Recent Trends in the Regulation of Biotechnology Products in Latin America

Session Chairs: Daniela Marreco Cerquiera, ANVISA and Ana Padua, Merck Serono S.A.
Panel Members

- Carolina Damas Rocha Zarate Blades, ANVISA-Brazilian National Health Surveillance Agency, Brazil
- Eliana Caballero Vedia, AGEMED, Ministry of Health, Bolivia
- Julio Rolón, MSPBS-Ministry of Public Health and Social Welfare, Paraguay
- Claudia Saidman, ANMAT-National Administration of Medicines, Food and Medical Technology, Argentina
- Isabel Slepak, Ministry of Public Health, Uruguay
Regional regulatory agencies are rapidly establishing new, and updating existing, internal policies and procedures to assess and monitor biotherapeutic products.

These efforts were encouraged by industry attendees as facilitating their ability to design the most appropriate dossiers for submission to each agency.

The OS45 pilot program launched by ANVISA in 2017 was slow to be adopted by industry (lack of industry awareness of it?), but 2018 had a great increase in requests from sponsors. Although data so far show it has already been a success in reducing backlog, ANVISA is extended the pilot period and will evaluate the status in July 2019.
Recent Trends in the Regulation of Biotechnology Products in Latin America

Panel Discussion
How many assessors in each agency are working on biological product dossiers?
- It varies widely among regional authorities.
- ANVISA has ~20 people on all aspects of pre and post approval;
- Argentina has one group for preclin/clin issues of biologics/biosimilars, a different group for vaccines; one group ~20 for biologics/biosimilars review and PAC Quality (CMC) who do reviews and inspections;
- Bolivia has 2 assessors for biologics (with only 30 days to make approve/reject decisions), and has constraints on hiring new staff; Paraguay has 3 biologics Quality (CMC) assessors;
- Uruguay has 5 biologics assessors. A big review challenge is also review timelines

Challenges with internal timelines?
- ANVISA now has mandatory timelines they did not set but absolutely must meet
- Other agencies have different timelines, but fewer people to meet them.
- Most had adaptive review (and clinical) processes for critical unmet needs, rare diseases, emerging infectious diseases
Product approval decisions from high vigilance regulatory agencies are considered in various ways across the regions; one key element is exactly which types of documentation are required to support the basis of those approvals?

- All regional agency value information from high vigilance agency reviews.
- In most cases, the more details that can be provided by sponsors, the better. The assessors need more than just what is publicly available from other agency approvals.
- ANVISA has found many of their questions were the same as those from these other agencies, so it saves effort to provide these up front.
- Also, it is important for assessors to know what (if anything) has changed in the dossier between the FDA/EMA approval and what is being presented for review now.
- But the exact set of assessment documents required by each regional authority varied slightly.
- Industry requested as much clarity and consistency as possible from each agency in the set of supportive review documents they need for assessments.

What are the most challenging issues regulators have seen in import, especially of non-registered (investigational) drugs?

- PARAGUAY - new decrees require producers and testing information to be provided, but found some importers/exporters did not have it
- One industry issue can be the long timelines when queing for review after documents are provided to agency, eg Uruguay (Uruguay was sympathetic, but indicated they are not empowered to change the que system at this time)
- ARGENTINA - sees gaps in quality data and lack of necessary certificates (75% of issues); new resolution coming for critical non-registered drugs specifically requested by patients/physician; past bad experiences with fake/poor quality drugs so had to change the process.
What is the process for each region to draft guidances/norms and issue for public comment?
- Bolivia - a pharmacist has been hired to review other norms from high surveillance agencies, plus the WHO standards to update/add policies; public comment period is 60 business days; information is posted on webpage and bulletins are sent to alert industry to give them time to respond.
- Agency websites update information on status of guidances so industry should check them frequently
- Each agency presentation had URLs for their relevant regulatory documents

How have new biologics norms/rules been applied to existing legacy biological products?
- Paraguay - first generation products are adapting to them now and 90% have been able to meet the new requirements;
- ANVISA - updating of old biological products began in 2002, and they have widely conformed by now;
- Argentina - As of 2015 began asking industry to update existing biologicals, which they are doing well.

How are regulatory agencies addressing new modalities like gene and cell therapies?
- ANVISA has a group for gene therapies with norms about to be issued for public comment (people are already knocking on the door!); Bolivia will use existing biologics regulations and adapt them as needed for advanced therapies;
- Argentina has draft norms out for comments, based on FDA guidance, and a committee has been formed for CAR-T products; doors not knocking yet but expect it soon.

What mechanisms are available for introducing new technologies for biological products (eg rapid micro methods, single use technologies)?
- Each agency depends upon sponsors to propose such technologies via their product dossiers, where it can be evaluated as applied to specific products.
- They cannot make theoretical decisions about approving new technologies, they can only assess its suitability when there is an application with sufficient data on how it performs for a given product.
What are the agency’s official position on Interchangeability for BSP?
- PARAGUAY and URUGUAY do not currently have interchangeability for biosimilars
- ANVISA has clarification note about it, but no official interchangeable status, it is up to clinicians
- ARGENTINA recognizes that clinicians will ultimately make the patient-based decisions on which product to use, but noted that among long term patients exposed to interchangeable versions of their drugs
- But some patients complained about switching their biological meds over the course of their treatments, so ARGENTINA now requires clinicians to use the same medication on a patient throughout their therapy

What are the regional naming conventions for each biosimilar product (BSP)?
- URUGUAY - BSP must use brand name
- PARAGUAY - BSP must use the brand name with abbreviation designating it a biosimilar version
- ANVISA - BSP uses brand name, commercial name and logo as biosimilar API;
- ARGENTINA - commercial name plus name of API noted as biosimilar

Does your country require official control labs to do confirmatory testing of drug products? If so, are they able to test biological products too?
- BOLIVIA has an official control testing lab for drugs (CONCAMYT); lab only perform physiochemical testing; they don’t do specialty tests for biotherapeutics but can send to outside labs that can do these tests
- ARGENTINA has ANMAT central lab to do confirmatory testing of three lots of clin lots, one (first) commercial lot.
- ANVISA requires validation of shipping chain so can rely on sponsor testing; vaccines testing is required (varies with info)
- PARAGUAY has no official labs; uses private labs for testing prior to approval to confirm C of A; new director looking at updating assays
- URUGUAY must analyze all imported drugs, but can waiver for biotechs if there are technology challenges
REGULATORY SESSION PANEL DISCUSSIONS

➢ What are agency perspectives on engaging in international and regional harmonization or convergence activities?
  ➢ Generally each agency has very positive views on aligning policies and procedures with other established and emerging norms for biologics
  ➢ They definitely welcomed increased dialog on global regulatory issues with other agencies and with industry for improving mutual understanding of the issues all around (industry agreed such dialog helps them too)
  ➢ ANVISA said that their participation in ICH has been very beneficial, but noted it does require a commitment of staff that must be considered in resource management

➢ Seems that there is good agency agreement on the concept of regulatory convergence, but what is holding up the actual implementation of common practices?
  ➢ Each regional authority must first stay within their legal constraints, not able to change existing laws;
  ➢ Beyond that, most are empowered to generate policies and procedures with aligned common principles
  ➢ But their internal administrative procedural systems can take a long time to issue a final guidance.

➢ What are the agency perspectives on knowledge sharing/regulatory capacity building for CMC issues with biologics, especially rapidly emerging products and technologies?
  ➢ All agencies expressed desire for increased access to knowledge on various types of biologics for mutual understandings.
  ➢ Also indicated accessible training on relevant issues would be most valuable to them and their teams.
  ➢ ANVISA indicated on-site meetings and training have been best for staff to attend with minimal disruption of their workload.
  ➢ ARG reported how much they have benefited from attending WCBP, and encouraged other regulators to do so.
  ➢ PARAGUAY said the wish list would include having greater access to as much information as possible;
  ➢ URUGUAY and BOLIVIA definitely agreed with this knowledge sharing wish.
  ➢ CASSS will take this back for discussions on options to facilitate this
ICH CTD Structure for Module 3 for Biotech

Session Chairs: Joe Kutza, AstraZeneca and Carmilia Jiménez Ramírez, Ajinomoto Bio-Pharma Services
Panel Members

- Flavia Firmino, Pfizer, Inc.
- Nadine Ritter, Global Biotech Experts, USA
- Hugo Hamel, Health Canada
- Livia Partika, Biogen Idec Brazil Produtos Farmaceuticos
HC is ICH member since 2015. CTD MQ4 adopted by HC in 2003.

BEFORE: Paper-based binders with information in different places

AFTER: Paper-based binders with index and format to find specific information

Discussed advantages of adoption of CTD format

M4Q indicates where and how, but not the what.

General guidance documents for CTD issued by HC in 2004 (under review) for biologics, and for conventional biotech products (venoms, allergenic substances)

Module 1 details

Module 3.2.R details

For minor misplacements of sections, HC has a screening process of the documentation that can detect this and allow proceeding with review. This reduces delays with review and approval process.

Sponsors may consult on the content and format of CTD sections in pre-submission meetings, and the sponsors are invited to share previous discussions with other regulatory agencies

HC Post-approval changes guidance is aligned with WHO guidelines and specify the CTD sections where the supporting data should be placed in Module 3.
Implementation of the ICH CTD Structure for Module 3 for Biotech: Health Canada’s Experience
Hugo Hamel, Health Canada (HC)

- Reliance on international agencies for review waivers is in progress (Foreign Review)
  - A draft guidance document has been issued for external consultation and comments
  - Sponsors should confirm in writing that the document submitted is identical to the one submitted to a qualified international regulatory agency or highlight any differences
Advantages and Challenges with Using CTD Module 3 for CMC Information
Flavia Firmino, Pfizer, Inc. Brazil

- Description of required format and information required for Modules 2-5 of CTD
- Module 3 format is modeled after ICH Quality Guideline
- Application of ICHQ12 guidelines and MQ4 guidance
  - No specific locations are described in for established conditions (EC) in MQ4. Suggest to include this information in QOS section.
Analytical Elements of Module 3 for Biopharm Products: Beyond S.4 and P.5

Nadine Ritter, Global Biotech Experts, LLC

- Use of S.4 and P.5 as “analytical storyboard”
- ICH Q6B for Biologics acknowledges complexity of these products, requires characterization and control of heterogeneity
  - Manufacturing process capability
  - Stability
  - Nature of pre-clinical and clinical material
  - Analytical capability
- Multiple analytical methodologies are needed to measure all relevant characteristics drug substance and drug product, including
  - Characterization of function and impurities (product and process related)
  - Reference standard establishments
  - Qualification of methods
  - Validation of methods
- The “Rhino” example
Some examples of information placement in 3.2.R section (regional section)

- Establishment of biosimilarity - Still requires S.4 and P.5 data for the actual biosimilar
ICH CTD Structure for Module 3 for Biotech

Panel Discussion
Commentary: For PMDA (Japan) reviews, they use M4Q CTD format, but are looking for an expanded Module 2.3 (QOS). They are also expecting ECs (ICH Q12) to be presented in Module 1.

Regarding submission of a prospective post-approval protocol for comparability with acceptance criteria, has this concept materialized as a regulatory relief for the original marketing application (MA)?

- It is necessary to lock down analytical methodology and acceptance criteria for comparability. Once the Sponsor realizes the complexity of the prospective post-approval protocol at initial submission, they typically shy away from submission.

- Often, the pace under which filing timelines are framed is too fast to submit prospective protocols in the original MA. Post-approval protocols after MA approval are more often submitted with more success of obtaining regulatory relief.

- With ICH Q12 coming to realization, HC will begin accepting post-approval protocols from Sponsors.
Who/what is the most appropriate person/department to author Module 3 CTD sections? What do you consider the best approach to submit CTD sections to agencies with experience with CTD vs agencies that have not adopted the format?

- Usually the Manufacturing team has the knowledge and skill to author these sections.
- Global companies are able to provide training to smaller/less experience companies in this aspect.
- ANVISA allows for a transition period to adopt CTD format. Partnership between Sponsors and agencies is key for this process.
- The content and story you want to tell about your product is the meat of Module 3. Some LatAm countries may need to indicate when the study started. Others don’t; include this information. Some companies have developed their own model for content. Sharing information with adopting CTD format allows expedition of submissions.
- The HC approach of not rejecting an application for misplacement of information is useful to the Sponsors and gives them a chance to submit the data in the right sections on the next scheduled update of the submission.
- Useful to perform a pre-work of the source documents upfront. Substance with style, so the technical content can be conveyed in a simple form.
Regarding the draft guidance from ANVISA for CTD content

- What have been the most commented topics or input gathered from industry?
- What kind of input/comments have industry leaders provided?

For biological products, most of the global companies are able to submit CTD format even if not required by ANVISA yet, as dossiers are easier to review. Specific questions regarding the provided input/comments might be addressed by the ICH coordination of ANVISA (not able to be present in the meeting).

Commentary: Would it not be a good idea for companies to start implementing the CTD format on their own to gain some timing advantage for review from regulatory agencies?

For local regulators, how easy is to convert the nCTD submissions to the local format?

- Information in the QOS is very useful to convert to the local format. It saves time and effort. Global CMC spends a lot of time filling out forms for PAC.
- It’s a challenge to create the Global dossier and when sent to LatAm and emerging markets partners, it takes a lot of time reworking the CTD dossier to fulfill the checklists of each of these countries. In the end, the patient suffers the delay in submission approval of about 2-3 years. Granting access to the patient would be much quicker if content was accepted as is. Also useful to leverage reference regulatory agencies.
Aside from EU IMPD, why does the panel think that an ICH global standard has not been established for clinical studies?

- EMA addresses stage appropriate method validation
- FDA has issued EC conditions guidance
- HC guidance document was developed knowing the need for content for clinical studies. HC suggested that this could be suggested to ICH at the next call out for topics.

For industry members: Provide examples on how CTD content and format are leveraged in your typical submission

- Bolivian importer - The order and content helps greatly in review and assembling content. What is the experience with pre-clinical and clinical studies (Module 4)? What format is recommended for the presentation?

- Global dossier may be translated to local requirements per country accompanied with assembly of source documents specific to the country. Often, these documents take 6 more months to become available after the CTD Module 3 content is issued. The hold up comes when the ancillary documents need to be legalized/notarized. When global supply chain is more complex, gathering this documentation in a short period of time is challenging.
Can ANMAT give more details on their experience with interchangeability?

From the clinical perspective for biosimilar national approval, the University hospital manages whatever arrives under license. Treatment will was offered on reference product and biosimilars coming from different sources. A debate ensued internally for how to treat short term courses for oncology, to harmonize and require use of the same product beginning to end. The ministry finally heard the suggestions, Currently it is required to use the same product.

For long term therapies, the story is different. Interchangeability is usually more common for treatment of chronic diseases. We will have to rely in regulatory convergence to define a plan and regulations.

Does WHO have plans for guidance for advanced therapies?

Since 2007, WHO started working with biosimilars guidance with little to no support from the rest of the community. Now it is well developed and effective. Two articles have been published on approach for advanced therapies. An official publication is planned.
Is there any possibility for some form of LatAm region convergence?

- Drive through PANDRA and PAHO regional harmonization initiatives. For example: Translation of guidelines to Spanish. Use a proactive approach, instead of a reactive approach. Propose to harmonize processes for advance therapies upfront, where regulations are not established yet.

- Paraguay will accept information approved by reference agencies and are amenable to accepting Module 3 CTD format as a suitable document for submissions. As leadership change over time, we have the opportunity to revise documents and practices. We have a working draft for these items. Case study of a product commercialized in Argentina, with a stability study approved for climactic zone II use. Paraguay accepted this product submission even though the climactic zone is different in Paraguay (zone IV).

- ANMAT agrees with T. Schreitmueller with proactive approach and support of changes in regulations from the industry and regulatory communities as effectors for change. Often, not being able to align with ICH guidelines stem from country-specific economic and legal reasons.

- Bolivia is very receptive to harmonization and convergence.

- The reality for regional regulatory agencies are staffing, time and financial constraints for adopting these changes.

- Uruguay intends to adopt CTD format soon.
Regulations for Post Approval Changes of Bio Therapeutics- Global Development and Opportunities for the Region

Session Chairs: Rosana Mastelaro, SINDUSFARMA and Thomas Schreitmüeller, F. Hoffman-La Roche, LTD.
Panel Members

- Rosana Mastelaro, SINDUSFARMA
- Thomas Schreitmüeller, F. Hoffman-La Roche, LTD.
- Hugo Hamel, Health Canada
- Maria Pina, AbbVie
- Elkiane Rama, ANVISA
- HyeNa Kang, WHO
- Carolina Damas Rocha Z. Blades, ANVISA
- Patricia Aprea, ANMAT
Why We Need Effective LCM Regulatory Systems
Now and Even More in the Future - An Introduction

Thomas Schreitmueller, F. Hoffman-La Roche, AG.

- Presenting on behalf of FIFARMA (Federación Latinoamericana de la Industria Farmacéutica)
  FIFARMA is the regional voice of the innovative pharmaceutical industry and as such engage in
  the development of policies that foster the access to high quality pharmaceutical innovations.
  It has a unique position as an official non-state actor with PAHO.

- Post-approval changes are challenging, in particular when registration has a global scope.
  - Different expectations, requirements, timelines per country.
  - Lack of post-approval change procedures in many countries.
  - Lengthy process. May take years.

- Harmonizing regulations for post-approval changes these days is more important since ever
  before.
  - Science is constantly evolving. New products and modalities (eg. CAR-T, gene therapy,
    combination therapy).
  - Clinical trials are more and more targeted and faster: Many indications and one specific bio-
    marker with positive patient response.
    - Patient numbers will be smaller for trials. More specific clinical experience as target is identified early
      on.
    - Regulatory Systems enablers for these new development approaches are:
      Expedited registration processes including accelerated approval pathways, mutual recognition, possibility
      for post-approval commitments, strong pharmacovigilance systems and very important efficient life-cycle
      management.
Why We Need Effective LCM Regulatory Systems Now and Even More in the Future - An Introduction

Thomas Schreitmueller, F. Hoffman-La Roche, AG.

- What we need to increase efficiency in the post approval space:
  - Globally harmonized risk-based change classification
  - Novel regulatory systems and tools
  - Reliance and mutual recognition
  - Clear and transparent timelines

- Solutions: Adopt complementary post approval change (PAC) guidelines in all LATAM countries
  - WHO PAC guideline indicates how to classify and justify the change
    - Additional considerations: Expedited review procedures and documentation requirements
  - ICH Q12 indicates what is actually change relevant
    - Additional considerations: Post Approval Change Management Protocol (PACMP) will increase efficiency in a proactive manner

- FIFARMA's ask for regulatory agencies in LatAm
  - Implement alternative registration pathways
  - Adopt collaborative decision-making process (Caribbean countries example)
  - Establish pilot program to adopt reliance-based procedures
  - Align requirements for post-approval changes for biologics and vaccines
New WHO Guidelines on Procedures and Data Requirements for Changes to Approved Biotherapeutic Products: Evaluation Principles in the New Guidelines

HyeNa Kang, WHO

- The WHO guidelines for similar biotherapeutic products (SBPs) were adopted in 2009. During international consultations on the development of these WHO guidelines, and during their implementation, it became clear that there was a need to develop specific WHO guidelines on changes to approved biotherapeutic products. In addition, it had been recommended during the 16th ICDRA that WHO assist Member States in ensuring regulatory oversight throughout the life-cycle of biotherapeutic products.

- WHO Q&A document on SBP guidelines has been recently published. It is intended to provide clarity concerning questions that may arise during the use of such guidelines.
  - Several questions relate to post-approval changes are provided in the section of pharmacovigilance.

- WHO Expert Committee on Biological Standardization (ECBS) recognized that the 2009 Guidelines remained valid and did not therefore require revision at this point (ECBS meeting, Oct 2018).
New WHO Guidelines on Procedures and Data Requirements for Changes to Approved Biotherapeutic Products: Evaluation Principles in the New Guidelines

HyeNa Kang, WHO

- WHO guidelines for post-approval changes of biotherapeutic products are intended to serve as a guide for establishing national requirements. It aims to provide guidance on the procedure and criteria for categorization and reporting of changes. New regulations in country should not impact product supply and patient access.

- WHO guidelines for post-approval changes of biotherapeutics are mostly aligned with the requirements from major regulatory jurisdictions (FDA, HC, PMDA, EMA) with a few exceptions:
  - Moderate changes: Prior approval supplement required to confirm absence of negative impact of the change on the product.
  - Minor changes: Divided in two categories
    - Minor changes - requires notification
    - Changes with no impact - does not require notification
Four reporting categories for quality changes: Major, Moderate, Minor, No Impact.

- **Major and moderate changes** must be submitted to the regulatory agency and approved before implementation by the Sponsor.

- **Minor changes** do not require submission of supplemental documentation, but Sponsors should be able to provide the documentation to the agency if requested. The agency must be notified but no review or approval is required.

- **Changes with no impact** do not need notification or review from the regulatory agency. These changes must be retained as part of the manufacturer’s GMP records or marketing authorization holder’s product records, as applicable.
  

Discussed examples of drug substance and drug product quality changes.
If any conditions are not fulfilled for a change, the reporting category is automatically upgraded to the next level. Scientific justification should be provided by the Sponsor if any of the supporting data outlined for a given change are not provided.

For changes not captured in the guideline examples:
- Use scientific judgement to propose category
- Leverage previous regulatory guidance

Use Appendix 4 for guidance when changes impact safety, efficacy and labelling. These changes require prior approval by the regulatory agency.

Multiple major or moderate changes may be filed in the same submission or supplement. If the reporting categories are different between changes, the regulatory agency may change classification to next higher level.
Reviewing Process of the Stability and Post-Approval Changes Regulations for Biological Products in Brazil

Carolina Damas Rocha, ANVISA (presented by: E. Rama)

- ANVISA participating as ICH member since 2016. ANVISA has been reviewing their current regulations to improve regulatory system, implement regulatory convergence and provide more flexibility.

- ANVISA participating in WHO informal consultation for guidance on post-approval changes.

- Changes to stability conditions and regulations adopting ICH guidelines and international guidelines.

- For post-approval change on stability programs, use of WHO guidance on post-approval changes, WHO Annex 4 for vaccines and HC guidance.
Reviewing Process of the Stability and Post-Approval Changes Regulations for Biological Products in Brazil

Carolina Damas Rocha, ANVISA (presented by: E. Rama)

- ANVISA resolution draft is very similar to WHO guidance in general for any post-approval changes. This includes risk categorization, reporting categories for quality changes, review timelines:
  - WRT to timelines, ANVISA has aligned them to the required government laws in Brazil. VERY SHORT, in most instances!

- OS45/FEB2018, Expedited Review Procedure - Pilot Program
  - RELIANCE tool. Not a tool for mutual recognition. Requires documented approval of FDA/EMA
  - Additional documents required:
    - Stability studies
    - QOS (Module 2)
    - Transport chain validation
Reviewing Process of the Stability and Post-Approval Changes Regulations for Biological Products in Brazil

Carolina Damas Rocha, ANVISA (presented by: E. Rama)

- Resolutions on stability and post-approval changes - Progress to date
  - Impact analysis and draft in progress
  - Public consultation expected by Q2/Q3 2019
  - Complete process by end of 2019
Case Study: How can we use WHO Guidelines on Procedures and Data Requirements for Changes to Approved Biotherapeutic Products in Real-Life Examples?
Maria Pina, AbbVie

- Typical questions to Global CMC teams
  - What are regulatory requirements?
  - How long will the change implementation take?

- Case study: New manufacturing site for DS, change in scale and new QC testing site (Multiple changes in one submissions)
  - Determine reporting category for each proposed change
  - Identify supporting data: GMP certifications, process validation, comparability, manufacturing site information, supporting batches (no concurrency required, historical data accepted), stability data, technology transfer qualification
Post-approval Changes Regulation in Argentina: Development Phase, Current Status of Public Consultation and Next Steps
Patricia Aprea, ANMAT

- Requisites for biotherapeutics
  - PRE-AUTHORIZATION: Registration dossier approval includes certification from ANMAT. Commercialization cannot begin until all data submitted in the dossier is verified with import testing or first production lot after approval.
  - POST-AUTHORIZATION: Any changes to this approved dossier, the Sponsor needs to update their registration submission and re-registration every 5 years. These are just as important as initial submissions.

- Modifications post-authorization are classified in a new system
  - Administrative changes
  - Qualitative Changes
  - Changes in safety, efficacy and pharmacovigilance

- After classification, conditions must be established for the change and supporting documentation is submitted.
- Minor changes require sworn declaration submitted within 12 months of change. Major changes require approval prior to implementation.
- Proposed changes are under public consultation.
Regulations for Post Approval Changes of Bio Therapeutics- Global Development and Opportunities for the Region

Panel Discussion
What is the timeline for public consultation and effective date for ANMAT’s proposed regulations for post-approval changes?

- Public consultation is complete. Modification to draft is in progress. Thereafter, a meeting with industry will ensue. We expect process to be complete in 3 months, with implementation of electronic submission platform.

During the consultation period of developing the WHO PAC guidelines, WHO has received several requests from regulators to develop a template for the annual report of minor changes. What’s the opinion of industry and regulators?

- Industry is on board with this proposal

- HC uses a fillable form that includes a drop-down list of all minor changes listed in the guidance document. The sponsors are also required to certify on the form that all conditions for minor change categorization have been fulfilled. HC would consider sharing this template with WHO.

- Paraguay considers that by adapting WHO guidance first hand and using a template is very beneficial.

- Uruguay does not have regulation for post-approval changes, but intends to adopt WHO guidelines when.

- Bolivia would like to know if fellow regulators from LatAm have established timelines for post-approval change review.

  - Paraguay does not have regulations in place yet. They are currently evaluating average timelines for evaluation. It would be useful to know the rationale behind established timelines for review in other agencies and how WHO determined the timelines in their guidance.
Has Brazil a “positive law” rule, meaning that ICH should be implementing as a law/regulation, instead of a guideline? How did HC develop its relationship with WHO and come about developing the guideline?

HC was not aware of the “positive law” rule. For HC, adopting ICH guidelines simply implies applying the concept and not necessarily enforcing law.

H. Hamel explained that when he started with Health Canada 20 years ago, in the absence of clear guidelines, he and his colleagues were receiving 5-6 calls per day from Sponsor inquiring on how to file post-approval changes. In order to be consistent, they would consult amongst themselves and started scoring the nature of the responses to Sponsors. This information was put in a guidance document, extensively consulted with the industry, and officially released in 2009. In 2016, WHO was looking around the world for consensus on a guideline and found the details in the HC guideline very useful. This was used as platform for global public consultation for the final WHO guideline.

ANVISA clarifies that implementing ICH guideline does not imply enforcing a resolution or regulation. If the guideline is part of requirement from the agency, it is included in the RDC. A resolution (RDC) may be written with open statements or flexible statements for implementation. For example, adding provisions around number of batches needed for stability packages. The legal authorities determine whether the guideline will be adopted as regulation or ANVISA’s guideline.
J. Kutza from AZ clarifies that ICH guidelines are NOT requirements and should not be embedded in laws.

ANIVSA is reviewing and trying to ensure that the current public consultation on post-approval changes takes into consideration the flexibility factor. ANVISA’s proposal for PAC for stability includes allowance of justification submitted when conditions cannot be met.

Resolutions (RDC) in Brazil are different than laws. Laws are issued by Congress. RDCs are not as easy to revise as guidelines. RDC implementation and approval requires consultation with their regulatory and legal departments. For example, initially, the RDC was proposed as a cover page with reference to ICH guideline for stability. The RDC proposal was refused by the regulatory department.

Industry question: Can you provide context on the process to follow RDCs? Are they legally binding?

Yes. RDCs are legally binding. If the RDC is prescriptive, it must be followed. No discussion. If the RDC has flexible language for justifications, it will be evaluated by ANVISA technical team.
What is the difference between minor quality changes and changes with no impact?

HC: There are many every day changes in manufacturing processes that are considered “no impact”. Things like correcting spelling mistakes and editorial changes made to SOPs, changing specification for compendial raw materials, replacing equipment with an identical equipment, etc. It is impossible to list all changes, but WHO has provided a list of examples of quality changes with no impact. Minor changes are listed in Appendix 2 and 3 in the guidance.

Can you give successful examples of submissions with post-approval changes under this guidance? Have you assessed how timelines have been reduced upon adoption of the guidance?

HC: Initially, implementation of the HC guidelines had some gaps with regards to conditions and risk assessments. The guidance has been revised to addressed those gaps about 5 times. This guidance is a living document.

HC: Yes. The screening process is much more efficient as the supporting data that need to be provided for a specific change are clearly described. In turn, the review process is expedited.

WHO: We don’t have direct information from NRAs regarding implementation successes. During the consultation period in 2016-2017, NRAs commented on the benefits
Stability for Biotechnological Products

Session Chairs: Lori McCaig, Genentech, a Member of the Roche Group and Camilla Santos, Amgen Inc.
Panel Members

- Carolina Damas Rocha Zarate Blades, ANVISA - Brazilian National Health Surveillance Agency, Brazil
- Laura Giribaldi, Amgega Biotech, Argentina
- Kavita Ramalingam Iyer, Merck Sharp & Dohme Corporation, USA
- Carmilia Jiménez Ramirez, Ajinomoto Bio-Pharma Services, USA
- Joseph Kutza, AstraZeneca, USA
- Germán Lastra, Amgen Limited, United Kingdom
- Donnie Pulliam, Biogen, USA
STABILITY SESSION SUMMARY

➢ Regionally-different requirements for amount of stability for biologicals are a huge challenge for industry to generate for a global product
➢ Major stability differences are in required # lots, required amt of time, magnitude of study designs, content/format data)
➢ Case studies were presented to show the impact of regional differences on:
   ➢ In-use/compatibility studies (extreme multiplicity of data sets; common range needed for ‘RT’)
   ➢ Shelf life at approval/annual commitment (cannot use “lean stability” strategies to reduce annual stability timepoints/# batches)
   ➢ Data to support PAC (full data sets for all tests/timepoints, specific report elements eg signatures, # PAC batches needed, minimum amt of real time data)
   ➢ Data needed in biosimilarity studies (use of comparative forced degradation data to demonstrate similarity)
➢ Another challenge is the mandatory timeframe for answering request for data (esp if real-time data is needed; very long timelines)
➢ Some regional authorities are adopting ICH guidelines for biological product stability (IHCQ5C) along with the other ICH stability guides (ICHQ1 series), and WHO guidelines
➢ But even when aligning with these global stability guides, some agencies still have extreme formatting and ancillary information needs that do not seem to add scientific value to the data
Stability for Biotechnological Products
Panel Discussion
Industry Clarifications to Regulatory Agencies on Considering Flexible Stability Strategies:

- Allowing flexibility in regional guidances does not obligate a reviewer to accept all kinds of data packages; reviewers always have the ability to determine there is insufficient data to make a decision.
- But when a package comes in that is sufficiently justified and has adequate data, it provides regulator with a mechanism to let them make a good decision (flexibility is not opening the barn door!)
- A major review benefit to streamlined stability packages (when justified) is the reduced amount of data that will require detailed regulatory review; 2000+ data points is onerous to generate AND to review

Paraguay - 99% of biologicals are imported product; it is zone VI but all data were at zone II; question was about what temps it was at between origin and recipient locations; they had to start stability studies at zone VI to answer assessor questions in order to support use in PARA at RT conditions in this region. What would industry propose?

- For a refrigerated product, industry typically does numerous shipping support studies for the entire supply chain conditions, eg short term excursions
- For extreme excursions at high and low temps, industry usually use small-scale studies of exposure cycles to be sure cold-chain products can be handled reliably in short term and over shelf life
- For cold chain product intended use by patients at home, ambient storage convenience (if needed by patient for travel or emergencies)

What do regional regulators expect for support of RT in their climate locations?

- ANVISA - Cycling studies that are sufficiently rigorous and include long-term real time data after cycling are generally accepted if the contain data the cover the region’s climate conditions; case by case but worth discussing
- If it is always used in controlled RT (eg hospital) then 25C ok, but any other “RT” location requires 30C data (must consider all uses, inc clinical sites, physician offices, patient homes)
What about products licensed for use in climate zones outside of zone II regions, especially those that have natural disasters with no electricity for extended periods?
- Some cycling studies could cover this for a short period of time but hard to plan prospective data sets for all possible contingencies; might be good idea for future discussions to talk to.

How is the ICH harmonization work going forward day to day at ANVISA?
- They have had good training on the details of the ICH guidelines and they understand the need to improve flexibility especially for post-approval changes (PAC).
- Challenge to implement because of the legal administrative issues (conversion of ICH into legally enforceable documents); having to work within their existing administrative systems.

How can you use ICHQ1E for biological products?
- Can use the statistical approaches to analysis of data sets, but may not be able to use poolability criteria for all characteristics.
- Might need to use alternative statistical models but will have to justify them with limited poolability of data.
- Flow charts are based on chemical drugs so might not fit for biologics, but should leverage the entire body of stability data to support shelf life determination strategies.

Did you get agency buy-in on accepting the ‘lean stability’ approaches for biologics for registration and annual?
- For new registration package, yes. For annual commitment, did not get pushback because it was supported by existing sound stability packages for the product.
EU PRIME program for urgent therapies/rare diseases have considered allowing shelf life assignments based on extrapolation; could regional LATAM agencies do so?

- ANVISA - Yes, the directive for rare diseases offers the assessor flexibility in consideration of required stability data, eg ongoing stability data.
- PARAGUAY has ability to judge what is necessary for rare diseases for individual patients; it is not for full registration; could discuss this internally about making a guide on this
- URUGUAY - can bring in non-registered medication for patients and so far has no requests for extrapolated shelf life
- BOLIVIA - also can bring in a non-registered product for patients; they just have to bring in the invoice to address customs issues
- ARGENTINA has the ability to make clinical decision for patients in special rare cases when supported with quality data
- CANADA - has flexibility to discuss number of lots and extension of shelf life for rare disease, backed up with post market commitments to monitor stability

Confusion between “RT” and “Controlled RT” terminology

- ANVISA controlled RT = 15-30C; uncontrolled RT
- Others?
- Some regional pharmacopoeias have very wide ranges defined for “room temperature” (eg JP: room temp is 15C - 30C!)
- General recognition that Zone IV regions will have different actual ambient temps than Zone II regions, even with HVAC systems in some areas, so stability of heat-sensitive products must include testing ranges likely to be encountered in the regional distribution chain from origin to point of use