Practical implementation of reliance models:

What are the barriers and facilitators to the successful application of these models for innovative medicines, generics and variations?

7-8 March 2018
Sandton, South Africa

WORKSHOP REPORT

CIRS Centre for Innovation in Regulatory Science

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Report date: 15 June 2018

Section1. Executive Summary

Background to the Workshop

A ***reliance model*** is defined by the World Health Organization 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". At the 2017 CIRS Workshop in Sao Paulo on this topic, it became clear that many agencies are interested in implementing these types of risk-based evaluations and would like to understand when and how they could and should practically implement a reliance model within their jurisdictions. Other agencies currently utilising some form of reliance model are interested on how to enable their use more effectively across different activities that an agency conducts.

At the Workshop, a number of recommendations were made to explore reliance models further, to identify good reliance practices as well as the practical implications of the different ways to benefit from such a model. Indeed it was suggested that although important for the review of new medicines, the concept of reliance can also be utilised for other aspects of an agency's work, such as the review of variations and generics, inspections, vigilance/surveillance and quality control. The key is having access to trusted reports from trusted sources.

Indeed, across mature agencies we have seen the increasing development of prioritised risk-based approaches to decision making and sharing of resources with such activities: e.g., reliance on inspections between EMA and US FDA; in the generics area, the ACSS Consortium (Australia, Canada, Singapore and Switzerland) have an initiative that has the aim of facilitating greater availability of generic drugs through the convergence of regulatory requirements and assessment approaches. The hope is to promote more efficient use of available resources, reducing regulatory burden and duplication of effort, as well as improving application approval times. The International Generic Drug Regulators Programme (IGDRP) has been created to promote collaboration and convergence in generic drug regulatory programs in order to address the challenges posed by increasing workloads, globalisation and complexity of scientific issues.

At the CIRS Workshop in Sao Paulo in 2017 it was recommended that agencies should also consider applying reliance approaches to post-approval activities**.** It was also suggested that it would be useful if models or experiences describing mechanisms in place by agencies for implementing risk-based approaches for post-approval changes based on reliance or other efficiencies could be discussed. For example, in the area of variations, agencies are starting to utilize risk-based approaches to identify changes that do not impact or have a minimal risk to the quality, safety or efficacy of a medicine; addressing a more efficient approach to submitting and reviewing these variations will reduce regulatory burden on the industry and in turn reduce unnecessary assessment work for the agency. Such approaches are in use by the EMA and are currently being evaluated by agencies like TGA in Australia.

Therefore, as countries are developing their regulatory capabilities they are evolving to implement reliance or risk-based evaluation approaches which address resource issues as well as compliance and product risks.

The question is not if, but when, will agencies be able to implement a reliance model. Indeed, the continuing limitations of resources has the potential to drive greater focus toward risk-based/reliance models, focusing on what is locally critical (i.e., value-added) vs. what can be leveraged/relied upon from other trusted authorities, leading to improved allocation of scant local resources and improved medicine availability. These approaches allow agencies time to build their regulatory technical capacity in line with their mission and funding, but at the same time enable patient access to good quality medicines that are safe and effective. However, implementation of these prioritization approaches faces a number of challenges including legal, political, methodological, cultural and organizational. These can be helped by ensuring that agencies have the relevant capabilities, decision making frameworks and practices in place.

This Workshop was a follow-on from that held in 2017 in Sao Paulo entitled "Facilitating the review of new medicines through risk-based evaluations: How can a stratification process be utilised to achieve an effective use of resources?". This programme was reviewed and developed in discussion with the South *African Health Products Regulatory Authority*.

Workshop objectives

- Discuss when reliance models can and should be used (by design or default) as well as the frameworks, data and trust that need to be in place to enable effective and efficient utilisation of reliance models.
- Understand how to practically implement reliance models for decision making in the review of medicines, variations and generics and how agencies/consortia can overcome the implementation hurdles and focus on the benefits of utilising these approaches.
- Recommend practical and acceptable reliance models for evaluating new medicines, generics and variations and how to ensure the success of these as approaches to decision making that allow agencies to focus on value-added activities and provide timely patient availability to safe, effective good-quality medicines.

Welcome

Portia Nkambule, *Acting Chief Executive Officer (CEO), South Africa South African Health Products Regulatory Authority (SAHPRA)* welcomed representative from 13 countries to the CIRS Workshop, saying that the effectiveness of the plans and approach used to address the legally, technically and scientifically complex challenges of pharmaceutical regulation depends upon strategic-level leadership and new ways of working around the globe. This growing landscape requires regulators to consider regional, continental, and international collaboration approaches. South Africa supports all efforts to increase confidence and collaboration among regulators with the hope to promote more efficient use of available resources, reducing duplication of effort, and regulatory burden for both industry and regulators, as well as expediting approval timelines, which will facilitate timely patient access to much-needed medicines.

Key points from presentations

Centre for Innovation in Regulatory Science (CIRS) Executive Director, **Dr Lawrence Liberti** discussed the use of facilitated regulatory pathways (FRPs) based on reliance and recognition assessments, saying that these pathways flow from principles of good regulatory practices and require transparency and trust: in processes and systems and in regulatory decisions and their rationales these FRPs allow for added-value activities; that is, doing locally what is important without duplication, with efficient resource use. These pathways can reduce review times and expedite access to medicines and may have broader applicability than new molecular entities.

Dr Luther Gwaza, *Technical Officer, Regulatory Systems Strengthening, World Health Organization* agreed that use of the shared responsibility model is characteristic of the modern regulator who employs smart regulation including reliance, collaboration and work sharing, while differentiating regulatory tasks that cannot be fulfilled through reliance on other agencies. Through the use of such reliance methods as the WHO Prequalification Procedure and the Zazibona work-sharing collaborative as well as its laboratories for the testing and certification of pharmaceuticals and biologics, the World Health Organization is helping national regulatory agencies in low-income countries become part of regulatory networks to facilitate their need to apply appropriate standards that are scientifically justified and risk proportionate to protect public health while ensuring economic and industrial interests are not hindered.

The newly formed South Africa Health Products Regulatory Authority (SAHPRA) is exploring methods to manage a surge in generic applications and review backlog as well as resource constraints. **Andy Gray,** *Senior Lecturer, Division of Pharmacology, Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal, South Africa* explained that whilst SAHPRA recognition of other national regulatory authorities is challenging because of variable maturity levels of the potential reference agencies, absence of mutual agreements and challenges to ensuring sovereign decision-making South Africa is part of the successful and newly expanded Zazibona model of work-sharing and there is also potential for expanded use of the WHO Prequalification Collaborative Procedure. In addition, legal enablements are now in place for a potential new reliance approach that will include consideration of South Africa-specific factors and risk management issues in the South African context.

Ana Carolina Marino, *Advisor for the Directorate of Authorization and Registration,* the *Agência Nacional de Vigilância Sanitária (ANVISA), Brazil* reported that in February 2018, ANVISA initiated an optimised and detailed review process for the full review of applications for registration and post-approval changes for biological products previously registered by the US FDA and EMA. Requirements for this review include US FDA and EMA reports and the Product Leaflet. Other documents used to inform ANVISA's decision include Packaging Information; quality documents, or technical reports such as those for stability; transport validation and quality, safety and efficacy summaries from Module 2 of the Common Technical Document (in Portuguese). A similar approach to the review of new chemical entities is being developed and a strategy to

simplify the generic review process involving the European Directorate for the Quality of Medicines and Healthcare Certification of Suitability to the monographs of the European Pharmacopoeia is under discussion.

In Singapore, the Health Science Authority (HSA) employs a hybrid system of reliance-based and independent reviews. To leverage the work of reference agencies without compromising the robustness of the decisions HSA makes for the Singapore population, **Dr Agnes Chan,** *Director, Therapeutic Products Branch, Health Products Regulation Group, Health Science Authority, Singapore,* explained that the agency identifies elements in reference agency's benefit-risk assessment that are critical in the local context, bridging the benefit-risk assessments to local patients. Elements of reference evaluation that are relatively objective can be leveraged such as pre-clinical and early phase clinical study evaluation as well as CMC assessments with the same quality specifications; region-specific stability data may be needed to inform the local decision.

To further enhance cooperation among regulators, optimise work efficiency and improve workload management and regulatory assessment duration, the Association of Southeast Asian Nations (ASEAN) proposed the ASEAN Joint Assessment procedure for marketing authorisations in which the same application is simultaneously submitted to all participating ASEAN national regulatory agencies (NRAs) and assessment work is carried out as a group with one report but with each NRA making its own final decision. **Dr Ramli Zainal,** *Director, National Pharmaceutical Regulatory Agency (NPRA), Malaysia,* informed Workshop participants that in addition to participating in the ASEAN Joint Assessment procedure, NPRA is considering other risk-based approaches to regulation in which the agency would rely on the word of other trusted regulatory agencies and focus on those areas which present the greatest risk to the population of Malaysia. The agency is also taking steps to optimise the use of available regulatory resources in the categories of structure, process and outcomes.

In the European Union, regulatory reliance through mutually recognised European Commission procedures reduces the duplication of effort and facilitates the review of an average of the 40 applications for marketing authorisation for new active substances and 1500 applications for generic medicines that are submitted each year. **Dr Siu Ping Lam,** *Director, Licensing Division, Medicines and Healthcare products Regulatory Agency (MHRA), UK* detailed the three routes for licencing of medicines in the EU. In the National route, a single EU member state provides marketing authorisation for a new product, which is only recognised in that member state; in the Mutual Recognition/Decentralised routes, a single EC member state provides marketing authorisation which is recognised by selected or all EC member states and in the Centralised route, a "community" marketing authorisation is recognised by all EC member states. Generic medicines are typically reviewed through the National route but the Centralised procedure can be used for the review of generics of centrally authorised new active substances of significant therapeutic, scientific or technical innovation or in interests of patients at community level.

Bruce Randall, *Director, Bureau of Therapeutic Sciences, Therapeutic Products Directorate, Health Canada* discussed the Generic Medicines Work-Sharing Trial (GMWST), an initiative of the consortium of regulatory authorities in Australia, Canada, Switzerland and Singapore (ACSS), focussed on information- and work-sharing projects as proof of concept for larger-scale initiatives. In the GMWST, similar to the EU Decentralised

Procedure, marketing authorisation applications were sought for submission to a Reference Regulatory Agency and three or four Concerned Regulatory Agencies. In the first trial, good communication and coordination proved to be essential. The complexity of the first submission required extra time to respond to questions and an extra round of evaluation, resulting in a timeframe of 9 months rather than the targeted 5 months; however, this still represented time and cost savings for both regulatory agencies and sponsor. An agreement has been reached to expand the scope of the project and submissions for additional trials are currently being sought.

Harmonisation and work sharing are feasible and remain the best reliance models to address the challenge of access to essential medicines in low- and middle-income countries. In discussing this model in terms of the accomplishment and yet-to-be-achieved goals of the East African Community (EAC) Medicines Regulatory Harmonization Programme, **Dr Yonah Hebron**, *Manager, Medicines and Cosmetics Laboratory, Tanzania Food and Drug Authority* reminded the Workshop that the existence of structured national medical regulatory authorities in EAC Partner States is important to realise the goals of medical regulatory harmonisation and a robust, regional binding legal framework is required; furthermore, regulatory decisions must have legal force. Medical regulatory harmonisation, however, is an important goal that can result in effective control, reduced cost and faster and expanded access to medicines and increased treatment options.

Dr Paul Huckle, *Chief Regulatory Officer and Senior Vice President, GlaxoSmithKline, USA* described the overwhelming number of global applications for post-approval product changes which, combined with extreme divergence in regulatory classification and procedures can result in lengthy delays in worldwide approvals. Adopting a risk-based approach to the review of post-approval changes would focus resources on changes with potential for biggest impact. Further convergence toward a global standard for data requirements and the implementation of international guidelines would reduce complexity and also expedite approvals. Industry can facilitate the use of reliance pathways by actively promoting convergence, trust and transparency and by exploring available alternatives. Implementing these recommendations will result in better use of regulatory resources, a reduction in complexity and development cycle time for industry and ultimately, in expedited access to medicines.

The abundance and diversity of global supply chains, manufacturing sites and processes and tests and analyses have exponentially increased the number and complexity of variances for approved medicines. **Dr Paul Dearden,** *Head, International, Regulatory Policy and Intelligence, AbbVie, UK* proposed four potential solutions to the challenges posed by global variations. The first is regulators' use of a consistent, standardised variation classification system that is tiered or risk based. Second is industry's development of best practices for the management of variations and utilization of accepted change management processes before and during the implementation of those practices. Third is regulators' adoption of the aligned data and documentation requirements developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the World Health Organization (WHO) and other groups. Finally, regulators should have transparent and predicable timelines for review and implementation of variations.

Dr Jenny Burnett, *Director, Scientific Operations Management, Scientific Evaluation Branch, Therapeutic Goods Administration (TGA),* Australia explained the implementation of the Medicines and Medical Device Reform in Australia as it applies to post-market variations. In the first phase of this implementation in 2017, TGA established a consistency across all classes of goods regarding self-assessment variation types, consistent with other regulatory agencies such as the European Medicines Agency and an automated process to manage risk. The new notification process is now nearly fully automated, consisting of an electronic application, payment of invoice, acknowledgement, submission to the Australian Register of Therapeutic Goods and filing of the variation. Within the new system, there are set options and validation rules built into the electronic form and automatic recording of notifiable change. When using the new system, sponsors select correct variation type, sign off on assurances that conditions have been met but must written TGA approval before variation implementation. Critically, there is ongoing assurance of compliance with good manufacturing processes. These changes have resulted in very low TGA risk and effort for these notifiable change variations

Recommendations from across the Roundtable discussions

Building trust into the reliance approach: What are the building blocks that need to be in place and how can companies and agencies facilitate the process?

- Develop a constructive benchmarking model for the elements of trust contained within current systems.
- Engage in programmes of training and capacity building in the development and regulation of medicine, such as the World Health Organization Centres of Excellence.
- Ensure the ability of authorities using reliance-based reviews to continue to make their own informed decisions to protect public health.

Practical implementation of an abridged review process for new medicines: where should an agency focus and what are the practical steps needed to change process and mind-sets?

- CIRS should carry out a study identifying the requirements of different agencies conducting abridged reviews.
- Determine what reports and data are available from different reference agencies, including whether they are redacted and the timelines for their availability.
- CIRS should develop a database consolidating available information concerning what agencies evaluate in an abridged review.

Opportunities for applying reliance approaches to variations (CMC and safety) and impact on local labelling

- In the short term, establish a classification system for CMC variations that is harmonised and converged. In the long term, align CMC variations with ICH Q12.
- Consider regional work sharing to expedite safety variations.
- Establish baseline timelines for variation changes and periodically reassess after implementation of reliance-based models to assess effectiveness.
- Continue to build confidence and trust through the exchange of reports under mutual recognition agreements, training of assessors through exposure to the reports of reference regulators, the convention of workshops, conferences and webinars, the publication of reliance success stories and the cross-regional exposure of maturing to established agencies.

Instigating a reliance review model for generics – How could this be done practically and what would be needed from companies and agencies?

- Harmonise data requirements for generic medicines.
- Develop tools or guidance on good review practices to facilitate use of the reliance or risk-based approaches.
- Provide information or publication on all the reliance models that exist including implementation models or roadmaps and agencies can select options suitable for their context based on workload and or regulatory capacity and capability.
- Agencies should benchmark timelines and monitor performance for different pathways.
- Develop a credible and appropriate model for increasing access to generic medicines.

PROGRAMME

SESSION: RELIANCE MODELS FOR THE REVIEW OF NEW MEDICINES: PRACTICAL IMPLICATIONS AND POTENTIAL OPPORTUNITIES	
Chair's welcome and introduction	**Professor Helen Rees,** *Chair, Board of South African Health Products Regulatory Authority (SAHPRA)*
Country welcome and introduction	**Portia Nkambule**, *Acting CEO, SAHPRA, South Africa South African Health Products Regulatory Authority (SAHPRA)*
Reliance based models of review - How do these fit within good regulatory and good review practices?	**Dr Lawrence Liberti**, *Executive Director, CIRS*
21st century best regulatory practice: The role of good reliance practices	**Dr Luther Gwaza**, *Technical Officer, Regulatory Systems Strengthening, World Health Organization*
What are the opportunities for the review of new medicines in South Africa with the establishment of the South African Health Products Regulatory Authority (SAHPRA)?	**Andy Gray,** *Senior Lecturer, Division of Pharmacology, Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal, South Africa*
Chair's welcome	**Mandisa Hela,** *Deputy Chair of SAHPRA Board South Africa*
Practical considerations to implement a reliance-based model of review	**Ana Carolina Marino,** *Advisor for the Directorate of Authorization and Registration, Agência Nacional de Vigilância Sanitária (ANVISA), Brazil*
Reliance model: access and use of assessment reports of the reference agency	**Dr Agnes Chan,** *Director, Therapeutic Products Branch, Health Products Regulation Group, Health Science Authority, Singapore*
How the reliance model has changed the process and mindset	**Dr Ramli Zainal**, *Director, National Pharmaceutical Regulatory Agency, Malaysia*
Saudi Food and Drug Authority approach to verification and abridged reviews	**Thamer Alsubi,** *Director of Standard setting Department Drug Sector Saudi Food and Drug Authority, Saudi Arabia*
What role do companies play to enable an agency implementing a reliance model to be successful?	**Dr Paul Huckle**, *Chief Regulatory Officer and Senior Vice President, GlaxoSmithKline, USA*
SESSION: BEYOND THE REVIEW OF NEW MEDICINES: WHAT ROLE COULD A RELIANCE MIND-SET HAVE TO AID COUNTRIES TO RESOURCE APPROPRIATELY?	
Chair's introduction	**Gugu Mahlangu,** *Director General, Medicines Control Authority, Zimbabwe*
Stringent regulatory agency processes to ensure an effective and efficient review process for generics	**Dr Siu Ping Lam,** *Director, Licensing Division, MHRA, UK*
ACSS Generic Medicines Work-Sharing Trial	**Bruce Randall,** *Director, Bureau of Therapeutic Sciences, Therapeutic Products Directorate, Health Canada*
East African Community Medicines Regulatory Harmonization Programme	**Dr Yonah Hebron**, *Manager, Medicines and Cosmetics Laboratory, Tanzania Food and Drug Authority*

Chair's introduction	**Dr Tomas Salmonson,** *Chair, CHMP, European Medicines Agency*
Variations and their impact on the current regulatory landscape – What are the main issues companies and countries are facing in their review? Company viewpoint	**Dr Paul Dearden,** *Head of Emerging Markets, Regulatory Policy and Intelligence, AbbVie, UK*
Risk-based evaluation of variations to Australian Register of Therapeutic Goods entries for prescription medicines	**Jenny Burnett,** *Director, Scientific Operations Management, Scientific Evaluation Branch, TGA,* Australia
Panel discussion- Optimising post-approval variations: What are the opportunities for implementing reliance approaches?	**Mabatane Davis Mahlatji,** *Deputy Director: Medicines Evaluation and Research, South African Health Products Regulatory Authority (SAHPRA)* **Dr Susan Forda,** *Vice President-Global Regulatory Affairs-International, Eli Lilly and Company, UK* **Dr Siu Ping Lam**, *Director, Licensing Division, MHRA, UK*
SESSION 3: ROUNDTABLE DISCUSSIONS	
Roundtable A: ***Building trust into the reliance approach: What are the building blocks that need to be in place and how can companies and agencies facilitate the process?***	**Chair: Prof Hubert Leufkens,** *Professor of Pharmaceutical Policy and Regulatory Science,Utrecht University, The Netherlands* **Rapporteur: Nevena Miletic,** *Regulatory Policy Lead, F.Hoffmann-La Roche Ltd, Switzerland*
Roundtable B: ***Practical implementation of an abridged review process for new medicines: where should an agency focus and what are the practical steps needed to change process and mind-sets?***	**Chair: Prof John Lim,** *Executive Director, Centre of Regulatory Excellence & Professor of Practice, Duke-NUS Medical School and Senior Advisor, Singapore Ministry of Health* **Rapporteur: Andrea Keyter,** *Deputy Director Medical Devices, South African Health Products Regulatory Authority (SAHPRA*)
Roundtable C: ***Opportunities for applying reliance approaches to variations (CMC and safety) and impact on local labelling***	**Chair: Dr David Jeffreys,** *Senior Vice President, Global Regulatory, Government Relations, Public Affairs and European Product Safety, Eisai Europe Ltd, UK* **Rapporteur: Dr Judy Coates,** *Scientific and Regulatory Affairs Manager, Innovative Pharmaceutical Association South Africa (IPASA)*
Roundtable D: Instigating a reliance review model for generics – How could this be done practically and what would be needed from companies and agencies?	**Chair: Prof Henry Leng**, Regulatory Affairs Consultant, South African Health Products Regulatory Authority (SAHPRA) **Rapporteur: Dr Luther Gwaza**, Technical Officer, Regulatory Systems Strengthening, WHO

Chair's introduction	**Prof Sir Alasdair Breckenridge,** *Former Chair, Medicines and Healthcare products Regulatory Agency (MHRA)*
Panel reflection from roundtable session	**Dr Tomas Salmonson,** Chair, CHMP, European Medicines Agency **Prof Stuart Walker,** Founder, CIRS **Dr Paul Dearden,** Head of Emerging Markets, Regulatory Policy and Intelligence, AbbVie, UK **Prof Shabir Banoo,** Chief Technical Specialist – Pharmaceutical Policy and Programmes, Right to Care and University of the Witwatersrand, South Africa **Prof Hubert Leufkens,** Professor of Pharmaceutical Policy and Regulatory Science, Utrecht University, The Netherlands

Section 2. Presentations

Reliance-based models of review: How do these fit with good regulatory and good review practices?

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

At the 2017 CIRS Workshop in Sao Paulo, Brazil, Mike Ward, Coordinator of the Regulatory System Strengthening Team at the World Health Organization (WHO), reported that the use of reliance-based regulatory review is currently globally pervasive, even amongst some well resourced regulatory agencies.[1]

Reliance-based models of review depend on the principles of good regulatory practice and require transparency and trust in processes and systems and in regulatory decisions and the rationale for those decisions. These principles of good submission and review practices have been well defined and are readily available for stakeholders to employ. Of those elements, participants at a recent CIRS Workshop in Lima, Peru particularly emphasised the need for predictable structured processes associated with appropriate timelines (Figure 1).[2]

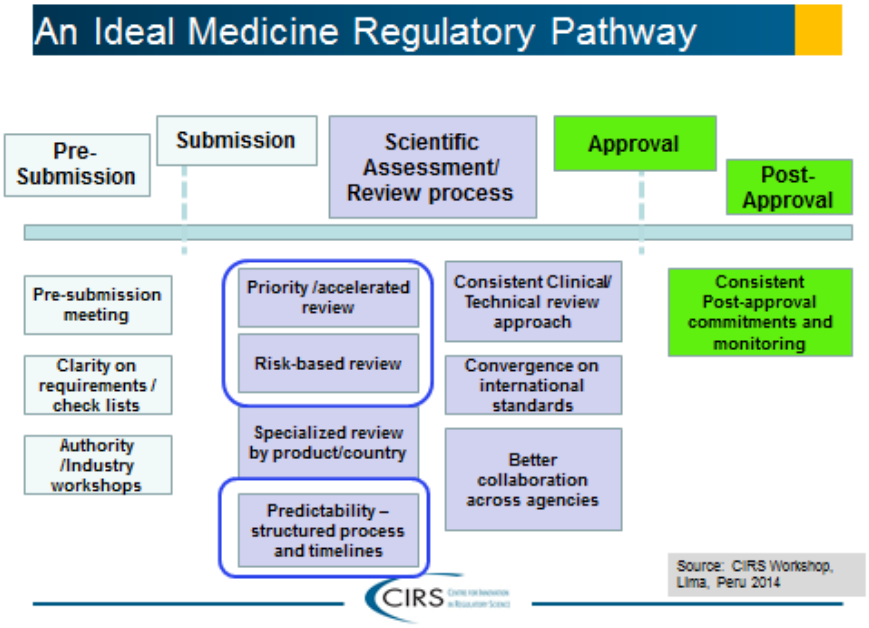

Figure 1. CIRS Workshop participants included structured processes and timelines as important elements of primary and secondary facilitated regulatory pathways.

Timelines for structured processes can be accelerated through priority or risk-based facilitated regulatory pathways (FRPs) that expedite the development and review of medicines while assuring their quality, efficacy and safety. Priority-based FRPs include primary FRPs, pathways that are typically implemented by a reference or stringent regulatory agency (SRA) for a first review that is not dependent upon the assessment by another agency. Internationally, these include pathways such as Accelerated Approval, Accelerated Assessment, Priority Review, , Conditional Marketing Authorisation, Marketing Authorisation under Exceptional Circumstances. Pathways such as Breakthrough Therapy designation, PRIME and Sakigake give the sponsor and agency greater opportunities for early interactions with the goal of making development most efficient. Most primary FRPs support the assessment of medicines targeting unmet medical need. In

secondary FRPs, national regulatory agencies or regional regulatory initiatives can expedite their decisions through the reliance on or recognition of prior reviews. These include approaches such as a verification or abridged review and the use of the WHO Prequalification and Collaborative Registration processes.

In Sao Paulo, Mike Ward cited three levels of reliance amongst regulatory agencies. At the first or foundational level, an equivalence of requirements between two regulatory bodies is determined and information sharing results in confidence building. At the second or reliance level, regulators benefit through work sharing whilst maintaining ultimate responsibility for decision making. At the third or recognition level, regulatory agencies achieve maximal benefit in regard to optimising resources by accepting another agency's decision whilst surrendering some sovereignty with regard to decision making [1]

Reliance-based reviews are based on the level of risk that an agency is prepared to accept. Risk-based stratification criteria include the number and location of prior approvals, the length of time a product may have been on the market, the quality (similarity) of the product, local medical standard of care and benefit-risk considerations and unmet medical need. In verification reviews, the agency recognises a previous authorisation of a product by a reference or benchmark agency. In this process, the agency validates this prior review while ensuring that the product conforms to local requirements and authorised product specifications. When using an abridged review, the agency conducts a more detailed assessment, relies on prior evaluations to inform local decisions, evaluating the product under local conditions and regulatory requirements.

In full reviews, the agency has the resources and expertise to carry out a full assessment of quality and pre-clinical and clinical safety and efficacy. Prior registration elsewhere may or may not be a prerequisite for authorisation.

As might be expected, these types of risk-based reviews are each associated with timelines commensurate with the amount of regulatory resource required. In Singapore, for example, verification reviews have agency timelines of 60 working days and abridged reviews, 180 working days, compared with 270 working days targeted for full reviews. Accordingly, agency goals for use of reliance-based reviews include acceleration of review timelines. Indeed, CIRS data from international pharmaceutical companies for maturing agencies show that median timing for regulatory approval was shorter for verification reviews than that for abridged reviews and the timing for abridged reviews was shorter than that for full reviews (Figure 2).

Such approaches are being used by a growing number of agencies. In 2016 faced with a rapidly increasing number of annual submissions and supported by CIRS analyses, the Saudi Food and Drug Administration instituted a risk stratification approach to regulatory review to reduce timelines.[3] Equivalence agreements represent another form of risk-based review. Also reported at the 2017 CIRS Workshop in Brazil, Mexico's equivalence agreement with the US, Canada, Australia, Switzerland and the European Union has resulted in a significant reduction in the timing for regulatory review in that country.[1] Regulatory timing may also be reduced in some low- or middle-income countries, through use of regional or joint reviews for WHO Prequalification of medicines.[1] The many different ways that agencies can use reliance-based FRPs to accelerate regulatory review are represented in the "Metro Map" as shown in Dr Liberti's thesis Globally

applicable facilitated regulatory pathways to improve equitable access to medicines.[4]

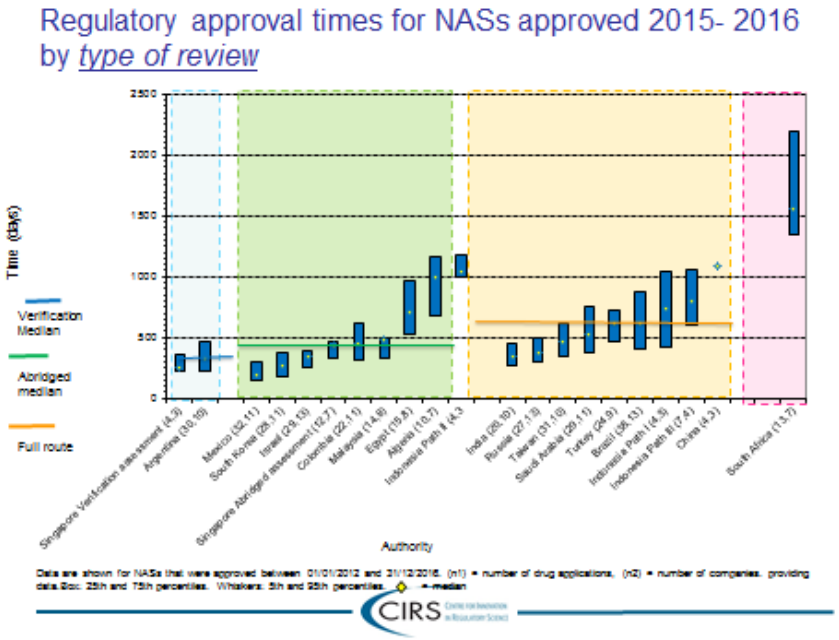

Figure 2. Median timelines for regulatory approval according to the type of review used.

The benefits of risk-based reliance pathways include the efficient use of staff and advisors, the ability for national regulators to focus on added-value activities and the alignment or convergence with international standards. In addition these pathways may help to reduce the burden of duplication for sponsors, improve process predictability and help to reduce the backlog of post-authorisation commitments, labelling changes and variations and generic applications.

Conclusions

Good regulatory practices form the basis of a review process so trust in decisions can be established across stakeholders. Using a trusted assessment forms the basis of reliance- and recognition-based assessment FRPs. These ”secondary reliance pathways” informed by prior decisions allow for added-value activities important in the local context, reducing duplication and facilitating the efficient use of resources. Their use can reduce review times expediting access to medicines and may have broader applicability in addition to new molecular entities.

“Secondary reliance pathways” informed by prior decisions allow for added-value activities important in the local context, reducing duplication and facilitating the efficient use of resources.

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21st century best regulatory practice: The role of good reliance practices

Dr Luther Gwaza, *Technical Officer, Regulatory Systems Strengthening, World Health Organization*

General and specific standards for pharmaceutical regulation

According to the World Health Organization (WHO) all pharmaceutical products should be used in a country only after approval by the national or regional authority and regulatory authorities should require a pharmaceutical product to meet good manufacturing processes, quality control specifications and where applicable, pharmaceutical product interchangeability.[1]

In addition to these universal regulatory practices, there are issues that are of particular importance in low-income countries, where regulators frequently must balance the economic concerns of their jurisdiction against matters of public health and patient access. In practical terms, medicines must be regulated in a country of millions of people, where hundreds of applications for the review of medicines must be handled by an extremely limited number of review staff. In addition, only a very small percentage of those applications are for innovative products, representing less than 10% of registered products on the essential medicines list. Because there may be only one or two local manufacturers, as much as 99% of medicines are imported.

Standards for pharmaceutical regulation in lower income countries have been considered. According to a report from the Committee on Strengthening Core Elements of Regulatory Systems in Developing Countries Institutes of Health, robust regulatory systems are ones that apply correct standards that are globally acceptable, at the same time having a good risk management system that ensures that the level of control is proportionate to the level of public health risk[2]. A good regulatory system is responsive, outcome oriented, independent, predictable and risk-proportionate. Regulators, however, must also always consider how to get needed quality product to patients faster and more efficiently using available resources. Accordingly, use of the shared responsibility model is characteristic of the modern regulator who employs smart regulation including reliance, collaboration and work sharing, while differentiating and focusing on regulatory tasks that cannot be fulfilled through reliance on other agencies.

Use of the shared responsibility model is characteristic of the modern regulator who employs smart regulation including reliance, collaboration and work sharing, while differentiating regulatory tasks that cannot be fulfilled through reliance on other agencies.

These add-value functions form the minimum that every country should have in place and include tasks such as licensing of premises, controlling import and exports and vigilance. The work of other regulatory agencies can be relied on for other functions such as review of applications for marketing authorisation and good manufacturing process inspection of foreign facilities. Regardless of the size of the agency or the model of review, however, the outcomes should be the same; that is, access to safe, effective, quality medicines and health technologies.

Reliance and recognition

Reliance is defined as the act whereby a regulatory authority in one jurisdiction may take into account/give significant weight to work performed by another regulator or other trusted institution in reaching its own

decision. *Recognition*, on the other hand, is the routine acceptance of the regulatory decision of another regulator or other trusted institution. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B. National regulatory agency pathway approaches can range from full assessment and inspection to recognition of decisions made by others; abridged reviews developed through reliance on the work of other reviewers, work-sharing and joint assessments or inspections.

One of the reliance models used by national regulatory agencies is the WHO Pre-Qualification (PQ) collaborative procedure, in which WHO shares detailed outcomes of its assessment and inspections with regulators to support decision making in exchange for a commitment for expedited review by the national regulatory agency. As of December 2017, 299 products in 31 countries have been approved through the use of WHO PQ, within a median of 85 days.

In the Zazibona collaborative process, Zambia, Zimbabwe. Botswana, Namibia and South Africa cooperate in the assessment and inspections of essential medicines in order to reduce workloads, shorten time to registration, develop mutual regulatory confidence and trust and provide training for regulatory capacity building. In this procedure, primary dossier assessment and inspection reports are conducted by rapporteurs and inspectors and circulated to participating countries for comments. Assessors meet four times a year to reach consensus on the reports and inspections, reviewing an average of 12 products per session. The WHO provides technical assistance and quality assurance for the assessment reports. Since 2013, the review of 109 products has been completed in 16 sessions. In addition, 17 GMP inspections have been conducted and 13 training sessions have provided the opportunity for regulatory capacity building. The average time to registration for all finalised products was 286 days (sponsor + regulator), which is close to the target of 270 days (Figure 3).

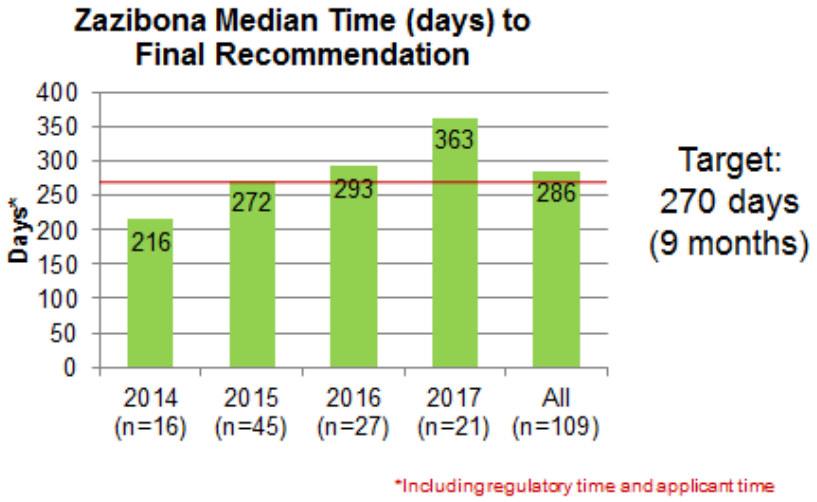

Figure 3. Median time to registration of essential medicines reviewed through the Zazibona work-sharing initiative.

Through the use of such reliance methods as PQ procedure and work-sharing collaboration as well as its laboratories for the testing and certification of pharmaceuticals and biologics, the WHO is helping national regulatory agencies in low-income countries become part of regulatory networks to facilitate their need to apply appropriate standards that are scientifically justified and risk proportionate to protect public health while ensuring economic and industrial interests are supported.

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What are the opportunities for the review of new medicines in South Africa with the establishment of the South *African Health Products Regulatory Authority (SAHPRA)?*

Andy Gray, *Senior Lecturer, Division of Pharmacology, Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal, South Africa*

The regulatory environment in South Africa has experienced a series of legal challenges for over two decades, culminating in the replacement of the South Africa Medicines Control Council (MCC) in February 2018 with the South African Health Products Regulatory Authority (SAHPRA). In the new SAHPRA regulatory model, decision-making power is vested in the Chief Executive Officer, who is able to appoint advisory committees. In this new model, advisory committee recommendations will not be binding on the CEO and staff.

Previous MCC regulations specified that "essential" medicines be subject to procedures that will expedite their registration within nine months, including "an abbreviated medicine review process as determined by the Council, where registration has been granted by other medicines regulatory authorities recognised by the Council". Unfortunately, as reported by Leng and colleagues, under this regulation an unlimited number of generic versions of essential medicines could be submitted for expedited review. Combined with a review backlog and limited regulatory resources, this glut of generic applications may have contributed to access delays for innovative and affordable medicines in South Africa.[1] The amended medicines Act has removed the enabling provision for "expedited" registration, and the new General Regulations do not specify what processes will be followed in order to deal with priority applications.

South Africa does have existing international relationships that can be used to develop liaisons and cooperative agreements to enable the legally mandated expedited reviews.

South Africa does have existing international relationships that can be used to develop liaisons and cooperative agreements to enable priority reviews. The country is a member of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), an observer at the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and a member of the International Medical Devices Regulators Forum (IMDRF), the International Generic Drug Regulators Programme (IGDRP), the African Vaccine Regulatory Forum (AVAREF), the newly expanded Zazibona initiative, and the nascent African Medicines Agency initiative. In addition, South Africa has memoranda of understanding with various national medical regulatory authorities.

Current examples of South African reliance include:

Recognition or the routine mutual acceptance of the regulatory decision of another regulator

As PIC/S member, SAHPRA makes use of good manufacturing process inspection reports. However, it remains challenging to establish recognition between national regulatory agencies of variable maturity and there is a potential for wider ICH involvement in this issue. Furthermore, in the absence of agreements, "black

box" recognition can be considered a challenge to national sovereign decisions. Recognition may need to be considered as a long-term goal for the yet-to-be-developed African Medicines Agency.

Work sharing or two or more regulators sharing workload by evaluating (different) parts of a dossier

Because of ongoing challenges for recognition-based approaches, work-sharing may be relatively easier to accomplish. Indeed, the Zazibona initiative as described by Dr Gwaza is a good example of work sharing in Africa. In addition, there is also the potential for expanded use of another form of work sharing in the WHO Prequalification collaborative procedure, also described by Dr Gwaza.

Reliance, or taking into account work performed by another regulator

To date, the reliance approach has been poorly developed in South Africa. However, a new approach has been proposed by the Harmonisation Task Team, which draws heavily on the Australian Therapeutic Goods Administration proposals and which is to be finalised by SAHPRA as part of its new operating model. It is envisioned that this reliance would involve submission of a full application in Common Technical Document (CTD) format including the South African-specific administrative Module 1 and submission of unredacted copies of reference evaluation reports, completed by a national regulatory agency with which SAHPRA aligns itself, with appropriate certifications and/or authentication of such reports. In addition, evidence would be required that the medicine is identical to the one approved by the reference agency, and in particular that it is presented in the same dosage form, strength and formulation, is manufactured by the same manufacturer, by means of a manufacturing process identical to that used to manufacture the medicine which will be marketed in South Africa, and that is intended for the same indications, and based on the same supportive documentation/evidence. The final product release and stability specifications must also be identical, and a declaration submitted that there are no specific issues regarding applicability of the product to the South African clinical context. Finally, details would need to be provided about the outcomes of the application in all jurisdictions where it has been submitted. An abbreviated SAHPRA review of the application may consist of verification that the necessary certifications have been received and are correct; consideration of any South Africa-specific factors, related to local demographics, climatic conditions, disease epidemiology, and clinical practice and any risk management measures that are necessary in the South African context. Finally approval must be issued for South African-specific labelling, Professional Information and Patient Information Leaflet.

Some questions still surround this future reliance model, including which national regulatory agencies will be considered and whether this list will be open to change. The current list includes the US Food and Drug Administration, European Medicines Agency, Japanese Pharmaceuticals and Medical Devices Agency, Swissmedic, Health Canada and Australia's Therapeutic Goods Administration. In addition, it remains to be determined if public assessment reports help to build confidence in the "unredacted reports" and how much reliance can be placed on the declaration that there will be no specific local issues. It must also be decided if the programme will be for new chemical entities only or if some generics or biosimilars will be included, if there will still be a need for extensive regulator-to-regulator agreements and whether timelines will be feasible and enforceable.

Reliance and recognition approaches provide an opportunity for South Africa to expedite the review of needed medicines, without detracting from work-sharing and harmonisation efforts. The necessary legal enablements for reliance are now in place in South Africa and these questions may best be answered through trials of this process.

Reference

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Practical considerations to implement a reliance-based model of review

Ana Carolina Moreira Marino Araujo, *Advisor for the Directorate of Authorization and Registration, Agência Nacional de Vigilância Sanitária (ANVISA), Brazil*

Challenges to development of a reliance-based model

There are multiple stakeholders in the implementation of a reliance-based model of review of medicines. Internally, there are assessors, their managers and the head of the agency, while externally there are pharmaceutical companies, the government and society. These internal assessors, who have been trained to perform comprehensive reviews, may be resistant to change, may believe that they need to review all elements of every dossier, may only trust their own work and may believe that they are ultimately in danger of losing their autonomy. In addition, assessors may be frustrated in their attempts to acquire more resources in order to deal with the pressure of backlogs. Whilst assessors may have experienced some progress toward the development of efficiency in the agency work process, they understand that more improvement is required. Externally, contact with other agencies' work is required to build trust.

Assessor and company involvement

Development of a reliance-based regulatory model should not be expected to be accomplished quickly. Assessors must be involved in the process of developing these models, including the harmonisation of the dossier format through implementation of the Common Technical Document and through strengthening of good review practices and the development of reliance-based review templates such as that of the CIRS Unified Methodologies for Benefit-Risk Assessment (UMBRA). In addition, regulatory reviewers should learn about other agencies' review processes and requirements even while establishing the local requirements of their jurisdictions. Finally, the regulatory review team must be trained to use new tools and to review the dossier using the a review model. For their part, companies should provide dossiers structured in the best possible way to accelerate their review as well as other agencies' full reports of their evaluations. Global companies should share full clinical and development data with their local or regional affiliates.

Assessors must be involved in the process of developing these models, including. . . strengthening of good review practices and the development of reliance-based review templates

New ANVISA optimised review process

In February 2018, ANVISA initiated an optimised and detailed review process for the review of applications for registration and post-approval changes for *biological products* previously registered by the US FDA and EMA. This is not, however, a pathway for priority review. Documents that support this reliance review include US FDA and EMA reports and the Product Leaflet, which includes product indication, treatment scheme, dosage, adverse events and warnings. Approval conditions that differ from the Leaflet must be discussed and verified. Other necessary documents include Packaging Information; Quality documents, or technical reports such as

those for stability; transport validation and quality, safety and efficacy summaries from Module 2 of the Common Technical Document in Portuguese.

A similar approach to the review of *new chemical entities* is being developed and a strategy to simplify the generic review process involving the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certification of Suitability to the monographs of the European Pharmacopoeia (CEP) is under discussion.

Reliance model: access and use of assessment reports of the reference agency

Dr Agnes Chan, *Director, Therapeutic Products Branch, Health Products Regulation Group, Health Science Authority, Singapore*

Drug registration in Singapore

In Singapore, the Health Science Authority (HSA) employs a hybrid system of reliance-based and independent review. In 1998, the country first developed the capability to perform a full first-in-world evaluation of medicines and later, HSA implemented verification and abridged reviews, which leverage the work of regulatory reference agencies to minimise duplication of effort. HSA in-house capabilities are complemented by external experts and advisory committees. HSA reference agencies (RAs) include the US Food and Drug Administration (US FDA), the European Medicines Agency (EMA), the UK Medicines and Healthcare products Regulatory Agency (MHRA), Australia's Therapeutic Goods Administration (TGA) and Health Canada.

In the HSA risk-based approach, the depth of regulatory evaluation is calibrated according to prior approvals and includes the potential to use one of three evaluation routes with different turnaround times, thereby maximising flexibility. For products with no prior regulatory evaluation, HSA performs a full review of quality and clinical data. For products with at least one prior approval by any regulatory authority, HSA performs an abridged review consisting of a quality review stratified according to prior approvals and a clinical review focusing on phase II and III clinical data. For identical products with at least two RA' approvals, HSA performs a verification review in which the benefit-risk assessment of the selected RA is verified based on quality and clinical evaluations within the assessment report. There is an ongoing fine-tuning and re-calibration of these processes, guided by risk appetites, national policies and international environments (Figure 4).

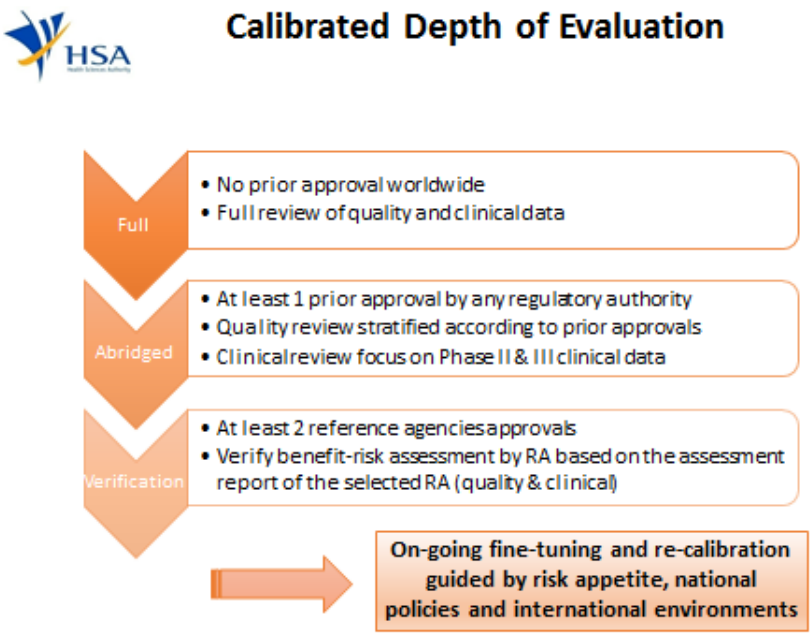

Figure 4. The depth of Health Science Authority (HSA) review in Singapore is calibrated according to prior regulatory approvals.

At HSA, the abridged review has been the route most preferred by industry. Within the past ten years, approximately 85% to 90% of products have been assessed via the abridged process, 5% to 10% via verification and 5% to 10% through the full review. Using the abridged route provides the flexibility to seek approval for clinical indication or quality specifications that may not be the same as those approved by reference agencies and avoids the necessity for submission of full assessment reports from the RA; however, the abridged route requires an independent review by HSA. The verification route represents the true reliance model, in which HSA can technically leverage an RA assessment to make a regulatory decision for marketing approval.

Although the extent and basis of reliance depends on the risk threshold and policy of an individual country, for effective reliance on RA approvals, HSA needs access to RA reports to understand the scientific basis of the RA approval in order to determine if the benefit-risk assessment made by the RA; regarding, for example, the clinical relevance of an endpoint or the magnitude of benefit, is relevant in Singapore's context. In addition, access to RA reports helps to ensure that there is no knowledge gap in a product's post-approval life-cycle management (Figure 5).

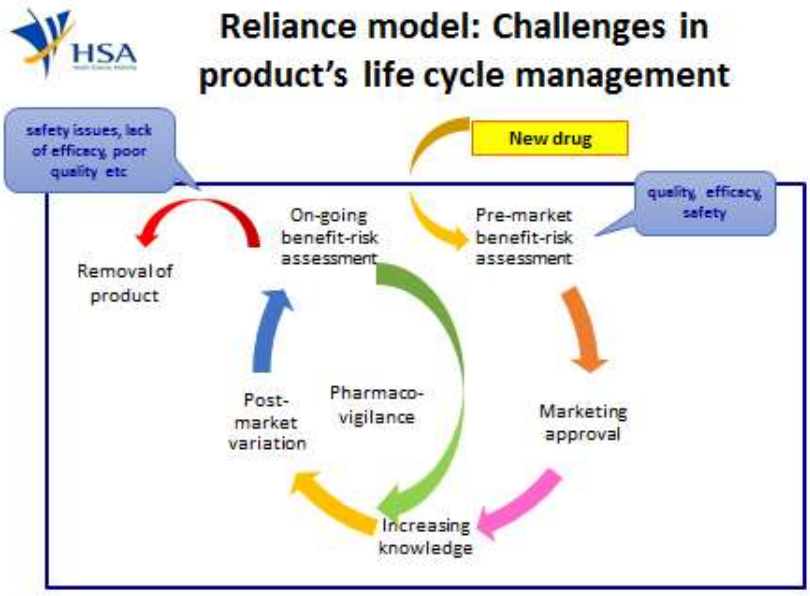

Figure 5. Access to reports from reference regulatory agencies helps HSA to ensure that there is no knowledge gap in a product's post-approval life-cycle management.

Technical aspects of using a reliance model

In the quality review of a product, HSA accepts international quality standards and specifications. The RA Drug Master File or Certification of Suitability to the monographs of the European Pharmacopoeia (CEP) provide the necessary basis for verifying that all aspects of a product meet international standards. HSA conducts an additional independent review for regional-specific stability data requirements, which does not preclude reliance on the RA assessment on other quality aspects.

In the absence of significant differences in disease epidemiology, patient population or clinical practice, HSA has typically arrived at the same benefit-risk evaluation as the reference RA in the clinical review of a product. However, within the past two years, as the amount of evidence required and risk threshold for approval increasingly differs across RAs, there appear to be more cases in which HSA has made a different benefit-risk decision from the RAs, although there is as yet insufficient data to observe a trend in this occurrence.

Can HSA make a regulatory decision based entirely on the assessment by reference agencies?

In the review of a product's quality, reliance is generally straightforward, as quality standards are often common across major jurisdictions and those determined by the RA are considered adequate for Singapore. Reliance for clinical reviews tends to be more challenging, even if the same dataset had been reviewed by the RA, as threshold for benefit-risk may not be identical. In addition, differences in regulatory approval pathways such as the US FDA Breakthrough Therapy pathway may enable new drugs to obtain approval based on reduced or early-phase data, subject to post-approval commitments. Countries without the same regulatory pathway of vigilance capabilities may not be able to rely fully on such approvals. Furthermore, differences in disease epidemiology, demographics and clinical practice may lead to different evaluations of benefit-risk.

Other reasons why access to an RA report may be critical include the influences of other non-scientific factors such as government policies, industry or consumer lobbying and pharmaceutical company filing strategies. There may be differing clinical indications, chemistry, manufacturing and controls (CMC) data and quality specifications for different markets, and potential knowledge gaps in the evaluation of post-approval variations throughout a product life cycle.

HSA identifies elements in RA benefit-risk assessment that are critical in the local context, bridging the benefit-risk assessments performed by RAs to local patients.

With 35 evaluators for clinical and quality assessments, HSA has limited resources and capacity and it is impractical to reproduce the depth of evaluation by major agencies such as FDA and EMA. To leverage the work of RAs without compromising the robustness of the decisions HSA makes for the Singapore population, the agency identifies elements in RA benefit-risk assessment that are critical in the local context, bridging the benefit-risk assessments performed by RAs to local patients. Elements of RA evaluation that are relatively objective can be leveraged such as pre-clinical and early phase clinical study evaluation as well as CMC assessments with the same quality specifications, except for region-specific data.

The reliance model is not confined to new drug approvals, but is possible to extend to post-approval variations such as new indications or manufacturing changes, if companies are willing to file for the same variation as approved by RAs and are able to confirm that changes are identical.

Observations from HSA experience

Bridging benefit-risk assessments performed by RAs to the Singapore population is a key HSA consideration. This includes an interpretation of results with the identification of differences in terms of patient population, disease profile, epidemiology, clinical setting and demographics. HSA needs to be aware of RA policies that may influence their risk threshold for approval.

Risk-based evaluation remains the most pragmatic approach for HSA regulator review, enabling the agency to optimise limited resources effectively while ensuring regulatory and scientific rigour. Capabilities to perform independent review remains strategically critical to HSA in order to provide support for growth of regional biomedical research and development, particularly for therapies for diseases of local public health importance and unmet medical needs (e.g.,dengue).

How the reliance model has changed the process and mindset

Dr Ramli Zainal, *Director, National Pharmaceutical Regulatory Agency (NPRA), Malaysia*

Malaysia and the National Pharmaceutical Regulatory Agency

Among Malaysia's population of 31 million, non-communicable diseases account for 70% of all deaths. Heart disease is the leading cause of health-related mortality, followed by stroke, respiratory diseases and cancer and the country has one of the highest prevalence of diabetes in the Asia-Pacific. This increase of non-communicable diseases along with a rapidly aging population is expected to increase the country's demand for multinational pharmaceutical products, already estimated at $2.3 billion in 2015.

Imported medicines comprise 70% of Malaysia's total drug market and foreign pharmaceutical imports were worth $1.3 billion in 2016. Malaysia has a fast-growing domestic pharmaceutical manufacturing industry with a total of 251 licenced manufacturers, primarily for generic drugs. In addition, there are 7,000 general practitioners: 184 private and 144 government hospitals and 3220 government clinics.

The National Pharmaceutical Regulatory Agency (NPRA) of Malaysia was created in 1985 and in 1999, the agency was designated as a World Health Organization (WHO) Collaborating Center for Regulatory Control of Pharmaceuticals. In 2002 Malaysia became a member of the Pharmaceutical Inspection Cooperation Scheme (PIC/s) and in 2013 joined the Organisation for Economic Cooperation and Development (OECD) system for the Mutual Acceptance of Data (MAD) in the Assessment of Chemicals. In 2015, NPRA was certified for International Organization for Standardization/International Electrotechnical Commission (ISO/IEC) 17025 (testing and calibration) and ISO 9001 (quality management). According to the WHO Global Benchmarking Tool for evaluation of national regulatory systems, NPRA has attained Maturity Level 3, meaning that the agency has a stable well-functioning and integrated system of oversight for medical products.

Association of Southeast Asian Nations Joint Assessment

Ten countries make up the Association of Southeast Asian Nations (ASEAN), Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei, Vietnam, Laos, Burma and Cambodia. ASEAN represents 620 million people with a combined gross domestic national product of US$2.4 trillion. After China, the European Union is ASEAN"s second leading trade partner, and EU-ASEAN trade totals US$ 229.7 billion in 2016.

In 2015, with WHO support, the ASEAN Pharmaceutical Product Working Group (PPWG) proposed the ASEAN Joint Assessment (JA) procedure for marketing authorisations, to be implemented as a pilot starting in January 2017 and continuing for up to two years. A JA is a formal procedure in which the same application is simultaneously submitted to all participating ASEAN national regulatory agencies (NRAs). Assessment work is then carried out together by all participating NRAs and a JA report is prepared. Each individual NRA then makes a final decision on the application through their normal decision-making processes within established

timelines based on the JA report and, where applicable, nationally relevant considerations. The objectives of the JA procedure are to further enhance cooperation among regulators to optimise work efficiency and improve workload management and assessment duration; to overcome divergence in interpretation of harmonised requirements, to generate stronger mutual understanding and trust and to strengthen the overall capacity of ASEAN regulators to ensure the ASEAN accessibility of medicines of assured quality, safety and efficacy.

Challenges for the JA procedure include potentially unrealistic expectations from industry regarding shorter timelines for the new route. In addition, suitable products to be evaluated through the JA procedure that fulfil ASEAN member state requirements need to be identified. Importantly, there is as yet no mutually recognised framework for JA nor is there long-term funding to support the initiative. Finally, change management strategies are required to prepare and support individuals, teams and organisations in making organisational changes (Figure 6).

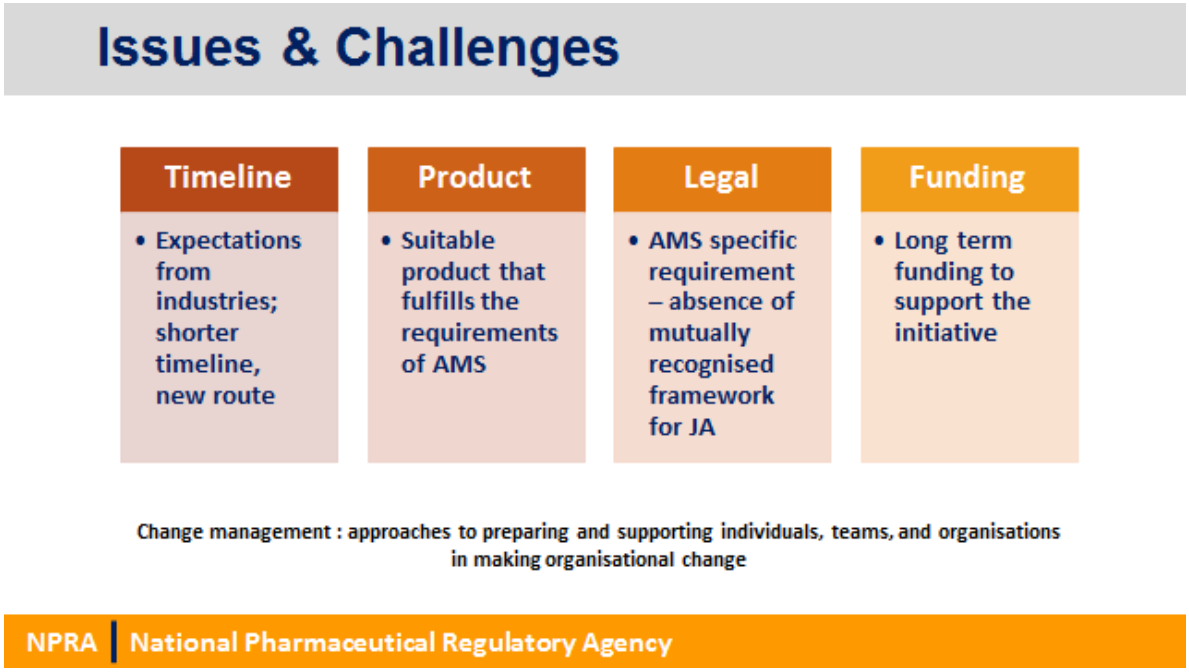

Figure 6. Potential hurdles to the ASEAN Joint Action procedure.

NPRA steps toward improved application time

In addition to participation in the ASEAN JA procedure, NPRA is considering other risk-based approaches to regulation in which the agency would rely on the word of other trusted regulatory agencies and focus on those areas which present the greatest risk to the population of Malaysia. The agency is also taking steps to optimise the use of available resources in the three categories of the Donabendian quality framework for healthcare, namely, *structure, process* and

The agency is also taking steps to optimise the use of available resources in the three categories of the Donabendian quality framework for healthcare, namely, *structure, process* and *outcomes*.

outcomes. *Structurally*, NPRA is developing Human Resource Technology Guidelines and together with industry and academia, are producing a structured regulatory training programme and identifying good submission and review practices including key performance indicators and key criteria for evaluation. Information technology in the form of Quest3, the NPRA online submission system, is being upgraded to include user guidelines. *Procedurally*, the agency is considering new pathways and approaches to regulation such as the ASEAN Joint Assessment procedure and other reliance-based programmes. The envisioned *outcomes* to these modifications are improved application timelines and the reduction of regulatory burden and duplication of work (figure 7).

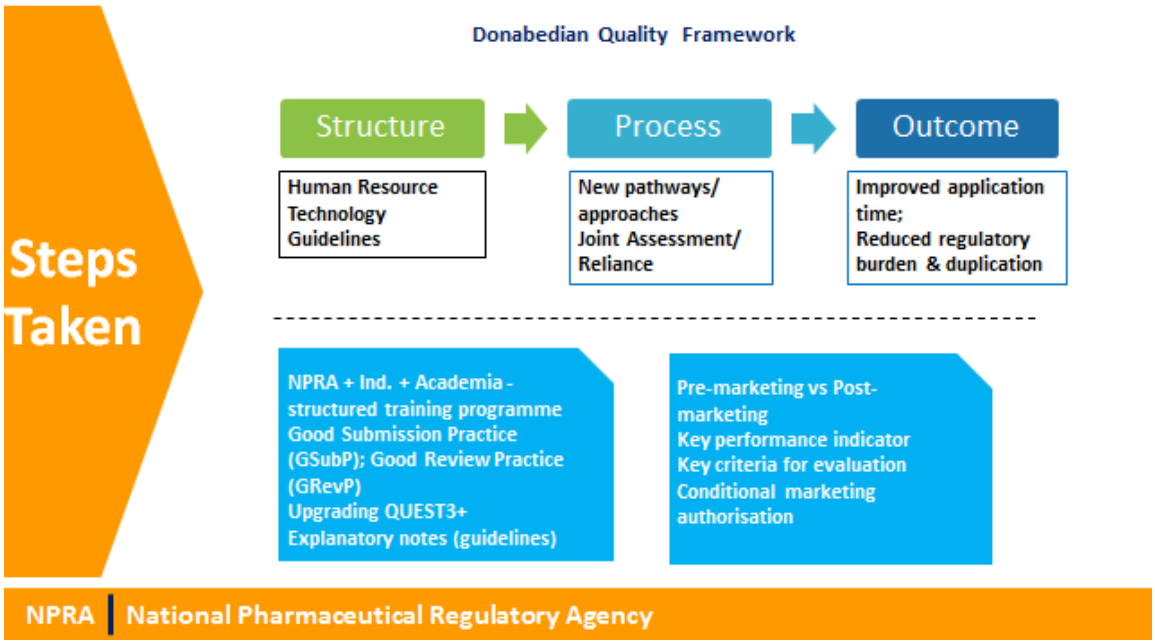

Figure 7. The NPRA has taken positive action toward reducing regulatory burden and shortening timelines for regulatory review.

Saudi Food and Drug Authority approach to verification and abridged reviews

Thamer Alsubi, *Director of Standard Setting Department, Drug Sector, Saudi Food and Drug Authority*
Presented by
Prof Stuart Walker, *Founder, Centre for Innovation in Regulatory Science*

With a rapidly growing and aging population currently at 30 million people, the healthcare budget for Saudi Arabia increased from $13 billion USD in 2013 to $39.2 billion USD in 2017 with the amount spent on pharmaceuticals increasing from $5.1 billion USD in 2012 to $7 billion USD in 2018. The Saudi Food and Drug Authority (SFDA) acquired the responsibilities for pharmaceutical regulation from the Ministry of Health in 2009. Its mission is to ensure the safety of food; the safety, quality and efficacy of drugs; and the safety and effectiveness of medical devices, by developing and enforcing an appropriate regulatory system.

The number of applications for the review of medicines that are submitted to the SFDA continues to increase each year, particularly the number of applications for generic medicines (Figure 8).

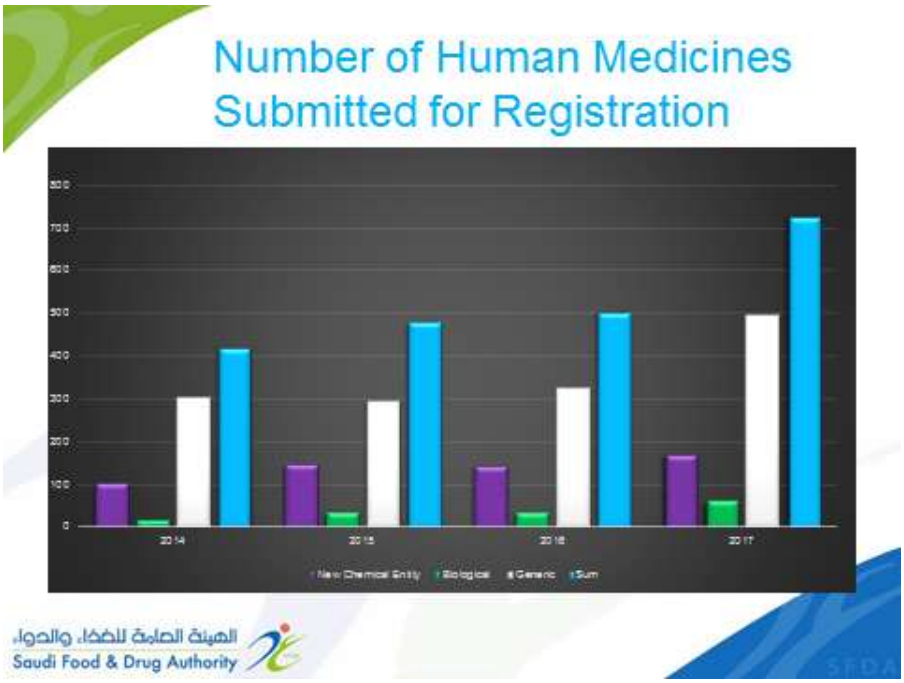

Figure 8. The number of applications for the review of medicines to the SFDA continues to increase each year.

The SFDA Regulatory Framework specifies a timeframe within which different types of applications must be reviewed (Figure 9). Although the median time for dossier review has fallen within those time limits since 2014, the time taken by sponsors to respond to SFDA questions has not been factored into that time.

Process	Total Performance Target[5]
Marketing Authorization Application for Generics	165 days
Marketing Authorization Application for New Drugs	290 days
Marketing Authorization Application for New Drugs not registered in an SRA	415 days
Marketing Authorization Application for Biologicals	290 days
Marketing Authorization Application for Biologicals not registered in an SRA	415 days
Marketing Authorization Application for Radiopharmaceuticals	290 days
Marketing Authorization Application for Veterinary drugs	175 days
Marketing Authorization Application for Herbal & Health products	155 days
Renewal of Marketing Authorization	70 days
Variation to a Marketing Authorization Type IA	60 days
Variation to a Marketing Authorization Type IB	120 days
Variation to a Marketing Authorization Type II	145 days

Figure 9. SFDA performance target timing for regulatory review.

Like many other regulatory agencies, SFDA resources remain limited, despite continuing increases in the number of submissions, resulting in challenges to agency target timelines. SFDA strives to meet those challenges and in 2016 adopted of a risk-based approach to the triage of drug applications, applying abridged and verification procedures.

Verification registration is a regulatory process that can be used for products that have been approved and by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and marketed in the US and EU. Abridged registration is a regulatory process that can be used for products that have been approved by either of those two agencies. Both verification and abridged procedures can only be used for the review of new chemical entities or biological products, excluding blood products or vaccines. The product must be submitted to the SFDA within two years from the date of approval by the US FDA and/or EMA. The product and its intended use, including indications, dosage information, and patient groups must not have been rejected, withdrawn or suspended by any drug regulatory agency for safety and/or efficacy reasons.

The electronic common technical document (eCTD) submission should be the same as was submitted to the reference drug regulatory agency US FDA and/or EMA for modules M 2-5. A complete clinical and quality assessment report is required, including (if applicable) assessment on the Question & Answer documents between the Sponsor and Agency and all annexes. Also required are assessment reports and/or documents pertaining to post-approval variations, if applicable and a stability study performed according to the Gulf Cooperation Council guidelines. Submitted assessment reports must be unredacted or unedited and include

details of imposed licensing conditions, final product labelling, chemistry and clinical review and other information in relation to the product's approval. Reports obtained from the public domain are deemed unacceptable. The stability study(s) must also conform to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines for stability testing. A declaration letter issued by the product owner/applicant is also required, stating that all aspects of the drug product's quality, including but not limited to the formulation, manufacturing site(s), release and shelf life specifications , primary packaging and active pharmaceutical ingredient(s) source are identical to that currently approved by the reference agency at the time of submission. It should be recognized that approval by these reference drug regulatory agencies does not oblige the SFDA to approve the application.

Target timing for verification procedures is 30 days and 60 days for abridged procedures. Through its use of verification and abridged procedures the SFDA intends to successfully leverage the work of reference agencies to provide access to needed medicines without prolonged timelines, although to date there has been no indication of how many products have been reviewed using this risk stratification approach.

What role do companies play to enable an agency implementing a reliance model to be successful?

Dr Paul Huckle, *Chief Regulatory Officer and Senior Vice President, GlaxoSmithKline, USA*

Challenges of post-approval variations

Although obtaining the initial market authorisation may take as much as 6 years, it only represents the beginning of series of challenges in the life cycle of a medicine in which changes can extend for more than 30 years. Globally, hundreds of thousands of these changes occur each year for reasons such as enhancing the robustness and efficiency of manufacturing process, improving quality control techniques, responding to changes in regulatory requirements, upgrading state-of-the-art facilities and changing supply chain arrangements. Each product is likely to experience multiple changes throughout its life cycle, as portfolio expansions drive new indications, formulations and packs; safety reviews result label changes and updates and manufacturing improvements or supply chain changes can cause chemistry, manufacturing and control (CMC) variations. In addition, each product will require regular licence renewals and product packs may be shared across countries to achieve scale for manufacturing. However, there is a lack of ability to 'bundle' changes into single applications and variations must be sequenced even though pending review of variation can preclude further filings. Furthermore, because of the international divergence in regulatory classification of and procedures for the changes, individual alterations can take up to 5 years to be implemented globally.

In its position paper on the optimisation of post-approval change, the European Federation of Pharmaceutical Industries and Associations (EFPIA) recommended several solutions to these and other challenges to post-approval changes. The challenge represented by heterogeneous national variation classification systems and specific local requirements could be met by converging national requirements through adoption of international standards such as those of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)and the World Health Organization (WHO) and adopting a risk-based approach to the classification of variations, data requirements and timelines. Unpredictable and variable approval timelines and implementation periods could be mitigated through the stepwise collaboration among regional national regulatory agencies that enables work-sharing, mutual reliance on assessments and, in the longer term, mutual recognition of approvals. The lengthy and unpredictable process for safety changes could be dealt with through a focus of resources to ensure that important public health issues such as the supervision of supply chains, protection against counterfeits and pharmacovigilance are addressed.[1]

The challenge represented by heterogeneous national variation classification systems and specific local requirements could be met by converging national requirements through adoption of international standards

Reliance and expedited pathways in maturing markets

An EFPIA White paper on reliance and expedited registration pathways in emerging markets cited an increasing number of regulatory agencies that are implementing alternative pathways to speed up development, submission and reviews for certain products (Figure 10). These pathways were of two types.

Reliance pathways to facilitate regulatory decisions: Registration pathways used by national regulatory agencies (NRAs) or regional regulatory initiatives (RRIs) wherein their decisions regarding the approval of any

type of product can be accelerated by the reliance on or recognition of prior reviews by stringent regulatory authorities. This type of review is used by regulatory authorities in Singapore, Saudi Arabia, Egypt, Serbia, Bosnia and Herzegovina, Albania, Jordan, Panama, Argentina, Costa Rica, Dominican Republic, Ecuador, El Salvador, Indonesia, Macedonia, Mexico, Montenegro, Ukraine, Taiwan and Thailand,

Expedited regulatory pathways for medicines targeting unmet medical need: Registration pathways that speed the development, review and approval of a product which fulfils the national requirements for unmet medical need; typically implemented by a stringent regulatory authority, for a first non-dependent review, where no prior approval exists. This type of review pathway is used by the European Union (EU), USA, Canada, Japan, China, Brazil, Taiwan, Turkey, South Korea, Kuwait, Saudi Arabia, Australia, Egypt, Indonesia, Israel and Switzerland.

Finally countries that use pathways that are **both expedited and reliance based include** Singapore, Saudi Arabia, Egypt, Taiwan and Indonesia.[2]

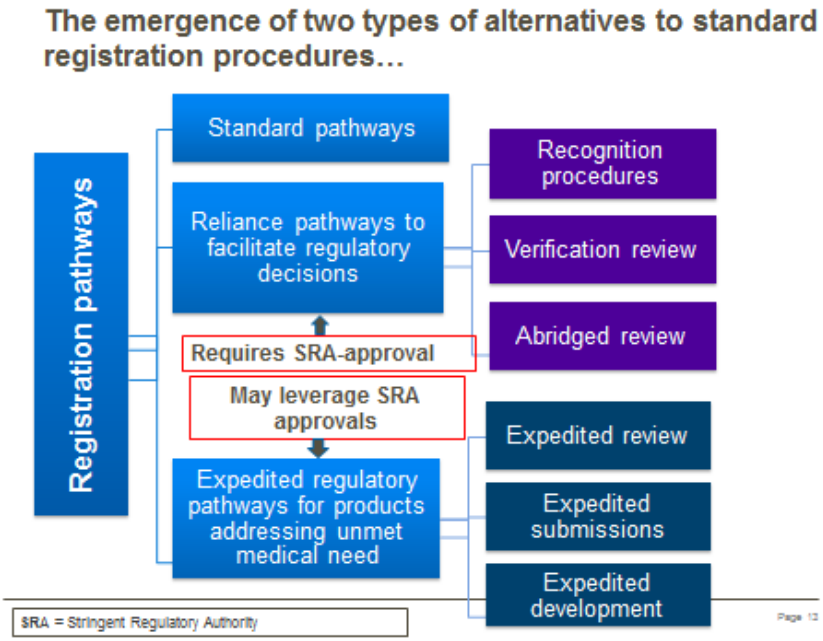

Figure 10. Standard, reliance and expedited pathways of regulatory review.

Industry should play an important role in facilitating regulatory reliance, convergence, transparency and trust. Pharmaceutical companies should actively promote regulatory agency convergence toward global standards through ICH, WHO or stringent regulatory agency guidelines. For its own part, industry should also align its own change control processes and models toward those international standards and increase alignment on submission aspects such as the format of data, their presentation in a dossier and the level of detail contained within submissions.

Industry can encourage regulatory trust by continuously improving processes and systems, continuing to innovate, consistently delivering quality output and by engaging in dialogue and explaining what they do.

Transparency can be encouraged by facilitating access to assessment reports and exploring digital solutions such as electronic data transfer. Industry should explore available alternatives by sharing experiences with existing alternative pathways among companies and by discussing those shared industry experiences with regulatory authorities to improve processes.

Conclusions

Successful collaboration among regulators should include reducing duplicative review and adopting a risk-based approach to the review of post-approval changes, allowing a focus of resources on changes with the most impact. Further convergence toward a single and global regulatory standard for data requirements and a drive for implementation of ICH and WHO guidelines is also required.

Major benefits of these changes include better use of limited regulatory resources, the reduction of development cycle time through reduced complexity and ultimately, increased patient access to new and needed products.

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What are the processes in place within stringent regulatory authorities to ensure an effective and efficient review process for generics?

Dr Siu Ping Lam, *Director, Licensing Division,*
Medicines and Healthcare products Regulatory Agency (MHRA), UK

Need for reliance

In the European Union (EU), regulatory reliance through mutually recognised European Commission (EC) procedures reduces the duplication of effort and facilitates the review of an average of the 40 applications for marketing authorisation for new active substances and 1500 applications for generic medicines that are submitted each year.

In the EU, regulatory reliance through mutually recognised EC procedures reduces the duplication of effort and facilitates the review of an average of the 40 MAAs for NASs and 1500 applications for generic medicines submitted each year.

This reliance requires a common legal framework and EC Article 6. Directive 2001/83 states that "no medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State." This directive includes generic medicines the legal definition of which has also been specified: "the same qualitative and quantitative composition in active substances as the reference medicinal product, the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies."

EU submissions for regulatory review must be made using the Common Technical Document (CTD), which sets out an extensive and detailed hierarchical structure for the content of the supporting technical information submitted in support of all marketing authorisations or variations for all product types harmonised across the EU, USA and Japan. The Directive also requires that "All information .. relevant ... whether favourable or unfavourable .. In particular …incomplete or abandoned (preclinical) or clinical test or trial relating to the … product and/or completed trials concerning indications not covered by the application."

EU licencing routes

There are three routes for licencing of medicines in the EU. In the National route, a single EU member state provides marketing authorisation for a new product, which is only recognised in that member state. The target timeline for the UK national procedure, which yields marketing authorisation in the UK only, is 210 days (Figure 11). In the UK, the National procedure is authorisation processes for generics.

In the Mutual Recognition (Figure 12) / Decentralised (Figure 13) route, a single EC member state provides marketing authorisation which is recognised by selected or all EC member states. In 2016 there were 270 Mutual Recognition Procedures for 181 products and 1264 Decentralised procedures for 1272 products. In 2016-2017, the UK was the Reference Member State for 48% of all products reviewed through a Decentralised procedure. In the Centralised route, a "community" marketing authorisation is recognised by all EC member states. This route is mandatory for certain product types and therapeutic areas but there is limited access to this procedure for the review of generic medicines. However, according to Article 3(2) & 3(3) of

European Commission Regulation 726 in 2004, the Centralised procedure can be used for the review of generics of centrally authorised new active substances of significant therapeutic, scientific or technical innovation or in interests of patients at community level. In the Centralised procedure, a marketing authorisation application is submitted to the European Medicines Agency for assessment and a Committee for Medicinal Products for Human Use (CHMP) Rapporteur and Co-Rapporteur are assigned. Voluntary assessment may also be performed by any other EU Member State. Assessment is conducted through six scientific committees such as the CHMP which are represented by the National Competition Authorities. A scientific opinion/ recommendation is prepared and there is a legally binding Commission decision to grant, refuse, suspend or revoke marketing authorisation. The Council of the European Union makes final decision in case of a dispute (Figure 14).

CMS = concerned member state; MAA = marketing authorisation application; RFI = request for information; RMS = reference member state.

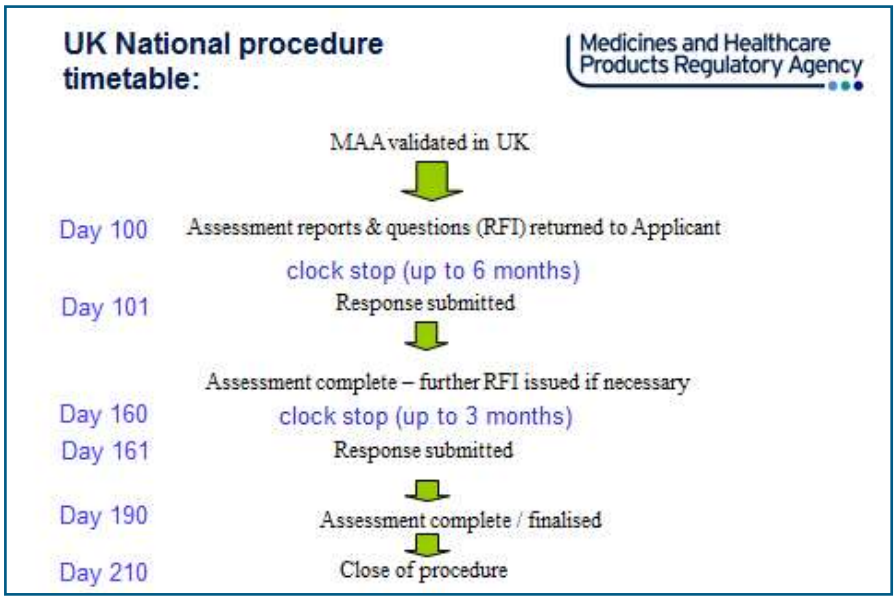


Figure 11. The UK National procedure

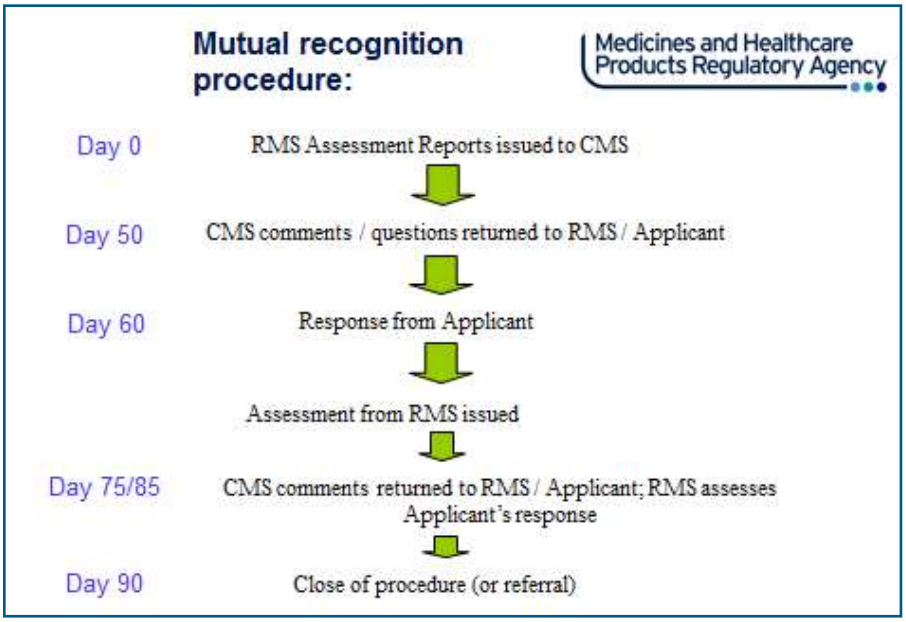
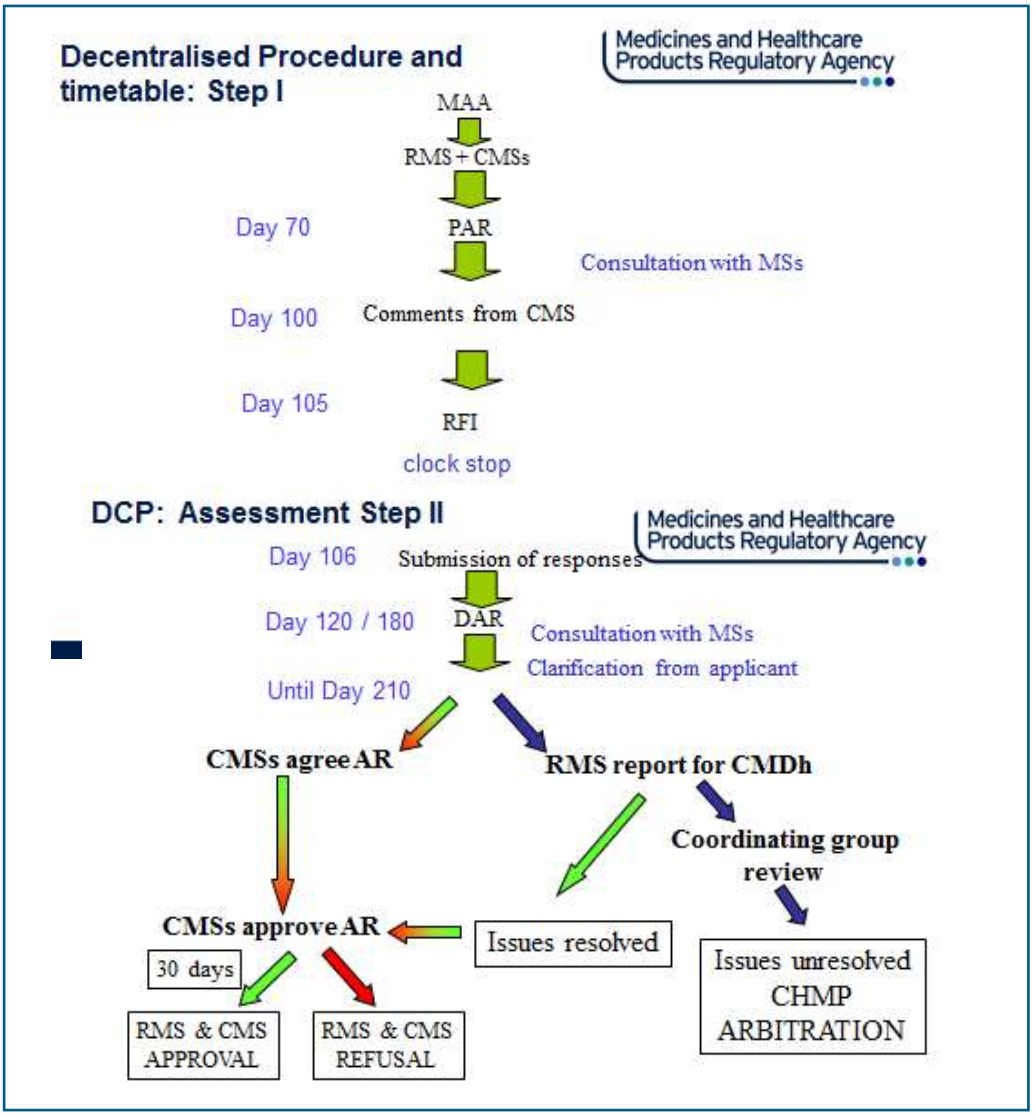


Figure 12. The EU mutual recognition procedure.



AR= assessment report; CHMP = Committee for Medicinal Products for Human Use; CMDh = Co-ordination group for Mutual recognition and Decentralised procedures – human; CMS = concerned member state; DAR = draft assessment report; eCTD = electronic common technical document; LoQ = list of questions; MAA = marketing authorisation application; MSs= member states; PAR = public assessment report; RFI = request for information; RMS = reference member state.

Figure 13. The EU Decentralised procedure.

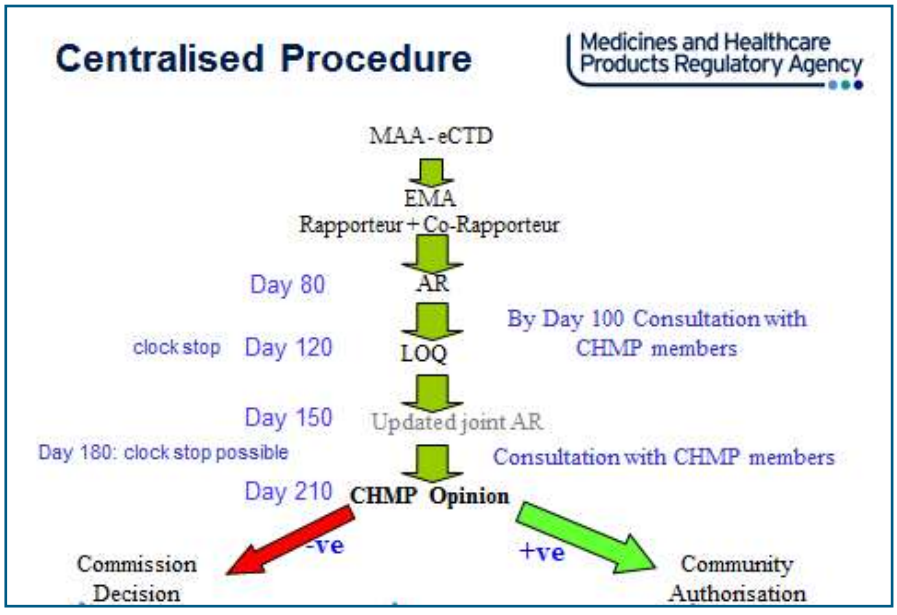


Figure 14. The EU Centralised procedure.

Australia, Canada, Singapore and Switzerland (ACSS) Generic medicines work-sharing trial

Bruce Randall, *Director, Bureau of Therapeutic Sciences, Therapeutic Products Directorate, Health Canada*

Four like-minded regulatory authorities, Australia, Canada, Singapore and Switzerland (ACSS) have formed the ACSS Consortium to focus on information- and work-sharing projects that might provide a proof of concept for larger scale initiatives. ACSS Working Groups include those for New Chemical Entities, Complementary Herbal Products, Information Technology/Communications, Pharmacovigilance, Compliance and Enforcement (Good Manufacturing Processes; GMP) and Generic Medicines.

The Generic Medicines Working Group (GMWG) was established in 2012 with a specific focus on issues relating to generic medicines to create opportunities and benefits for regulatory programmes through greater alignment of regulatory approaches and technical requirements, more efficient use of resources through information and work sharing and the establishment of an effective network among similar, trusted, regulatory authorities. It was envisioned that the GWMG would both produce immediate and ongoing results in priority work areas and serve as a proof of concept for other international regulatory cooperation initiatives such as the International Generic Drug Regulators Programme (IGDRP). To this end, the group has focused on quality, bioequivalence, and multi-disciplinary projects on issues associated with generic applications.

Governance

A detailed operational workplan of the GMWG calls for bi-annual face-to-face meetings and interim teleconference calls with the host of a meeting fulfilling the duties of the GMWG Chair for the subsequent six months. The two GMWG sub-working groups are those for Quality and Bioequivalence. There is a secure IT platform hosted by Swissmedic for reporting and other group communications, regular updates and progress reports are made by the ACSS Heads of Agencies and there is an ACSS Consortium page on members' organisational websites.

ACSS priority work areas

Each agency shares information of notable developments in their respective regulatory programmes. The ACSS Quality Working Group has developed Quality Assessment Report templates and Guidance for Quality Assessors of Drug Substance/Drug Product and similarly, the ACSS Bioequivalence Working Group has produced a Bioequivalence Assessment Report template and Guidance for Bioequivalence Assessors. Multidisciplinary projects include the Repository of Technical Issues of Interest (ROTII) for issues relating to Common Technical Document Modules 1, 3, 5; sharing of procedures and best practice, and procedures for the use of foreign assessment reports.

Generic Medicines Work-Sharing Trial

The GMWG is a trial of an innovative review model with the coordinated assessment of an application submitted simultaneously to the ACSS members. One agency acts as the Reference Regulatory Agency (RRA) and the other agencies as Concerned Regulatory Agencies. Potential benefits of the work-sharing model include an opportunity for a unique global collaboration between regulatory authorities and the pharmaceutical industry, the development of a model that could be adopted on an even larger scale, a reduction in regulatory burden, for example, the filing of common dossiers and the concurrent receipt of marketing authorisations of a medicine to multiple markets.

The first application was filed in June 2016 and has completed the pilot in April 2017. Valuable experience has been gained that will inform internal procedures for the use of foreign assessment reports as well as for international collaborative work.

The first trial was limited to a medicine with simple dosage forms (solutions and immediate-release solid orals). Applications were submitted to three of the four ACSS countries, with a RRA and CRAs, similar to the EU Decentralised Procedure. To encourage applications, completion was targeted for five months after acceptance (Figure 15).

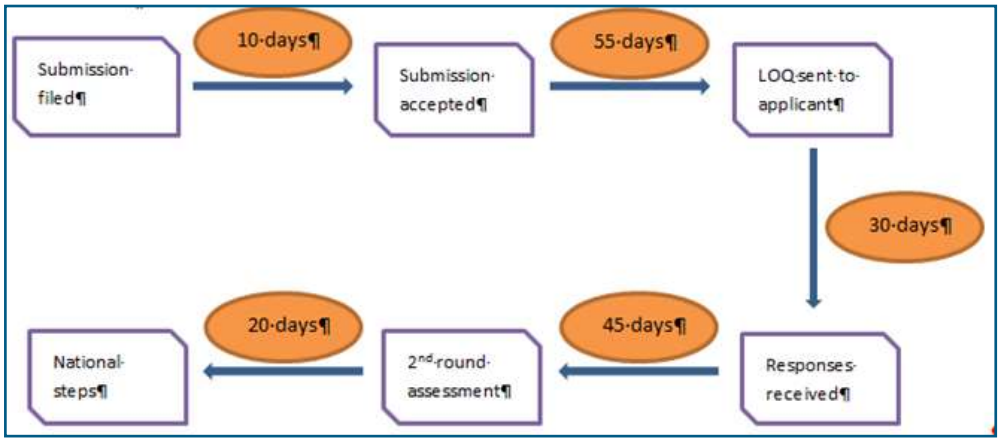


Figure 15. Target completion for the first GMWG trial was five months. LOQ = list of questions.

The difference in pre-acceptance procedures among the four agencies was a potential obstacle for the first submission, requiring significant pre-submission communication. Differences in agency requirements were identified through these communications, ensuring a complete dataset at submission.

Australia's Therapeutic Goods Administration (TGA) acted as the RRA in the first trial, with Health Canada and Swissmedic as CRAs. The questions from all three agencies were put to the applicant within targeted timing, but the time for response was extended and a second round of questions was needed. The application was approved in Switzerland in late March 2017 and in both Australia and Canada in early April 2017. The time to these decisions in all countries was ~9 months. According to the applicant, this timing was approximately the same with standard reviews in Canada, 3 months quicker than usual in Australia, and 8 months quicker than usual in Switzerland (Figure 16).

[the Generic Medicines Work-Sharing Trial] nevertheless represented a time saving from normal procedures, with this earlier approval reducing costs for both applicant and governments

Lessons learned

Pre-submission communications were important and good communication and coordination within the ACSS agencies and with the Applicant were essential throughout the application process. The first submission was more complex than anticipated and extra time was required by the applicant to respond to the first round of questions. Evaluation also took an extra round and the RRA will need to include sufficient detail in the Assessment Reports to enable an appropriate peer review by the CRAs. The overall timeframe was 9 months rather than the targeted 5 months, but this nevertheless represented a time saving from normal procedures,

with this earlier approval reducing costs for both applicant and governments. Applicants were able to submit to multiple agencies simultaneously and answer a single consolidated list of questions at a known time.

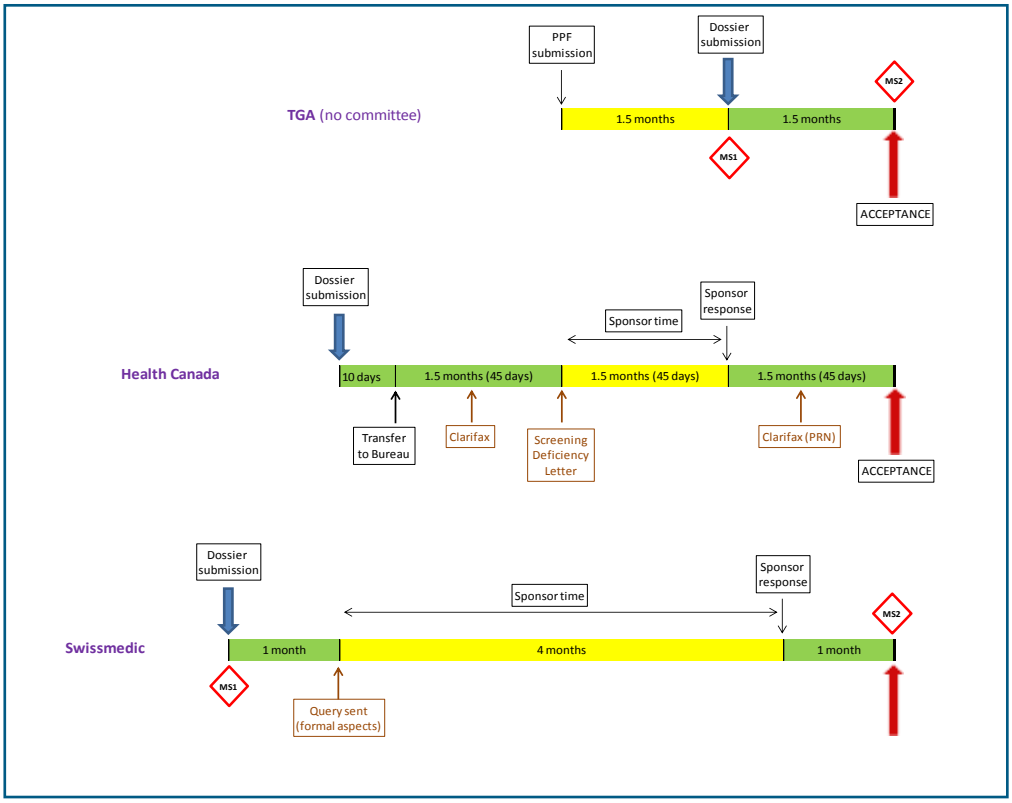


Figure 16. Timeline from submission to acceptance at three agencies in GMWG pilot trial.

General considerations and conclusions

The GMWST represented a significant upfront investment for all stakeholders. Differences in review regimens, including timelines, systems, nomenclature and data requirements needed to be identified. Specific downstream processes needed to be performed such as a biostudy to support formulary processes in Canada. In addition, intellectual property issues remain a key component of where and when generic companies file submissions and generic companies may need to use local formulations to address intellectual property in the various jurisdictions. Although there are key international players a significant number of generic companies remain regional.

Next steps

The ACSS agencies have agreed to expand the scope of the pilot to medicines with all dosage forms and allow applications to be filed with a minimum of 2 of the 4 agencies. Key governance documents have been finalised to guide the pilot including an internal project plan, an Expression of Interest (EOI) form, a Q&A document, and Operational Procedures document. On December 2017 a request for EOIs was posted on the websites of all four agencies. An in March 2018, an article describing the trial was published in the *DIA Global Forum*.[1] The ACSS is actively soliciting further submissions.

Reference

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East African Community Medicines Regulatory Harmonization Programme

Dr Yonah Hebron, *Manager, Medicines and Cosmetics Laboratory, Tanzania Food and Drug Authority*

EAC Medical Regulatory Harmonization

Established in 1999 and headquartered in Arusha Tanzania, the East African Community (EAC) is an intergovernmental organisation that includes the republics of Burundi, Kenya, Rwanda, Uganda, United Republic of Tanzania, Zanzibar and the newest member, South Sudan. There are six national medical regulatory agencies (NMRAs) operating within the EAC and 165 million people live in the region, with a gross domestic product of $158 billion USD in 2016.

The EAC Medicines Regulatory Harmonization (MRH) Programme was launched in 2012 in Arusha, Tanzania to increase the rapid availability and free movement of good-quality, safe and effective essential medicines for the treatment of conditions of public health importance. The goal of the EAC MRH is the development of a harmonised and functioning medicines regulatory system within the EAC region. Technical support for the programme is provided by the World Health Organization (WHO) and Swissmedic and funding by the Bill and Melinda Gates Foundation and the UK Government Department for International Development. All stakeholders – government, manufacturers, donors and patients – stand to benefit from medical regulatory harmonisation, which can result in effective control, reduced cost and faster and expanded access to medicines and increased treatment options (Figure 17).

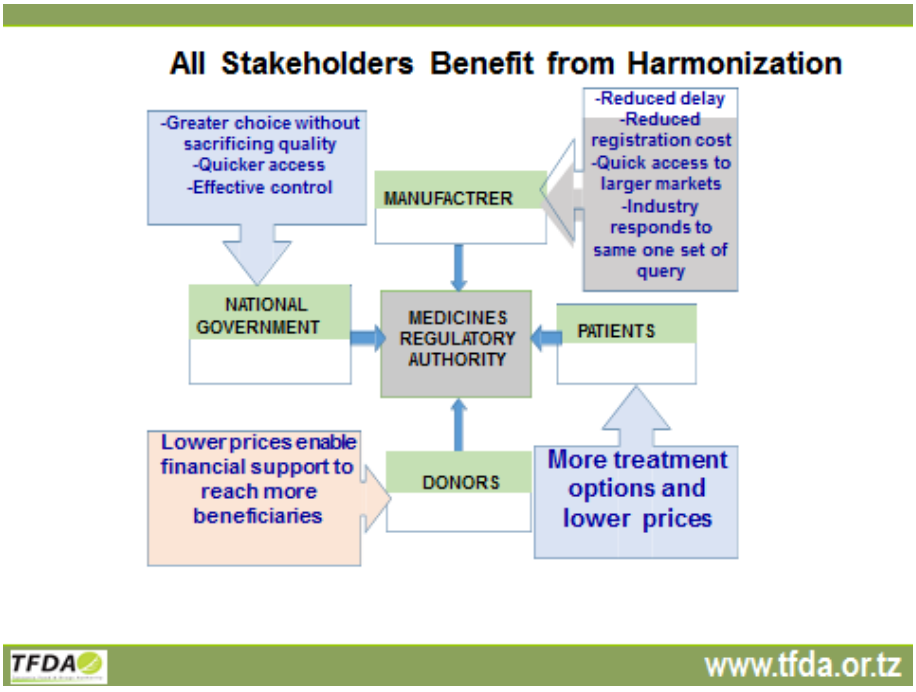

Figure 17. The benefits of medical regulatory harmonisation.

Progress toward EAC MRH milestones

Six milestones were envisioned for accomplishment by 2017, which was year five of the EAC MRH programme.

1) Implementation of the Common Technical Document (CTD) for the registration of medicines
2) Establishment and integration of an information management system in all EAC Partner States
3) Implementation of a quality management system
4) Building of institutional, human and infrastructural capacity
5) Establishment of a platform for information sharing for a harmonised medicines regulatory system
6) Development and implementation of a framework for mutual recognition of regulatory decisions made by Partner States NMRAs

Progress toward milestone 1: Implementation of the Common Technical Document (CTD) for the registration of medicines

The CTD was developed and rolled out in 2015 with robust CTD Guidelines. The CTD is based on WHO and International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) CTDs, and the same dossier is sent to all NMRAs. Challenges to the use of the CTD include the fact that manufacturers of active pharmaceutical ingredients (API) may not be willing to share the data master file with domestic manufacturers and there is a lack of domestic centres of excellence to conduct bioequivalence studies for these manufacturers. The number of applications submitted with the CTD continues to grow at EAC NMRAs and timelines for review have been shortened (Figure 18).

EAC – MRH Progress

Impact CTD on number of applications 2012-2017 at national level

		Using old guidelines	Using CTD
NMRA	CTD	Appl.	Appl.
Zanzibar – ZFDA	2015	26	42
Tanzania- TFDA	2015	1,595	1,683
Uganda - NDA	2013	568	2,694
Rwanda - RPTF	2015	-	-
Kenya – PPB	2015	-	15,428
Burundi - DPML	2015	-	518

TFDA

EAC – MRH Progress

Impact CTD on application submission and timelines

		Growth of applications		Timelines	
NMRA	CTD	Pre – CTD (%)	Post – CTD (%)	Pre – CTD (Months)	Post – CTD (Months)
Zanzibar - ZFDA	2015	37	- 78	24	16 - 18
Tanzania- TFDA	2015	4	34	24	10 – 12
Uganda - NDA	2013	5	3	18	14 -16
Rwanda - RPTF	2015	-	-	30	-
Kenya – PPB	2015	19	17	24	8 – 14
Burundi - DPML	2015	-	-	-	9 – 12

TFDA www.tfda.or.tz

Figure 18. The number of applications using the CTD at East African Community National Medical Regulatory Agencies and the timelines for their review.

CTD and joint assessments

The use of the CTD has had an impact at the regional level by facilitating joint regional assessments across the EAC through one application. Companies responding to an invitation for an expression of interest have submitted a dossier and payment of the relevant fees to the lead NMRA, the Tanzania Food and Drug Administration (TFDA), which screens the submission for obvious omissions or errors and appoints first and second assessors who review the application ahead of the joint assessment. The report of these assessors is discussed at the joint assessment meeting of all NMRAs and if the application is successful, the applicant can apply for registration at each of the other NMRAs. Challenges to the use of joint assessments include the administrative burden of registration, dossier submission and payment of fees to all NMRAs, with no single contact point. In addition, there is inadequate dossier screening, leading to avoidable later queries, a lack of transparency regarding the calendar and joint assessment timeline, poor follow-up to queries and no verification that an applicant registers with all NMRAs.

CTD and joint GMP inspections

Good Manufacturing Process (GMP) certification is required as part of the joint assessment application and accordingly, GMP inspection guidelines, *Compendium of Good Manufacturing Practices (GMP) Technical Documents for Harmonization of Medicines Regulation in the East African Community*, based on WHO GMP Inspection guidelines were developed and rolled out. An applicant site that has applied for GMP inspection in at least two NMRAs is identified as a site of common interest. The GMP Working Group decides whether an inspection of the site is required or a desk review will suffice. In a joint GMP inspection, the lead GMP NMRA allocates inspectors from a national pool. If the plant is compliant, the lead agency issues the applicant a GMP certificate and the applicant then applies for the GMP certificate at each of the other NMRAs and pays the applicable fees. To date, 13 joint inspections have been carried out in EAC, India and Egypt and 10 GMP inspection certificates have been issued since 2016. Challenges to joint inspections include the fact that scheduling is not effective at the national level and GMP inspection fees are negotiated for each inspection rather than being pre-defined. In addition, the number of Corrective and Preventive Action (CAPA) reviews and timelines to respond are not defined, there is limited coordination of joint GMP inspections with the joint assessment process and limited leverage of stringent regulatory authority certification and use of desk reviews, ever after WHO inspection.

Progress toward Milestone 2: **Establishment and integration of an information management system in all EAC Partner States**

Information management systems are fully operational in Kenya and Tanzania, partially operational in Uganda and Rwanda and under testing in Burundi and Zanzibar. However, these systems all differ and are not regionally integrated.

Progress toward Milestone 3: Implementation of a quality management system

Two NMRAs, Tanzania and Zanzibar are International Standards Organization (ISO)-certified and ISO certification was expected to be achieved in Uganda by end of 2017 and Kenya by March 2018. In Rwanda, an audit was planned in 2017. There is currently no ISO certification in Burundi.

Progress toward Milestone 4: Building of institutional, human and infrastructural capacity

Over 500 staff in EAC NMRAs have received training in Medicines Evaluation and Registration: ~178; Good Manufacturing Process: ~149; Quality Management Systems: ~62, Information Management Systems: ~139, and Pharmacovigilance: ~29. In addition, three Regional Centres of Excellence (RCOREs) have been established. A consortium of Muhimbili University of Health and Allied Sciences (MUHAS) and Tanzania Food and Drugs Authority (TFDA) was designated as a Medicines Evaluation and Registration RCORE. The University of Nairobi and the Pharmacy and Poisons Board (PPB) Kenya were approved as a Pharmacovigilance RCORE and Makerere University and the Uganda National Drug Authority (NDA) were named as a Good Manufacturing Practice RCORE.

Progress toward Milestone 5: Establishment of a platform for information sharing for a harmonised medicines regulatory system

Currently, websites for sharing regulatory information are only available in Uganda and Tanzania and no formal information sharing on registered medicines is available from EAC NMRAs. Although semi-autonomous NMRAs have not yet been created in Burundi or Rwanda, a Rwandan law to create this type of regulatory agency is under parliamentary review.

Progress toward Milestone 6: Development and implementation of a framework for mutual recognition of regulatory decisions made by Partner States NMRAs

To date, a framework for mutual recognition of regulatory decisions implemented in line with Chapter 21, Article 118 of the EAC Treaty has not been developed due to different levels of development within EAC NMRAs, nor have information-sharing agreements been developed nor adopted. The Council of Ministers have however, adopted Chapter 21, Article 118 on Regional Cooperation on Health.

The way forward

A Forum of the Heads of EAC NMRAs is working to fast track registration of jointly assessed products and the harmonisation of medicines registration and regulation remains a key policy. To that end, EAC expert working groups have been developed in Medicines Evaluation and Registration, Good Manufacturing Processes, Quality Management Systems and Information Management Systems. Financial and technical support continues through New Partnership for Africa's Development, the African Medical Regulatory Harmonisation, WHO, Bill and Melinda Gates Foundation, the UK Government Department for International Development and World Bank.

Plans have been made to clear the backlog for both joint assessment and inspection and additional joint assessments were scheduled for March and June 2018. In 2018 and 2019, harmonisation efforts will be

extended to medical and diagnostic devices, with the TFDA to take the lead. In addition, a pharmacovigilance business plan will be implemented and a framework prepared for the long-term (2020-2022) establishment of a regional EAC Health Care Products Agency. It is envisioned that this agency will coordinate the assessment of the most complex, innovative or priority products not eligible for WHO prequalification, ensure maximum utilisation of all experts at the regional level, issue recommendations that are binding for all NMRAs throughout the EAC and facilitate mutual recognition agreements among NMRAs to accelerate registration throughout the region of generic and other less complex products.

Conclusions

Harmonisation and work sharing are feasible and remain the best reliance model to address the challenge of access to essential medicines in low- and middle-income countries. The existence of structured NMRAs in EAC Partner States is important to realise the goals of medical regulatory harmonisation and a robust, regional binding legal framework is required. Regulatory decisions that are issued must have legal force with automatic entitled implementation. For the financial sustainability of a future EAC Health Care Products Agency, its activities must be partly financed by fees or contributions from partner states and NMRAs.

Harmonisation and work sharing are feasible and remain the best reliance model to address the challenge of access to essential medicines in low- and middle-income countries.

Variations and their impact on the current regulatory landscape –
What are the main issues companies and countries are facing in their review?

Paul Dearden
Head, International, Regulatory Policy and Intelligence, AbbVie, UK

The challenge of global variations

Variations are the inevitable part of the lifecycle of medicines that are necessary to ensure their quality, needed improvements, innovation and availability. These may be mandatory adaptations arising from supplier changes, regulatory commitments, corrective and preventive action reviews or pharmacopoeia updates or they may be discretionary changes such as new manufacturing sites or equipment, process improvements or changes in control strategy. Although these changes may be overwhelmingly positive, the abundance and diversity of global supply chains, manufacturing sites and processes and tests and analyses have exponentially increased their number and complexity. The resulting burden for regulators and industry has increased to the point at which global approval for a simple variation can take up to five years. As an example, an application for a simple change in supplier for an approved medicine submitted to over 100 global agencies in 2016, might need to be submitted to half of those agencies as a major variation, to a quarter of the agencies as a minor variation and for the final quarter, require no submission at all. Following those submissions, the sponsor would need to participate in approximately 75 separate and repetitive regulatory reviews and question and answer sessions for the variation, resulting in the last global approval of the change in supplier taking place in 2021 (Figure 19). The supply and logistic challenges that occur during such an extended period may result in drug shortages or even the complete withdrawal of a medicine from a market when it can no longer meet local requirements.

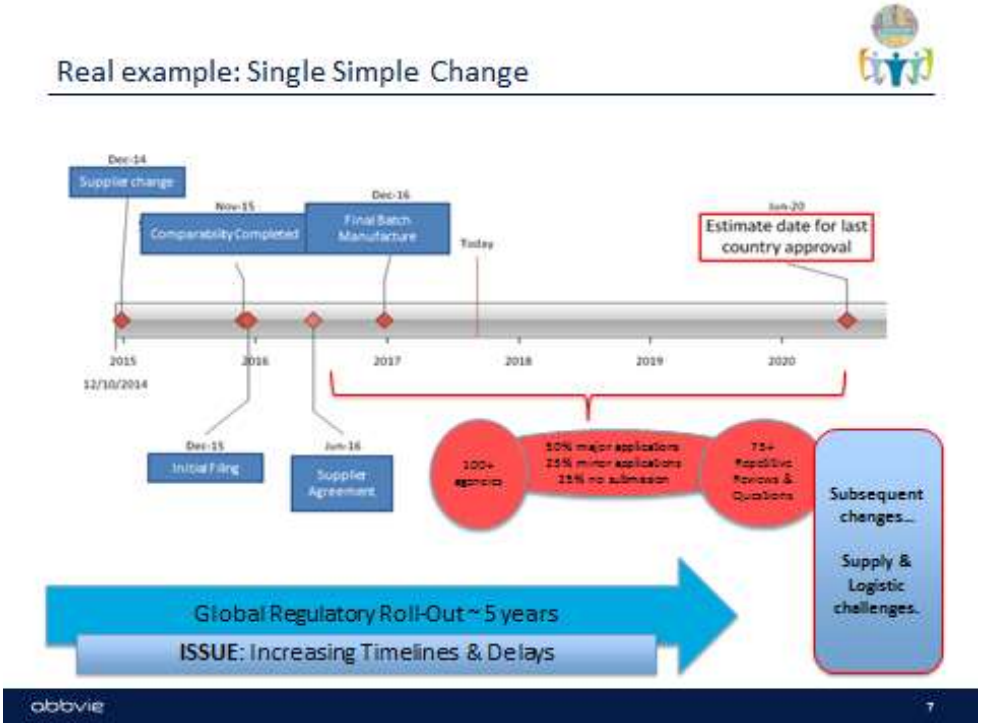

Figure 19. Global approval for a simple variation can now take up to five years.

Potential solutions for global variation challenges

To reduce regulatory burden and duplication by efficient use of limited resources, thereby reducing approval timelines of variations, four strategies may be employed (Figure 20). The first is the use of consistent, standardised variation classification system that is tiered or risk based. Second, industry needs to develop best practices for the management of variations and utilise accepted change management processes before and during the implementation of those practices. Third, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), World Health Organization (WHO) and other groups have developed or are developing aligned data and documentation requirements for variations. The adoption of these aligned requirements would reduce complexity and redundancies. Finally, transparent and predicable timelines for review and implementation are required.

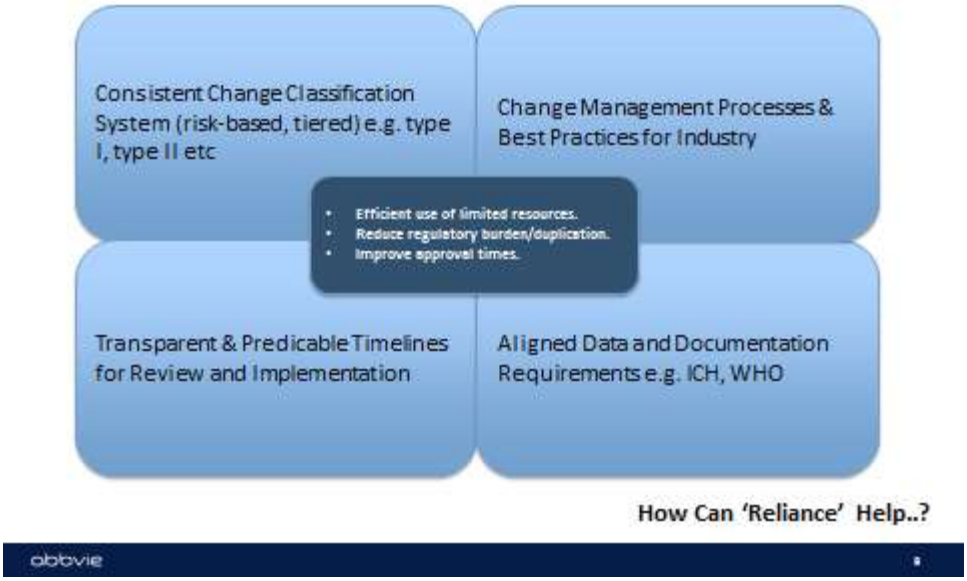

Figure 20. Strategies to manage the variations landscape.

Conclusions

Rather than a "rubber stamping "approach that cedes responsibility, reliance should be regarded as a regulatory enabler, facilitating decisions made as part of global alignment. The inherent value of this pragmatic philosophy is dependent on local needs, enabling the optimal use of available resources regardless of the application type and freeing capacity to focus on progress toward convergence.

Rather than a "rubber stamping "approach that cedes responsibility, reliance should be regarded as a regulatory enabler, facilitating decisions made as part of global alignment

Risk-based evaluation of variations to Australian Register of Therapeutic Goods entries for prescription medicines

Jenny Burnett, *Director, Scientific Operations Management, Scientific Evaluation Branch, Therapeutic Goods Administration,* Australia

As a cost-recovery agency, Australia's Therapeutic Goods Administration (TGA) attempts to match risk, effort and fees in its evaluation of post-approval variations. Three types of variation risk have been identified in Australian legislation, the low risk associated with simple corrections, the slightly higher risk of changes that improve a product's safety and the higher risk attached to changes with potential to affect a product's quality, safety or efficacy. Data requirements for these variations also varie according to the level of assumed risk. No data are required for submission of variations that had been self-assessed by companies as being one of a listed group of products of lower risk, dealing, for example, with sterile versus non-sterile goods or simple versus complex medicines. Varying data requirements apply to products not fitting into this lower risk group. While the risk varies between these two types of products, the amount of effort to be expended by TGA in their evaluation remained high.

The Medicines and Medical Device Reform (MMDR) in Australia in 2017 was set to be implemented in two phases. The first phase involved implementation of notifications and improved electronic forms while the second phase will encompass further review of variations and additional automation. After external consultation with industry and internal consultation among various TGA business areas as well as a review of technology requirements TGA established a consistency across all classes of goods regarding self-assessment variation types, consistent with other regulatory agencies such as the European Medicines Agency through an automated process to manage risk. The new notification process is now nearly fully automated, consisting of an electronic application, payment of fee, acknowledgement, submission to the Australian Register of Therapeutic Goods (ARTG) and filing of the variation (Figure 21). Effort and risk for TGA were greatly reduced with this notifications process for variations (Figure 22).

Effort and risk for TGA were greatly reduced with the implementation of the the notifications process for variations

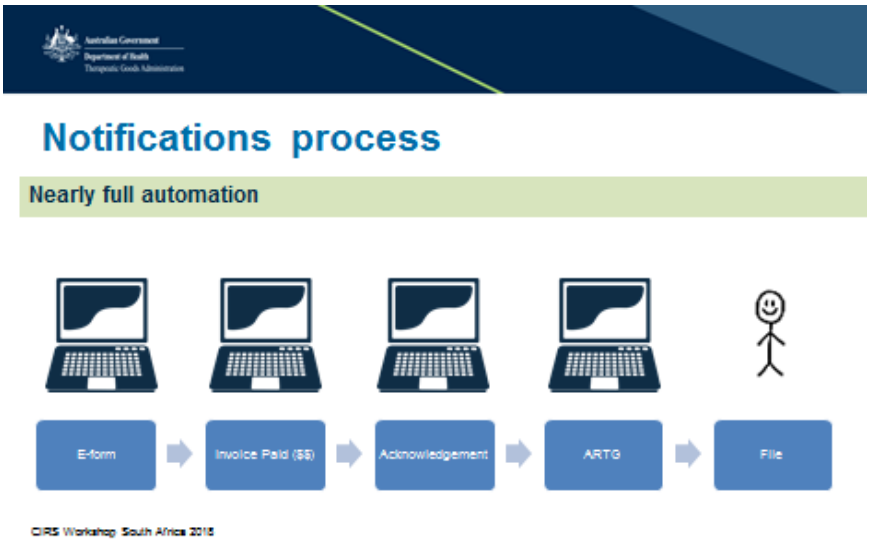

Figure 21. The notifications process for variations submitted to TGA.

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Figure 22. Effort and risk for TGA were greatly reduced with the implementation of the notifications system for post-approval variations.

Challenges during implementation included refinement of variation types for reclassification, confidence building for internal stakeholders and issues surrounding TGA legacy internet technology systems. After implementation it was determined that data in electronic TGA records was inconsistent. Further refinement of variation types, user education to select correct variation type and additional re-assessment of internal processes to reduce regulatory burden will be required. It remains to be determined if compliance review will be needed and if multi-level variation requests can be consolidated into a single submission.

Panel discussion

Optimising post-approval variations: Opportunities for implementing reliance approaches

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

The variability or lack of uniform consistent regulatory reviews of variations in chemistry, manufacturing and controls (CMC) for approved products presents multiple challenges to industry. As has already been noted, it can take 2 to 4 years for complete approvals of a moderate to major change in every country where a global product is registered. These long regulatory approval timelines add complexity when different versions of the product are required to supply multiple countries, further increasing the potential for challenges in enabling reliable supply to every country. Reliance models for CMC variations would best be implemented in a way that minimises complexity and extent of review (Figure 23).

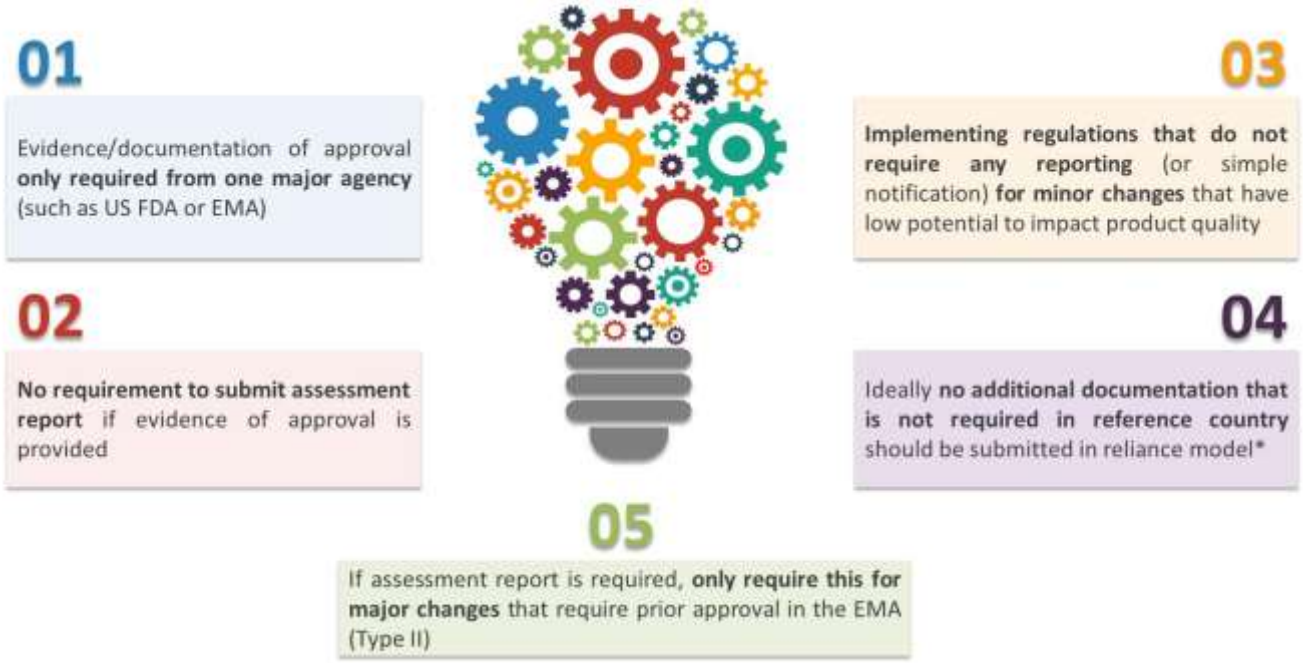
Requiring an assessment report from a reference agency for variations that are minor or moderate changes can be a major barrier to reliance models. The US FDA provides approval letters for moderate but not minor changes and does not provide assessment reports for any type of variation. Data requirements that are not consistent with the EMA or US risked-based approaches for CMC variation would present challenges for a reliance model or render the model essentially valueless. Some countries are implementing risk-based approaches to CMC variations. This is extremely helpful when only changes that have a moderate-to-high potential to impact product quality require submission or at least prior approval before implementation. Harmonising CMC variation requirements with ICH requirements would result in the same data requirements in all countries, facilitating the use of reliance models. This is especially important for stability data that are needed to support process or product changes. Reliance models offer a potential improvement in the speed at which CMC variations could be approved. This would improve reliability of the continuous supply of high-quality product to all countries.

Dr Siu Ping Lam, *Director, Licensing Division, MHRA, UK*

As many as 4200 applications for medicinal product variations are made each month in the EU and since 2005, these variations have been classified by the European Commission depending on the level of risk to public health (Type IA, IB, II) and the impact on the quality, safety and efficacy.

Type 1A mutual recognition variations are minor administrative variations. Decisions for these variations are the sole responsibility of the Reference Member State (RMS) and an automated system for these variations is being developed. The RMS is also solely responsible for the evaluation of Type 1B variations, which are also considered minor. For Type II major variations, the Concerned Member State performs a targeted assessment of the RMS evaluation (on which it significantly relies} and raises only important points for RMS consideration.

Work sharing for variations in the EU also provides a tremendous opportunity for regulators and industry to minimise the number of procedures for the same type of variation or group of variations across a number of member states. For example, after a significant update to a marketing authorisation arose as the result of clinical studies, one marketing authorisation holder could have submitted 18 individual variations for a branded product and its generic duplicate in multiple member states. By applying grouping and work sharing procedures, however, the number of variations was reduced to only 4.



*** That is, no GMP supporting documents, such as raw data, validation reports, chromatograms, declarations**

Figure 23. Reliance models for post-approval variations would best be implemented in a way that minimises complexity and extent of review.

Mabatane Davis Mahlatji, *Deputy Director, Medicine Evaluation And Research, South African Health Products Regulatory Authority (SAHPRA)*

In 2003, in response to a backlog of post-approval variations, the Medicines Control Council of South Africa first developed an "appetite for risk" approach when it published guidelines for post-approval amendments (variations) for medicines. These guidelines, which were similar to those in the UK, specified variations as Type A, those that did not require prior approval and that could be implemented without prior notification, Type B, those that required notification only, Type C, those that required prior approval and Type D, those that were considered new applications. These new guidelines resulted in the approval of approval of approximately 70% of applications in less than 30 days.

However, over time, a significant increase in applications, combined with the constraint in resources faced by many regulatory agencies has again resulted in a backlog, with the result that it will become necessary for the newly formed South African Health Products Regulatory Authority (SAHPRA) to also increase its appetite for risk to expedite the review of these applications. It is anticipated that provisions within the new legislation will enable the agency to address this need and develop processes to reduce regulatory burden through collaborative work sharing that has been outlined here today as well as on the reliance on the work of other agencies.

Section 3: Roundtable Discussions

Roundtable A Discussion

Building trust into the reliance approach: What are the building blocks that need to be in place and how can companies and agencies facilitate the process?
Chair: Prof Hubert Leufkens, Professor of Pharmaceutical Policy and Regulatory Science, Utrecht University, The Netherlands
Rapporteur: Nevena Miletic, Regulatory Policy Lead, F.Hoffmann-La Roche Ltd, Switzerland

Background

A *reliance model* is defined by the 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*"*. At the 2017 CIRS Workshop in Sao Paulo on this topic, it became clear that many agencies are interested in risk-based evaluations and would like to understand when and how they could and should practically implement a reliance model within their jurisdictions. Indeed, it was further suggested that the concept of reliance could also be utilised for other aspects of an agency's work, such as the review of variations and generics, inspections, vigilance/ surveillance and quality control. However, irrespective of the reliance model used, agencies still need to consider differences in local benefit-risk decisions as well as how medicines will be used within their healthcare systems.

A number of reliance models have been established including the prequalification process of WHO; regional and consortium work sharing and verification and abridged regulatory pathways (which vary dependent on whether medicines have been reviewed by a comparable or reference agency). The European regulatory system is often seen as a potential model for other regions in regard to building trust. Through its centralised and decentralised systems Europe has developed effective cooperation and what can be considered a mutual reliance model. The key to reliance is having and building trust between agencies and also having access to trusted reports from trusted sources. However, there are still potential barriers, which can include the lack of a legal framework, secure information technology platforms or political will. Although reference agencies may have a higher level of capability, agencies must consider the criteria or areas that need to be aligned or similar to build trust between agencies including risk tolerance, objectives and goals, standards and technical guidelines, predictability in review process, integrity of decision making and transparent communication of processes and decision making.

The focus for this Roundtable was on methods for building trust into the reliance approach, the building blocks that need to be in place and how companies and agencies can facilitate the process.

Definitions: *Trust:* firm belief in the reliability, truth, or ability of another. *Reliance***:** act whereby a regulatory authority in one jurisdiction may take into account/give significant weight to work performed by another regulator or other trusted institution in reaching its own decision. (M. Ward, Presentation, Jan 2017)

Questions for consideration

1. As trust is the foundation of any reliance model, how would the group define trust as it relates to reliance models?
2. What are the main building blocks on which one agency needs to have to rely on or have trust in another agency?
3. Should there be a one-size-fits-all approach or a set of different criteria to be used depending on the type of reliance model, agency maturity level or resource constraints? If the former, what might this look like?
4. What processes and mechanisms should be in place to build mutual confidence to enable reliance models? How can care and confidentiality in the sharing of information be best ensured?
5. What are the potential barriers to building trust and how can these best be overcome?
6. What would a trust framework look like for agencies considering developing a reliance model for their review system?
7. What role do pharmaceutical companies play in helping to build trust? For example, consent for information exchange among reference and maturing regulatory agencies
8. What training in how to regulate through reliance is required for regulators? What would be important components that any training programme would need to consider?

Discussion results

Critical issues

Trust building is a long-term learning process that entails an acceptance of the risk of failure. Building trust needs a face; that is, its growth is best facilitated through the development of personal relationships. It is the long-term effect of an accumulation of individual cases in which trust is bestowed.

Participants in this Roundtable agreed that dialogue, communication and transparency are key to successful trust building, but also specified that national and regional political will and the legal framework to work on trust are also required.

The necessary trust for medical regulatory reliance can be negatively affected through a lack of communication arising from issues unrelated to the regulation of medicines, as occurred as the result of a mining dispute between Peru and Chile. There are multiple examples, however, of successful trust-building initiatives like the Australia, Canada, Switzerland, Singapore Consortium (ACSS see page 41)

Trust must be built among all stakeholders. Industry and agencies can build trust through early dialogue in which the parameters of compliance and liability and a secured environment for information sharing are established. Regulatory authorities can build trust with each other through the convergence of regulatory requirements and the use of common approaches (e.g. good review practices). Citizens and health technology assessment can build trust in each other through instances of engagement but it should be recognised that issues that appear to limit healthcare affordability and access can have an ultimate impact on trust for these stakeholders.

Although trust is built through relationships, it should be regarded as an institutional goal, and it should be a governmental policy decision to work on trust and to reinforce trust building, with defined criteria. Roundtable participants agreed, however, that reliance and trust building are driven by capacity and resource constraints and training and capacity building are prerequisites for success. A fair balance should be established between trust givers and accepters and reciprocity in active or passive roles should not be a condition of the development of trust among stakeholders. The mandate for good manufacturing processes and inspections could be a starting point for the development of trust relationships as it was between the US FDA and EMA.

Stakeholders may wish to develop parameters for special types of trust building such as might be necessary with the development and regulation of novel therapies. Finally, constructive benchmarking could be established to measure the elements of trust in current systems

Recommendations

- Develop a constructive benchmarking model for the elements of trust contained within current systems.
- Engage in programmes of training and capacity building in the development and regulation of medicine, such as the World Health Organization Centres of Excellence.
- Ensure the ability of authorities using reliance-based reviews to continue to make their own informed decisions to protect public health.

Roundtable Discussion B

Practical implementation of an abridged review process for new medicines: where should an agency focus and what are the practical steps needed to change process and mind-sets?
Chair: Prof John Lim, Executive Director, Centre of Regulatory Excellence & Professor of Practice, Duke-NUS Medical School and Senior Advisor, Singapore Ministry of Health
Rapporteur: **Andrea Keyter,** Deputy Director Medical Devices, South African Health Products Regulatory Authority (SAHPRA)

Background

The European Federation of Pharmaceutical Industries and Associations (EFPIA) has defined an **abridged review procedure: "**This model relies on assessments of scientific supporting data that has been reviewed and accepted by stringent regulatory authorities, but includes an 'abridged' independent review of a certain part of the registration dossier of the product (e.g., relevant to use under local conditions). This might include a review of the pharmaceutical quality (CMC) data in relation to climatic conditions and distribution infrastructure and a benefit-risk assessment in relation to use in the local ethnic population, medical practice/culture and patterns of disease and nutrition."[1]

At the 2017 CIRS Workshop in Sao Paulo on this topic, it became clear that many agencies are interested in risk-based evaluations and would like to understand when and how they could and should practically implement a reliance model within their jurisdictions. It has been suggested that countries developing regulatory capabilities should consider a risk-based approach to the review of new medicines. Indeed, a number of agencies have recently adopted verification and abridged routes of regulatory review, which include consideration of reviews undertaken by reference agencies and which have the potential to accelerate timelines compared with standard reviews. Accelerating the review process should not compromise the safety, quality and efficacy of medicines and irrespective of the reliance model, agencies still need to consider the local benefit-risk decisions as well as use of the medicine within their healthcare system. The disadvantages of such systems are the need to wait for a prior approval and appropriate documentation such as a Certificate of Pharmaceutical Product (CPP). However, the advantages are the ability to focus on locally critical issues and conserve regulatory resources and the opportunity to accelerate availability of medicines.

Information requirements and agency activities for these approaches have been proposed based on models developed by agencies such as the Health Sciences Authority in Singapore.[2] Agencies evaluating this approach must consider what areas they would evaluate specifically and at what depth they should rely on reference agencies and what detailed information from those agencies they should require.

The focus for this Roundtable was the practical implementation of an abridged review process for new medicines and where an agency should focus to ensure in the added value of it its review and the practical steps needed to change processes and mind-sets.

Questions for consideration

1. What is the experience of the group with utilising abridged-based approaches, either as a company submitting a product or an agency using or developing an abridged-based approach? What are the pro and cons?
2. What practical steps does an agency require to implement an abridged approach in regard to process and the mind-set of its stakeholders? What is the best approach for companies and agencies to agree on whether an abridged review is the best choice for a particular review?
3. What type of skill sets do agencies need in order to adopt abridged based approaches and how are they best achieved?
4. Utilising the following table as a reference, where should an agency focus its review for an abridged process? Are the sections proposed for submission adequate from the perspective of both agencies and companies?
5. An abridged-based approach requires documentation from reference agencies. What are the critical components of documentation that agencies need from the reference agency approval and the company submission? Is the CPP still a fit-for-purpose way to provide information on product quality?
6. What are the pros and cons to submitting a complete Common Technical Document (CTD) for an abridged review? Does Module 1 of the CTD need to be designed to provide the key information for an abridged review?
7. How much does the success of an abridge approach rely on trusting reference agencies and the level of information companies provide to the agency?
8. What training is required for regulators in using an abridged route? What would be important components that any training programme would need to consider and why?

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Discussion results

Critical issues

This Roundtable agreed that there are multiple benefits associated with abridged approaches to regulatory review including the better management of resources. Moreover, in addition to shorter timelines compared with full reviews, studying the assessments of reference agencies can add value and potentially improve review quality for agencies using abridged models.

There are challenges to using abridged approaches, however, including identifying what should be included in the review and how it should be conducted. Training must be provided to local reviewers including education regarding the differences between full and abridged reviews, identification of suitable candidates for shortened reviews and contextualising the abridged approach within the national setting.

This training, provided for both companies and agencies is among the enablers of abridged approaches, which also includes internal and external stakeholder engagement. Abridged reviews are also facilitated through convergence among agencies in the requirements for abridged application, the methods for review of abridged applications and the required documentation.

Elements that jurisdictions must determine to constitute an abridged application include the number of required assessment reports from stringent regulatory authorities, and the type of products eligible for abridged review; for example, new active substance, biologicals or orphan drugs. Abridged applications typically include a full dossier, a declaration that the substance to be reviewed is identical to the substance in the original application or the identity of differences and the assessment report, including public and reviewers' assessment and questions and answers. Target times for abridged reviews vary among jurisdictions.

Parts of the dossier on which reviewers should focus in an abridged review are chemistry, manufacturing and controls (CMC), with changes highlighted by the reference agency or sponsor. The good manufacturing processes (GMP) status of listed manufacturers or the active pharmaceutical ingredient (API) source and stability data should be reviewed. Non-clinical data and human pharmacology data are not routinely evaluated. Summary data for phase II/III are evaluated unless specific issues in the reference agency assessment indicate a more detailed evaluation is necessary.

Recommendations

- CIRS should carry out a study identifying the requirements of different agencies conducting abridged reviews.
- Determine what reports and data are available from different reference agencies, including whether they are redacted and the timelines for their availability.
- CIRS should develop a database consolidating available information concerning what agencies evaluate in an abridged review.

Roundtable Discussion C

Opportunities for applying reliance approaches to variations (CMC and safety) and impact on local labelling
Chairman: Dr David Jeffreys, Senior Vice President, Global Regulatory, Government Relations, Public Affairs and European Product Safety, Eisai Europe Ltd, UK
Rapporteur: Dr Judy Coates, Scientific and Regulatory Affairs Manager, Innovative Pharmaceutical Association South Africa (IPASA)

Background

A *reliance model* is defined by the World Health Organization 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". At the CIRS Workshop in Sao Paulo in 2017 on risk-based evaluation, participants recommended that reliance models should be applied to post-approval changes more commonly known as variations. It was also suggested that it would be useful to discuss experiences, models or mechanisms currently in place for implementing risk-based approaches for post-approval changes based on reliance or other efficiencies. For example, agencies are starting to use risk-based approaches to identify variation changes with no or minimal risk to the quality, safety or efficacy of a medicine, thereby reducing unnecessary industry and agency review burden. Such approaches are in use by the European Medicines Agency and are currently being evaluated by agencies like Therapeutic Goods Administration in Australia.

Variations occur for many reasons including changes in regulatory requirements, manufacturing processes or facilities or the knowledge base for a product's safety profile. These variations are introduced routinely worldwide so that patients and healthcare professionals can be made aware of new or changed information in a product labels/prescribing information. These variations and their notifications are currently heterogeneously classified globally and the same changes can differ significantly depending on local requirements. It remains to be decided whether global convergence of regulatory guidelines will result in a more efficient or complex environment for the review of variations in multiple markets. A recent white paper from EFPIA identified issues including specific local requirements, unpredictable and variable approval timelines, divergent decisions by regulatory bodies and variable implementation periods. See page 62 for EFPIA recommendations and for more information.

In order to successfully implement a reliance approach for variations, appropriate policies and structures need to be in place and there needs to be an understanding of the impact of the approach on local labelling. The focus for this Roundtable was to identify the opportunities for applying reliance approaches to variations (CMC and safety) and impact on local labelling.

Questions for consideration

1. What types of variations should/could a reliance model be used for? (e.g., CMC changes, safety changes, efficacy)?
2. What are the different company and agency perceptions on the critical issues in regard to variations impacting the timing and content of the submission, review and availability of new information for patients and healthcare providers?
3. What kind of reliance models can best be used to manage variations and what would this look like. Would this entail instigating risk stratification by type of variation?
4. How might the various reliance models for variations operate/look like? The Roundtable should illustrate 2 or 3 possible models
5. Would the global convergence of requirements enable the use of a reliance model and would this convergence be both possible and practical?
6. What kind of metrics of indicators could an agency put in place to measure the effectiveness of any reliance model?
7. What training would be required for regulators to regulate variations through reliance? What important components would any training programme need to consider and why?

In a 2017 position paper, the European Federation of Pharmaceutical Industries and Associations recommended a set of actions for variations that are summarised in the following tables.[1]

Table 1. Recommended actions for variations.

Short to mid-term	Longer term
Converge requirements through the adoption of international standards (WHO) through a risk-based approach to the classification of variations, data requirements, and timelines.	
	Implement in a stepwise manner collaboration among regional NRAs that enables work-sharing, mutual reliance of assessments and, in the longer term, mutual recognition of approvals
Minimize the number of country-specific requirements (examples are provided in the paper)	
Consider how best to focus resources to ensure that important public health aspects i.e. supervision of supply chain, counterfeits, pharmacovigilance, are in place. These measures may be more impactful in ensuring quality of medicines to its population than re-assessing a change already evaluated by other agencies.	
Encourage exchange of knowledge between the review and inspection departments	Implement best practices and principles from ICH Q12. Increasingly rely on the companies' Pharmaceutical Quality Systems (PQS) to effectively manage minor changes without the need to file variations
Dedicate resources for the review and approval of safety labelling variations in an accelerated manner	Implement broad acceptance of e-labelling and progressive deletion of paper leaflets in the pack, in line with information technology capability in countries worldwide
Allow flexible implementation periods for technical and labelling variations	
Industry to improve planning of changes through the product life-cycle and seek to adopt new mechanisms that are expected in the future such as Post Approval Change Management Protocol (PACMP).	

Table 2. Outline of current situation and proposals for improvement.

Current Situation		Proposals for Improvement
Heterogeneous classification systems	QUALITY	Implement a unified risk-based variation classification system Introduce mechanisms to allow simultaneous submissions (i.e. grouping) Create opportunities for regulatory agencies to work together and develop further convergence
Specific local requirements		Converge administrative requirements for the submission of variations, and eliminate unnecessary submission of data
Unpredictable and variable approval timelines		Define and follow clear procedural guidance with appropriate and aligned timelines Seek future opportunities and solutions to enhance life cycle management
Divergent decisions by regulatory bodies		Mechanisms described above will optimise convergent decisions
Variable implementation periods		Agree on common market implementation (QA release) time-periods for introducing the product with the new change.
Safety labelling review and implementation process can be lengthy, and unpredictable	SAFETY LABEL	Safety labelling should follow a dedicated and expedited process, independent from quality and technical variations
		Longer term, electronic labels should be considered (after suitable pilot assessments), as a mechanism to enable direct access to the most recent product information.

Discussion results

Critical issues

As the issue of reliance for the review of post-approval chemistry, manufacturing and controls (CMC) and safety variations is a relatively new area for consideration with few established models, this Roundtable agreed that an alignment of classifications of the variations and clustering of types would be helpful.

It should be recognised that reliance for CMC variations needs to be considered both for products approved through standard registration and through reliance models. Implementation of CMC variations for products approved through reliance can be achieved through two models. For example, for products within two months of approval, an active approach could be for tacit approval, based on the same reliance registration approval, whilst a passive approach would entail automatic recognition, based on the agency making a declaration to accept all associated changes and variations to the original approval.

CMC variations for products already on the market can be implemented by aligning with European Union (EU) classifications with regard to ICH Q12, *Technical and regulatory considerations for pharmaceutical product lifecycle management* (http://www.ich.org/products/guidelines/quality/quality-single/article/technical-and-regulatory-considerations-for-pharmaceutical-product-lifecycle-management.html) . It is understood, however, that this is a solution for many but not all countries.

As has been noted by several Workshop speakers, post-registration amendments can encompass many variations and require a long timeframe for approval. In South Africa for example, it may take as long as eight years to receive approvals for all variations for a single product. Discussion participants proposed that the principles of reliance be applied and the dossier plus all variations be considered a new product for registration and include a statement that the product and the product variations are identical to those approved by reference agencies. This may be challenging as regulators may legally only be able to issue approvals based on evidence available at the time of submission and also may decide not to approve based on new information or data.

A collaborative approach might be appropriate for products on the essential medicines list. This may be possible if only applied to a particular suite of variations. This situation would not imply a common dossier or a dossier reset. Risk stratification would apply and consideration would still need to be made with respect to the local context.

There are broader considerations from an industry perspective including the strategic management of variations, a cost analysis of the changes to be submitted, the time to implement the variations and the regulatory risk in maintaining the variations. These need to be considered versus potential product benefits, requirements for compliance and overall risk.

Pharmacovigilance

Pharmacovigilance concerns include a necessary awareness of risks to patients, companies and regulators. The onus remains on industry to provide timely urgent safety information. However, the final output of variation convergence may not have been fully defined. Are stakeholders agreeing on a common label for a product? When using reliance and convergence models, it may be challenging to implement divergent clinical updates.

Regional work sharing such as that practiced through the Zazibona initiative may be effective for safety variations, with the original leading agency continuing to direct regulatory work for the variations. The Roundtable cited industry's current successful engagement with the Zazibona initiative in efforts to standardise labelling in the region, which would assist with indication changes using the reliance approach.

The pharmacovigilance landscape is still developing and many considerations are required. What the reliance framework for pharmacovigilance variations would look like within and between regions and methods for practical implementation would need to be determined. It was recognised that timelines for getting changes into information packs for distribution might be lengthened in the process and that alignment with World Health Organization (WHO)-listed stringent regulatory authorities may be challenging. Any reliance models should take all post-registration activities into consideration including periodic safety update reports (PSURs) and renewals.

Effectiveness of new models can be assessed by establishing baseline timelines with periodic reassessment for changes. Trust and confidence must be developed by fully understanding the systems, processes and use of guidelines of other regulatory agencies and the exchange of reports under mutual recognition agreements.

Assessors who will be using reliance approaches can be trained through exposure to the reports of reference regulators. Workshops such as those convened by Asia Pacific Economic Cooperation (APEC) forum can act as a springboard for reliance as can other types of conferences and webinars. In addition to ongoing efforts in training and confidence building by WHO, the World Bank, the Bill and Melinda Gates Foundation and the New Partnership for Africa's Development (NEPAD), CIRS has published articles sharing the reliance success stories in Jordan and Saudi Arabia and strived to bring cross regional exposure to more agencies in countries in with emerging pharmaceutical markets.

Recommendations

- In the short term, establish a classification system for CMC variations that is harmonised and converged. In the long term, align CMC variations with ICH Q12.
- Consider regional work sharing to expedite safety variations.
- Establish baseline timelines for variation changes and periodically reassess after implementation of reliance-based models to assess effectiveness.
- Continue to build confidence and trust through the exchange of reports under mutual recognition agreements, training of assessors through exposure to the reports of reference regulators, the convention of workshops, conferences and webinars, the publication of reliance success stories and the cross-regional exposure of maturing to established agencies.

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Roundtable Discussion D

Instigating a reliance review model for generics – How could this be done practically and what would be needed from companies and agencies?
Chair: Chair: Prof Henry Leng, Regulatory Affairs Consultant, South African Health Products Regulatory Authority (SAHPRA)
Rapporteur: Dr Luther Gwaza, Technical Officer, Regulatory Systems Strengthening, WHO

Background

The worldwide growth in generic medicines has resulted in increased regulatory pressure because of a greatly increased workload as well as the increased sophistication of the products and the risks associated with their complex global supply chains. A number of recent regulatory initiatives have been established to exchange information on issues of mutual interest, enable cooperation, maximise synergies and avoid duplication of effort. These include the International Generic Drug Regulators Programme (IGDRP), the work of which includes Quality Guidelines for Assessors and which has now merged with International Pharmaceutical Regulators Forum (IPRF) to form the International Pharmaceutical Regulators Programme (IPRP). The Generic Medicines Working Group within the Australia, Canada, Singapore, and Switzerland (ACSS) Consortium have also developed and successfully piloted a decentralised model for generic review which has resulted in a decreased regulatory process timeline compared to that for standard generic review. Other models include prequalification through the WHO and other collaborative initiatives such as the East African Community (EAC) and the work being under taken by Zazibona. South Africa joined this initiative in 2016 and it has now been adopted as an official South Africa Development (SADC) project. Such collaborative models do have challenges as well as benefits.

In addition to work-sharing models, individual countries can use a reliance model similar to the verification and abridged models used by Singapore. It is important that regulatory systems be science based, respect international standards and best practices, and adopt an approach that focuses on leveraging the work of other trusted agencies. When considering the review of a generic medicine, agencies must clearly define how their activities “add value” especially when there are positive recommendations from reference agencies. This value may be a local jurisdictional confirmation that the product meets the required standards or is appropriate for the local population. Because of complex generic supply chains, however, no single review system will suffice and flexible review options are needed. The focus for this Roundtable was the practical aspects and needs for instigating a reliance review for generic medicines.

Questions for consideration

1. What are the major challenges facing regulators with respect to generics today and why could a reliance- or risk-based model be of value?

2. What types of models currently exist or are being piloted for generic review and how can these reduce the pressure on agencies and in what way?
3. Which approaches or models can serve as a basis for efficiency in generic reviews? What are the strengths and weaknesses of these approaches? How can weaknesses be overcome?
4. What are the key considerations of an agency looking to develop a reliance/work share mechanism for generics? Are there special considerations for evaluating complex generics such as multi-component products or difficult-to-manufacture dosage forms?
5. Can realistic timelines be set for the various components of reliance-based generic reviews? What would agency and company response timelines look like in ideal scenarios for verification, and abridged reviews? What are the causes of extended timelines from the agency and company perspective?
6. What metrics should be used to determine the effectiveness of risk-based review strategies? What are the measures of agency activity and of company activity that should be evaluated? What quality measures (beyond timelines) should be assessed?
7. What training is required for regulators in how best to regulate variations through reliance? What would be important components that any training programme would need to consider and why?
8. Is there a role for addressing the review of biosimilars using the current or proposed pathways for generics? What are the pros and cons or issues that will need to be addressed to make biosimilars assessments efficient?

Discussion results

Critical issues

General issues discussed by this Roundtable included the possible differences in interpretation of the application of the terms reliance and recognition in relation to the characteristics of generics, which include biostudies to demonstrate equivalence to an acceptable reference product. The level of data requirements for these products may differ based on the reliance model, but in general, full data submission is expected as well as review or inspection reports from the reference authorities. The group focussed on responses to the discussion questions that were supplied.

Question: What are the major challenges facing regulators with respect to generics today and why could a reliance- or risk-based model be of value?

Challenges include the volume of submissions versus the regulatory capacity to handle them. The submission of variations increases this workload. In addition, there is no global harmonisation for generic approvals in mature markets. Generics can be complex and industry is challenged to meet the country-specific requirements for generics in a global market, as different standards are applied by generic manufacturers to different markets; for example, the standards for facilities may differ in mature and emerging markets.

Question: What types of models currently exist?

The EU system with the centralised procedure and decentralised model is likely the best model for reliance and mutual recognition. Other models include the so-called Singapore model of abridged and verification reviews and the work sharing and joint reviews practiced by groups such as Zazibona, East Africa Community (EAC), Association of Southeast Asian Nations (ASEAN), Caribbean Community (CARICOM) and Australian, Canada, Switzerland, Singapore (ACSS) Consortium. Reliance is also represented by use of the Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) for active pharmaceutical ingredients (APIs) and the WHO prequalification and collaborative procedures.

Other special regulatory programmes for reliance or recognition include the Swiss Medic Marketing Authorisation for Global Health Products (MAGHP) procedure, the Committee for Medicinal Products for Human Use (CHMP) EU Article 58 which allows the Agency's to give opinions in co-operation with WHO on medicinal products for human use that are intended exclusively for markets outside of the EU and the US FDA tentative approval letters, which are issued if a generic drug product is ready for approval before the expiration of any patents or exclusivities accorded to the reference listed drug product.

Question: How can they reduce pressure on agencies and in what way?

Reducing timelines, harmonisation of requirements and increase in resources or decrease in the level of effort required.

Question: Which approaches or models can serve as a basis for efficiency in generic reviews? What are the strengths and weaknesses of these approaches? How can weaknesses be overcome?

There is an inherent lack of trust with some of the models being used. Including recipient countries in the review process, for example, through participation in EU Article 58 and Swiss Medic MAGHP procedures, may address these trust issues. Use of the CEP and certificate of pharmaceutical quality reduces data requirements for manufacturers and reduces duplication and time in review of API. Publishing information on the different reliance models available would allow agencies to evaluate options suitable for their situation.

Question: What are the key considerations for an agency looking to develop a reliance or work sharing mechanism for generics?

Agencies need to consider local registration requirements compared with the reference agencies and whether

the reference product is marketed in their own country. Mechanisms are needed for information sharing between regulators or industry regarding selecting reference products to overcome country-specific requirements. Agencies should consider different scenarios relating to reference product and how to address these issues. Definitions of generic drug may differ between jurisdictions and need to be established as will the definition of similarity. A knowledge of the reference agency decision-making process is required as is knowledge regarding whether the product is in clinical use or marketed in the reference country. The agency capacity and capability need to be considered and their learning and training should be balanced between full

regulation and the use of reliance models. Agencies must establish the difference between critical and non-critical reviews and develop heterogeneous standards and approaches in the review process.

Question: Are there special considerations for evaluating complex generics such as multi-component products or difficult-to-manufacture dosage forms?

The considerations are similar to those for non-complex products but agencies may wish to consider the number of reference authorities that have approved the product and the maturity of the manufacturer. Work sharing might be a viable option for the review of these products.

Question: Is there a role for addressing the review of biosimilars using the current or proposed pathways for generics? What are the pros and cons or issues that will need to be addressed to make biosimilars assessments efficient?

Yes, there is a role for these pathways for biosimilars. The same issues cited for complex generics could apply here.

Question: Can realistic timelines be set for the various components of reliance-based generic reviews?

Agencies should set timelines that take into account the level of reliance pathways required; for example, full recognition, reliance or work sharing. Agency timelines used without reliance models should also be

considered and benchmarked based on existing models. Work sharing may reduce workloads but not necessarily reduce timelines.

Question: What are the causes of extended timelines for verification and abridged reviews from the agency and company perspective?

Timelines may be extended because data are not readily available. In addition, where requirements are not harmonised, additional tests or data need to be generated for specific countries, submission quality may not be sufficient and companies may request time extensions to respond to issues.

Question: What metrics should be used to determine the effectiveness of risk-based review strategies (in addressing the intended problems; volume, capacity and review effort, without compromising quality)? What are the measures of agency activity and of company activity that should be evaluated? What quality measures (beyond timelines) should be assessed?

Timelines are an important metric for risk-based reviews as is the proportion of products going through the reliance models, the time lag between approval at the reference authority and submission to the agency using reliance reviews; review effort, that is, the number of review cycles.

Question: What training is required for regulators in how best to regulate generics through reliance? What would be important components that any training programme would need to consider and why?

An important focus for regulator and industry training might be the different review approaches and data requirements for different regulatory pathways. Important components of that training might include performing desk reviews for inspection reports, abridged and verification review for assessment reports, change managements and the responsibilities of reviewers, interpretation of the guidelines for both industry and regulators and risk management science or risk-based approaches to regulation.

Recommendations

- Harmonise data requirements for generic medicine applications.
- Develop tools or guidances on good review practices to facilitate use of the reliance or risk-based approaches.
- Provide information or publications on the reliance models that exist including implementation models or roadmaps and agencies can select options suitable for their context based on workload and or regulatory capacity and capability.
- Agencies should benchmark timelines and monitor performance for different pathways.
- Develop a credible and appropriate model for increasing access to generic medicines.

FINAL REFLECTIONS

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

The regulation of medicines today is such a massive undertaking, that with one possible exception, no single agency can handle it themselves. All agencies, large and small, must deal with the realities of constrained resources and focus on tasks that with the most potential return on investment. The role of regulators is neither to expedite nor to block medicines' market entry but rather to use the most efficient pathway to add value to the assessment of the product to ensure its quality, safety and efficacy contribute to the public health.

.Avoiding the duplication of work through collaboration among a global network of regulators is the only way forward in this regard. Rather than a loss of sovereignty or independence, this reliance should be regarded as an indication of true empowerment and strength.

Once regulators realise that reliance is absolutely required, it becomes important to determine how to develop the necessary trust for this reliance. It would be valuable for CIRS to identify examples of successful trust building among regulators and distinguish the methods used to build trust in these instances. A necessary element for trust building in Europe has been legal support, without which progress in this area would have taken significantly longer. As a result of EU legal mandates, cooperative regulatory decision making has been "forced" in a positive way.

Finally, as mentioned by Roundtable C, with the possible exception of generic medicines, the life cycle approach to reliance, rather than focusing on initial approval is critical. As regulators recognise each other's work in both approval decisions and in labelling, post-approval work is enabled an expedited.

Question: Initially the regulator's role was to improve the public health by keeping bad products off the market. Now the role of the regulator is still to improve the public health but it is also to facilitate new products to come on to the market. Would you agree with that?

Dr Salmonson: I certainly agree, and I think that regulators have different roles in different countries where they may or may not have a greater task in trying to provide assessments for downstream stakeholders. Also, not approving a product or delaying approval of a variation because of a lack of resources is a huge responsibility. If safety updates are not approved because of a backlog, it can have important consequences for patients and for an agency's creditability and reputation.

Prof Stuart Walker, *Founder, CIRS*

The pharmaceutical industry and regulatory agencies have undergone amazing changes over the last decades. One of the most important of these changes has been through the growth of trust through relationships, transparency and communications.

No project or process is going to be successful unless there is a relationship between the various stakeholders, that is, agencies, industry, patients, physicians and health technology assessment agencies. In 2017 CIRS was privileged to arrange seven workshops for agencies in the last year. Some agencies are very comfortable with bringing in industry to share in discussions at those workshops, signifying the existence of trust and relationships between those two groups, whereas other agencies do not accept that the workshops should include companies, potentially signifying a lack of relationships as well as an element of mistrust.

When reliance was discussed 10 or 15 years ago, many agencies indicated that they could not possibly put any reliance on any other agency because of issues in sovereignty or because they needed to take ultimate responsibility for the products that they had reviewed. I believe that along with many contributors, CIRS has played a key role in the growth of reliance among agencies through its position in bringing together stakeholders to share information and build trust.

My second reflection concerns abridged reviews. In the Roundtable group in which I participated, it was clear that defining *abridged review* was difficult as there is a whole range of meanings for this term within various agencies and companies. Some agencies have indicated that they wish to undertake this form of review but may be uncertain as to how to proceed. Because of its work with some 25 regulatory agencies around the world, CIRS is now in a unique position to fulfil the first recommendation from our Roundtable namely to *Clarify the elements that make up an abridged review.*

The second recommendation from the group was to *Identify what information is available from the reviews conducted by reference agencies in different countries, when it is available and if it is redacted.* Some pharmaceutical companies have already generated lists containing this information and have indicated that they may be willing to share that information so that agencies that want to conduct abridged reviews can more easily understand what information is available.

The third recommendation from the Roundtable was to *Identify what agencies currently evaluate when performing an abridged review.* Agencies wishing to begin to use abridged reviews may be uncertain as to what needs to be reviewed. CIRS are now planning to conduct a survey to determine what other authorities review, whether it is human pharmacology, phase two or three or summaries or full reports from the reference agencies. The results of this survey could be anonymised and put into a database to be shared and would have the potential to be very helpful to those agencies beginning to employ abridged reviews.

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

Although industry typically focusses pragmatically on the speed of regulatory review, the perspective of maturing regulatory agencies, who are trying to develop the expertise and experience is understandable, even in an atmosphere of increased global harmonisation. This perspective is likely to remain an important consideration. The balance lies in trying to find the best way to support those agencies in their efforts to increase their capabilities while encouraging them to recognise the benefits to collaboration and reliance and conserve limited resources. To this end, whilst reliance or collaborative models may prove useful, many agencies may wish to remain flexible and adapt those models using approaches they find most appropriate.

There is a critical need for education and training on guidelines, agency procedures and good submission and review practices. There may be many options for this training. ICH training is very useful, but may not be available for jurisdictions who are not yet members or who are observers. If the availability of training were made more clear, industry might lend some support and experts may be more willing to contribute their knowledge. It is important to realise, however, that often trust can only be built through actually working with other stakeholders and may first require a leap of faith. Collaboration that starts with a simple project in good manufacturing processes can start the conversation and build the trust going forward.

At the recent APEC meeting of the Regulatory Harmonization Steering Committee meeting, Professor John Lim presented ideas on key performance indicators for agencies. Although agency approval times were discussed, what was actually being measured with convergence and reliance and we should exercise caution in measuring convergence and reliance by agency approval times, which may or may not be good indicators.

CIRS does a wonderful job in bringing together industry and regulators and academia as a strategic and practical level, but there are a number of mid-sized and smaller agencies that would truly benefit from hearing these kinds of discussions and appreciate being in the room with top-level regulators. It would be very beneficial if they could also be invited to future meetings.

Although industry would be happy to provide the necessary support for agencies like Saudi Arabia in their efforts to implement abridged and verification models, it is a more appropriate role for CIRS to share some of the learnings from agencies that have already successfully incorporated these reviews routes.

Question: Prof John Lim, would you like to reflect on what Paul was saying about the APEC meeting?

Prof John Lim: There has been a push to measure the degree of convergence amongst the 21 APEC economies by 2020 from the APEC High-Level Committee. Therefore, at the APEC meeting in Singapore in February 2018, we tried to move that thinking forward and assess where APEC economies are in terms of some practical things like their Pharmaceutical Inspection Cooperation Scheme (PIC/S) membership, whether they continue to use Certificates of Pharmaceutical Product (CPPs) and whether they require multiple licences for products produced in two different sites. The idea was to consider these characteristics as potential indicators of convergence or reliance because convergence in agency requirements and standards can facilitate the use of standardised models of review.

Prof Shabir Banoo, *Chief Technical Specialist – Pharmaceutical Policy and Programmes, Right to Care and University of the Witwatersrand, South Africa*

This Workshop comes at a time when SAHPRA has the opportunity to learn from the past, deal with today's challenges and to move forward with the best available tools and frameworks. It has been acknowledged that the regulator is both a gatekeeper and enabler of public health and most stakeholders would likely agree that reliance frameworks promote public health. The challenge for SAHPRA is to implement a framework that is driven by high levels of procedural efficiency and integrity but that also aligns with global frameworks for health products regulation. While I agree that the concept of zero duplication of work is critical for agencies with limited resources and that there are elements in a reliance framework that SAHPRA may wish to consider and progress, the primary current challenge for the agency is to complete the backlog of work, which may call for a more drastic approach.

An understanding of what reference countries are doing in terms of pharmacovigilance and post-approval surveillance will support product stewardship in maturing agencies and facilitate the growth of knowledge regarding the safety issues for therapeutic products. In fact, resources that regulators are able to conserve through the use of reliance frameworks may best be used in the area of post-approval product surveillance.

Developing a culture of regulatory science requires extending training and capacity building not only to regulators but to industry and other stakeholders and may need to include the provision of undergraduate courses for healthcare workers at all levels and the development of both national and regional regulatory science institutes. A number of initiatives in the African Medicines Regulatory Harmonization programme are moving in that direction but this would afford an opportunity to integrate best practices in current standards of operation as well as in mechanisms for reliance.

Prof Hubert Leufkens, *Professor of Pharmaceutical Policy and Regulatory Science, Utrecht University, The Netherlands*

Currently, conversations about reliance have very much been kept between regulators and industry. Patients and healthcare providers expect the availability of efficacious, safe and high-quality products and are unaware of reliance needs or of issues in constrained regulatory resources. Communication with these external stakeholders about the need for investment in regulatory reliance and its potential global benefits is necessary.

Reliance and trust have a face and it is possible for learned and respected people to arrive at different interpretations of the same data for the same product. In a study by Giovanni Tafuri of the Italian Medicines Agency, myself and others, regulators from the US FDA and EMA were interviewed to determine factors in decision making for approximately 50 oncology products. It was determined that although there were more similarities among the regulators than differences, different decisions were made, primarily as the result of "informal" factors.[1] I anticipate that these types of different regulatory decisions will occur more frequently in the future because of the proliferation of advanced complex therapies. It has become important, therefore, to

understand why decisions are made differently and to communicate that information to patients, healthcare providers and politicians.

It is also important to realise that duplication of work is not always a waste of resources. For example, the Committee for Medicinal Products for Human Use (CHMP) of the EMA relies on the reports of the Rapporteurs but welcomes and values additional comments from different member states, whether they are supportive or critical of the Rapporteur reports. Some may see these additional reviews as duplicative and unnecessary, but I believe that they are critical to the integrity of the system. It should also be understood that the initial implementation of reliance may actually require *more* time and resources than is expected.

Similarly, there should include "buy-in" from regions that are affected by reliance-based decisions. Originally, when the Pharmacovigilance Risk Assessment Committee (PRAC) was formed as a result of 2012 European legislation, the plan was for committee experts to examine safety issues for products and make decisions based on those issues. It was eventually decided though that there should be discussion and buy-in from countries affected by the safety issues. Although this is not always easy, it is essential.

Ultimately, reliance represents a delicate balance between receiving and giving and may not only be understood through quantification and metrics. Understanding and respect of the interests, emotions and cultural differences of all decision makers are key for sustainable reliance models.

Reference

1. Tafuri G et al. How do the EMA and FDA decide which anticancer drugs make it to the market? A comparative qualitative study on decision makers' views. *Ann Oncol.* 2014;25:265-269.

APPENDIX: WORKSHOP ATTENDEES

Regulatory agencies, regional associations and centres of excellence		
Dr Denize Ainbinder	*Head of Drug Registration Department*	**Ministry of Health, Israel**
Prof Sir Alasdair Breckenridge	*Former Chair*	**MHRA, UK**
Dr Jenny Burnett – RF	*Director, Scientific Operations Management, Scientific Evaluation Branch*	**Therapeutic Goods Administration, Australia**
Agnes Chan	*Director, Therapeutic Products Branch, Health Products Regulation Group*	**Health Sciences Authority, Singapore**
Jo-Feng Chi	*Deputy Director, Division of Medicinal Product*	**Food and Drug Administration, Taiwan**
Deeksha Ganga	*Technical Officer*	**CARPHA CRS, Trinidad & Tobago**
Dr Churn-Shiouh Gau	*Executive Director*	**Center for Drug Evaluation, Taiwan**
Dr Yonah Hebron	*Manager, Medicines and Cosmetics Laboratory*	**Tanzania Food and Drug Authority**
Mandisa Hela	*Deputy Chair*	**South African Health Products Regulatory Authority (SAHPRA)**
Norita Kesuma	*Senior Evaluator, New Drug Evaluation*	**NADFC, Indonesia**
Andrea Keyter	*Deputy Director, Medical Devices*	**South African Health Products Regulatory Authority (SAHPRA)**
Dr Siu Ping Lam	*Director, Licensing Division*	**MHRA, UK**
Dr Henry Leng	*Regulatory Affairs Consultant*	**South African Health Products Regulatory Authority (SAHPRA)**
Prof John Lim	*Executive Director, Professor of Practice and Senior Advisor*	**Centre of Regulatory Excellence, Duke-NUS Medical School. Singapore Ministry of Health**
Hitekani Mabunda	*Medicine Registration Officer*	**National Department of Health, South Africa**
Mabatane Davis Mahlatji	*Deputy Director, Medicine Evaluation And Research*	**South African Health Products Regulatory Authority (SAHPRA)**
Gugu Mahlangu	*Director-General*	**Medicines Control Authority, Zimbabwe**
Ana Carolina Marino	*Advisor for the Directorate of Authorization and Registration*	**ANVISA, Brazil**
Brian Mutale Ng'andu	*Monitoring and Evaluation Officer, AMRH and Health Programmes*	**NEPAD, South Africa**
Khamusi Mutoti	*Deputy Director, Biological Medicines*	**South African Health Products Regulatory Authority (SAHPRA)**
Portia Nkambule	*Acting Cluster Manager: Food Control, Pharmaceutical Trade and Products Regulations*	**Ministry of Health, South Africa**
Themba Nukeri	*Medicines Control Officer*	**South African Health Products Regulatory Authority (SAHPRA)**
Sybil Nana Ama Ossi-Agyeman-Yeboah	*Professional Officer/Essential Medicines and Vaccines, Pharmaceutical and Quality Assurance Analyst*	**West African Health Orgnization (WAHO), Burkina Faso**

Regulatory agencies, regional associations and centres of excellence (CONT)		
Bruce Randall	*Director, Bureau of Therapeutic Sciences, Therapeutic Products Directorate*	**Health Canada**
Prof Helen Rees	*Chair of Board*	**South African Health Products Regulatory Authority (SAHPRA)**
Dr Tomas Salmonson	*Chair*	**CHMP, EMA**
Tohlang Sehloho	*Deputy Director, Clinical Pre-Registration Evaluations*	**South African Health Products Regulatory Authority (SAHPRA)**
Dr Alain Some	*Head of Registration Service, Directorate for the Continuity of Regulatory Pharmaceutical Activities,*	**Ministry of Health, Burkina Faso**
Nanik Sundari	*Senior Evaluator, New Drug Evaluation*	**NADFC, Indonesia**
Dr Ramli Zainal	*Director*	**NPRA, Malaysia**
Pharmaceutical companies and associations		
Yaser Alhagan	Scientific Office, Public Policy and Government Affairs Director	**Merck, Sharp & Dohme, Saudi Arabia**
Zainab Aziz	RA Portfolio Manager	**Novartis, South Africa**
Sjaak Bot	Head of EMEA Regulatory Affairs	**Janssen, The Netherlands**
Jaime César de Moura Oliveira	Director for Regulatory Policy and Intelligence Latin America	**Bayer, Brazil**
Thomas Brookland		**Roche, Switzerland**
Isil Canset Canturk	Regulatory Affairs Manager for Business Area Near East, Russia and CIS	**Novo Nordisk, Turkey**
Trevor Charters	Senior Regulatory Affairs Manager – SSA and FSA Markets	**AstraZeneca Pharmaceuticals, South Africa**
Dr Judy Coates	Scientific and Regulatory Affairs Manager	**IPASA**
Dr Paul Dearden	Head of Emerging Markets, Regulatory Policy and Intelligence	**AbbVie, UK**
Dr Bettina Fiedler	Head Regulatory Eastern Europe, Middle East and Africa	**Bayer AG, Germany**
Dr Susan Forda	Vice President-Global Regulatory Affairs-International	**Eli Lilly and Company, UK**
Dr Paul Huckle	Chief Regulatory Officer and Senior Vice President,	**GlaxoSmithKline, USA**
Elzaan Human	Senior Regulatory Affairs Pharmacist	**Sanofi, South Africa**
Dr David Jefferys	Senior Vice President, Global Regulatory, Government Relations, Public Affairs and European Product Safety	**Eisai Europe Ltd, UK**
Sanjay Lakha	Senior Regulatory Affairs Manager – South Africa	**AstraZeneca Pharmaceuticals, South Africa**
Fayrooz Lambey	Regulatory Affairs Manager	**Roche Products (Pty) Ltd, South Africa**
Mavis Mwashita	Regulatory Affairs Pharmacist	**Pfizer Laboratories, South Africa**

Pharmaceutical companies and associations (CONT)		
Puvinesvarie Naidoo	Head of Regulatory Affairs Nigeria, East and Southern Africa Cluster (and Head of Regulatory Affairs South Africa)	**Pfizer Inc, South Africa**
Yolanda Peens	Senior Regulatory Affairs Manager	**Amgen (Pty) Ltd, South Africa**
Euganthri Pillay	Regulatory, Quality and Safety Manager	**Novo Nordisk, South Africa**
Jo-Anne Poley	Head of Regulatory Affairs and Quality	**Takeda, South Africa**
Shamima Rashid	Regulatory Affairs Pharmacist Lead	**Astellas Pharma Ltd, South Africa**
Hemphill Matyeka	Quality Assurance Pharmacist, Medical & Development Department	**Astellas Pharma Ltd, South Africa**
Dr Reinard McPherson	Medical Director	**Astellas Pharma Ltd, South Africa**
Nevena Miletic	Regulatory Policy Lead	**F.Hoffmann-La Roche Ltd, Switzerland**
Varsha Mistry	Director, Regulatory Strategy – Africa Middle East (Oncology and Vaccines)	**Pfizer Inc, South Africa**
Flucia Molokwane	Regulatory Affairs Manager	**Bayer, South Africa**
Youna Moodley	Regulatory Affairs Pharmacist	**Pfizer Laboratories, South Africa**
Githa Singh	Regulatory and Quality Affairs Director	**AbbVie Ltd, South Africa**
Lynette Terblanché	Director Regulatory Affairs, South Africa and EPA	**MSD (Pty) Ltd, South Africa**
Universities and non-profit organisations		
Prof Shabir Banoo	Chief Technical Specialist – Pharmaceutical Policy and Programmes	**Right to Care and University of the Witwatersrand, South Africa**
Dr Shyam Bhaskaran	Program Officer	**Bill and Melinda Gates Foundation, USA**
Andy Gray	Senior Lecturer, Division of Pharmacology, Discipline of Pharmaceutical Sciences	**University of KwaZulu-Natal, South Africa**
Dr Luther Gwaza	Technical Officer, Regulatory Systems Strengthening	**World Health Organisation**
Prof Hubert Leufkens	Professor of Pharmaceutical Policy and Regulatory Science	**Utrecht University, The Netherlands**
Prof Andrew Walubo	Head, Department of Pharmacology	**University of the Free State, South Africa**
Centre for Innovation in Regulatory Science		
Magda Bujar	Project Manager	
Patricia Connelly	Manager, Communications	
Dr Lawrence Liberti	Executive Director	
Dr Neil McAuslane	Director	
Prof Stuart Walker	Founder	