOPs
- Provide pre-submission meetings and early scientific advice (jointly with HTA bodies if such system exists) to encourage a more consistent review and better use of resources
- Improve transparency

What are perceived as the main barriers or challenges that agencies face in implementing activities that can improve the effectiveness of the review process?

Challenges	Solutions
Change of mindset in agency e.g. relying on others, both at individual and agency level	Implement culture change from the top, with a clear direction and effective change management strategy Run pilots, increasing scale and scope over time Assess gaps that are preventing trust Increase acceptance to take risks e.g. use risk-based approach as part of the learning pathway Leverage where industry may be able to support agencies Promote opportunities for knowledge sharing e.g. secondments for reviewers
Quality and complexity of submission	Provide training on different topics e.g. Common Technical Document (CTD), new clinical trials approaches Work in partnership with mature regulatory agencies. Develop a robust IT platform to manage drug submissions, while ensuring the right IP protection and exchanging information with other agencies.

Lack of systematic quality management systems and training on decision making	Promote structured approach to quality decision making using tools such as Quality of Decision-Making Orientation Scheme (QoDoS) and implementing training
Resource, skillset and/or legislation may need to change	Consider support from external advisors, subject matter experts and industry. Promote agency collaborations
Knowledge barriers as new areas of technology evolve	Hire new staff or train staff, possibly by experts at other agencies Leverage where industry may be able to support agencies
Transition period	Run the 'old' and 'new' systems in parallel until the benefits of the new system are realised. However, this approach may require more energy.
Convergence, harmonisation, adoption of international standards	Have clear international guidance e.g. from WHO, PAHO, ICH and other international organisations to speed up training and adoption of international standards. Harmonise competing international and domestic requirements

Breakout B

What would be the key performance indicators that an agency should consider that would provide feedback to the agency and other stakeholders on the effectiveness of their regulatory approval process?		
15th September (Asia meeting)	**Chair**	**Dr Alizera Khadem,** *Scientist, WHO, Switzerland*
	Rapporteur	**Dr Sannie Chong,** *Asia Pacific Technical Regulatory Policy, Roche, Singapore*
16th September (Americas meeting)	**Chair**	**Dr Jude Nwokike,** *Vice President & Director, US Pharmacopeial, USA*
	Rapporteur	**Leonardo Semprun,** *Global Regulatory Policy Director – LatAm, MSD, Panama*

Please note: the breakout groups on both days were asked to examine the same three questions, so the results presented here are an amalgamation of the key discussion points from both groups.

Background

Regulatory authorities are already being evaluated quantitatively, measuring the overall time spent on the approval of new medicines, and qualitatively to assess the quality of the regulatory review process as defined by Good Review Practices.

Improving agencies' performance needs a clear understanding of systems and processes in place. This requires operational measures to be put in place. CIRS through the OpERA programme is enabling agencies to embed a performance driven culture to measure where time is spent in the approval process, both their time and company time.

The question for agencies when identifying areas that need improvement is how to go beyond efficiency and ensure that they are also effective (doing the right thing - goals) focusing on the right aspects of the review and utilising the correct pathways/tools so that they are adding value to the process and the quality of the review is not being compromised. It is therefore important that agencies also have measures of effectiveness but ensure that these are balanced with an efficient process.

One measure of an agency's effectiveness could be whether they are meeting the objective of ensuring availability of safe, efficacious and quality medicines to patients in a timely manner. However, to achieve this, agencies need to build into the review system both effective and efficient (doing the process in a timely, correct manner) processes and activities as well as implementing how these will be measured.

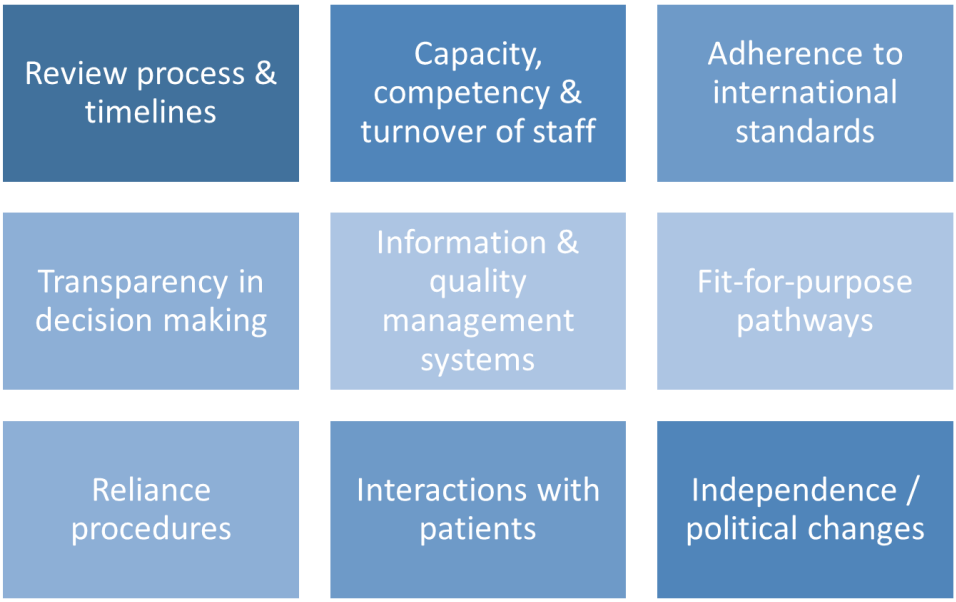
Regarding what measures of effectiveness an agency should employ, the key considerations for discussion and recommendation from this breakout are:

- What **areas of the approval process** should an agency have Key Performance Indicators (KPIs) for?
- What **would be the KPIs** that an agency should consider that provide feedback to the agency and to other stakeholders- companies, patients, policy makers?
- As a proxy measure, **what information should agencies seek from stakeholders** to determine the effectiveness of the agency's processes?

Discussion results

*What are the main activities/processes that an agency undertakes in the approval of medicines for which KPIs for effectiveness need to be considered?**

Agencies should consider developing KPIs for effectiveness in relation to:



*Due to limited time, specific KPIs were not suggested for all the above areas so further development may be needed.

What KPIs (either direct or proxy measures) would be the effectiveness KPIs that an agency should consider that provide feedback to the agency and to other stakeholders (companies, patients, policy makers)?

Activity/Area	Effectiveness KPI
Regulatory process and timelines	% of products (New Drug Applications, post-approval variations, reliance pathways etc) processed within published timelines % of products backlogged in the queue, time taken to pick out product from queue to start of evaluation Predictability and turnaround time on post-approval variations Post-marketing surveillance including alerts and recalls Supply chain integrity
Capacity and competency of staff	Reviewer's risk-based approach, effective reliance (based on information sharing) rather than full review in the name of reliance Number of products using reliance pathways Quality of questions, limited cycles of List of Questions

Applicability of international standards to review process	Level of adoption of international standards vs local mechanism % applications in Common Technical Document (CTD) format
Information management system/Quality management system	Use of electronic/digital platforms Tracking systems in place for applications and processes Communications with other agencies and stakeholders
Reliance procedures (and other non-standard regulatory pathways)	% of reviews guided by reference agency Public Assessment Reports (PARs) or unredacted assessment reports Level of engagement with health authorities in information sharing initiatives, work sharing or reliance
Transparency in decision making	Compliance with Good Regulatory Practices and Good Review Practices Number of regulations - regulatory impact analysis Communication channels in place that allow input from stakeholders e.g. audience, hearings, interactions, dialogue Patient involvement in regulatory process
Adequate and appropriate pathways	Review timelines for various pathways, including accelerated pathways for products with unmet medical needs

Stakeholder feedback can also be utilised to measure the agency effectiveness of the review process. Therefore, if an agency wanted to survey companies as to their perception of the agency's effectiveness, what would be the key components/areas or activities that would be of value in order to help an agency optimise their effectiveness?

From a company perspective, **transparency** and communication are key areas in which an agency can optimise its effectiveness. Assessment reports must be publicly available to inform stakeholders on the basis for the decision, in addition to a list of approved products. There should be clarity in an agency's requirements and processes and clear communication channels for which an open dialogue can easily be pursued.

In relation to **risk-based approaches**, companies may wish for agency feedback on whether the decisions of mature agencies were considered. In addition, companies would find it useful to know how different agency activities are aligning or work sharing e.g. GMP inspections as well as other types of joint decision making.

Agency **outcome measures** that companies would find valuable include number of first cycle reviews, number of requests for additional information during review and common deficiencies observed in dossiers and how to avoid them. Agencies may also find value in seeking company feedback on the relevance and quality of reviewer questions as well as the predictability and consistency of the review process.

Breakout C

How could the actions/activities of applicants/sponsors be improved to enable agencies to improve their review effectiveness?		
15th September (Asia meeting)	**Chair**	**Dr Virginia Acha,** *Associate VP and Global Lead, Global Regulatory Policy, MSD, UK*
	Rapporteur	**Dr Vivien Woodworth,** *Regulatory Science Specialist, H.Lundbeck A/S, Denmark*
16th September (Americas meeting)	**Chair**	**Ginny Beakes-Read,** *Executive Director GRR&D Policy, Amgen, USA*
	Rapporteur	**Raul Stucchi,** *Director, Regulatory Affairs, Latin America, Eli Lilly and Co, Peru*

Please note: the breakout groups on both days were asked to examine the same three questions, so the results presented here are an amalgamation of the key discussion points from both groups.

Background

As regulatory agencies seek to enhance the efficiency and effectiveness of their dossier assessment process, they are introducing many measures that will help them achieve this. These include system indicators relating to efficiency, which look at input (e.g. number of applications received), output (e.g. number of applications reviewed), performance (e.g. % approvals completed within the timeframe), resource per output (e.g. time to undertake the clinical/CMC\safety review) and quality of the process.

One area that regulators agree can have a major influence on the effectiveness of the review are the actions and activities of sponsors, particularly regarding the quality of the submission.

However, regarding an agency's effectiveness, although this can be perceived differently by stakeholders (i.e. a company perspective will differ from that of the reviewer on what makes up an effective regulatory approval process) agencies and companies do understand that for agencies to maximise their effectiveness and meet their targets, input should be made from all stakeholders.

This has led to the development and promotion of Good Submission Practices (GSubP) and Good Review Practices (GRevP) as a way of building quality into both the submission and review, which in turn will improve the effectiveness of the review process.

This breakout group were asked to consider how and in what way the **actions/activities of applicants/sponsors can be improved** to enable agencies to improve their review effectiveness?

The key considerations for discussion were:

- What activities can a sponsor/applicant do to help enable an effective review process?
- What activities can an agency do to help sponsors implement these activities?
- How can these be used to improve agencies' review effectiveness?

Discussion results

What activities can a sponsor/applicant do to help enable an effective review process?

Dossier quality

Identify issues within the dossier before submission, considering mitigation strategy and review prioritisation.

Ensure same information is submitted that was submitted to reference agencies.

Convey clear messages throughout the dossier.

Engagement

Engage in dialogue even before submission (collaboration model).

Be well prepared for pre submission meetings.

Ensure a scientific focus to all dialogue.

Contribute to building agency competency e.g. through trade association.

Transparency

Provide all core documents to support reliance models and build trust.

Avoid hiding weaknesses in the dataset.

Seek clarity on what the agency is asking for in order to provide the right documents and avoid post submission requests.

Efficiency

Align with agencies' expectations in terms of timing and review efficiency e.g. responding promptly to questions.

Answer questions efficiently without 'nice to have' information, which could potentially lead to more questions

What activities can an agency do to help the sponsor/applicant implement these activities?

Review predictability

Clearly define requirements, guidelines, review practices

Track review milestones

Transparency in decision making – offer feedback on outcome

Engagement

Clear and open communication with sponsors

Let sponsors know about concerns – before submission and during the review process

Transparency

Ensure review process is visible e.g. timelines, decision making

Support reliance models by providing documents and tools to sponsors

Evaluate need for translations

Digital

Consider using electronic tools/documents for more efficient communication throughout the review process

What are the main effectiveness outcomes that an agency and applicant will achieve if the previously identified activities are implemented?

Potential outcomes	For whom	
	Agency	Applicant
Reduction of backlogs	✓	✓
Open communication / dialogue	✓	✓
Optimise predictability (quicker path to the right decisions)	✓	
Focusing resources more mindfully and avoiding duplication	✓	
Increased trust and transparency	✓	✓
More timely availability of medicines	Ultimately for patients	

Other issues for consideration

One issue that was raised during the breakout but could not be discussed in the time available was how sponsors might be able to provide training to enable agencies to improve their review effectiveness. It will be important to consider what type of training would have the most impact and how this could be provided/facilitated by sponsors without causing a conflict of interest.

Breakout D

Focus on the utilisation of an abridged reliance review process: what does an agency need from their reference agencies and from the applicant that can improve the effectiveness and efficiency of their reliance route?		
15th September (Asia meeting)	**Chair**	**Dr William Wekwete,** *Head, Evaluations and Registration, Medicines Control Authority, Zimbabwe*
	Rapporteur	**Dr Bettina Doepner,** *Global Lead Regulatory Intelligence and Policy, Director, CSL Behring, Germany*
16th September (Americas meeting)	**Chair**	**Sebastian Duarte,** *Director of the Institutional Relations and Regulation, ANMAT, Argentina*
	Rapporteur	**Michael Cunha,** *Senior Director, Regulatory Policy and Intelligence, Bayer, USA*

Please note: the breakout groups on both days were asked to examine the same three questions, so the results presented here are an amalgamation of the key discussion points from both groups.

Background

To ensure they are using their resources effectively and efficiently, regulators are increasingly using "abridged assessment routes" in which they review selected portions of submission documents to help inform their decision, allowing them to rely on observations from prior analyses so as to be able to focus on added value assessment not readily supported by the reference agency(s) decision documentation. As a reminder:

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; prequalification process of WHO; regional and consortium work sharing; and individual agencies regulatory pathways (verification and abridged reviews) which will vary, depending on whether the medicines has already been reviewed by one or more comparable or reference agency.

An abridged review can be used when the product has been registered by a reference regulatory authority; the abridged assessment evaluates use under local conditions and regarding local regulatory requirements while relying on prior decisions to inform the local decision. This model conserves resources by not re-assessing scientific supporting data that has been reviewed and accepted elsewhere. For example, this may focus on:

- a review of the pharmaceutical (CMC) data in relation to climatic conditions etc
- benefit-risk assessment in relation to use in the local ethnic population.

Recently, several agencies have implemented reliance-based abridged routes. These pathways have raised questions; importantly for this breakout:

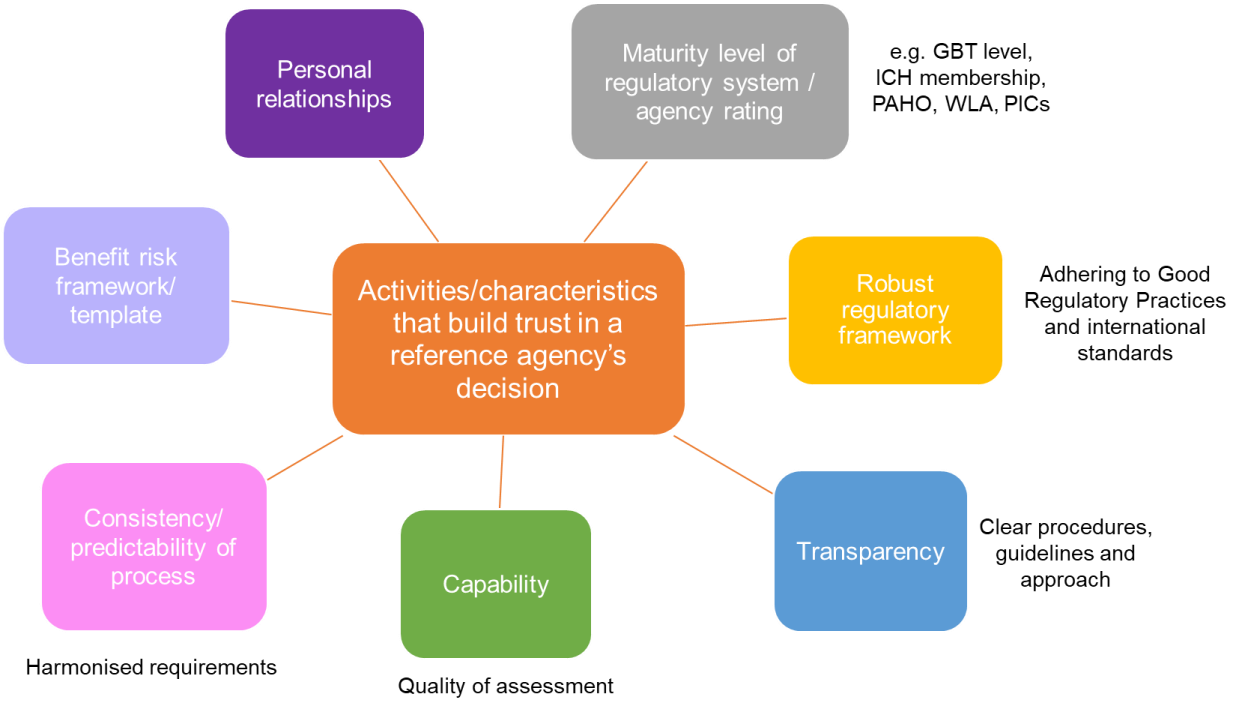
- What information should an agency request from the reference agency and from the sponsor?
- What are the areas a company can proactively aid an agency with an abridged review reliance model?

- What are the sections of the submission the agency should specifically review and in what depth?

Therefore, in respect to the use of an abridged reliance review process, the key question for this syndicate can be summarised as: What does an **agency need** from their reference agencies and the applicant that can **improve the effectiveness and efficiency** of their reliance route?

Discussion results

What are the main domain areas that one agency needs to see are in place in another (reference) agency if they wish to rely on or have trust in the decision made by the other agency?



*What are the types of documents that an agency would like to have from a **reference agency** to support its decision making when using an abridged review process?*

- Redacted (or unredacted) assessment report – a good starting point with enough information to inform a benefit-risk decision
- Summary of the approval process including the criteria considered for the decision
- Scientific comments and responses from the applicant (Q&A documents) – facilitate review by avoiding duplication / same questions being asked
- Communications and interactions with other agencies – may help to improve the relying agency's understanding and provide a more detailed explanation of key areas that may be encountered, therefore avoiding duplication.
- Inspection documents
- Certification of Pharmaceutical Product (CPP) – provides a level of confidence that 'sets the tone' for review. The CPP is a legal requirement in some countries e.g. Brazil, Argentina and should be issued by the certifying authority rather than the manufacturing site.
- Post marketing experience

*What are the types of documents that an agency would like to have from the **submitting company** to support its decision making when using an abridged review process?*

- Full dossier and Q&A
- Proof that the product is identical (verifying the source of Active Pharmaceutical Ingredient) or if there are differences, these should be disclosed and a justification provided
- Common Technical Document (CTD) – there may be challenges providing all sections of the CTD due to confidentiality and limited data protection in some countries, but sections that address local requirements around stability studies, container closure etc are important.
- For post approval changes – designation of classification of change in reference country
- Ongoing benefit-risk assessments

Other issues for consideration

An issue that were raised during the breakouts but could not be considered during the time available was the expectation of each stakeholder involved in abridged review (relying agency, reference agency and sponsor). In addition, there was a discussion on the redacting of documents e.g. how much commercially sensitive information is necessary for an abridged review? EMA redacts personal data and confidential commercial information, unless the company agrees or there is a confidentiality arrangement in place. Chemistry, Manufacturing and Controls (CMC) is considered the most commercially sensitive information but is probably the most useful for reliance.

Future thinking - improving the effectiveness of the submission and review using Cloud-based approaches

Dr Thomas Kühler, *Head of Global Regulatory Science and Policy EU/AMEE, Sanofi, France*

Dr Felipe Dolz, *Head, Global Regulatory Science & Policy, Sanofi, USA*

Please note – these speakers gave separate presentations[‡] but this summary amalgamates key points from both.

Currently, regulatory filings (dossiers) represent a static snapshot in time of the available information on a product's benefit-risk (BR) profile. A dossier is replicated multiple times at company and agency levels and global registration requires multiple and repetitive filings. Organisational structures on both sides tend to contribute towards creating barriers to effective intra and intermural information sharing.

The static nature of dossiers and the administrative burden associated with filings could be overcome and reduced by using a common (Cloud-based) platform as a single global data repository. Cloud-based is nothing new but the 'norm' for contemporary data storage and handling: namely a distributed set of servers that could be owned and operated in a central or federated fashion. This provides a contemporary and scalable online architecture that is accessible 24/7. Indeed, once data has been captured and uploaded to the Cloud, it could be accessed and assessed by a regulatory agency (or even multiple agencies) in real time.

In addition, Cloud-based platforms are amenable to the integration of advanced analytics such as artificial intelligence (AI) and machine learning (ML) technologies. This could create a sort of self-learning and self-sustaining system, monitoring that the BR criteria remain within prespecified boundaries. As new data is gathered, these advanced analytics technologies could lay the foundation for regulatory actions such as label expansions or pharmacovigilance follow-up measures. If the data ever fell outside of the agreed operating space, the regulators would be alerted and could then act accordingly e.g. request more studies, re-negotiate the label, or request a product recall.

Cloud-based solutions must be cybersafe to ensure that patient-sensitive data is kept secure and that commercial confidentiality for the sponsor is maintained. Integrated AI or ML technologies must also be protected from potential alteration or manipulation that could result in a change in outcomes.

Cloud-based regulatory filings have several benefits, including being paperless, available in real time, collaborative, transversal, innovative, and can facilitate work-sharing between regulators, see infographic below. However, there are also a number of issues that need to be addressed, such as:

- Who owns the data platform - third party(ies), regulator(s), sponsor(s), or private-public partnership(s)?
- Does the platform need to be mirrored or replicated for security and accessibility reasons?
- Who is responsible for guaranteeing the quality and safety of the platform and its operations – are service level agreements required?
- Who should have access to the platform and to what level?
- Are data sharing agreements needed – is consent from patients and other stakeholders required to upload sensitive data?

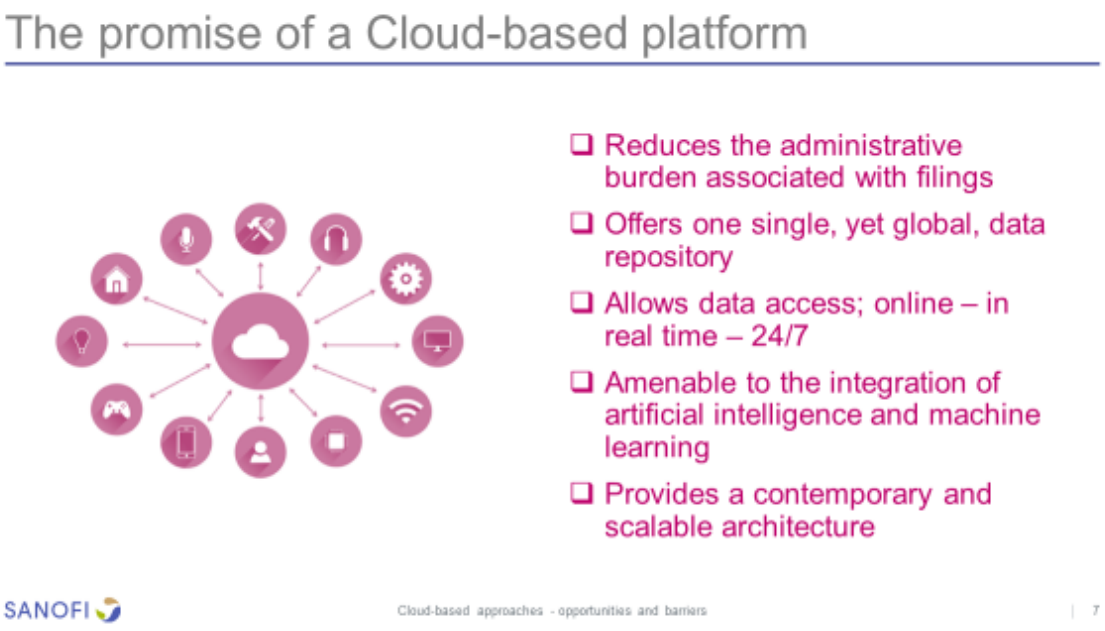
[‡] Dr Kühler spoke at the Asia meeting on 15 September and Dr Dolz spoke at the Americas meeting on 16 September.

- What do the legal frameworks in different countries allow one to do and not to do?
- What are the 'cultural considerations' for working in this way e.g. are agencies concerned about the impact on revenue streams and fees?

Sanofi is discussing Cloud-based regulatory filings with a number of stakeholders through different channels, including industry fora, public consultations, conferences, think tanks, publications and directly with regulators including the FDA on its Technology Modernisation Action Plan, the EMA, the Dutch Medicines Evaluation Board and the UK's MHRA. At the global level, the Hever and Charles groups, which is made up of R&D heads of top pharmaceutical companies and heads of Regulatory Affairs, respectively, have signed off on a pilot Cloud submission system called Accumulus Synergy. This will be run as a non-profit and is being initially financed by 10 leading pharma companies.

At the EU level, a number of member states have launched Project GAIA-X, which aims to create a data infrastructure in Europe for not only the pharma sector but also for any sector where huge data sets need to be shared in an open and secure way. The European Federation of Pharmaceutical Industries and Associations (EFPIA) has also created a working group to better understand what dynamic regulatory assessment will mean for regulators and industry in the EU and to reduce Cloud-based concepts into tangible practice.

In summary, multinational companies have signalled that they are ready to partner to accelerate adoption of Cloud-based strategies and regulatory authorities have expressed an interest in a continued dialogue. These are positive steps towards the integration of Cloud-enabled practices in drug regulation, though several issues remain to be addressed. A coordinated strategy between industry and regulators will be essential for taking this vision of a dynamic assessment model forward.



Appendix: Workshop attendees

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