



Focus on Latin America:

**Building quality submission and review processes and practices –
Overcoming challenges and meeting expectations**

23-24 January 2014
Lima Peru

WORKSHOP SYNOPSIS



Synopsis authors

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BACKGROUND TO THE WORKSHOP

In general, all agencies follow the same mission of ensuring that patients have timely access to safe, effective and high-quality new medicines. The technical requirements for the development of a new medicine are harmonised in the ICH countries, with the adoption or adaptation of these guidelines occurring in the non-ICH countries. In addition to the efforts to harmonise the technical guidelines for the development of new medicines, developing countries are proactively looking to align their activities regionally through the efforts of overarching groups such as ICH GCG, LSIF and APEC or ASEAN in Asia, EAC and SADC in Africa, and in Latin America, PAHO, PANDRH, and MERCOSUR.* Discussions are ongoing regarding the development of methodologies for cooperation and sharing information such as safety data and the results of clinical site and manufacturing inspections to use resources more effectively to assess novel medicines for their respective populations agencies further the discussions. The challenge, however, centres on the current variability in agency skill sets and processes.

As more agencies develop their processes and practices to take a science-based approach to regulation and risk-based decision making, a common understanding and regulatory language is being developed. This understanding includes clarity around what constitutes a quality review and the necessity to have good review practices (GRevP) embedded within the agencies. Accordingly, agencies in Asia Pacific and Latin America are actively developing and evolving their practices so that these can be in line with more widely followed good review practices. The key questions in this evolution are

- what are the underpinning components that ensure good regulatory decision making and
- what are the regulatory science tools that can be built in and used to ensure a timely, high-quality, predictable and transparent process whilst ensuring an effective and efficient use of resources?

Agencies are challenged to identify these components and to ensure that rather than adherence to an esoteric guideline, ultimately, knowledge, attitude and practices are all aligned as good practices become part of the behaviours and practices of all staff members.

This Workshop was held to discuss how agencies are building quality into their review process and to identify the challenges involved in moving from a guidance document to the use of good review practice in the daily workings of an agency and how this can help underpin good regulatory decisions, performance measurement, and quality. The themes of this Workshop carry forward a discussion begun in 2011 by CIRS amongst agencies at the Workshop in Kuala Lumpur, Malaysia and revisited this past January 2013 at the Workshop in Beijing, China.

*APEC = Asia Pacific Economic Cooperation; ASEAN; EAC = East African Community; ICH GCC =, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Global Cooperation Group; LSIF = Life Sciences Innovation Forum; MERCOSUR = Mercado Común del Sur (Southern Common Market); PAHO = Pan American Health Organization; PANDRH = Pan American Network for Drug Regulatory Harmonisation; SADC = South African Development Community.

PROGRAMME

DAY 1: 23 JANUARY 2014

SESSION 1: GLOBAL FOCUS ON BUILDING QUALITY REVIEW PROCESS: THE ROLE OF GOOD REVIEW PRACTICES	
Chairman's welcome and introduction	Dr Murray Lumpkin , Deputy Director, Regulatory Affairs, Global Regulatory Systems, Bill & Melinda Gates Foundation
Country welcome and introduction by host agency	Dr. Paulina Esther Giusti , Vice Minister of Health Provision and Insurance, Peru
Building a quality submission and review process: Why is this critical to the future evolution of agencies and regional regulatory alignment?	
PAHO/PANDRH experience: reference agencies, mutual recognition and information sharing	Dr José Peña José Peña Ruz , QF Regional Advisor, Medicines and Health Technologies, Pan-American Health Organisation (PAHO) / WHO
Brazil experience	Dr Renato Porto , Director of Health Regulation, ANVISA, Brazil
Good review practices: What are the challenges and benefits?	
Global consideration for developing GRevP	Mike Ward , Manager, International Programs Division, Health Canada
Country perspective – Canadian experience	Catherine Parker , Executive Director, Biologics and Genetics Therapies Directorate, Health Products and Food Branch, Health Canada
Company perspective – How can GRevP enhance communication, transparency and clarity of submission and review expectations?	Anthony Ventura , Senior Director, Head, Latin America Region, Pfizer Inc, USA
Measuring good review practices: from guidance document to utilisation	Dr Neil McAuslane , Scientific Director, CIRS
A structured benefit-risk framework; more clarity and transparency?	Prof Hans-Georg Eichler , Senior Medical Officer, European Medicines Agency

SESSION 2: FOCUS ON LATIN AMERICA	
Chairman's welcome and introduction	Dr José Peña , <i>QF Regional Advisor, Medicines and Health Technologies, Pan-American Health Organisation (PAHO) / WHO</i>
Focus on Latin America: Adoption of good review practices – an assessment of where agencies excel and areas for improvement	
CIRS Survey Feedback	Prisha Patel , <i>Manager, Emerging Markets Programme</i>
A Regional Viewpoint- the PRAIS initiative: PAHO	Dr Analía Porrás , <i>Advisor, Medicines and Health Technologies, Pan-American Health Organisation (PAHO)/ WHO</i>
Panel Discussion: Focus on Latin America: Submission requirements and review procedures: how are these converging?	Dra Helen Rosenbluth , <i>Head, Licensing Department ANAMED, Chile</i> QF Lidia Luz Castillo Solorzano , <i>Executive Director, Sanitary Authorisations, DIGEMID</i> Beatriz Luna , <i>Head of Evaluation – Technical Director, MSP, Uruguay</i>
SESSION 3: ROUNDTABLE SESSIONS	
Roundtable A: Regional alignment	Chair: Emer Cooke , <i>Head of International Affairs, European Medicines Agency</i> Rapporteur: Patrick O'Malley , <i>Senior Director, Regulatory Affairs, Eli Lilly</i>
Roundtable B: Elements of good-quality review and decision making	Chair: Mike Ward , <i>Manager, International Programs Division, Health Canada</i> Rapporteur: Jill Jarusiewicz , <i>Director, Regulatory Affairs, Celgene</i>
Roundtable C: Facilitating the review process	Chair: Prof Hans- Georg Eichler , <i>Senior Medical Officer, European Medicines Agency</i> Rapporteur: Aldo Topasio , <i>EMAP Policy and Strategy Director, Global Regulatory Affairs, GSK, Chile</i>
Roundtable D: How to optimise stakeholder interactions?	Chair: Dr. Murray Lumpkin , <i>Deputy Director, Regulatory Affairs, Global Regulatory Systems, Bill & Melinda Gates Foundation</i> Rapporteur: Dorte Strobel , <i>Senior Regulatory Intelligence Manager, Novo Nordisk, Denmark</i>
Roundtable E: Regulatory pathway for biosimilars	Chair: Catherine Parker , <i>Executive Director, Biologics and Genetics Therapies Directorate, Health Products and Food Branch, Health Canada</i> Rapporteur: Birgitta Hedin , <i>Head of Regional Regulatory Affairs, Boehringer, Ingelheim, Germany</i>

DAY 2: 24 JANUARY 2014

SESSION 3: ROUNDTABLE SESSIONS CONTINUE

Roundtable discussions resume

Chairman's introduction

Professor Sir Alasdair Breckenridge, Former Chairman, MHRA, UK

Feedback by roundtable session facilitators

Panel reflection from roundtable session – What are the next steps in Latin America in the implementation of GRevP?

Mike Ward, *Manager, International Programs Division, Health Canada*
Dr Cristina Alonso Alija, *Head, Regulatory Affairs, Latin America, Bayer Healthcare*
Lawrence Liberti, *Executive Director, CIRS*
Q.F Lidia Luz Castillo Solórzano, *DIGEMID, Peru*

SESSION 4: FOCUS ON INTERNATIONAL INITIATIVES

Regulatory cooperation: A nicety or a necessity?

Dr Lembit Rāgo, *Coordinator Quality Assurance and Safety: Medicines, World Health Organization*

Regulatory cooperation – How does this work in practice and how do stakeholders ensure equity and quality of process?

Dr. Mario Alanis Garza, *Advisor to the Commissioner, COFEPRIS*

Addressing the multinational complexity product submission in a non-converged environment: a pharmaceutical company viewpoint

Dr Susan Forda, *Vice President, Global Regulatory Affairs, Eli Lilly, UK*

Panel reflection on regional convergence initiatives: What can be learnt from these activities?

Transnational Agency consortia: Is this another route to the same place?

Catherine Parker, *Executive Director, Biologics and Genetics Therapies Directorate, Health Products and Food Branch, Health Canada*

Regional convergence from a company viewpoint

Sharon Olmstead, *Global Head, Development and Regulatory Policy, Novartis, USA*

European viewpoint

Emer Cooke, *Head of International Affairs, European Medicines Agency*

NGO viewpoint

Dr Murray Lumpkin, *Deputy Director, Regulatory Affairs, Global Regulatory Systems, Bill & Melinda Gates Foundation*

Chairman's summary and close of Workshop

WORKSHOP OBJECTIVES

- Identify current initiatives/approaches being used by agencies in building quality review systems and the role of good review practice in decision making
- Discuss the challenges of aligning knowledge of, attitude toward and practice of GRevP within agencies as they evolve their processes and procedures
- Recommend approaches to build quality and efficiency into agency review processes and practices
- Understand the challenges faced by the pharmaceutical industry in meeting diverse agency requirements and multiple requests for information during dossier reviews

INTRODUCTIONS

Centre for Innovation in Regulatory Science – CIRS Executive Director **Lawrence Liberti** welcomed to the Workshop representatives from eighteen international research-based pharmaceutical companies travelling from as far as Europe and Japan as well as a number of non-profit organisations such as the Bill and Melinda Gates Foundation and the World Health Organization. He expressed his thanks to representatives from the European Medicines Agency, Health Canada, the six Latin American regulatory agencies and PAHO who invested the time to participate in this international meeting as well as colleagues from the Peruvian Regulatory Agency Dirección General de Medicamentos, Insumos y Drogas (DIGEMID) who helped to make the Workshop a reality.

Day 1 Morning Chair, Dr Murray Lumpkin, *Deputy Director – Regulatory Affairs, Lead for Global Regulatory Systems Initiatives, Global Health/Integrated Development, Bill and Melinda Gates Foundation* initiated the Workshop, by inviting participant to take part in stimulating, informative interactions and provide insights and practical recommendations to ensure the efficient use of regulatory time and research, with a common goal of making quality medication available in a timely manner to all patients.

Her Excellency Dr. Paulina Esther Giusti – *Vice Minister of Health Provision and Insurance, Peru* detailed the reformation process at the Ministry of Peru, which centres on three axes: the increase of public insurance coverage based upon the expansion of the public health system, the improvement in the quality of service of the insurance system and the protection of the rights of the patient. These enhancements include the provision of essential medicines for public insurance patients with chronic illnesses through private pharmacies and the implementation of good manufacturing processes for pharmaceuticals. She reflected that this Workshop would assist in the efforts to allow the population of countries with developing pharmaceutical markets to have timely access to quality medicines.

Recommendations from across the Roundtable Discussions

General recommendations

1. Create more opportunities for regulatory agencies to understand each other's systems, strengths and challenges.
2. Increase the interaction and exchange of reviewers among countries.
3. Build on some of the progress related to GMP inspections such as medical devices inspection; use the WHO prequalification to expedite reviews; share inspection information and reduce the burden to produce GMP certificates.
4. Consider alignment on a common review template.
5. Industry should fulfill regulatory requirements or proactively explain why they cannot
6. Industry should answer regulatory questions completely or proactively explain why they cannot
7. Regulatory agencies should ensure a legal framework is in place for appropriate interaction with industry and establish transparent processes and goals for these interactions.
8. Regulatory agencies could enact fees that are linked to performance expectations to alleviate resource constraints.
9. CIRS should investigate existing mechanisms used by mature agencies to recommend appropriate legal frameworks and processes for interactions between agencies and industry.

Latin America-specific recommendations

1. Target sub-regional country alignments based on strengths, weaknesses and common objectives; consider leveraging the PAHO system.
2. Survey the use of submission formats in the region; evaluate the expanded use of the CTD format
3. Latin American regulatory agencies should provide the opportunity for pre-submission meetings on a case-by-case basis.
4. Latin American regulators should clarify CMC requirements, especially as they apply to the DTC.
5. Industry and regulatory agencies in Latin America should continue to conduct agency-industry workshops as a vehicle for the communication of requirements and expectations of both stakeholders.
6. Latin American regulators should explore further opportunities for collaboration with other regulatory agencies, including exchange programmes with more mature agencies.
7. ICH should conduct discussions regarding guidelines for biosimilars including regulators from Latin America and Asia. Topics that should be addressed include definition, chemical characterisation, requirements to show efficacy and safety, methods to monitor safety and acceptability of a reference product.
8. Regulatory agencies must conduct discussions with one another regarding naming, especially modification of international non-proprietary names for biosimilars as well as pharmacovigilance.
9. Regulatory pathways for biosimilars should be aligned across regulatory agencies, potentially using ICH guidance.

Roundtable Discussions

Roundtable Discussion A

Regional alignment and cross-agency recognition: What are the opportunities for regulators and companies?

Chair	Emer Cooke , <i>Head of International Affairs, European Medicines Agency</i>
Rapporteur	Patrick O'Malley , <i>Senior Director, Regulatory Affairs, Eli Lilly and Co</i>

Background

No single agency will be able to address the review needs of the future. Accordingly, careful consideration is being given to regional alignment of regulatory requirements and review activities. Experience has now been gained with the maturity of the EMA together with the newer experiences across the Four-Agency Consortium, Asia Pacific Economic Cooperation (APEC), the Gulf Cooperation Council (GCC) and most recently in the East African Community (EAC). Alignment can provide clarity and efficiency for companies with regard to consistency of regulatory expectations across jurisdictions, thereby streamlining the dossier development and submission processes. This Roundtable was dedicated to discussing the elements of a regionally aligned process that could benefit Latin American regulatory agencies.

Questions for consideration

- In general, what are the motivating factors for regional alignment as seen from the agency point of view?
- What are the motivating factors for regional alignment as seen from the company/sponsor point of view?
- What are the activities that can be aligned? Which ones are easier to align than others?
- Is mutual recognition of decisions possible and practical? What are the factors that need to be in place for mutual recognition of an approval?
- Around the world, what have been the experiences of the participants in creating submissions or doing reviews that involved shared activities across two or more agencies? How could these experiences be applied to Latin America?
- Are there any experiences from other regional alignment initiatives that can build onto the PAHO initiatives?
- How can companies benefit from processes that are aligned across regulatory agencies submission?
- PAHO has been active in developing cross-agency recognition approaches for Latin American; for example, by using the reference Agency designation. What have been the successes and limitations of these activities?

Critical issues

This Roundtable agreed that agencies and industry would benefit by having a better understanding of the motivating factors for regulatory alignment. For agencies, those benefits include a reduced workload, the ability to emphasise and focus on the most important information for review, the incorporation of agency-specific views or needs, and an increase of opportunities to participate in global development such as the development of clinical trial standards. In addition, alignment would make it easier to understand and compare other agencies' review considerations and decisions and create opportunities for mutual recognition. Industry would benefit through the creation of an aligned global product development and submission data package, which would reduce the potential for repetitive studies, questions and inspections

It was further agreed, however, that there are barriers to regulatory alignment, including the legal frameworks of individual countries. Certain activities such as product analytical testing or good manufacturing inspections may be mandated in certain jurisdictions and other variables include the extent of import or export of products within a country and the government's aspiration for growth and development of the pharmaceutical sector within a country.

There are differences between "alignment" and "cooperation between agencies," as there is between the sharing of and reliance on information and harmonisation and mutual recognition. For all of those activities, however, trust and confidence in other regional regulators are the foundation for convergence.

Recommendations

1. Create more opportunities for regulatory agencies to understand each other's systems, strengths and challenges.
2. Latin America-specific recommendation: Target sub-regional country alignments based on strengths, weaknesses and common objectives; consider leveraging the PAHO levelling system.
3. Increase the interaction and exchange of reviewers among countries.
4. Build on some of the progress related to GMP inspections such as medical devices inspection; use the WHO prequalification to expedite reviews; share inspection information and reduce the burden to produce GMP certificates.
5. Consider the alignment on a common review template.
6. Latin America-specific recommendation: Survey the use of submission formats in the region; evaluate the expanded use of the CTD format.

Roundtable Discussion B

Elements of good-quality submission and review	
Chair	Mike Ward , <i>Manager, International Programs Division, Health Canada</i>
Rapporteur	Jill Jarusiewicz , <i>Director, Regulatory Affairs, Celgene, USA</i>

Background

The goals of good review practice are to enable the timeliness, predictability, consistency, transparency, clarity, efficiency and quality of the review process and management. A good-quality submission is not just about the robust nature of the evidence generated but also both the delivery of the message (organisation, presentation and language) and the quality of the message (purpose, context, logic and content) being fit for purpose for an agency. Although GRevP can be built in and monitored internally, it is challenging to determine the methodology of measurement of a good quality review/submission objectively and its components. Is it just a direct measure of adherence to the process or is it also an assessment of the nature of the decision taken? Should measurement only be performed by agencies or sponsors using internal metrics of either direct or relationship measurements? If so, which ones should be used and is there a role for agencies and companies in providing feedback on the process and elements of good review and submission practices?

Questions for consideration

- Do sponsors have a role in aiding agencies in delivering good-quality review standards? If so, what?
- Do sponsors have a role in ensuring good submission practices? If so, what are they and how can they be measured?

Critical issues

Of the elements of GRevP: timeliness, consistency, predictability, transparency, clarity, efficiency and adherence to GrevP, it has been agreed by both regulators and industry that transparency is the most important. This element is intertwined with clarity, and communication is also part of concept. Regarding the other aspects, consistency and predictability are intertwined as are efficiency and timeliness. Active communication, approachability and dialogue are critical and should also be considered elements of GRevP. It should be remembered, however, that metrics may not be specific to each of these parameters and may change over time.

Transparency, communication and clarity

Industry and the public would have more confidence in the regulatory process if regulators were more transparent in the way they arrive at their decisions. These parameters apply to many regulatory components such as applications, draft regulations, final regulations and timelines. To industry, communication regarding a delay in timelines is far better than no communication. Although communication represents a significant investment in resources, it is always critical to industry that they understand the rules.

Ways to improve transparency, communication and clarity include increased dialogue between agencies, training of agency and company staff, clearly separating the regulatory issues from the legal administrative issues, and ensuring that queries are addressed to and handled by the correct staff members. It should be determined if the Health Authority has a public rule-making process and if there is an opportunity for review and comments on draft legislation and guidances. An updated Q&A from regulators about common deficiencies, issues and questions posted to their website would also be of value in the enhancement of transparency, communication and clarity.

Metrics for the measurement of transparency, communication and clarity are accessed mostly via survey tools but also include face-to-face meetings with industry and industry associations where the outcomes to these meetings are documented and shared. Relevant questions include: Is there a website? How often is it updated? Can industry or regulators meet and ask questions? How may desired discussion occur? For example, regulators in Uruguay have an open door every other Friday.

Efficiency

Efficiency is important in aspects other than the initial approval of a medicine; for example, in an agency's evaluation of post-marketing variations, is a risk-based approach employed or does every change need to be reviewed in similar detail? Some Health Authorities have extremely limited resources; is it possible to rely more on other regulators and work in networks? Can complexity be reduced or eliminated in non-value added activities? How can third party reviews contribute to efficiency (as is done in Mexico)

Dialogue between agencies is important to build operational excellence. Additionally, peer review and senior review validation provide links to predictability. Other tools to increase efficiency include the use of project management systems and internal agency benchmarking. The metrics of efficiency are more than adherence to published timelines and could be shared between agencies to identify best practices.

Consistency and predictability

Challenges to the quality of the review can include the slow progress of agency staff in accepting and adapting to new or changed regulations. It was agreed by this Roundtable that it is better to have a delayed "good" decision than a "bad" fast one.

Tools to improve consistency and predictability of decision-making include the exchange of staff among regulatory agencies, potentially funded through industry or third parties such as PAHO. Other tools for improvement include: the use of GRevPs, interagency dialogue and defined mechanisms for training.

Recommendations

1. Industry should fulfil regulatory requirements or proactively explain why they cannot
2. Industry should answer regulatory questions completely or proactively explain why they cannot

Roundtable Discussion C

Facilitating the review	
Chair	Prof Hans- Georg Eichler , <i>Senior Medical Officer, European Medicines Agency</i>
Rapporteur	Aldo Topasio , <i>EMAP Policy and Strategy Director, Global Regulatory Affairs, GSK, Chile</i>

Background

Having an efficient and effective review process in place can shorten the time to approval by maximising the use of an agency’s resources. Furthermore, ensuring that submission dossiers are well constructed and meet the needs of the reviewers can streamline the review process. From a process standpoint, having systems to recognise approvals by other jurisdictions is one way to expedite the regulatory approval process. Other processes may also help expedite the review of medicines. This Roundtable investigated those practices that an agency can employ to efficiently use their resources to ensure that new medicines undergo a quality review within target times. Further, the group discussed ways that special expedited review pathways can be used to more quickly approve medicines of critical need, especially where few therapeutic alternatives exist.

Questions for consideration

- In general, what factors contribute to an efficient and timely regulatory review process?
- What practical pathways could be considered to ensure that important medicines where there is high unmet medical need are reviewed quickly? What are those that work best (eg, CPP, EMA Article 58, Singapore model review)?

- What processes are in place in your country to benefit from prior experience by other agencies with a new medicine? How is this used to expedite a new product review?
- What types of cross-agency recognition can reduce the duplicative work of agency internal staff?
- The better constructed a dossier is, the fewer questions and rounds of re-submission can occur. What are the factors that can contribute to companies making a well-constructed dossier?
- How can agencies share their experiences to help implement best practices at other agencies?
- How can activity assessment (benchmarking) form the basis for continuous improvement?

Critical issues

It was the consensus of this Roundtable to consider the elements of the review process as a continuum, with parameters of importance that should be considered that occur both before and after the actual review (Figure 5). For example, pre-submission discussions and meetings between industry and agencies represent an opportunity to simplify and expedite submissions; however, this communication does not typically occur in Latin America. Developing the flexibility to include pre-submission meetings on a case-by-case basis would represent an opportunity for agency-industry interactions in the region.

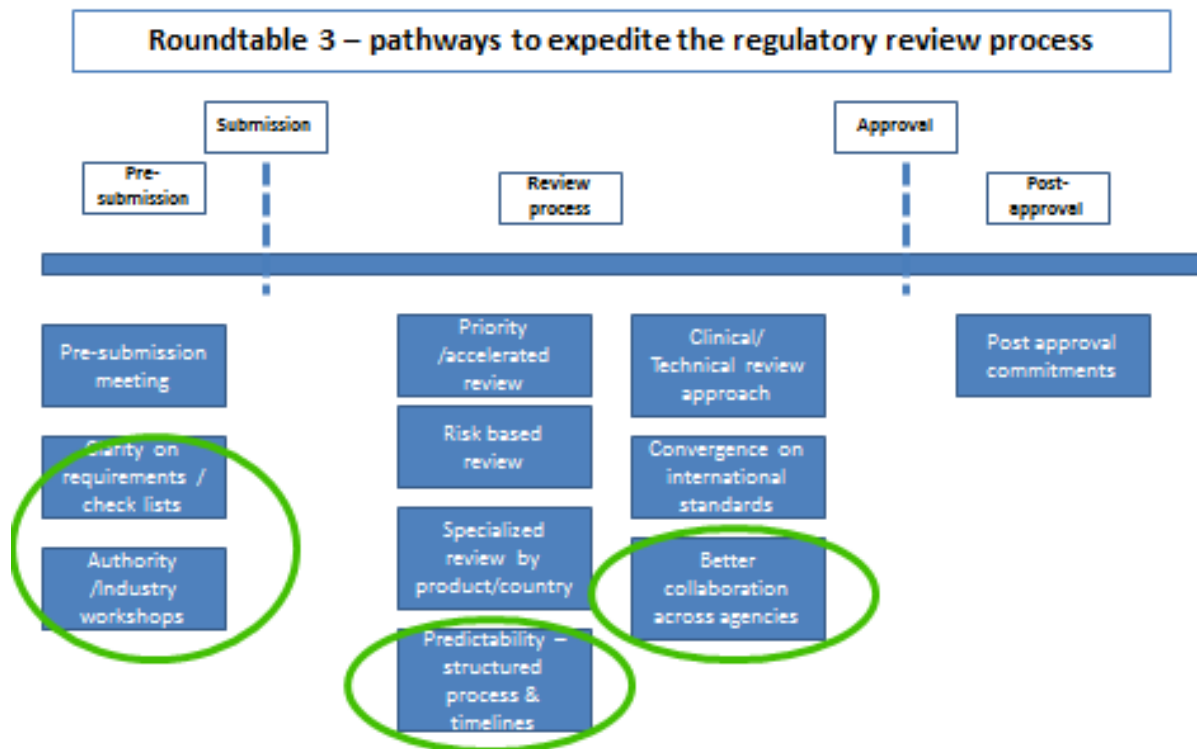


Figure 5. Opportunities to expedite the regulatory review process occur throughout the life cycle of a medicine.

Potentially even more important than pre-submission meetings, clarity of regulatory expectations and requirements is vitally important for the submission of a quality dossier, especially when new regulations are issued. In some countries the most difficult-to-understand regulatory requirements surround chemistry, manufacturing and controls (CMC) and increased clarity in this regard, especially as it applies to the granularity of information required in the CTD, would be extremely helpful. Agency-industry workshops that are currently ongoing in the region are perceived as being of great value and could be important tactics in the ongoing communication of the expectations of regulators.

Convergence in international standards is linked to better collaboration across the agencies. In addition to the ongoing efforts of PAHO for agency-agency collaboration, Latin American regulators may wish to consider exchange programmes with other more mature agencies. This type of mentoring activity, which has been employed by the EMA and other agencies, has been shown to result in increased knowledge, capacity and expertise. Predictable and structured processes and time targets with defined milestones were perceived as very important elements of quality reviews and as a win-win prospect for both the industry and the authorities.

Even though there are limited opportunities for expedited review in the region, authorities have provided the opportunity for acceleration for certain products and have indicated a willingness to continue this process-linked to a risk-based evaluation system. Although streamlining processes for the review of specialised products in the region was discussed, it was the perception of the group that agency capacity and experience should increase before this specialisation can occur. Post-approval commitments may play a role in the reduction of review time in the future, but detailed discussions of this must still occur.

Recommendations

1. Latin American regulatory agencies should continue to provide the opportunity for pre-submission meetings on a case-by-case basis.
2. Latin American regulators should clarify CMC requirements, especially as they apply to the CTD.
3. Industry and regulatory agencies in Latin America should continue to conduct agency-industry workshops as a vehicle for the communication of requirements and expectations of both stakeholders.
4. Latin American regulators should explore further opportunities for collaboration with other regulatory agencies, including exchange programmes with more mature agencies.

Roundtable Discussion D

How to optimise stakeholder interactions	
Chair	Dr Murray Lumpkin , <i>Deputy Directory, Regulatory Affairs, Global Regulatory Systems, Bill & Melinda Gates Foundation</i>
Rapporteur	Dorte Strobel , <i>Senior Regulatory Intelligence Manager, Novo Nordisk, Denmark</i>

Background

Interactions and transparency of process and decision making between a regulatory agency and its stakeholders are critical enablers of good review practice and process, as they build trust in the review and decision process, thus enabling accountability. Communication amongst stakeholders should be a routine process but what are the best ways to optimise these interactions and what role does transparency play in regard to agency interactions with companies, other agencies and other stakeholders such as physicians and patients? Indeed, many initiatives have encouraged greater transparency amongst stakeholders. These include regional initiatives such as the PRAIS through the Pan American Health Organisation (PAHO). This initiative has given stakeholders a neutral platform to facilitate the development of linkages between stakeholders for innovation in health systems that extend beyond institutional, country and sector boundaries. This Roundtable was asked to discuss the area of stakeholder interaction and methods for optimisation as well as the role transparency has in encouraging interactions and in enabling GRevP.

Questions for consideration

- What are the appropriate routes and methods and timing for company/agency interactions?
- What are the critical considerations for companies to seek and agencies to provide an interaction channel and how can this aid quality of the submission and review?
- How can these interactions be optimised, what could both companies and agencies consider to ensure that any interaction is of value to both stakeholders?
- What constitutes good stakeholder interaction practice between companies and agencies, what issues need to be considered; for example, conflict of interest?
- How can a transparent process contribute to improving patients' access to medicine?
- How can a transparent process contribute to improving patients' access to medicine?
- What activities, process and decisions should be transparent and how can this enable interactions between different stakeholders?
- What types of tools can encourage transparency/interactions?
- Agency-to-agency interactions, what is in this for agencies and how could this be best facilitated?

Critical issues

Roundtable D agreed that industry needs to include countries with emerging pharmaceutical markets in their business development strategies. This would entail knowledge and understanding of the countries' regulatory requirements and the implementation of responses to those requirements in a suitable manner. Although regulators may request specific information they deem necessary to license a product for patients in their country, industry often expresses frustration with regulatory requirements that are additional to those specified by ICH guidelines as they wish to avoid costly duplicative studies that may ultimately slow access to the medicine.

At the same time it should be recognised that one department of an agency may not know the product is being reviewed or be familiar with data from its clinical trials; situations like this can occur in countries such as Peru, where clinical trial applications are not handled by the regulatory agency DIGEMID, but by a different agency.

Regulatory agencies should have more interactions with industry in general regarding overall requirements but also more interactions with individual companies regarding specific applications. These interactions should include pre-submission meetings and dialogue during reviews. In addition to dialogue with the local industry affiliate, it may be necessary for agencies to communicate with the corporate office.

Despite the need for ongoing communication with industry, it is recognised that it is important that the agency is seen as performing independent reviews and that no inappropriate agency-industry interaction occurs. Other agency challenges include a lack of resources or basic infrastructure limitations such as a shortage of suitable private meeting rooms.

Recommendations

1. Regulatory agencies should ensure a legal framework is in place for appropriate interaction with industry and establish transparent processes and goals for these interactions.
2. Regulatory agencies could enact fees that are linked to performance expectations to alleviate resource constraints.
3. CIRS should investigate existing mechanisms used by mature agencies to recommend appropriate legal frameworks and processes for interactions between agencies and industry.

Roundtable Discussion E

The regulatory pathway and approval process for biosimilars	
Chair	Catherine Parker , <i>Executive Director, Biologics and Genetics Therapies Directorate, Health Products and Food Branch, Health Canada</i>
Rapporteur	Birgitta Hedin , <i>Head of Regional Regulatory Affairs, Boehringer, Ingelheim, Germany</i>

Background

The availability of biosimilar products has been followed by the introduction of new legislation across a number of countries. The regulatory pathway for these complex molecules is diverse and the lack of alignment in terms of diverging priorities and evidence needed for approval. This provides challenges for both agencies and companies and this was the focus for this Roundtable Discussion.

Questions for consideration

- How do you define a *biosimilar*?
- Is the regulatory pathway for biosimilars clear in all Latin American Countries and how aligned are they?
- What are possible pathways and what are believed to be appropriate routes for approval of biosimilars?
- What key criteria should be adopted by agencies for the reference product when assessing a biosimilar?
- What are the elements which can be used to establish biosimilarity and what evidence requires to be generated by companies for agencies?
- What are the main regulatory challenges for companies in developing and achieving approval of a biosimilar?
- What are the main challenges for a regulatory agency reviewing and approving a biosimilar?

Critical issues

The definition of *biosimilar* used by Health Canada is generally accepted by agencies and companies: “A well characterized recombinant DNA product entering the market after an innovator comes off patent”. In this definition, direct comparison with the innovator is required for authorisation, although it is not necessary to compare the drug with a local product. That is, the biosimilar is similar to the innovator but not identical. In general, the WHO guideline for *similar biotherapeutic product* also serves as the basis for many countries: “a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference

biotherapeutic product.” The elements that can be used to establish biosimilarity are chemical comparability, clinical efficacy, and clinical safety.

Health Canada has no per se regulations for biosimilars but legal interpretation of the current medical regulation notes that data requirements can be incorporated into guidelines and guidance documents. The agency has further advanced specific demands for different product groups. The Canadian definition has been adopted in Peru although there is still no approved regulation, and other definitions are still being evaluated. Colombia is examining the definitions of the US FDA and EMA and draft legislation is available.

There is a need for consistent guidance since some biosimilars have been approved like generics with limited data. ICH is currently creating a working party for biosimilars.

The regulatory pathway is not clear or aligned for biosimilars in all Latin American countries. For example, there are no guidelines for biosimilars in ANVISA, but there are two pathways for biotechnology products, de novo or comparability testing. Some countries like Venezuela have based their pathways on WHO guidelines and some countries like Colombia have established abbreviated pathways. The Colombian pathway, however, is based on the acceptance of “any data” with the health authority to decide if they are sufficient. Not all countries have biosimilar legislations and some are working on guidelines; Argentina has just issued a biotechnology guideline, specifying the requirement for full dossiers but no need for a certificate of pharmaceutical product (CPP).

This Roundtable agreed that the main regulatory challenges for companies in developing and achieving approval of a biosimilar are poor understanding of the local requirements, a lack of harmonisation, the need for training of the authorities (although consensus was not reached in this regard), a lack of patent protections for some biosimilars, the need for pharmacovigilance systems and automatic substitutions without regard for risks such as immunogenicity. Challenges for authorities include extrapolation of efficacy and interchangeability of indications to reference product and off-label use.

There is an urgent need for guidelines for biosimilars to be discussed within ICH. Discussions must include regulators also from Latin America and Asia. Topics that should be addressed include definition, chemical characterisation, requirements to show efficacy and safety based on an acceptable reference product, and methods to monitor safety including the development of an integrated pharmacovigilance system .

Additionally, authority-to-authority discussions are needed regarding the naming of biosimilars. With no differentiation in the international non-proprietary name (INN), it is difficult to monitor the safety of the biosimilar product versus the innovator when a safety report uses simply a common generic name. Also the interchangeable use of products at the practitioner level could raise safety and efficacy issues.

Recommendations

1. ICH should conduct discussions regarding guidelines for biosimilars including regulators from Latin America and Asia. Topics that should be addressed include definition, chemical characterisation, requirements to show efficacy and safety, and methods to establish integrated pharmacovigilance systems to monitor safety compared to the reference product.
2. Regulatory agencies must conduct discussions with one another regarding naming, especially modification of international non-proprietary names for biosimilars.
3. Regulatory pathways for biosimilars should be aligned across regulatory agencies, potentially using a common ICH guidance.