

More Structured, Interactive Process to Drive Convergence in Latin America Advocated by Biotech Product Regulators and Industry at CMC Strategy Forum in Brasilia

The need for a more structured, interactive process to drive convergence and resource sharing among the regulatory agencies of Central and South America – potentially drawing on elements of the European model – was a dominant theme among the industry and regulator participants in the second annual CMC Strategy Forum Latin America held again in late August 2015 in Brazil’s capitol city Brasilia.

The two-day forum, sponsored by CASSS with the support of the key regulatory agencies in the region, brought together industry and regulator CMC experts to review: • the significant progress that has been made in recent years in strengthening the biopharmaceutical regulatory capacities in the region • where the shortfalls remain, and • how the region can move into closer alignment with the US, Europe and Japan, and keep pace with their evolving processes.

In her summary of the presentations and discussions presented at the forum’s conclusion, industry consultant Nadine Ritter (Global Biotech Experts) highlighted the consistency among the participants in wanting to strengthen the foundation for increased regulatory convergence and resource sharing – a desire heightened by the challenges that biotechnology presents and the limited resources available at the individual agency level to address them. [Ritter’s in-depth summary is provided in full below.]

Pointing to the increased involvement of countries in the region with international organizations like the World Health Organization (WHO), the Pan American Network for Drug Regulatory Authorities (PANDRA) and the Pan American Health Organization (PAHO), Ritter noted the desire echoed across the agencies represented to have more permanent interactions at that international level.

“A really strong message came from everyone that they wanted to promote increased interaction among their agencies to advance their understanding and even to advance internal training on technical issues specific to biotech and biosimilar products,” she stressed in her summary.

Heightening this desire is the recognition that “these are definitely different products. They require different complex systems, and they require different CMC considerations to support their safety and efficacy and stability.”

In her summary, Ritter reviewed the regional and global collaborative efforts that the Latin America regulatory agencies presenting at the forum were engaged in to further the harmonization of their policies. She noted the point made by Chilean regulator Fabiola Espinoza that the absence of a permanent CMC working group among the regulatory authorities in the region is hindering progress and should be created as quickly as possible.

Convergence, Predictability, Transparency in Focus

The opening session of the forum focused on “regulatory convergence, predictability, transparency and priority reviews in Latin America.” It included presentations by the regulatory agencies of Brazil (ANVISA), Peru (DIGEMID), Chile (ISP) and Mexico (COFEPRIS). Updates and comments were also provided related to the themes of the session by representatives from the EU and FDA, and from Grupo Farma Brasil and the Latin America Federation of the Pharmaceutical Industry (FIFARMA). An extended panel discussion followed.

Regulatory Convergence Panel Discussion Participants

A presentation session and panel discussion on “Regulatory Convergence, Predictability, Transparency, and Priority Reviews in Latin America” held at the CASSS forum was moderated by ANVISA’s Marcelo Moreira and EFPIA LATAM Network Chair Ana Padua. The presenters and participants in the panel discussion were:

Edith Roxana Vásquez Alayo (DIGEMID, Peru)

Reginaldo Braga Arcuri (Grupo Farma Brasil)

Niklas Ekman (Finnish Medicines Agency)

Sarah Kennett (FDA, USA)

Marcelo Moreira (ANVISA, Brazil)

Fabiola Muñoz (Public Health Institute, Chile)

Thomas Schreitmueller (FIFARMA)

Esenbeckia Yureri Torres Guzman (COFEPRIS, Mexico)

Following the pattern of the foreign CMC Strategy Forums, the opening regulatory session led into targeted sessions with industry and regulator presentations and panel discussions exploring some of the key technical challenges in the biotech arena. In focus, respectively, at the two-day Brasilia forum were: • the characterization, control and regulation of protein glycosylation • technology transfer, and • cold chain management and product transportation qualification. *[Editor’s Note: See [IPO September 29](#) and [IPO September 30](#) for a review of the presentations and discussion at the tech transfer session.]*

CMC Strategy Forums are also held annually in Europe in May and Japan/Asia in the late fall. Next year’s Latin American forum will be held in Mexico City.

A pair of forums are held in the US in conjunction with the CASSS Well Characterized Biotechnology Product (WCBP) conference in late January and another during July. The WCBP conference will again be in Washington, D.C. with forums scheduled on January 25 – the day before the WCBP conference begins – on the “technical and regulatory considerations for pharmaceutical product lifecycle management” and “production cell line development and control of product consistency during cell cultivation,” respectively.

Panel Probes International Opportunities

The panel discussion at the opening regulatory session in Brasilia gave the presenters the opportunity to explore further how the goals of transparency and convergence relate to each other, why they are important to pursue, and how their realization can be furthered.

KEY QUESTIONS FOR REGULATOR PANEL AT LATIN AMERICA FORUM

The following were the important questions driving the regulatory panel discussions at the opening session of the CMC Strategy Forum Latin America on "regulatory convergence, predictability, transparency and priority reviews."

- **Predictability:** What are the measures planned and implemented to enable the correct estimate of evaluation review deadlines?
- **Convergence:** Considering the Latin America regulatory environment, what are the barriers for development of integration and cooperation among national regulatory agencies (NRAs) in order to promote regulatory convergence? What are the main hurdles and how could they be overcome?
- **Transparency:** In the context of regulatory convergence, it is evident that transparency is required. How could transparency be provided? What tools could be used? How could transparency in regulatory decision be ensured?
- **Priority Reviews:** Are there priority review programs in place or under implementation in your country? What has been the experience and timelines achieved?
- **2015 Priorities:** What have been the top three priorities established in your regulatory agencies and industry organizations for 2015? What about the evolution of these priorities during the past months?
- **2016 Priorities:** What are the most important regulatory perspectives for 2016?

In his presentation, Roche Biologics Regulatory Policy Head Thomas Schreitmueller, who heads up FIFARMA's Regulatory and Biologics Working Group, explained the association's concern, in particular, with the current lack of a harmonized risk-based approach to biologic product lifecycle management and outlined FIFARMA's thinking on the pathway to achievement ([*IPO December 28, 2015*](#)).

During the panel discussion, Schreitmueller reemphasized that convergence is "in the interest of everybody," with the potential to bring resource spending down by mutually recognized decision making based on similar regulations.

He cited the biosimilar example of how the convergence process can start from the global organization WHO, flow down through PAHO and then spread out to individual countries.

The key ingredient is the building of trust, which can only happen through transparency, the Roche FIFARMA representative stressed. He cited the European Public Assessment Report (EPAR) as an example of the transparency/trust relationship at work.

Finnish Medicines Agency biologics quality assessor Niklas Ekman, who updated the forum on the EU's adaptive pathway and transparency initiatives, agreed with Schreitmuller that transparency "is a crucial thing for harmonization and convergence."

Ekman noted that the content of the EPAR, which provides the basis for the regulatory decision and has the company's buy in, continues to increase. "To be transparent and come out with information that the regulatory decision is based on," he maintained, "is a win-win situation for all."

It was noted during the transparency discussions that the Asia Pacific Economic Cooperation (APEC) initiative has a working group that is looking at developing a guidance for international product review summaries based on the EPAR model.

Seeding Convergence with Training

CDER Office of Biotechnology Products (OBP) Division of Monoclonal Antibodies Review Chief Sarah Kennett, who provided the FDA update at the session, suggested that, rather than "100% convergence," the initial focus should be on "regulatory consistency," which in itself would be "very, very beneficial."

Different laws and regulations create convergence hurdles that take time to cross and there are different risk benefit/tolerance levels and intellectual property sharing concerns that factor in as well, she noted.

A key to making progress is training, Kennett emphasized. She noted that knowing how to do efficient and consistent application reviews and write them up is a concern on which FDA has been focused internally – having the training systems in place "so people know what is expected of them and they start doing things the same way every time."

Ekman concurred that product assessment is increasingly challenging, and commented that the EMA has been expanding its international training efforts, in which assessors from Latin America have participated.

He pointed out that Europe is dealing with the resource constraints through its harmonized assessment system and mutual recognition. With its four biotech reviewers, the Finnish agency "could never handle all the applications that are going around in Europe. Our agency would need to be at least ten times bigger than it is currently."

Peru DIGEMID's Edith Alayo highlighted the challenge faced by the seven regulators at her agency involved with biologic evaluations in handling the divergent products. Training is important, she stressed, adding that the more senior people in the agency should also be attending these types of meetings and that video conferences could help promote mutual understanding and regulatory advancement.

Mexico COFEPRIS' Esenbeckia Guzman commented that academic and industry experts should be involved along with regulators to advise and collaborate on new approaches and help streamline the convergence process.

ANVISA's Marcelo Moreira offered a more general comment on the ability of Latin America to address its individual agency resource constraints by moving directly to the mutual recognition-type system established in Europe.

Europe has shown that language issues can be dealt with. However, Moreira stressed, harmonizing around the technical criteria and requirements is a necessary first step on the mutual recognition pathway, followed by transparency around the registration approval process. While mutual recognition is a worthwhile goal, "we have a long way to go" to reach it, he said.

PAHO and the ASEAN/APEC Models

In presenting FIFARMA's recommendations during his presentation and again in the discussions, Schreitmueller pointed to the need for PAHO to be more actively engaged in driving the convergence process "to the next level" in Latin America.

What is needed is more "political will" behind the effort in Latin America, he said, equivalent to what is taking place in the Asia Pacific region under the Association of Southeast Asian Nations (ASEAN) and through APEC ([IPO July 27, 2014](#)), where countries are working to harmonize through a "top-down approach," which could lead toward a EU-type collaborative system.

Schreitmueller cited a suggestion made publicly by CDER Director Janet Woodcock that with all the disparate initiatives going on globally around convergence, what may be needed now is a global umbrella steering committee to minimize duplication of efforts and provide strategic direction.

ANVISA's Moreira noted that it is usually the same subject matter experts involved in the different regional/international groups, resulting in more harmonization among the various initiatives than their diversity would imply.

The regulatory session concluded with a review by the various panelists of their top priorities during 2015 and how they would evolve in the coming year.

Increasing regulatory efficiency and effectiveness through more transparency and international collaboration on guidelines, inspections, and pharmacovigilance appeared high on the priority lists.

[Story continues on the next page...]

CLOSING SUMMARY OF 2015 CMC STRATEGY FORUM LATIN AMERICA BY INDUSTRY CONSULTANT NADINE RITTER

At the conclusion of the 2015 CMC Strategy Forum Latin America, industry consultant Nadine Ritter gave the following summary of the four sessions comprising the two-day forum. The opening session of the forum, focused on "regulatory convergence, predictability, transparency and priority reviews in Latin America," included presentations by the regulatory agencies of Brazil (ANVISA), Peru (DIGEMID), Chile (ISP) and Mexico (COFEPRIS). Updates and comments were also provided related to the themes of the session by representatives from the EU and FDA and from Grupo Farma Brasil and the Latin America Federation of the Pharmaceutical Industry (FIFARMA). An extended panel discussion followed. "Technical" sessions were then held focused on three challenging areas in the biotech arena: • the characterization, control and regulation of protein glycosylation • technology transfer, and • cold chain management and product transportation qualification.

General Observations

In the first part of this, I am going to talk about my general observations – what I heard and what I saw from the Latin American regulatory authorities' presentations. And there was actually amazingly a lot of consistency in some of the points.

It is very clear from everyone's presentation that since around 2009 this region has been undergoing **significant regulatory adaptations**, specifically for biotech and biosimilar products. And these are not only changes in technical guidances that are being issued, but also the legal framework for these products in terms of their registration processes.

There has been an amazing amount of work that has gone on in this region just within the last six or so years. You guys have been extremely busy. And many of the initiatives have required updated regulatory guidance documents that separate historical registration pathways of chemicals from biologicals and establish specific processes for biosimilar products – the emerging class of biotech products, which of course are global.

And while we do not have full convergence across all of the regional agencies in this area, **most align closely** with WHO, EMA, and FDA guidance for biosimilars, and ICH guidances on things like the common technical document [CTD] format and the specific ICH guidances, especially the Q5 series for biopharmaceutical products. And so even though there were some regional logistical difficulties, the philosophies and strategies are actually very similar for many of the elements.

We just learned a minute ago in the last session that there were still some significantly different practices in a few elements like shipping. But by and large for the development of these kinds of products, a lot of the CMC elements are very similar.

We did learn that there is increasing involvement with a lot of other agencies in this area – other organizations like **PANDRH** [the Pan American Network for Drug Regulatory Harmonization] and **PAHO** [the Pan American Health Organization]. And you will see that there has been an increase in requests for more involvement with PAHO.

Each of the agencies and many of the audience members really desire to have more permanent interactions at that level. And one of the comments made about the ASEAN [Association of South East Asian Nations] countries is that they became very strong when they began to collaborate on their practices – not necessarily mutual recognition, but certainly in getting a permanent working group together to converge and harmonize for efficiencies.

There will still be some differences. And one of the issues that is most difficult is **interchangeability extrapolation**. But that is not unique to this region – it is a global concern. There is still not harmonization on this globally.

Also **priority reviews** are not necessarily possible logistically in every region and every authority in this area.

And then there are **traceability requirements**, where there are some differences between what the proposals are from WHO and what the requirements are regionally for labeling of products.

A really strong message came from everyone that they wanted to promote **increased interaction** among their agencies to advance their understanding, and even to advance internal training on technical issues specific to biotech and biosimilar products. These are definitely different products. They require different complex systems. And they require different CMC considerations to support their safety and efficacy and stability.

One thing I am going to note here for myself because, as I mentioned, the notes from the slides here will be put up on the CASSS website, and ultimately they will be transcribed into the publication International Pharmaceutical Quality. I have a note here that each of the regulators did a fantastic job, I thought, of putting the detailed links to their websites and specific regulatory guidance documents in their slides.

And so what I am going to do is work with [IPQ Editor-in-Chief Bill Paulson] and make sure that those things are put into the IPQ article, so that we can all have access to them (**links are provided below**). Because one of the hardest things sometimes is knowing that you do not know where to find something. And having these all available at this time and current was really an achievement and we really appreciate that.

Now just a couple of notes: I am not going to summarize anyone's slides. It was mentioned that the individual speaker slides, where permission was granted, are going to be put up on the CASS website. So I am not going to reiterate any of the slides here other than to say a couple of points that stuck out for me.

Key Points from Regulators

One point was from **ANVISA** – this is just something that popped out as being unique: They were not necessarily agreeing with all of the elements of the WHO proposal for naming conventions. In fact, they made the comment that even regions are not harmonized on what to call the things – that they are 'biosimilars,' 'follow-on biologics,' 'similar biological products,' or 'subsequent entry biologics.' So getting down to the level of granularity of an INN [International Nonproprietary Name] is perhaps a bit premature now if we cannot even call them the same things as a class of product.

From **Peru**, they have indicated some major updates in their regulatory approaches for biotech and biosimilar products. And now they have two different registration options for dossiers for a *de novo* product or a similar

bioprocess product. They encourage us to look at their reference documents. They generally reflect the WHO guidance. But they also consider elements of EMA and FDA guidances in there as well.

Chile was indicating that all of their biological products are registered as new products. They do not have the CTD format yet. But they do emphasize the value of a well-organized dossier in their review process. And certainly, having worked many times with other health authority officials, having a well-organized dossier is not to be underestimated. We can debate about the value of CTD document. But the organization of information is important.

Chile also indicated that they are collaborating with other regional health authorities like WHO and PANDRH to be able to further harmonize and converge policies. They indicated that the absence of a permanent CMC working group in this region is hindering progress. They really advocated a permanent working group among the regulatory authorities in this region to advance these issues as quickly as possible.

They emphasized the deficits that occur in training, and that having trained reviewers to be available to look at these complex products is a very important element. So having staff is good. But having trained staff is essential.

Mexico is also working in a very collaborative way with other health authorities like Health Canada, EMA, FDA, the Swiss and Australia – the TGA. They are trying to move toward better predictability via emergency equivalence agreements with these regulatory authorities. So there are a lot of very positive things going on in our sector in this region of the world that we have heard in the last couple of days.

And also in Mexico, priority review is currently limited to disasters and emergencies. But they are working to get that high priority status for high demand products. However, they do have to go through their federal executive, which is a legal process that is out of their control.

Now some of the things that we have heard from the EU, from the **EMA** representative, is that the centralized procedure for a market authorization through a centralized review is necessary for biotech and biosimilar products. The review is actually done by regional representatives, but it is authorized through the EMA.

And there is a new innovative approach – the adaptive licensing model – which is being piloted now. It is in the middle of its pilot process. Initial authorization is given followed by a progressive staggered review approach before final authorization. The details about this are still being worked out. But it involves multiple iterative phases of data gathering of the CMC elements. And that combines with iterative license adaptations according to the stage that you are in.

It means that you will likely provide them with a limited package at the time of first authorization, which will involve a rolling review of CMC data as it comes in. However, CMC could be a gating item if there are deficiencies in data sets that are related to patient safety. So they have to have enough CMC data to at least understand that the material you are making is not going to risk the patient safety in a period between initial approval and full approval.

FDA had a couple of notes from their representatives. They know that most of the US products that they work on are globally produced. Even though their jurisdiction is the US, they are not unaware of the fact that almost

all the sponsors are globally producing the products. And they are in fact heavily involved in global convergence discussions, which I did not realize until Sarah showed it. It goes back to the original FD&C Act about the expectation of working with global regulatory agencies.

But as she said, it is easier said than done, because there are only a certain number of people, and you have stressed resources. You want to get your reviews and inspections done. But the global interactions are valuable activities. And so they do provide for that in their plans.

They just recently signed on with PIC/S for inspections. They have worked forever with ICH and ICDRA [the International Conference of Drug Regulatory Authorities] to be able to exchange information. However, there is no formal mutual recognition agreement yet. In other words, they still have to review their dossiers individually because of jurisdictional requirements. They cannot just sign off on someone else's approval or someone else's inspection. I have to say that probably from my experience the inspection side is a little closer to that, although it is not there yet.

There are expedited review processes in place, but there are no major CMC shortcuts for either breakthrough or biosimilar products. Some orphan products do have flexibility in rolling CMC information, but that is based on the risk to patients and the type of product. But there are no major CMC shortcuts that are allowed, because CMC is what drives decisions on product quality and process control.

Both the **EU and US** said that they have heard from the industry and they have heard from patients, and they really have tried to implement the priority review status or rolling review status to be able to meet the demands of industry and patients. So the policies and procedures are in place that are facilitating this, but they have to have data.

So the good news is that the logistics are present, but the bad news is that you still have to get data. They cannot possibly approve a dossier, even a breakthrough or adaptive dossier, unless they have enough information to convince them that your production capabilities are in control, and that your product is sufficiently characterized, consistent, and stable for the intended use that it is going to be approved for in whatever legislation it is going to go through.

This means there is increased responsibility on the sponsors to understand these expectations and know how to get the right data at the right time to fulfill what the regulatory agencies need to conduct their reviews effectively.

Industry Groups on Post-Approval Changes

We had some notes from presentations by two industry groups that were really quite excellent – Grupo Pharma Brazil and FIFARMA. And some general things that I have pulled up are that they were quite laudable about the progress that has been going on globally for the preapproval requirements for biotech and biosimilar products. However, the next challenge is closing gaps on the **post-approval changes**.

And this is a theme that echoed through that whole session. The good news is that we have a lot more harmonization and understanding of preapproval requirements globally. The bad news is that once we get them approved it goes into a nightmare scenario of multiple iterative changes that are not in parallel.

They are mindful of the fact that there are **legal jurisdictions** that are constraining regional registered products – that you cannot violate the laws – but they still encourage discussion on the mechanisms of at least the convergence of CMC requirements for post-approval changes to be implemented as rapidly as possible worldwide for approved products.

This is not just a **benefit** for industry, obviously. The point remains that it will also minimize the burden on regulators by harmonizing the nature and amount of CMC data that they need to see to support approval of a post-approval change.

This means it will also **streamline the assessment** of those filing packets. If you have some consistency in the data sets that are expected, then like with the CTD for preapproval, you can go through and see what you are expecting to see to efficiently review the post-approval changes.

And something that came out during later discussions – it seems like such a system would also **minimize the burden** on the regional public facilities that are engaged in tech-transfers where global licensed products come in and they undergo changes during the time of the tech-transfer.

So it seems like there is a dual benefit there – that the public facilities that we heard from that are trying to affect these tech transfers would also have a significant benefit from a harmonized post-approval change, in that they can minimize the number of gaps that occur while something that is being tech-transferred in.

FIFARMA had a recommendation to WHO and PAHO to prepare and update guidance documents for this purpose, and harmonize or at least **converge** the data requirements for changes to biotech products. Currently, we have guidance documents on what can be done, but not how to do it globally. I think that the issue is not the technical part. It is, ‘what are the data sets that have to be submitted to the regulatory authorities for their review and approval?’

So we know what we have to do, like comparability protocols. We do not know how to actually get it through regulatory affairs logistics in each region easily. And the goal is to be sure that we can do this most effectively and efficiently.

They even went so far as providing a title for a guidance document just in case there needed to be a little bit more prompting. It would outline the change classification concept, the documentation required for regions for individual changes, and the procedures including timelines for post-approval changes. These are meant to be complementary to the existing technical guidance on what studies you do to do comparability, like analytical studies for process changes. This is one of the logistics of it.

Agency Transparency

In terms of transparency, which is one of the major issues, we saw very common statements.

ANVISA indicated that all of their applicable regulatory statutes and guidances are on their website. Plus they have now made their drug approval and refusal letters available for people to review.

Peru indicated the same thing – that their regulatory statutes and guidances are now on their website.

Chile was the same way, and include commission proceedings and evaluations from their debates and discussions.

Mexico indicated that their statutes and guidances are available.

EMA has had them on the website for a while. And EPARs [European Public Assessment Reports], which are summaries of the approvals, are available on the website. And they indicated that there is a considerable amount of detail available, because those are published in cooperation with sponsors so that any confidential information is negotiated before it is published.

Similarly, **FDA** has all their statutes and guidances published on their website. And they also publish their ‘Summary Basis of Approvals.’ However, those are heavily redacted, so they are generally a little smaller than the EPARs. But they are still quite valuable if you know what you are looking for.

So all of these agencies are using the Internet and using their websites to be able to make these documents available to us, if we can just mine them ourselves.

One little problem that has come up, and this came out in the CMC Forum in **Japan**, is that of course the documents are in their regional languages – they have to be. But to really facilitate global transparency for those who want to use them outside of the region it would be of great benefit be able to have access to **translated copies** of some of these documents.

And when we had the CMC forum in Japan in 2012 – this is an editorial comment that we did not talk about, but I want to put it out here – it was noted then that the Japanese guidance documents and regulations are all available, but they were only available in Japanese, obviously, because those are the people that wrote them and need them.

But a proposal was made at that forum that like the ICH and WHO documents, it would be very nice to have access to these documents in English. Could a regional industry group provide support? Because regulatory bodies cannot do this as they are stretched already.

And in fact that seems to have happened. I just noticed this morning that we have some provisionally translated documents that are available. And you can see the note – it says that the English version is only for reference. If there is a conflict between the original and this one, then the former prevails.

So I would like to just set it out there that maybe something can be done here. It would be nice to have just for an increased transparency of all the regional documents that have been so carefully and dedicatedly written.

Okay, let’s talk about interchangeability, extrapolation, and the naming convention. ANVISA did a very good job of overviewing what is currently the status of interchangeability.

Health Canada does not declare **interchangeability** for biosimilars. EMA has individual countries with different policies. FDA law permits FDA to designate a product as interchangeable. But the decisions do not occur at the FDA level, they occur at the pharmacy level, which is ruled by state laws.

ANVISA indicated that they consider interchangeability if there is sufficient clinical data to support that purpose.

Extrapolation is currently under discussion. There is a working group that is proposing a reflection paper that hopefully has enough information to support scientifically when extrapolation would be allowable.

And the internal rule for **INN** is in conflict right now with what the WHO is doing, and so that is something that they are discussing right now.

International Integration and Cooperation

Now let's go to a couple of questions: What are the **barriers** for development of integration and cooperation among the national regulatory agencies to promote convergence? What are the main hurdles? What are some of the comments that we had?

How can each agency maintain what is best for its own region? If the European Union could do this, so could this region. That was one of the comments that came out of the discussion.

It is recognized that each agency **cannot formally recognize** each other's dossier approvals. But they could review what other agencies approved and what considerations were taken by those agencies. A comment was, 'a mutual acceptance of a dossier, I mean the legal ability to sign off on else's review, is not the same thing as using the converged guidance documents to inform more consistent review outcomes.'

And so I think that the message there for us is that we will certainly, hopefully, get more consistent reviews, more predictable reviews. But I think it is a bit premature to expect legal mutual recognition of registered products based upon one review in one region.

It was noted that even though EU has an EMA review process, it is driven by one member state that takes the lead. And if that lead gets it approved, the other member states agree to follow it. And there is contribution to the lead review from other scientific advisory panels and other entities within the regions.

The US FDA does not have a **formal mechanism** for partnerships and reviewing CMC. There is an office of international programs at FDA that may have some other information available. But that is the preclinical and clinical side, not the CMC side.

FDA noted that they also struggle with staff versus **workload**, and that training is an issue, especially in crosschecking the CMC elements to other sections; that reviewing a BLA is quite complicated; and that the CMC has to tie to other elements.

Some of the **hurdles**: Everybody seemed to be uniform across the board that regulatory authorities need resources, time, training, and communications. And the national regulatory authorities here need more resources. They cannot just implement good ideas without adequately trained reviewers. Even if that training has to be done by videoconferencing, it is better than nothing.

EMA has workshops that have had participation of Latin American health authorities, but they do not have formally shared reviews.

Mexico indicated that they are attending more APEC [the Asia Pacific Economic Cooperation group] meetings as they move towards manufacturing and marketing in Mexico. And Peru is attending meetings on data protection for biotech products and similar biologic products. But there is no agreement yet on how that is going to be done internally.

And Chile is also engaged internationally with APEC and Korean health authorities for imported products that are going into Chile. So you can see that there is an enormous amount of interaction going on internationally from this region and other parts of the world.

In fact, a comment came out of the discussions: With all the industry and regulatory groups working on so many meetings, is it really **convergence or is it divergence?** The comment was made that it is usually the same people taking part in the same topics in the various regions. So it is more harmonized than it would appear. You have a lot of the same subject matter experts – [Finnish regulator Niklas Ekman], [Office of Biotech Products reviewer Sarah Kennett], and those kind of folks – who are perennials in our CMC hall of stars for these discussions. So it is more harmonized by their consistent participation.

In fact, Janet Woodcock of FDA noted that there are numerous parallel organizations working on convergence such that it almost begs some kind of global umbrella steering committee to minimize duplication of efforts.

It was also noted that APEC has sent out surveys to the field on how their guides are being used. And at this point they seem to be used as a checklist by the countries that use them, and not so much on how to improve convergent discussions. That could be an area for improvement.

And FIFARMA had kind of a bold statement: In the Latin America region, there has to be a stronger **political will** behind formal harmonization of the health authorities, like the ones that have occurred in Asia with ASEAN and APEC. And that those two agencies have had a great impact on biopharma development and approval logistics. So it is possible to do here.

The national regulatory authorities said there is not much local production of biopharma products yet. But that is changing with the tech-transfer of manufacturing of products here.

The political will for patient access to new and cost-effective drugs is definitely there. But they must educate the politicians about the need to have good regulatory review. It is not enough to say you are going to have new cost-effective drugs to the patients. The pipeline has to go through regulatory authorization. And maybe there are some folks within the political system that really need to understand that better.

And they need to be made aware of the critical link between their political initiatives for faster entry of products, the need for good regulatory policy, good regulatory practices on review, and approval of post-approval changes, if they really want to get them into the hands of the patients who need them.

We talked about **transparency** and some of the issues that are related to improving transparency and what tools would be available. In the EU it is a collaborative process with the health authorities and the individual

firms on what is published in the EPARs. This could possibly be a model for other regions that want to open their decision-making process to review from other people, with of course protection of confidential information.

APEC has a working group on a guidance for EPAR-like review. I think they are called IPARs. This might lead to the public consultation on a draft soon for international product review summaries.

Also ANVISA is tackling transparency with many different things. They have analysis rankings and abridged versions of **approval letters** that are available to us. And companies do get to see a draft of the summary before it is published to redact any confidential information.

They are also working to reduce what is considered confidential information. But they do expect that firms will resist a bit. Their goal is not to expose a firm, but to share whatever is valuable and what elements factored into the regulatory decision so that everyone can see what that predictability will be like for similar application.

The IPARs that are within the working group now would ideally have a harmonized format and much more common information that could possibly even be copied and pasted for each regional authorization letter. I think the timeframe for that was in the next one or two years. There are no official plans to disseminate this in Latin America. But it might be available for consideration once it becomes available.

ANVISA has launched the CTD format, and has found it very useful. I have another comment later where it is not being used.

Oligosaccharide Analysis for Glycosylated Proteins

Now lets' jump to the state of art of oligosaccharide analysis. We had some really spectacular presentations that gave us a snapshot on the current technology and applications of oligosaccharide analysis for glycosylated proteins.

The take home message is that it is not one technology. It is a **slate of technologies**. In fact, it is a massive slate of technologies that have to be used for complete analysis of carbohydrates, because carbohydrates are very complex structures and there are many biomolecular elements that can be interrogated.

In order to be able to provide an **adequate data set** on characterization of carbohydrates and for glycoproteins, FDA would expect a combination of methods to be used for comparison of two products for biosimilarity. They would expect to see many more features than what we would characterize in a novel product. Why? Because the purpose is to compare the features that are similar or different between the originator product and the biosimilar product.

The originator product is characterizing it for its own molecular entity. The biosimilar is characterizing it for the purpose of claiming comparison. And so it could require a drill down on things that the innovator did not do.

Also it was noted that different **methods for carbohydrate analysis** have different purposes. Methods used for clone selection – which turned out to be an extremely valuable aspect of biosimilar product development –

may be different, and should be different than process optimization methods vs. methods that are used for comparability and similarity. They are all considered carbohydrate analyses. But they have very different intended outcomes in the data sets.

The EU said the same thing. In fact, they said methods usually are not the problem when it comes to comparability, especially in glycan starches. That most companies do a very good job of characterization and assessing similarity of glycans. But the challenge is that when they see differences, what do they mean?

So the good news is they are getting a lot of good data. The bad news is that if they see differences you have to figure out if that has an impact on the safety or efficacy of the product.

The paper that was used, and I do recommend it, was a 2006 paper.

Have there been any updates to that since 2006? And the answer is that, in fact, these are still the tools that we use. The difference is that the paper was academic. And what typically happens in the evolution of analytical methods is they arise in an academic environment and ultimately get adapted into applied biotechnology. And so the tools that are there are still the same. It is the application that has changed since 2006.

What if any limitations exist with these technologies? Well, some technologies are not yet amenable to QC applications. We know that it could take a decade or more for an academic technique to practically move into applied biotechnology, usually from the R&D side of analytics. It could possibly move into a QC environment if it is determined to be robust enough, can be validated, and is demonstrating that it is measuring a product characteristic that is critical for the control of product quality.

But when the method does get into a QC lab, it is expected that it will be validated and maintained in a state of operational control with no excessive number of invalid runs. Anecdotally in the break – this was not a public conversation – we were noting that in some QC laboratories it is kind of a rule of thumb that you should have less than 10% invalids for your validated methods. Whether that holds true or not across the globe has yet to be seen.

What high throughput methods are there for carbohydrate analysis? There are a few that can be reasonably high throughput, but noted was that oftentimes in those cases it is the sample prep that is the gating item. Once you get the sample prepared and the extraction performed, loading it up on the auto sampler is not the problem. It is the sample prep that is usually the slow part of those kinds analyses, especially those that use auto samplers.

But in any event, it is not going to be high throughput if it keeps breaking down. You have to have good method development and optimization, including sample prep steps, that make the method more vs. less cumbersome to execute routinely. And so it is not inherent to the technology, it is inherent to the procedure that is utilizing the technology.

What strategies are used to define the criticality of glycosylation? EMA indicated that they expect comprehensive assessment in cell culture models based on the understanding of the mechanism of action for each type of product.

Efficacy is not the only parameter to consider. You need to look at things like PK and immunogenicity that could be different if different glycans are present. It is easier to assess the criticality of efficacy than it is other of these things because they require animal systems or complex testing systems that are not just the *in vitro* potency assay.

How do you correlate no clinically meaningful differences in glycosylations and *in vitro* assays based only on real world reports? Part of that requires good pharmacovigilance reporting in all regions. The only way you can really do this is with head-to-head trials of products. So when looking at historical or literature reports of post-marketing surveillance pharmacovigilance, you can only infer that there is no impact of glycosylation or bioassay differences when there are no adverse events reported between, say, a biosimilar and an innovator product.

It was critical in terms of when to start doing **glycosylation analysis of a reference licensed drug**. Comments that were made there were that you really want to do a pretty thorough characterization of the target reference license drug first, and then use that information to select the clone that you are going to use that matches the glycan range of the target product as well as possible.

It is much more challenging to select the clone and discover that it is not in the same glycan range, because you can only do minimal things to try to fix it. And so there is a drive for more biosimilar companies to do a lot of assessment up front in clone selection, especially for glycan patterns.

In fact, FDA commented that they have seen problems when the wrong clone is picked. Even a 2% change in fucosylation can lead to large differences *in vivo* that can affect the approvability of the biosimilar candidate. And also mentioning immunogenicity and PK, that sponsors do tend to forget when they talk about critical quality attributes, it is not just critical quality to efficacy, it is critical quality to everything it is doing someone's body.

A question about different expression systems, specifically NSO-zero to CHO between an originator and biosimilar product: The agencies indicated that this could be risky depending upon the kind of product being reproduced. So it is important to understand what the differences are in glycosylation based upon the biology of the system to determine if you are going to be able to mitigate those risks some other way.

What should be considered in designing a control strategy for glycosylation? Look at the critical quality attributes for all of the elements that they consider. And recognize that it is not just end product testing that is a part of this, it is a total control strategy, which is a concept that has been in the industry for a quite a while for biotech products.

How do we use sophisticated methods, like mass spec, for emerging markets and import testing?

Well, compared to the rest of the technologies needed it is complex, but it is transferable. It is just an instrument. You push the button and prepare some samples. It does require good training of analysts and well-validated methods.

You have to get good vendor support on instruments for the user laboratories. And there were a couple of meetings that were brought up where you tend to have a good interface with vendors who are providing these

instruments. And we can talk to them about things like invalid rates and method suitability for its intended use in its operating environment.

One thing that was noted: However you get there, it is expected that methods to be used under GMP will be validated to be robust in the lab operation environment. So that is a quality requirement. And there are many different ways you can get there.

What happens to interchangeability if a post-approval change causes changes in the glycan structure? The European agency indicated that their principle is that once a similar biologic product is authorized, it is now its own stand-alone product with no tie to the originator. So if one or the other changes, it is managed through a post-approval change comparability study for each product. So they are not necessarily linked hand-to-hand once they have been approved.

How would you notice if there was an adverse event reported in pharmacovigilance? How would you know if they were related among products unless someone drills down into the lot-by-lot assignment of what product batches have been attributed to the adverse events?

And the notation there was that the traceability of batches requiring lot numbers and sources would be a way that you could get those signals out of the data set. And the European agency indicated that Eprex is one of those cases where the signals were detected based on tracking specific lot numbers of the product. So this kind of puts pressure on the INN question: How do you know what the product is? And what is the lot number it came from to be able to do this pharmacovigilance that we need?

One question that came out was based upon a case study that was shown where the sponsor drilled way down into dissecting **assay performance differences between the similar and the reference product**. And when they found differences, they had to go back and make the assay less sensitive to determine what the functional differences were.

And the answer that we got from the regulatory bodies is that it is a challenging question, because you really do need to look at the totality of data and how it relates to the mechanism of action. And the sponsor indicated that they actually were asked by the regulatory body to add additional bioassay data and then to dissect the differences, and then later had to figure out the strategies about why those differences did not matter.

What FDA indicated, and what we were talking about, is that you do look for the most sensitive methods to see what the differences are. You cannot assess the differences unless you can see them. Then when you see them you determine how to do a risk assessment and determine what effect it could possibly have on product safety and efficacy.

It is the same question during post-approval changes for comparability for one product in the same company or between products. And you have to judge the impact of the differences or no impact of the differences on the clinical indication. So it is a body of data that goes out into great granularity, but then also has some less sensitive techniques to assess what the meaning is of some of these differences.

Biotech Product Tech Transfers

Then we went to tech transfer of biotech products. Some of my observations from those discussions were that:

- Regional public agencies have extensive experiences in biological products like vaccines and serums.
- In this region, there is a significant growth of the transfer of biotech products from local production of these complex protein products.
- Tech transfers that are occurring right now from private entities to public entities here require detailed discussions of all elements of the transfer activities including those for quality systems and quality agreements.

We had a lot of discussions about roles, responsibilities, liabilities, and lengths of time that these occur under quality agreements that were quite informative. The take home message, and this is from the public laboratory presentations and the industry presentations, is that it is highly critical to design and execute a comprehensive, systematic plan for generating the appropriate data to assess the material being produced at the recipient site against its intended characteristics to know whether or not that recipient entity is going to be able to make the materials it is supposed to make.

There were great case studies that were presented that can show what can go right and wrong in tech transfer projects, with specific points to consider. I do recommend that you look at the slides for all of these because they were far more detailed than I can summarize here. But here are a couple that caught my eye:

- **Operational disconnects:** This was actually from the public entity – that there were disconnects in testing capabilities. In one case the bioassay did not perform the same, the *in vivo* assay, because the animal food lacked iron, and the animals had different responses. In another case they had a mass spectrometer that was setup with the tech transfer partner. The brands were the same, but the models were different. So they had to negotiate how to manage those differences in that technology, which might not have been as subtle as you might expect, just because the models were different.

- At the analytical level, Mary was talking about the use of **stress stability studies** to reveal possible differences in pre- vs. post-transfer materials. She presented some very interesting case studies – three different case studies – where the two-stage statistical model that they had developed was extremely objective and highly sensitive to hidden differences, which saved them a lot of time – and I have to believe a lot of money – in chasing products that needed to have some remediation before they were ready to go.

- And then even culturally: [Biologics Consulting Group Senior Consultant Christina Vessely] pointed out some **cultural differences** that can affect successful transfer of technologies, including language. And I got it down, ‘Do not use Google Translate for SOP’s.’ I got it Chris. I will not do that.

And even when the tech transfer does occur smoothly and everything does finally get established in the recipient location, you have **change management**. And this was a part of the post-approval change discussion that we had. This is a major challenge for tech transfer of products into regional facilities, because the staggered global approval process can generate the need to run parallel products in the facility.

So they are really strongly pushing back not to tech transfer things until all the changes are approved globally, because they will get stuck in the middle where changes are in various places around the world. And actually

even sponsors deal with this all of the time in their own facilities. They have to run parallel processes sometimes until all the approvals are globally concluded.

What are the most time-consuming and costly aspects? We had two perspectives:

- From regional entities perspective, it was the cost of investment in **infrastructure** at the site. And we discussed what capital input and financial aid they can get from the sponsor vs. the government sector. Add to that the cost of the drug substance for the tech transfer.

Also they have issues regionally with the timing being less predictable, because they have a requirement from the government sector on the delivery of services and material. And any delay they have gets magnified. This happens in the private sector as well. It is just that we can usually yell louder and throw more resources to make it go away.

Anytime there is a lag in infrastructure it is going to have problems and have a domino effect on project timelines. That is definitely true. And they indicated towards the end of our discussions that even something as simple as getting enough drug substance by continuous harvesting can be a challenge to timelines and to costs.

- From the sponsor side, some of the costs were noted. The cost of the **drug product transfer**, which requires a lot of bulk API, can be very expensive. So they try to use surrogate materials in order to validate production processes, [such as] form/fill processes for drug product. Having to make that much API – not only does it cost a lot just for the API itself, but it takes production time away from API that you could be using to supply markets that are looking for the product.

Another comment was that tech transfer failures are extremely costly. Consecutive batches must pass or it would jeopardize the claim for success in tech transfer. And that is why there is so much attention paid to the design of the comparison study. The comparison can fail comparability – not because the products are different, but because the methods were not used appropriately or the data were not structured correctly for the analysis.

Analytical Considerations

How can sponsors and partners balance cutting edge technologies in emerging countries and markets?

One comment was made that the **instrument choices** should factor in what the unusual lag is going to be. Does it have to be the cutting edge technology because of the sensitivity of the measurement that is being made? Or are there standard techniques that are still just as suitable for use without the most high-end piece of equipment that you can get?

There are challenges in **old vs. new equipment** in QC. It is not that they are not compliant. Old equipment, simple equipment, can very much be compliant to GMP. But when it comes to being able to get the information for the product quality, they may not be sufficiently sensitive or specific.

One approach was that when you build a new lab, that is a good time to get new instruments. And you can bridge between technologies. It was indicated from the industry side that often they add new technologies

when they license a new product and then slowly retrofit that into legacy products by bridging to the old methods once they get experience in what that new technology is doing for them. If it is an advantage, then they will bridge it back to their existing legacy products.

In one of the product development **partnership agreements** it was noted that there are annexes specifically in terms of putting together a matrix based on each technology needed. They have these discussions with the private partners so that resources are available to be able to make sure they can accomplish the testing that they are supposed to accomplish by having the instruments they need for the project.

What are some of the practices in deciding whether to engage with multiple or single partners for manufacturing?

The cons were: • Multiple costs: Costs are increased because multiple sites increase cost. • You have to manage multiple streams of work. • There is the potential for divergent practices, and • Stability studies are a big cost for tech transfers, especially for those required for validating shipping stability, with large regional differences and requirements.

But there are some pros, and some of those are: • being able to improve supply chain robustness • being able to have access to things if you have an issue, and • it is more risky to be limited to a sole site or sole provider, especially when you have the potential for environmental disasters like wildfires, floods, and earthquakes. So there are some very practical reasons to want to have multiple sites in your product stream.

One of the questions from the audience was: What does FDA and EMA see in terms of reviewing post-approval changes and tech transfers in dossiers?

EMA said there was not a specific problem. All of them are possibly problematic depending upon the product and the sites. But they do not see much problem with stability data. It really depends on the data sets, the product, etc.

Most problems that they do see are actually in the comparability data sets when they get results that are not comparable. And then sponsors have to find out how to justify that the differences are acceptable.

FDA said that the biggest problem they see is that there is **not enough data** oftentimes to support the change or tech transfer that is being conducted. Of course the agencies indicated that they do not see what did not work. We tend to keep those under wraps. And we do not tend to share with the agencies all the things that we found that were problems and that we fixed. We only tend to submit to them what worked.

But even still, they see deficiencies in data sets, particularly in not directly correlating the changes that you are making, and then the studies that you are designing to assess those changes. Make sure that you are measuring the right parameters to cover the nature of the changes.

One of the things that is a mantra out there in biotechnology is that the further upstream in a process a change is made, everything downstream is subject to comparison. And if you do a tech transfer, that is considered the ultimate upstream. Everything is transferred. And so the nature of those comparability studies is not as simple

as just saying the release test for the drug substance are adequate. It is changing everything in terms of that process. We had some good examples from industry about what they did to assess those things.

What are the pros and cons of staging and testing stability samples at satellite sites? It is always risky for a lot of reasons. It is not just stability samples, it is release testing as well.

Small differences in analytical methods can generate different results. We had examples of integration differences, and that is a subtle one. LIMS systems and stability protocol computer systems may not talk to each other between the sites. And you may not be able to get all the raw data you needed from the site to ensure that the results are accurate.

This is my own note. I did not add it in discussion, but I will add it here. This is specifically for stability. There could be different local practices on how they hold samples after they come from ICH conditions. In other words, in some labs it is their practices to always freeze everything when they get it from a stability station. Well, is that okay or not okay?

Or they hold it at 5°C. Well, that is fine. But it was frozen when it was stored. Or do they hold it at the ICH temperature in their laboratory? There is no guidance on how to do that. It is a matter of what the lab will do. But when you have two different laboratories doing it, that is a source of disconnect that can occur very easily.

Different ranges in the temperature of the stability chambers could impart different rates of degradation. Amgen had an example that was quite intriguing. It was a slight change in temperature that affected the stability rate.

Another note was that the sample containers used for drug substance stability studies between the two sites can be slightly different. The drug substance is often sub-aliquoted into smaller versions of the container closure, and those have to be matched as much as possible to the bulk container. And there are some subtle differences in those that can be different.

Shipping Considerations and Cold Chain Management

Then the **shipping stability** came into its own in the next session. There were just a lot of issues. And the comment here was about shipping test samples. The shipping excursions that we were talking about in this section were all about shipping materials that were to be used for product. But even shipping test samples from one location to another is not a trivial issue, because you want to be sure that the results you get out the test sample is accurate for product quality, not based upon some excursion that that sample had that does not reflect the overall batch.

It was even noted that it is not a matter of two different entities – a single entity can have two different physical locations. So if you call it one site, it is a site, but they can be forty kilometers apart. And there is still shipping that has to occur of the test articles between those two locations before they get the results for the stability pull point.

The last section that we had was on **cold chain management**. These are my seat of the pants observations from that.

We had excellent highly detailed presentations on specific strategy studies and international vs. regional regulatory requirements, including a discussion of a major new guidance from Brazil and an annex from Chile, and the discussions that are necessary.

I would strongly refer you to the speaker slides that are going to be available on the CASSS website, because they had some really terrific detailed information about the designs of these studies.

It was recommended that you follow **good distribution practices**. It was also noted that there are several good PDA technical reports on shipping studies. Also discussed was the ANVISA guidance that clarified the expectations for Brazil. And I will note that [Bernardo Moreira's] presentation had thirty individual references associated with it for your information (*see below*). So you cannot say after this presentation that you did not know what was going to be expected.

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There are still some **regional differences** that are currently experienced by global companies – for example, the type and nature of the product stress stability studies throughout shelf life for all possible environmental scenarios including pharmacy and patient handling conditions. All possible real-world conditions must be factored into one study design.

And you have to be concerned about **terminology** – warm does not mean microwave. There are also requirements to validate all aspects of shipping conditions for both the packaging and the product, agitation, dropping, heat, light, water, and all seasonal variations in both hemispheres. This was reiterated several times in the presentations.

And although there are mechanical engineering standards for typical shipping test conditions, **human factor studies**, and even though it was mentioned in the question and answer portion, **user surveys**, are increasingly important for anticipating what should be tested in those studies. And the comment there was that it was just a continuous improvement element that you deal with from practical field experience. You just say, ‘I did not know you could do that. I guess we have to plan for that next time.’

And **excursions** have varying regulatory feedback. It is undoubtable that the impact on a protein product can be far more significant for excursions than on a chemical drug. So it is a very high-risk event for protein therapeutic products.

Some agencies even expect **anticipatory data**, including the robustness of shipping conditions to the hold temperature range that has been stated. Or whether or not there is support of stability brackets at the beginning of shelf life, at the end of shelf life, etc.

What are the main challenges? Planning all possible scenarios in advance. As was mentioned, use existing guidance documents and tech reports, but improvise as needed to support your own chain of custody and user practices. And remain vigilant to field reports about what is being done with your product.

Another challenge is navigating and coordinating all the regional variations required for **importation** of products. Geographical issues are very relevant to each regional agency, as are the data packages that are required for them to review to get your products into their sites.

Can multiple factors be combined into assessing shipping conditions and excursions?

And the answer was 'possibly,' if in the end the data can prove that the product will be stable throughout all of the shipping and handling conditions that it can experience throughout all of its shelf life. So the burden of proof is on the manufacturer to be able to get data sets that are meaningful enough to be able to make that assessment.

And [Amgen Contract and Product Quality VP Tony Mire-Sluis] mentioned that Amgen uses chamber robots where they can actually build in DOE studies with factorial designs and hundreds of replications with slight variances that can at least look at some physical conditions that they can model there.

So it might be possible in some regions. But there are still substantial gaps in the data sets required for shipping validation studies.

And then the last one that I have – this is an intriguing one, and I have a personal note for it too – **How much can the shipping conditions vary from the ICH stability conditions that have been established?**

These are the harmonized conditions around the world for stability data, right? So shouldn't they exactly match what we do for shipping? And the answer is that they actually do not. It depends upon the degree of excursion. Time and temperature is a factor for what impacts a protein product. And there is no harmonized approach across the agencies of how much difference there can be from these carefully controlled ICH conditions and the stated label conditions.

I have a footnote here to tell you that I inspected a laboratory in Japan where their control room storage temperature of the reagents had a sticker that said from zero to 30° C. Because the JP says room temperature is zero to 30° C. It may have changed. That was three years ago.

The concept was hopefully that these things would get reconciled eventually. But even the USP has it at 15° to 30°. There is not a relationship between what is label claim allowed by the pharmacopeias and what ICH has harmonized so carefully for stability data.

LINKS:

Brazil (ANVISA)

- [Comparability exercise, heparin, and interferon alpha guidelines; guideline for elaboration of clinical study reports](#)

Peru (DIGEMID)

- [Legal and technical development of biological products in Peru](#)

- [Registration of chemical and biological products](#)
- [Regulation of biological products](#)
- [Review of similar biological products](#)
- [Review of biotech products](#)

Chile (ISP)

- [ISP commission meeting proceedings](#)

Europe (EMA)

- [Adaptive licensing](#)
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