

FOCUS ON LATIN AMERICA:

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

23-24 JANUARY 2014
LIMA PERU

WORKSHOP REPORT

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

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QUALITY SUBMISSION AND REVIEW PROCESSES AND PRACTICES

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 and to assess novel medicines for their respective populations. 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 = Association of Southeast Asian Nations; 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.

Workshop 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 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 , Senior 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 Ruz , QF Regional Advisor, Medicines and Health Technologies, Pan-American Health Organisation (PAHO) / WHO
Focus on Latin America: Adoption of good review practices – an assessment of where agencies excel and areas for improvement	
CIRS survey feedback	Prisha Patel , Manager, Emerging Markets Programme
A regional viewpoint- the PRAIS initiative: PAHO	Dr Analía Porrás , Advisor, Medicines and Health Technologies, Pan-American Health Organisation (PAHO)/ WHO

<p>Panel Discussion: Focus on Latin America: Submission requirements and review procedures: how are these converging?</p>	<p>Dra Helen Rosenbluth, <i>Head, Licensing Department ANAMED, Chile</i></p> <p>QF Lidia Luz Castillo Solorzano, <i>Executive Director, Sanitary Authorisations, DIGEMID</i></p> <p>Beatriz Luna, <i>Head of Evaluation – Technical Director, MSP, Uruguay</i></p>
<p>SESSION 3: ROUNDTABLE SESSIONS</p>	
<p>Roundtable A: Regional alignment</p>	
<p>Chair</p>	<p>Emer Cooke, <i>Head of International Affairs, European Medicines Agency</i></p>
<p>Rapporteur</p>	<p>Patrick O'Malley, <i>Senior Director, Regulatory Affairs, Eli Lilly</i></p>
<p>Roundtable B: Elements of good-quality review and decision making</p>	
<p>Chair</p>	<p>Mike Ward, <i>Manager, International Programs Division, Health Canada</i></p>
<p>Rapporteur</p>	<p>Jill Jarusiewicz, <i>Director, Regulatory Affairs, Celgene</i></p>
<p>Roundtable C: Facilitating the review process</p>	
<p>Chair</p>	<p>Prof Hans- Georg Eichler, <i>Senior Medical Officer, European Medicines Agency</i></p>
<p>Rapporteur</p>	<p>Aldo Topasio, <i>EMAP Policy and Strategy Director, Global Regulatory Affairs, GSK, Chile</i></p>
<p>Roundtable D: How to optimise stakeholder interactions?</p>	
<p>Chair</p>	<p>Dr. Murray Lumpkin, <i>Deputy Directory, Regulatory Affairs, Global Regulatory Systems, Bill & Melinda Gates Foundation</i></p>
<p>Rapporteur</p>	<p>Dorte Strobel, <i>Senior Regulatory Intelligence Manager, Novo Nordisk, Denmark</i></p>
<p>Roundtable E: Regulatory pathway for biosimilars</p>	
<p>Chair</p>	<p>Catherine Parker, <i>Senior Executive Director, Biologics and Genetics Therapies Directorate, Health Products and Food Branch, Health Canada</i></p>
<p>Rapporteur</p>	<p>Birgitta Hedin, <i>Head of Regional Regulatory Affairs, Boehringer, Ingelheim, Germany</i></p>

DAY 2: 24 JANUARY 2014

SESSION 3: ROUNDTABLE SESSIONS CONTINUE

Roundtable discussions resume

Chairman's introduction	Professor Sir Alasdair Breckenridge , <i>Former Chairman, MHRA, UK</i>
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Feedback by roundtable session facilitators

Panel reflection from roundtable session – What are the next steps in Latin America in the implementation of GRevP?	<p>Mike Ward, <i>Manager, International Programs Division, Health Canada</i></p> <p>Dr Cristina Alonso Alija, <i>Head, Regulatory Affairs, Latin America, Bayer Healthcare</i></p> <p>Lawrence Liberti, <i>Executive Director, CIRS</i></p> <p>Q.F Lidia Luz Castillo Solórzano, <i>DIGEMID, Peru</i></p>
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SESSION 4: FOCUS ON INTERNATIONAL INITIATIVES

Regulatory cooperation: A nicety or a necessity?	Dr Lembit Rägo , <i>Coordinator Quality Assurance and Safety: Medicines, World Health Organization</i>
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Regulatory cooperation – How does this work in practice and how do stakeholders ensure equity and quality of process?	Dr. Mario Alanis Garza , <i>Advisor to the Commissioner, COFEPRIS</i>
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Addressing the multinational complexity of product submission in a non-converged environment: a pharmaceutical company viewpoint	Dr Susan Forda , <i>Vice President, Global Regulatory Affairs, Eli Lilly, UK</i>
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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 , <i>Senior Executive Director, Biologics and Genetics Therapies Directorate, Health Products and Food Branch, Health Canada</i>
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Regional convergence from a company viewpoint	Sharon Olmstead , <i>Global Head, Development and Regulatory Policy, Novartis, USA</i>
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European viewpoint	Emer Cooke , <i>Head of International Affairs, European Medicines Agency</i>
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NGO viewpoint	Dr Murray Lumpkin , <i>Deputy Director, Regulatory Affairs, Global Regulatory Systems, Bill & Melinda Gates Foundation</i>
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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

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.

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

PRESENTATION SUMMARIES

SESSION: GLOBAL FOCUS ON BUILDING QUALITY REVIEW PROCESS: THE ROLE OF GOOD REVIEW PRACTICES

In 2006, Mexico, Argentina, Brazil and Cuba along with PAHO began the Pan American Network for Drug Regulatory Harmonization (PANDRH), an initiative to strengthen the implementation of regulatory guidelines and recommendations and to create mechanisms for collaboration among countries in the region.

One of the primary goals of this collaboration, which was later joined by Chile, Columbia and Venezuela, was to develop confidence in each other's processes, structure and results through the establishment of a procedure for qualification of national reference regulatory agencies. **Dr José Peña Ruz**, QF Regional Advisor, Medicines and Health Technologies, Pan-American Health Organisation (PAHO) / WHO reported that using an instrument generated by the World Health Organization, regulatory agencies were evaluated against a number of critical indicators and assigned a designation of competency from a minimum of Level 1 to Level 4, which indicates that the National Regulatory Authority exercised "competent and efficient performance of the

functions of health regulation recommended by PAHO / WHO to ensure the effectiveness, safety and quality of medicines." (Figure 1)

From its assessment thus far of the regulatory agencies of twenty jurisdictions, PANDRH had learned that despite societal, commercial and geographic differences, there are certain key requirements for an independent, transparent and competent authority, which include a structured organisational system, legal support, the commitment of senior management, well-trained staff and a system for quality management.

Dr Renato Porto, Director of Health Regulation, ANVISA, Brazil detailed the efforts of Agência Nacional de Vigilância Sanitária (ANVISA) to continue to build quality processes and practices in the review of new medicines. For example, in recognition of the convergence of global regulation, ANVISA participates in international forums and cooperative projects with international organisations. Additionally, multiple activities are planned or ongoing to enhance the elements of good review practices.

Transparency is practiced through the provision of information regarding dossier analysis on the ANVISA website, an online product leaflet databank and the disclosure of the rationale for granting priority status to certain new medicines. Legislation revisions focus on health risks and convergence with international regulatory standards. Information systems are being upgraded with the gradual implementation of electronic submissions.

There has been an organisational restructure of ANVISA, with the establishment of units based on areas of knowledge and the implementation of audits on review process allows the rapid exchange of information between the analyst and industry. Finally, a project to improve the work process of the Drug General Office is identifying opportunities for improvements including information systems, processes and working structures.

There is an increasing recognition of the role that good review practices (GRevPs) play in enabling a well-functioning regulatory review system and inter-agency cooperation, irrespective of the size and maturity of the agency. Although not a panacea, GRevPs provide those involved in review and decision-making processes the best possible support and tools for ensuring consistent, science-based assessments that comply with legal requirements and are

Figure 1. Regulatory agencies that have been qualified as Level 4 reference agencies by PANDRH.

RESULTADOS EVALUACIÓN 2013				
Pais	Institución	Evaluación	Reevaluación	
	Chile Instituto de Salud Pública, Departamento Control Nacional	Agosto 2009 Nivel III	???	
	Colombia Instituto Nacional de Vigilancia de Medicamentos y Alimentos, INVIMA	Septiembre 2009 Nivel III	Julio 2010 Nivel IV	
	Cuba Centro para el Control Estatal de la Calidad de los Medicamentos, CECMED	Octubre 2009 Nivel III	Julio 2010 Nivel IV	
	Argentina Administración Nacional de Medicamentos, Alimentos y Tecnología Médica, ANMAT	Diciembre 2008 Nivel IV		
	Brazil Agencia Nacional de Vigilancia Sanitaria, ANVISA	Mayo 2010 Nivel IV		
	Mexico Comisión Federal Para la Protección Contra Riesgos Sanitarios, COFEPRIS	Junio 2012 Nivel IV		
	USA Food Drugs Administration, EEUU			
	Canada Health Canada			

essential in building trust and confidence in regulatory systems. **Mike Ward**, *Manager, International Programs Division, Health Canada* informed Workshop participants that among the increasing number of activities of evolutionary international regulatory networks, the APEC-WHO collaboration is producing the first international GRevP guidance document. This and other new guidance on GREVPs should help contribute to this conversation by providing common terms and tools for use by all regulatory agencies and even mature agencies can benefit from ongoing discussion and collaboration in this evolving discipline.

A Canadian perspective on the challenges and benefits of implementing and maintaining good review practices for biologic drugs was provided by **Catherine Parker**, *Senior Executive Director, Biologics and Genetics Therapies Directorate, Health Products and Food Branch, Health Canada*. The Good Review Practice Project was officially launched in Canada in 2004 as part of the Therapeutic Access Strategy, Health Canada's plan to become more efficient, transparent, accountable and responsive, which centred on communications, training and standard operating procedures and templates.

Although the first efforts succeeded in their primary goals to reduce a long-standing backlog of submissions and implement critically important quality systems, the new Good Review Practices Initiative for Biologics of 2012 has sought to respond to ongoing challenges by creating a GRevP Unit, conducting an inventory

of GRevP tools, extensively consulting review staff and creating a review-staff-only steering committee. Lessons learned to date include the fact that a dedicated, experienced resource is needed to oversee the development of GRevP and the development must involve review staff. Finally, in addition to GREVPs, regular communication with the review community and patients and a long-term commitment are also required for good regulatory decision making.

Anthony Ventura, *Senior Director, Head, Latin America Region, Pfizer Inc, USA* explained that from an industry perspective, an increasingly complicated supply chain to serve global markets poses significant regulatory and compliance challenges and the complicated nature of the supply chain is exacerbated by increasing divergence of global regulatory expectations, presenting substantial barriers to innovation (Figure 2). GRevP enables an agency-industry partnership to overcome barriers to innovation by providing global validation of quality assurance and facilitating mutual international recognition and regulatory harmonisation. Regulatory harmonisation in turn could reduce supply chain complexity, drug shortages and administrative costs for industry and regulatory authorities while simplifying compliance adherence and increasing the probability of simultaneous approvals and improving post-approval efficiency and change implementation.

Measurement of good review practice can aid agencies in their evolution of GRevP, understanding how well it is embedded and how it is perceived by their stakeholders. The challenge is to identify specific key performance indicators for the different goals of GRevP.

Dr Neil McAuslane, *Director, CIRS*, discussed several methods of GRevP measurement that have been employed by CIRS. A checklist or survey diagnostic gap analysis approach that characterises the current implementation of GRevP within an agency, can be used to assess processes and procedures in place, compared with standard review tools and compared with other agencies. It can aid in understanding agency needs, potential areas for training and the evolution of GRevP but does not measure actual use and usually represents the perspective of senior management. Conversely, undertaking a study to evaluate how embedded GRevP are within an agency can only be achieved by undertaking a survey across reviewers and management. This type of survey identifies the staff knowledge, practice and attitude to

Figure 2. GRevP can facilitate regulatory convergence to overcome diverse international regulatory requirements.



GRevP. It also provides a baseline of the agency's current situation, identifies what works well, areas for improvement, including the need for mentoring, training, review tools, processes and procedures and improves management's understanding of how GRevP are being utilised within the agency. A Quality Scorecard approach provides stakeholder perspectives on critical areas of the review process, procedures and management, feedback on a specific review regarding timeliness, transparency, consistency and clarity and improves agency – company dialogue. Although single scorecards are open to subjectivity, multiple scorecards can identify an agency's strengths and weaknesses and improve the quality of the review and GRevP adherence.

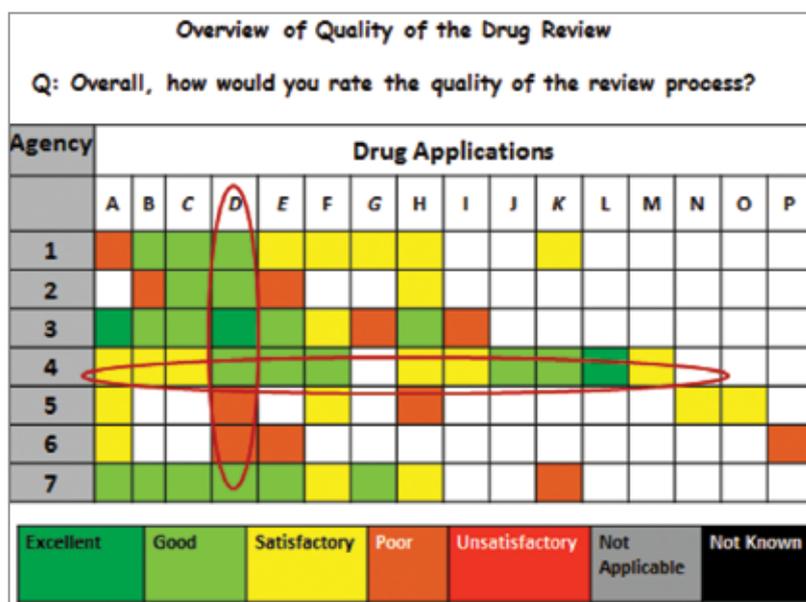
To make decisions around new medicines, regulators traditionally determined if the

benefits outweigh the risks and if the degree of uncertainty around these benefits and risks was acceptable. However, today's regulator is also responsible for accountability to stakeholders, defined as transparency, relevance and revisability. **Professor Hans Georg Eichler**, Senior Medical Officer, European Medicines Agency proposed that the use of a structured framework to make regulatory decisions may add relevance and transparency to decision making, potentially even affecting the outcome of the decision and improving the quality of public debate. Communicating decision options to patients as being risk-risk rather than benefit-risk may help decision makers surmount tendencies toward risk aversion. The biggest challenge in the development of frameworks for decision making, however, is likely to centre on addressing the uncertainty component.

SESSION: FOCUS ON LATIN AMERICA

As mentioned by Dr McAuslane, one approach to measuring good review practice used by CIRS is the Quality Scorecard System. **Prisha Patel**, Manager, Emerging Markets Programme, CIRS reported on the results of a CIRS Quality Scorecard study, in which six companies scored the reviews of sixteen products by seven

Figure 3. Six companies scored the reviews of sixteen products by seven Latin American regulatory agencies.



Latin American regulatory agencies in terms of transparency or communication, scientific competence, consistency and assessment reports. In addition to providing numeric scores of 1-5, in which 1 was unsatisfactory and 5 was excellent (Figure 3), companies were also afforded the option to specify ways in which agencies excelled as well as ways in which they could improve. The goals of this Latin American study were to obtain structured feedback on agency process related to application review; allow the cross-comparison of reviews of same or similar new drug applications carried out by regulatory authorities; enable best practices regarding the review to be shared with a view to improve the decision-making process, increase efficiency and identify the ways that good review practices are being used in agencies, to map these and therefore to identify the most likely opportunities for exchange of best practices amongst regulatory authorities. "The study found that at a high level, companies were satisfied with the agency review process but for some, areas were identified that would require improvement. Quality Scorecard studies in which agencies scored company's dossier submissions on application format, scientific consistency, technical content and communication and transparency have already been conducted by CIRS in mature markets and may also be conducted in countries with emerging pharmaceutical markets in the near future.

There is increasing cooperation among regulatory agencies in the Americas, with multiple new signed recognition and sharing agreements, capacity-building activities and cooperation through collaborative networks and seven regulatory authorities thus far have been assessed as reference agencies by WHO/PAHO. It is, however, a complex global regulatory landscape, with sub-regional development and several alternative ongoing initiatives for regulatory convergence. **Dr Analía Porrás**, *Advisor, Medicines and Health Technologies, Pan-American Health Organisation (PAHO)/WHO* discussed PRAIS, the Regional Platform on Access and Innovation for Health Technologies that was developed in view of these complexities. PRAIS is a platform to support and promote innovation, access, rational use and good governance in health technologies with a public health perspective for the purpose of providing access to and delivery and uptake of medicines. It is also intended to enable research and development and technological innovation for health, whilst developing governance and policies and improving regulation and regulatory capacity.

PRAIS seeks to accomplish these goals through the development of a participative knowledge base, linkages and cooperation, hosting relevant resources and information, raising awareness about key issues and priorities and facilitating technical cooperation. Current PRAIS features include the Observatory, which systematises the results from regulatory agency assessments and self-assessments; Social Networks which provide a space for agencies to interact and work together as well as for interaction with the other subsectors of health technologies; the Annotated Medicines List which is a “one-stop” information hub for essential and strategic medicines as well medicines procured through PAHO’s Strategic Fund and an Information Repository for national regulations and policies.

A Working Group consisting of US FDA, Health Canada, Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS) and PAHO is developing the business and technical requirements for the further implementation of PRAIS. Other future goals include the establishment of a governance structure and a sustainable financing mechanism. Features soon to be built include a capacity-building component using audio-visual material and PRAISsec, a virtual space for the exchange of confidential information between regulatory agencies.

Panel: Focus on Latin America: Submission requirements and review procedures: how are these converging?

Dr Helen Rosenbluth, *ANAMED, Chile*

Agencia Nacional de Medicamentos (ANAMED) is divided into authorisation, control, and surveillance functions, which are carried out through seven departments. Applications must first be reviewed for admissibility, a process that typically takes ten days. Dossiers are then evaluated by specialty experts for legal issues and quality, safety and efficacy who create reports that are considered in the rendering of a final decision by ANAMED. ANAMED uses checklists, guidelines and standard operating procedures and attempts to implement the good review practices of quality, transparency, efficiency and consistency. Quality is part of a system of continuous process improvement initiated by the agency in 2013 and standard operating procedures have been instituted to enhance efficiency. Transparency is accomplished through the posting of information regarding the review of products on the agency website, including approvals, denials and suspensions. Efforts to improve consistency include training, external consultation and peer review. ANAMED uses electronic template documentation and ninety percent of applications and procedures are implemented and tracked online. A structured methodology is also used for the assessment of benefits and risks that can be adapted throughout a product lifecycle. Because of these system enhancements, there was a significant improvement in the number of applications that were reviewed within pre-set time limits in 2013 when compared with 2012. Dr Rosenbluth expressed the hope that other regulatory agencies will also continue to develop and enhance their good review practices to increase confidence in one another’s systems and enable increased cooperation.

Dr Q.F Lidia Luz Castillo Solórzano, *DIGEMID, Peru*

In 2009, Law 29459 was enacted in Peru, which allowed DIGEMID to evaluate drugs’ safety, efficacy and quality, in accordance with three categories. Category 1: products whose active pharmaceutical ingredients or components were

included in the national essential drug request. Category 1 products have a 60-day evaluation period. Category 2: products whose active pharmaceutical ingredients or components were approved by high sanitary surveillance countries. These products have a 90-day evaluation period. Category 3: products whose active pharmaceutical ingredients were not considered in categories 1 and 2. These products have a 365-day evaluation period. Requirements differ according to each category. For other pharmaceutical products, such as biological products and medical devices, the new regulation is currently in the implementation process.

After the review of the dossier that accompanies the application and before the evaluation of each requirement, the companies have 48 hours to complete any missing requirements. This has to be completed before the dossier is accepted. The dossiers are randomly assigned to different evaluators for the assessment of quality, safety and efficacy and DIGEMID can also consult external experts. If there are any questions during the evaluation process, DIGEMID gives the companies 30 days to respond. The application then moves to a regulatory decision for the approval or denial of the registration dossier.

Because DIGEMID aimed to establish the criteria for the evaluation process of the pharmaceutical dossier in order to improve efficiency and effectiveness of the review and to guide its administration, a Manual of Good Practices for Review was developed and approved. The material was based on International Standards: Technical Guidelines for high sanitary surveillance countries, ICH and WHO. The Manual of Good Practices for Medicinal Gases Evaluation and for Sanitary Registry of Diagnostic Agents is currently in the development process. The manuals are also reviewed by Technical Directors of the pharmaceutical industry. Additionally, checklists for the administrators and evaluators of the initial dossier that accompanies the application have been developed. The Manual of Good Practices for Review is on the DIGEMID website.

Furthermore, DIGEMID is one of the eight entities that take part of the Foreign Trade Single Window (VUCE) in order to integrate and simplify processes and services of State institutions involved in foreign trade. Fifty-three administrative procedures have been implemented effectively by the use of the

electronic platform. Records are received virtually through the VUCE website, avoiding travel to the DIGEMID offices to carry out the related processes, thus, reducing costs and saving time.

DIGEMID began implementation of these processes in 2007 in accordance to the Quality Management System- ISO for sanitary registry procedures and is currently in the process of adding all processes to the system.

Finally, DIGEMID recognises that it is essential to strengthen capacity of professional staff through the use of internships and national and international educational courses.

QF Beatriz Luna, *Head of Evaluation – Technical Director, Ministerio de Salud Pública (MSP), Uruguay*

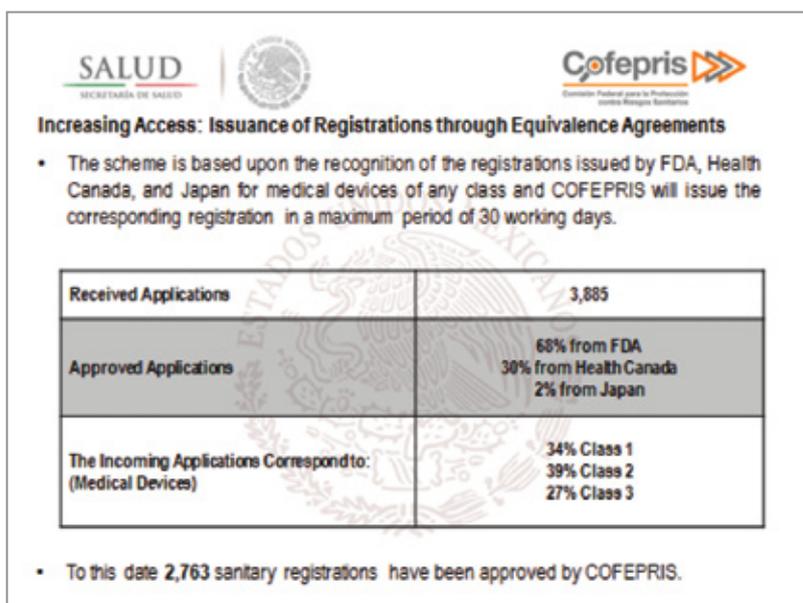
The legal framework for the registration of pharmaceuticals in Uruguay, which dated from 1984 and 1999, has been in the process of revision since 2007. Revisions began with those laws that concerned the quality control of imported drugs and the exchangeability of drugs and a process for the registration of biotechnology medications has also been drafted. All of these laws have been developed according to WHO guidelines. Companies may request new, renewal or modification registrations and the requirements that must be fulfilled for submission include the scientific protocol for the development of the medicine, certification of good manufacturing processes and of the right to market in the country of origin. Dossiers are reviewed by product or therapeutic area specialists within MSP and the advice of outside academic or scientific experts is solicited as necessary. Ongoing communication with sponsors is maintained throughout the review and MSP chemists and reviewers and can ask questions or schedule meetings as needed. Currently, requests for information about registered drugs must be in writing, but the Ministry of Public Health of Uruguay is in the process of improving its website in order to provide this information in a more timely and efficient manner. Marketing authorisation certificates are granted for five years.

SESSION: FOCUS ON INTERNATIONAL INITIATIVES

Science is advancing rapidly in today's complex and interlinked world and no single regulator can operate in isolation, or cope with all the work to be done. Whilst regulatory cooperation can be passive or active, legally mandated or voluntary, it results in the optimisation of resources and the facilitation of more quality decisions. **Dr Lembit Rāgo**, *Coordinator Quality Assurance and Safety: Medicines, World Health Organization* listed the requirements for regulatory cooperation, which include

- an enabling environment and foundation,
- the implementation of good governance principles,
- a flexible modern legal system,
- political will and a common vision,
- a comparable level of socioeconomic development among the participants,
- functional regulatory authorities with necessary capacity and resources,
- the willingness to invest into harmonisation and convergence,
- an inclination to cooperate and compromise
- and a commitment to an implementation that includes good regulatory practices and update and revision.

Figure 4. The acceptance of equivalence agreements by COFEPRIS has expedited access to innovative therapies to the people of Mexico



WHO will continue to promote regulatory collaboration, harmonisation and convergence in order to provide the best added value to public health. At the 14th ICDRA workshop for Medicines Regulatory Authorities in Singapore in 2010, it was recommended that regulators take account of one another's work with a view to improving the efficiency of the global regulatory system, commit resources to form cooperative networks based on uniformity of standards and inspection systems, engage with regional and international initiatives promoting harmonisation, information sharing and use of data generated by other regulators as a tool for improving timely access to medicines and medical products. It was recognised that although cooperation will not replace national sovereignty of regulatory decision making, the results of effective cooperation are an increasingly important part of integrated national regulatory decision making. It is hoped that opportunities to further develop regulatory convergence would be available at the next ICDRA meeting hosted by ANVISA 29 August 2014 in Rio De Janeiro, Brazil.

Dr. Mario Alanis Garza, *Advisor to the Commissioner, COFEPRIS* explained that the international strategy of the Mexican regulatory agency is based on harmonisation of its framework with the best international practices and direct action to increase access to health products while ensuring safety, efficacy and quality. Actions to implement this strategy that have taken place include recognition of COFEPRIS from the Pan-American Health Organization (PAHO) and by WHO for their primary reviews of vaccines and pharmaceutical products; initiation of the membership process for Pharmaceutical Inspection Cooperation Scheme (PICS); participation at the International Medical Device Regulatory Forum (IMDRF); the development of the assessment tool for medical device regulatory agencies; passage of an agreement for the promotion of innovation; recognition of Certificates of GMP; issuance of registrations through equivalence agreements (Figure 4) and recognition of product registrations from abroad. Benefits for the Mexican population are multiple and include access to innovative therapeutic options that increase quality of life and life expectancy, public and private savings due to market entry of generic drugs and increased competition in the pharmaceutical industry generating competitive market prices. Additionally, the increased participation of Mexico's health

agency in international harmonisation initiatives lowers costs, increases access, and promotes effective disease prevention. Finally, there is a causal relationship between the efficiency and transparency of health policy and economic growth. The market value of generic drugs increased by 77% in Mexico and the market volume increased by 56% from 2010-2012. Pharmaceutical spending as a percentage of total health expenditure in Mexico decreased from 28.3% in 2010 to 27.1% in 2011, a rate which is expected to continue to decrease and that has generated savings of 20 billion pesos in 2 years.

An industry perspective on the multinational complexity of product submission in a non-converged regulatory environment was offered by **Dr Susan Forda**, *Vice President, Global Regulatory Affairs, Eli Lilly, UK*, who maintained that regulatory harmonisation can result in tangible benefits for patients. Dr Forda provided examples of country-specific differences in preclinical, chemistry, manufacturing and control, import testing and clinical trial requirements and stated that even one additional clinical trial requirement can cause significant amount of additional work and delay submission timelines. These variable requirements can include longer clinical trial start-up times, regulations that limit the conduct of certain clinical studies, a lack of predictability in agency reviews and differing approaches to study endpoints and population requirements. The differences can result in a timeline delay for a national agency to receive new molecular entity dossiers and may impede future manufacturing and product improvements throughout the product lifecycle.

There have been instances of successful regulatory improvement efforts. Between 2009 and 2013 the Japanese regulatory agency PMDA achieved targets for on-time standard and priority reviews within medians of 12 and 9 months respectively and is currently the world's highest performing regulatory agency. Future opportunities for harmonisation include collaborations such as those of ICH and PANDRH to advance the consistency of regulatory standards across countries and regions worldwide. Topics that may benefit from additional deliberations on alignment include technical standards for chemistry manufacturing and controls (CMC) and good manufacturing practices (GMP), import testing, risk-based approaches to regulatory requirements, mutual regional recognition of regulatory activities and inspection outcome recognition between regulatory agencies with well-established practices.

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

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

Formed in 2007, the Four Agency Consortium is a very active international initiative for work and information sharing among Health Canada, the Therapeutic Goods Administration of Australia, the Health Science Authority of Singapore and Swissmedic. These mature, high-functioning, mid-sized regulatory agencies protect populations that are smaller than those overseen by the larger agencies such as the US FDA and EMA and could consequently be bypassed for access to important medicines as a result of company business decisions.

After an initial confidence-building period, a work-sharing plan was developed in 2010 for some of the issues that are most common to the four agencies such as those relating to criteria for foreign reference products, the development of common quality assessment templates and generic drug review. Other issues being addressed by the Consortium include common approaches to risk communication, and resource sharing through representative participation in technical working groups such as ICH and benefit-risk evaluation. Additionally preliminary discussions have taken place regarding work sharing in orphan drug regulation.

When considering potential work-sharing alliances, Latin American regulatory agencies may wish to replicate the success of this geographically far-ranging Consortium and look beyond their own borders for similar agency partners.

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

Regulatory agencies are approaching convergence for varying reasons including the optimisation of resources and the opportunity to provide regional leadership. For their part, as global submission timing becomes more simultaneous, industry would like to have the ability to develop a global application that can be used consistently across different regions. Additionally, ministers of trade are making free

trade agreements driven around intellectual property issues that inevitably have a regulatory component. Regulatory experts should be proactively engaging with their counterparts to determine that the appropriate legal frameworks exist within the countries covered by these agreements so that the industry can continue to provide safe, effective, and quality products to patients. All stakeholders are trying to get to the same place but may be taking different paths. Not all agencies have the resources to be an FDA or an EMA; therefore, balanced networks can be an extremely valuable source of expertise and experience.

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

The European Regulatory System is a model of regulatory convergence with potential applicability in Latin America. It is a testament to collaboration that 28 countries ranging in size from Germany (at about 80 million people) to other countries with populations of approximately 400,000 and 24 official languages have effectively implemented a single framework for marketing authorisation. This did not, of course, happen overnight. The legislation started in 1965 and real regulatory harmonisation began in 1995 when the EMA went from 15 national assessments to either coordination or common assessments. This harmonisation occurred because the EMA embraced the concept of the common technical document and understood that it was necessary to cooperate and be consistent and predictable.

Multiple learnings during the past 18 years include the identification of requirements such as common guidelines, templates, training and procedures and a common assessment report that explains decision rationales. The secure electronic linkage of internet technologies, databases and assessment systems is another complex but necessary element of the system. The existing legal basis for these actions and the voluntary spirit of EU members were distinct advantages to the development of the regulatory system. An established Secretariat was another important component of success.

Assessments of a product for a centralised application are conducted by a rapporteur and co-rapporteur, after which the decision is put to a committee of member states that must work together with a common understanding of context and of the decision framework. The

implementation of this process has evolved over time and multiple work-sharing agreements have arisen as a result. Although there is no work-sharing authorisation system for clinical trials, a group of member states have initiated a voluntary harmonisation procedure that now is becoming legislation. Additionally, all inspections are performed on behalf of the EU member states. Finally, trust and confidence are really central to a successfully converged regulatory system. Latin America may wish to consider PAHO as a resource to help develop an approach based on the learnings from the EMA.

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

The Bill and Melinda Gates Foundation (BMGF) is interested in trying to enhance the efficiency of regulatory systems in order to make quality products available more expeditiously to patients who need them in low- and middle-income countries (LMICs) without sacrificing product quality or patient safety. The Foundation has determined that by the time a product that is intended for people in the Sub-Saharan African countries actually reaches that population, it can be seven to eight years after the completion of its development programme. It was important to determine what causes these delays. A study commissioned by the BMGF determined that most global health products go through a three-step regulatory process before legal distribution in LMICs. After a product is authorised in its country of manufacture, it next goes through WHO prequalification and, finally, because there is no EMA-type central agency, in sub-Saharan Africa, companies next have to submit separate regulatory applications (often with different formats, languages, content requirements, etc) to each country in the region in which they wish to market their product. Often, the length of time between the submission to the first Sub-Saharan African country and the submission to the last country in that area can exceed five years, because, in most cases, there is no financial incentive for companies to expedite this process. Companies have indicated to the Foundation, however, that the alignment and harmonisation of regulatory agencies' requirements and processes in Sub-Saharan Africa, even if first only at the economic community level, would allow industry to submit fewer and more consistent applications to the region and greatly improve the efficiency of patient access to products there.

Realising that the creation of a pan-African Medical Agency was not feasible in the short term, leaders of the African Union capitalised on the existence of economic communities in the region, which are based on the principle of the free movement of goods. The African Union approached these various economic communities with a proposal of support from the Foundation and from other groups for the alignment of the regulation of pharmaceuticals within the economic community. The first of these communities to develop such a plan, which was subsequently vetted through WHO and other outside experts, was the East African Community (EAC), a group of five countries (Burundi, Kenya, Rwanda, Tanzania, and Uganda).

The EAC have developed four Working Groups that have created 44 guidelines for the community on submission format, procedures, GMP standards and internet technology, which have been agreed by the EAC ministers and which are now being further internationally vetted to assure they are consistent with international standards. They have also completed a pilot study of generic

drugs marketing applications review based on a work-sharing model. Using this model and many of the principles in the new guidelines, review times were reduced by 40%. Another pilot is underway. The ultimate goal is to develop eight or nine regional regulatory authorities in the continent through a program of alignment of processes and requirements, greater reliance on the work products of other trusted NRAs to inform decision-making, and a greater focus on value-added activities at the local level so as to best use the resources currently available. Dr Lumpkin proposed the consideration of a similar plans of action in other areas, building on the lessons learned in east Africa, and the further enhancement of the African efforts based on the successes of similar initiatives in other parts of the world.

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, *Head of International Affairs, European Medicines Agency*

Rapporteur Patrick O'Malley, *Senior Director, Regulatory Affairs, Eli Lilly and Co*

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)?

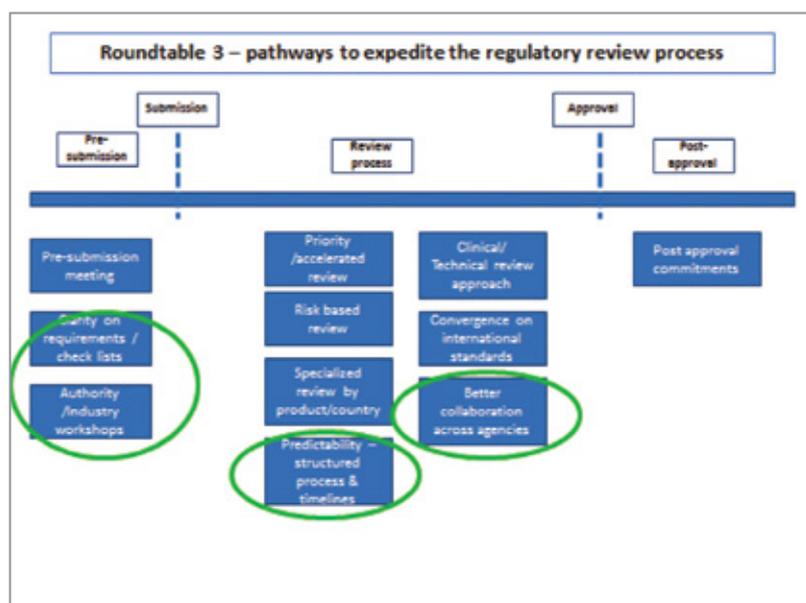
- What processes are in place in your country to benefit from prior experience by other agencies with a new medicine? How is this used to expedite a new product review?
- What types of cross-agency recognition can reduce the duplicative work of agency internal staff?
- The better constructed a dossier 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.

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

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



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 take place.

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 or 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 that 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>Senior 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 there is a 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?
- Are the regulatory pathways for biosimilars clear in all Latin American Countries and how aligned are they?
- What are possible pathways and 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 that can be used to establish biosimilarity and what evidence should be required?
- 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 products 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.

Reflections on Roundtable Discussions

Mike Ward, *Manager, International Programs Division, Health Canada*

- A commonality in all the Roundtable discussions was the idea of interagency cooperation, alignment and collaboration. The gradual evolution in common understanding among regulatory agencies has been accompanied by a spectrum of information and work sharing and even potentially, by reliance. Good review practices are a key component but should be considered necessary but not sufficient – other enablers are required.
- One such enabler that was discussed is staff exchange, such as occurred through the EU twinning projects. In addition to accelerating an understanding of one another's processes, staff exchange provides the opportunity to make personal connections among review managers and reviewers. The work-sharing consortium of Australia, Canada, Switzerland and Singapore is another successful form of this type of exchange.
- We are moving more toward the use of ICH and WHO guidance. In Latin America, the strategic goals of PANDRH are the strengthening of regulatory agency competencies and advancing regulatory science in the area. This group and the PRAIS initiative provide good platforms for the secure exchange of information between regulatory authorities.
- An important and timely idea was presented in the discussion of the leadership role that reference agencies can play in Latin America in assisting other agencies in the region and sub-regions. Strategic implementation of this concept that draws on the experience of Europe and other areas with mature regulatory agencies will advance regulatory convergence in the area.
- One of the themes of the strategic plan within the Americas is interconnectivity, but not just within the region. There is an opportunity in the International Pharmaceutical Regulators Forum to have a global discussion because many of the important issues facing regulators are not just national or regional, but rather are international in nature. Because all

agencies are struggling with some common issues it makes sense to try and adopt and share best practices and to explore common international solutions. As has been said many times, "think globally, act locally."

Dr Cristina Alonso Alija, *Head, Regulatory Affairs, Latin America, Bayer Healthcare*

- Both regulators and industry have a shared responsibility to enable access to innovation in the different countries of the world and cooperation is necessary to fulfil that responsibility. In the past several years quite a number of positive changes have occurred in Latin America but these must be reinforced and many tasks still remain to be accomplished.
- It is clear that not all drugs will have the same impact and differentiated regulatory review paths for differentiated drugs such as those in the breakthrough category are a necessity, but some agencies, for example in Mexico and Singapore have also created different regulatory paths in order that industry may choose the most appropriate one to bring a particular drug to market in a specific area.
- The issue of drug lag in which countries' access to medicine may occur four to five years after first launch in Europe or other mature markets should be examined by industry as a whole to determine if there is something that can be done differently. Regulators should also take actions to change this situation.
- An issue that emerged in all the group discussions is the necessity for dialogue and communication, especially as drugs increase in complexity. Early discussions between industry and regulators can ensure that the local context is considered in the evaluation of new medicines, and facilitate the evaluation of complex drugs.
- Even though implementation may be complex, simply aligning regulatory guidelines and format would overcome a huge hurdle for both industry and regulators and should be initiated as soon as possible, to make the regulatory process more efficient.
- Creating efficiencies, avoiding redundancies to optimise the use of resources and taking full advantage of the experience of mature agencies and industry are key to adding value to regulatory performance and bringing innovation to all countries.

Lawrence Liberti, *Executive Director, CIRS*

- International cooperative opportunities are moving forward within the confines of legal constructs but trust is required for cooperation and collaboration between and among agencies, companies and other stakeholders. Communication is another essential element of collaboration and as part of that communication, agencies need to clarify not only their expectations of companies but their own mission and goals. That is, the agency should communicate whether they have the capabilities to always perform full reviews or if their resources dictate more defined ambitions that may rely on shared activities. This information would lead naturally to discussion and awareness of timelines. In this regard, industry can aid agencies in their resource planning by formally or informally informing them of the timing of planned submissions.
- Some regulatory agencies such as Singapore currently take a risk-based approach to deciding whether a review will be verification, abridged or full. This risk-based decision making could be expanded to optimise available resources in Latin America by making risk-based label changes or enabling the risk-based prioritisation of company-agency interactions.
- Much insight can be gained through experience sharing or mentoring not only within agencies but between agencies and industry, potentially through industry-agency workshops. DIGEMID in Peru has initiated such an industry-agency project and other agencies may also be embarking on these kinds of interactions. Agencies may wish to consider micro-pilots for the exchange of review templates or templates for benefit-risk decision making, such as is currently being undertaken by CIRS or of pre-submission meetings. Again, initiation of or participation in these pilots can be based on risk-based prioritisation.

Q.F Lidia Luz Castillo Solórzano, *Executive Director, Sanitary Authorisations, DIGEMID, Peru*

- It is essential for national regulatory agencies to be aligned with the highest international norms. DIGEMID, as a national regulatory authority, grants certification of good manufacturing practices to the national manufacturing laboratories or

to foreign manufacturers from countries that are not considered to maintain high sanitary surveillance. It is challenging to establish mutual acknowledgement for granting this certification and to ensure that imported pharmaceutical products come from manufacturing laboratories that can document such quality assurance.

- In order to develop joint actions with other regulatory sanitary agencies to strengthen institutional capacity in the drug sanitary regulation and surveillance area, DIGEMID establishes cooperation agreements. For example, DIGEMID and ANVISA have signed a cooperation agreement to exchange experiences and information and to build capacity through expertise developed in workshops or internships. In addition, the Inter-institutional Cooperation Agreement has been signed by the Sanitary Authorities from the Pacific Alliance countries (Mexico, Colombia, Chile, and Peru and DIGEMID). The agreement is related to sanitary registries and the certification of good practices for the chemically synthesised manufacture of medicinal products.
- Furthermore, DIGEMID is a member of a working group that coordinates the harmonisation of the regulation of medicines and medical devices in APEC (Asia-Pacific Economic Cooperation) jurisdictions. Good Review Practices have been one of the discussion and development topics; however, regulatory agencies have to work on different levels since the good practices are related to their own processes.
- PAHO builds important instruments for harmonisation, which every country is free to adopt within their own regulations. In addition, every country can rely on the expertise of Latin American agencies that have been certified by PAHO as a National Regulatory Authority of Regional Reference thereby increasing cooperation and dialogue. DIGEMID has taken part in the processes of self-assessment and pre-assessment of indicators for the PAHO certification as a National Regulatory Authority of Regional Reference.
- Finally, the DIGEMID mission is to protect public health through its sanitary regulation to ensure timely access to quality products and devices with safety and efficacy.

Appendix: Workshop Attendees

Regulatory agencies		
Judy Castañeda Alcantara	Chief of Narcotics Control Bureau	DIGEMID / Ministry of Health, Peru
Diana Luzmila Medina Angulo	Chief of Regulatory Affairs for Cosmetics and Hygienic Products - EPSAN	DIGEMID / Ministry of Health, Peru
Prof Sir Alasdair Breckenridge	Former Chairman	Medicines and Healthcare Products Regulatory Agency, UK
Beatriz Adriana Luna Busto	Directora Departamento de Medicamentos	Ministerio de Salud Pública, Uruguay
Yane Carvalho	Specialist in Regulation and Health Surveillance	ANVISA, Brazil
Jaime Antonio Villegas Chiguala	Technical Consultant of General Directorate	DIGEMID / Ministry of Health, Peru
Leila Choy Chong	Chief of the Surveillance Area for Pharmaceutical Products, Medical Devices, Cosmetics and Hygienic Products	DIGEMID / Ministry of Health, Peru
Emer Cooke	Head of International Affairs	European Medicines Agency
Prof Hans-Georg Eichler	Senior Medical Officer	European Medicines Agency
Leandro Huayanay Falconi	Main Consultant of the General Directorate	DIGEMID / Ministry of Health, Peru
Dr Mario Alanis Garza	Advisor to the Federal Commissioner	COFEPRIS, Mexico
Walter Arango Gomez	Chief of Pharmaceutical Establishments Office	DIGEMID / Ministry of Health, Peru
Jesus Nieves Tipiana Jayo	Chief of Regulatory Affairs for Pharmaceutical Products – ERPF	DIGEMID / Ministry of Health, Peru
Dr Helen Rosenbluth Lopez	Jefa Subdepartamento Registro, Agencia Nacional de Medicamentos	Instituto de Salud Pública de Chile
Silvia Alvarez Martell	Team Leader, Pharmacovigilance and Pharmacoepidemiology Area	DIGEMID / Ministry of Health, Peru
Gloria Garcia Molina	Chief of the Surveillance Area for Pharmaceutical Establishments	DIGEMID / Ministry of Health, Peru
Rocio Delgado Montero	Consultant – International Affairs Area	DIGEMID / Ministry of Health, Peru
Catherine Parker	Senior Executive Director, Biologics and Genetics Therapies Directorate	Health Canada
Dr Renato Porto	Director of Health Regulation	ANVISA, Brazil
Dr Pedro Yarasca Purilla	Director of General Directorate of Medicines, Supplies and Drugs	DIGEMID / Ministry of Health, Peru
Celia Chuquichanca San Miguel	Chief of Regulatory Affairs for Medical Devices	DIGEMID / Ministry of Health, Peru
Lidia Luz Castillo Solórzano	Executive Director, Sanitary Authorisations	DIGEMID, Ministry of Health, Peru
Carmen Elvira Rojas Torres	Executive Director of Access and Rational Use of Medicines	DIGEMID / Ministry of Health
Vicky Flores Valenzuela	Executive Director of Directorate of Control and Health Surveillance	DIGEMID / Ministry of Health, Peru
Dr Hans Vásquez	Clinical Reviewer	DIGEMID / Ministry of Health, Peru
Mike Ward	Manager, International Programs Division	Health Canada

Non-profit agencies		
Dr Murray Lumpkin	Deputy Directory, Regulatory Affairs, Global Regulatory Systems	Bill & Melinda Gates Foundation, USA
Dr José Peña	QF Regional Advisor, Medicines and Health Technologies	PAHO/WHO
Dr Analía Porrás	Advisor, Medicines and Health Technologies	PAHO/WHO
Dr Lembit Rõgo	Coordinator Quality Assurance and Safety: Medicines	World Health Organization, Switzerland
Pharmaceutical companies		
Dr Cristina Alonso Alija	Vice President, Head, Global Regulatory Affairs, Latin America	Bayer Healthcare Pharmaceuticals Inc, USA
Simone Borup	Regulatory Director	Celgene, Brazil
Marisa Carcione	Head, Regulatory Affairs	Boehringer Ingelheim SA, Argentina
Odalís Estrada	Technical Director	AstraZeneca, Peru
Carla Olivera Fatacioli	Regulatory Affairs Manager, Peru and Bolivia	Pfizer, Peru
Dr Susan Forda	Vice President, Global Regulatory Affairs, International	Eli Lilly and Company Limited, UK
Doris Yaneth Gama	Regulatory Affairs and Quality Assurance Manager	Allergan de Colombia SA, Colombia
Birgitta Hedin	Head of RCC Coordination	Boehringer Ingelheim GMBH, Germany
Rocio Viladegut Hilares	Regulatory and Technical Affairs Manager	Productos Roche, Peru
Jill Jarusiewicz	Director, Latin America Regulatory Affairs	Celgene Corporation, USA
Dr David Jefferys	Senior Vice President, Global Regulatory	Eisai Europe Ltd
Dr Hiroki Kato	Director for R&D Strategy and Planning	Zeria Pharmaceutical Co Ltd, Japan
Thomas Kuhler	Vice President, Regulatory Policies and Intelligence	Novo Nordisk A/S, Denmark
Jan Leeuwinga	Director Strategic Initiatives, Regulatory Affairs	AbbVie, USA
Leyla Lister-Mora	Head of Emerging and Regional Affiliates Support	F.Hoffmann-La Roche Ltd, UK
Clara Sanchez Luna	Head, Regulatory Affairs BHC Peru	Bayer S.A, Peru
Ida Pena Molina	Regulatory Affairs Coordinator	Pfizer, Peru
Corina Nolasco	DRA Regulatory Director LATAM	Novartis Pharmaceuticals, Peru
Sharon Olmstead	Global Head, Development and Regulatory Policy	Novartis, USA
Patrick O'Malley	Senior Director, International Regulatory Affairs	Eli Lilly and Company, USA
Alexandra Sanchez	Regulatory Lead for Central America, Caribbean, Peru and Ecuador Markets	AstraZeneca, Costa Rica
Dr Joseph Scheeren	Senior Vice President, Head of Global Regulatory Affairs	Bayer Healthcare Company Ltd, China
Dellarika Schmitt	Senior Manager, Emerging Markets, Regulatory Policy	Pfizer, USA
Sonia Clarisa Seino	Latin America Regulatory Affairs Director	Eli Lilly and Company, Argentina
Dr Sampat Singhvi	Senior Director, International Regulatory Affairs	Takeda Pharmaceuticals, USA
Dorte Strobel	Senior Regulatory Intelligence Manager	Novo Nordisk A/S, Denmark

Aldo Topasio	EMAP Policy and Strategy Director, Global Regulatory Affairs	GlaxoSmithKline, Chile
Dr Jas Uppal	Director, Regulatory Affairs	Biogen Idec Limited, UK
David Verbraska	Vice President, Regulatory Policy	Pfizer Inc, USA
Anthony Ventura	Senior Director, Head of Latin America Region	Pfizer, USA
Cristina Wakiyama	LATAM Regulatory Head	Sanofi, Brazil
Centre for Innovation in Regulatory Science		
Patricia Connelly	Manager, Communications	
Lawrence Liberti	Executive Director	
Dr Neil McAuslane	Director	
Prisha Patel	Manager, Emerging Markets Programme	
Professor Stuart Walker	Founder	