

Asian Agencies Report on Progress in Addressing Emerging Regulatory Challenges at CASSS Biotech CMC Strategy Forum in Japan

Asian medicines agencies are joining those in the US and Europe in seeking to address the emerging regulatory challenges posed by: • new classes of products such as cell-based regenerative medicines and engineered antibodies • accelerated approval pathways • biosimilars • international convergence, and • validation lifecycle management.

Regulators from Asia provided insights on their agencies' strategies for dealing with these pressing issues and the progress they have made to date at the CMC Strategy Forum Japan, held in Tokyo in December 2014.

Sponsored by CASSS with the support of Japan's Pharmaceuticals and Medical Devices Agency (PMDA) as well as the Japan Pharmaceutical Manufacturers Association (JPMA) and the U.S. FDA, the forum provided the opportunity for regulator and industry experts from Asia to compare notes with those from the US and Europe on where viable solutions and harmonization pathways lie and the hurdles that have to be crossed to achieve them.

In their presentations, the various regulators discussed how their staffing, product classification and review processes are changing to deal with the new challenges, and the coordination, integration and streamlining efforts that are being pursued.

They also highlighted the regional and global organizations that they and their agencies are involved with, and the impact the organization working groups are having on their ability to handle the new review and inspection demands.

In a summary of the discussions at the two-day forum presented at its conclusion, industry consultant Nadine Ritter pointed out that "all speakers were acutely aware" of the increased filing and inspection workload and decreasing review timelines, which are "putting massive pressure on CMC reviews." [Ritter's full summary is included below.]

All of the agencies, she noted, reported that they are looking at: • staff expansion • assignment flexibility • streamlining and simplifying their internal reviews and inspections, and • coordinating and integrating reviews and inspections to reduce redundancies and maximize their efficiency.

A universal theme was the need to work with other global health authorities and industry groups to find ways to "increase communications, share experiences, align philosophies, harmonize policies and leverage information." On the other hand, the regulators also emphasized that industry needs to be aware of the legal constraints the agencies operate under in pursuing the convergence efforts.

The new classes of products are "requiring an adaptation of our traditional well-characterized models – balanced with the risks and benefits of patient safety and product availability," Ritter summarized.

She highlighted a key point made in one of the presentations that "regulators are the spokespersons for the patient population, and the need for the data that they have to have" to perform that role must be respected by industry accordingly.

At risk for industry, Ritter stressed, is the large negative impact of a prominent product failure "We have a lot of quiet successes in biotech," the industry consultant commented. "We have done amazing things in the last

30 years that the public really does not appreciate so much. But it only takes one loud product failure – one really spectacular patient population to be hurt – and it can bring parts of our business to a crashing halt.”

Cell-based Product Regulation Follows Biologics Models

The diversity of the number and types of cell-based regenerative medicine products makes addressing them as a product class difficult.

There was general agreement in the discussion at the forum among the US, European, and Asian industry and regulatory participants that while aspects of these products have to be dealt with on an individual basis, there are some common principles that can be extended from other complex biological products.

Because the cell-based products are heterogeneous mixtures like antibodies, the degree and control of that heterogeneity is important and needs to be demonstrated using appropriate analytical tools. Product characterization and control strategies that ensure the defined target product profile is met consistently for each batch of these complex and frequently very labile biological materials are also critical.

In discussing risk to the patient, participants asserted that risk mitigation plans should be in place for each product and its intended use, including: ● the traceability of the source material ● the chain of custody of the process material, with an emphasis on where it was made and the patient that gets it, and ● long-term safety follow-up for post-market surveillance. *[Editor’s Note: the current advanced therapy regulatory landscape in the US, Europe, and Asia and related harmonization efforts will be reviewed in an upcoming IPQ story.]*

Engineered Antibodies Use Conventional CMC Strategies

A new class of antibodies – for example, those that have been engineered to contain modified glycosylation patterns resulting in reduced levels of antibody-dependent cell-mediated cytotoxicity (ADCC) – requires sophisticated manufacturing technologies, but can successfully use conventional CMC strategies, workshop participants agreed.

The general consensus was that structure/function relationships of these antibodies can, for the most part, be characterized using tools similar to those used for conventional antibodies. For the stability-indicating methods, it is important to demonstrate that the method is capable of detecting structural differences as well as functional changes.

At the workshop, Roche Diagnostics’ Elisabeth Kirchisner gave a presentation on GAZYVA (obinutuzumab), the first approved glycoengineered antibody, which is used for treating chronic lymphocytic leukemia, non-Hodgkin’s lymphoma, and diffuse large B-cell lymphoma.

Kirchisner explained that “a full quality-by-design (QbD) approach was used for technical development of obinutuzumab,” which was granted both orphan drug and breakthrough status in the US, and approved by FDA in late 2013. Approval in the EU followed in 2014.

The manufacturing technology is based on the co-expression of the antibody with glycosylation-modifying enzymes during cell culture, which leads to a modified glycosylation pattern with reduced levels of core-fucosylation. The increased level of afucosylation results in an increase in ADCC.

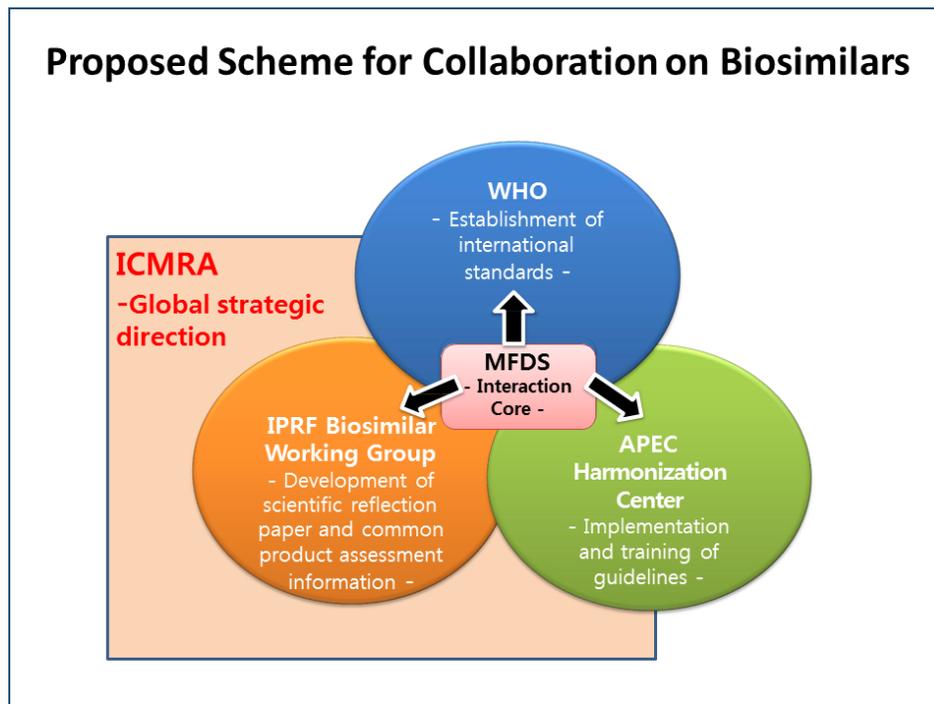
Biosimilar Regulations Progressing in Asia

A discussion of the status of biosimilar regulations in Asian countries revealed that while there has been some harmonization of the CMC requirements in the Common Technical Document (CTD) Module 3, agency policies on the use of non-national clinical trial data and reference drugs are highly diverse.

In addition, the types and amounts of analytical comparison required with the reference drug also varies, but in some cases can be overcome by the use of three-way bridging studies comparing analytical and/or clinical data with that of the reference drug.

Jeewon Joung, representing Korea's Ministry of Food and Drug Safety (MFDS), explained that while some Asian countries, such as Malaysia, have used the EU biosimilar guidelines as models, the Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC) has settled on the WHO biosimilar guidelines as its model for regulatory convergence in the APEC countries.

APEC is proposing that the convergence effort take place under the auspices of the International Coalition of Medicines Regulatory Authorities (ICMRA), a body sanctioned by WHO in 2013 (*see box below for the depiction presented by Joung*).



Serving a central role in the effort will be the International Pharmaceutical Regulators Forum (IPRF), which grew out of ICH, and Korea's MFDS.

The effort, Joung said, is intended to “aim for efficient and timely global development and access to biotherapeutics, including biosimilars.”

Also presenting at the session, Malaysia Ministry of Health Head Of Biotech Product Registration Arpah Abas discussed the issues her agency has been seeing that have caused non-approvals of biosimilar applications.

Application deficiencies her agency has seen include: • insufficient data on process • insufficient characterization of product • inadequate specifications • deficient strategy for analytics • no justification for the choice of the reference product • poorly designed technical studies • inadequate immunogenicity assessment, and • prescribing and product labeling problems.

In her summary of the forum discussions, Ritter commented that the deficiencies cited by Abas comprised “a laundry list that is probably something you would see similarly in other regulatory bodies as well.” *[Editor's*

Note: Ritter's summary is provided in full below.]

During the discussion period at the biosimilars session, a question was raised regarding whether current regulatory frameworks would allow approval of biosimilar vaccines.

Japan's PMDA responded that it would be dealt with on a case-by-case basis. EU and FDA regulators concurred that a biosimilar vaccine approval would be covered by their current regulations. However, under the Malaysian system, vaccines are not covered.

The Korean and Taiwan regulators commented that their agencies would consider a biosimilar vaccine if the product was well-characterized and therapeutic rather than prophylactic.

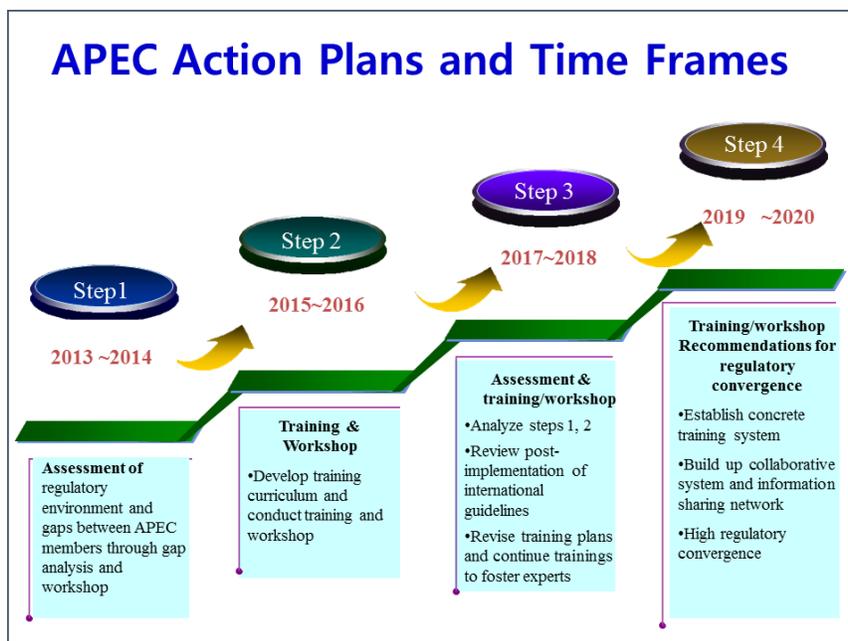
APEC Leads Asian Regulatory Convergence

There was general agreement at the workshop on the benefits of convergence of regulatory filing requirements across regions and agencies for both industry and regulators. Asian agency involvement with international harmonization and coordination efforts was a focal point at the conference.

It was noted in the discussions how challenging it has been to produce and get agreement on centralized procedures across the EU member states and the greater difficulty of achieving mutual recognition across Asian countries, which have unique jurisdictional requirements and are not linked legally in the way the countries in the EU are.

The most prominent and broadest-based efforts on regulatory harmonization and convergence of biotherapeutic regulations taking place across Asia are being spearheaded by APEC. [Editor's Note: More will be provided on APEC's current efforts in an upcoming IPQ story on regulatory convergence. See also [IPQ June 10, 2013](#). For a review of APEC's work on global supply chains, see [IPQ July 27, 2014](#).]

Joung emphasized that the APEC "Biotherapeutic Products Roadmap" has a goal of "reaching a high level of regulatory convergence by 2020" for recombinant DNA products, monoclonal antibodies, and therapeutic vaccines (*see box below*). Joung explained that vaccines, blood products and cell/gene therapy products are not within scope.



A survey was conducted by APEC in mid-2014 to understand the gaps and opportunities for regulatory convergence, in which ten of the 21 APEC economies responded. The results showed that nine of the ten respondents have already either partially or fully implemented the ICH guidelines.

However, Joung said, the “regulatory gap between harmonized and non-harmonized countries may be wide,” and “prioritization of what is needed for non-harmonized countries should be discussed.”

Initial areas identified in 2014 for convergence include post-approval changes and acceptance of foreign clinical data. “Training may be required on these topics for non-harmonized countries,” Joung pointed out.

In her summary of the regulatory harmonization discussion, Ritter commented on the important role that ICH Q12 on product lifecycle will play ([IPO December 26, 2014](#)).

ICH Q12 “is going to include things on review and inspections, which is that integrated approach that we were talking about. This is good because we want to drive better global harmonization and the better use of comparability protocols for post-market changes.”

Validation Terminology Needs Harmonizing

Dominating the discussion on validation lifecycle management at the CASSS workshop were concerns regarding the differences in terminology used in different regions and the impact that misunderstandings and translation errors can cause.

In her summary of the discussion, Ritter commented on the importance of understanding the various terms, such as validation, verification, continued versus continuous validation, and evaluation.

“This is not a trivial thing,” she stressed, “because it materially affects how much data you collect, when you collect it, what reviewers are expecting to see, and how they are interpreting what you are claiming by the set of data that you are generating for them. That is even complicated by the fact that we have different languages that have different translation subtleties associated with them.”

Ritter pointed to the assertion during the workshop by Germany Federal Institute for Drugs and Medical Devices (BfArM) Biotech and Biologics Inspections Head Brigitte Brake that harmonizing the terminology in this area would be valuable to both industry and regulators. “The use of common language,” Brake maintained, “will facilitate acceptability of the PV data package in different regions of the world.”

Ritter also commented that “we really should be harmonizing this terminology and making it a lot more clear so that for this extraordinarily expensive and labor intensive activity, we know exactly what regulators need to see and when they need to see it, so that we can be sure we generate the set of data that is expected.” *[Editor’s Note: For a discussion of the similarities and differences regarding process validation terminology in US and EU guidances, see [IPO May 31, 2012](#).]*

CPV Case Study Highlighted

Also presented at the workshop was a case study developed by the BioPhorum Operations Group (BPOG), whose membership includes 20 major biotech companies, on general approaches to implementing continuous process verification (CPV). The case study provides specific recommendations on the content of a CPV protocol and the associated rationale (*a link to the case study is provided below*).

The cross-company effort was compiled in response to the FDA’s 2011 process validation guidance, explained Pfizer Global CMC Biologics and Devices Research Fellow Stefanie Pluschkell, presenting on behalf of the

BPOG's CPV team.

BPOG was formed in 2008 and consists primarily of experts from biopharmaceutical drug substance operations, who meet and work together at face-to-face meetings in the US and Europe, and in regular teleconferences via web meetings. The group, Pluschkell said, "has established best practice on a wide variety of quality, engineering, and organizational topics considered central to the challenge of mastering effective biotech drug substance operations."

The purpose of the CPV case study, she noted, is to: • provide a new business process for the industry • leverage collective experience and expertise • include realistic examples in a case study format, and • provide groundwork for further useful discussion on implementation.

There are "very few" articles written by actual practitioners, Pluschkell asserted, and "most of the literature covers only some aspects of the topic."

Included is a "comprehensive industry example," which was based on the CMC Biotech Working Group 2009 A-MAb case study to leverage the industry work and familiarity with A-MAb. She noted, however, that the CPV case study does not include concepts associated with design space implementation, as in A-MAb.

LINK:

[BioPhorum CPV Case Study](#)

SUMMARY OF DECEMBER BIOTECH CMC STRATEGY FORUM JAPAN

The following is a summary of the presentations and discussions at the December biotech CMC Strategy Forum in Tokyo, provided by Global Biotech Experts' Nadine Ritter at the conclusion of the forum. The sessions at the two-day forum, which included presentations by industry and regulator experts from Asia, North America and Europe, and panel discussions, addressed: • recent trends in the regulation of biopharmaceutical products and practices • breakthrough products and accelerated approval • biosimilars • international regulatory convergence • cell-based products for regenerative medicines, • antibody engineering, and • the process validation lifecycle.

We heard from nine global regulatory authorities [Japan, U.S., Finland, Malaysia, Korea, Taiwan, Portugal, and Germany, with Health Canada not presenting but contributing to the discussions]. It was a fantastic representation certainly of the Asian countries and then some very notable representatives from some European and Western countries that have been leaders in some of the thoughts on biotech product regulation over the years and will be going into the future.

We had a very good set of case studies that were provided to us by industry on cell therapies, cell-based products, and a variety of antibody products. I am not going to summarize those because of time. But I will pull out some salient points that came out in the discussions. The same thing is true for the research projects that we saw that came from some fantastic laboratories. I will summarize only the pieces that are related to the discussions.

A great deal of discussion was held on the industry perspectives that were contributed by the speakers and the panel members. Those points and discussions will show up in the answers to the questions that were posed both ahead of the forum and during the discussions.

Recent Trends in Biopharmaceutical Product Regulation

These are the highest of the high points from the regulatory bodies that I captured. I grouped the first set under individual regulatory agencies.

Japan's PMDA

Japan's PMDA plans to significantly increase its staff size in the next few years.

It strongly supports the QbD initiatives that are going on. They were a pilot program observer.

The agency launched a "forerunner" package priority review known as 'Sakigake' and a rapid authorization program for off-label unapproved drugs that have an unmet medical need.

Also new is a regenerative medicine program that has arisen under the revised Pharmaceutical Affairs Law – PAL – and the pharmaceutical medical device act.

An update was provided on its science board considerations that affect the topics that we have been dealing with for biotech and biologic products.

PMDA has recently revised its process validation standards to be more in alignment with ICH and PIC/S and product lifecycle strategies, although there are still some points that are being assessed. We heard that Japan's perspectives on process validation are highly risk-driven for what they are going to decide to do. PMDA is now a member of PIC/S. We will talk about the global harmonization efforts – that was a major topic.

US FDA – CDER Office of Biotechnology Products (OBP)

One of the big things for those of us on that side of the pond is the reorganization of CDER that will better align the research, review, and inspection activities under one Office of Pharmaceutical Quality (OPQ). It actually is not a new approach for biotech products to have an integrated review and inspection system. They currently have a document internally – a MAPP – that describes the split of those activities within the discussion of the dossier.

OBP remains intact, but it will go from having two divisions – monoclonal antibodies and all of the therapeutic products – to four divisions that will allow them more flexibility in assigning resources.

The agency did define a sponsor meeting plan for biosimilar programs that matches to what we have for conventional product end-of-phase-two meeting, pre-IND meetings, etc. They outlined statistical discussions that they have had for assessing analytical similarity, and promised that the guideline on interchangeability might be due sometime in 2015.

Finland/EMA

The Finnish regulator – as did many others – wore multiple hats during his presentation. In addition to representing FIMEA, [Niklas Ekman] also represented some things from EMA and the Biologics Working Party [BWP].

The big news for us, I think, is that there is going to be a single clinical trial assessment pathway and that we will be utilizing an **EMA portal**, which he gave us a great deal of information about. Some of it was a bit scary – like if the portal crashes, you are suddenly approved....

It is a two-part assessment, but it has incredibly aggressive timelines. I had to look twice at the timeline to make sure it was saying 'days' instead of 'weeks.' I do not know how they are going to do it. Although with biotech products you can petition for a 50-day extension, and I suspect everyone will, with that kind of aggressiveness.

There is a tremendous emphasis on increasing the public **transparency** of the systems, including information regarding the experts who are involved in the assessments, the clinical trial programs, and the market authorization decision details, to try to improve information that goes to the agencies.

FIMEA has **adaptive licensing** for clinical plans. The CMC seems mostly the same, although the clinical side of it is more affected.

I was interested in the ‘valley of death’ concept for novice sponsors and the ‘baby medicines welfare clinic.’ That does not sound like what you think it means. It sounds like something that would involve pacifiers and bottles. But it is to provide regulatory support to companies that otherwise would crash and burn – that need some additional assistance to make better decisions.

Malaysia

They gave us a very spirited discussion on their activities, and also gave us a very good overview of the **ASEAN** [Association of Southeast Asian Nations] activities.

The CMC review of vaccine therapeutics and regenerative medicine products are all conducted by one group.

It has a **biosimilar guidance** that came out in 2008. It was emphasized that it has a very strong CMC package requirement and strong risk management plans with a lot of post-market surveillance. It was emphasized that they do not allow any quality shortcuts that could possibly compromise patient safety.

There is a big concern over safety risks of what are called ‘**bio-copies.**’ There was a paper that came out not long ago on the risk of some of those bio-copies to patient health. That is not a trivial concern as you will see later – what that can do to public opinion about these products.

Sponsors are allowed to choose the **reference product** for biosimilar products so long as it has a complete dossier and there is a sufficient duration/scope of commercial use of that reference product.

For **cell and tissue products**, there are tiered levels of review for high vs. low-risk product types.

Right now, **gene therapy products** are only getting licensed in Malaysia if they have been previously approved by a benchmark agency like US FDA, EMA, or Health Canada.

Korea

I am not sure Korea ever goes to sleep – there are so many things Korea is doing. I am impressed not only by the Korean regulatory strategy, but also all of the additional international organizations and the driving force that they seem to be in some of these global harmonization efforts.

They provided a summary of the Asia-Pacific Economic Cooperation [APEC] **regulatory harmonization steering committee** activities. There are nine roadmaps for pharmaceutical products. Vaccines, blood products, and cell and gene therapy products are in a separate area from the nine roadmaps.

There is a biotherapeutics global initiative goal to have the guidance documents from WHO and ICH rolled into APEC nations by 2020. They see a gap between the countries that have been harmonized with those international regulations vs. those that are not. They see quite a lot of disparity in practices when that situation occurs. A big problem is that there are no common languages that allow shared principles among those regional entities.

In 2015, a meeting is going to be held at which they are going to have discussions about convergence on a couple of different issues. A couple of key topics might be post-approval changes, immunogenicity assessments for biotherapeutics and biosimilars, and what degree of acceptance there may be for using foreign clinical trial data for biosimilar products.

It was also highlighted that there is a **Singapore Center of Excellence** that has been established that takes up issues of CMC questions for lifecycle management and post-approval changes.

Taiwan

Taiwan weighed in on the regulatory framework of Taiwan FDA and IMPRO [Integrated Medicinal Products Review Office], and highlighted the good review practices that guide them for looking at efficiency, quality, consistency, clarity and transparency in their review practices.

Taiwan has a **tiered review classification** system. Everybody seems to have a review classification system that allows some accelerated products and some regular products. After hearing all of the discussions today, I am not sure we are ever going to have regular products again – everybody is going to be accelerated, priority, or abbreviated, as far as I can see.

The agency likes to adopt best practices from many international organizations. They gave us a list of the organizations that they benchmark against in adopting their own internal practices. It has its own guidances on biosimilars.

The Taiwanese regulator Churn-Shiouh Gau who presented sees a **translational gap** from basic research to clinical development. It was brought up that there is a big disconnect between the academicians and the medical profession and the way they look at some of these products, especially some of the new products like advanced therapies, vs. those of us who have been for a long time on the development side, who know what it takes to get something through a regulatory review process for quality, safety, and ultimately, for efficacy.

For a biosimilar, it requires that the reference product be from Taiwan unless a justification for why it is not can be made.

Taiwan is now a PIC/S member.

Portugal

We had some wonderful discussions with Portugal's INFARMED. [Margarida Ferreira] also represented EMA's committee for advanced therapies [CAT], which was a predominant focus of her presentation.

Margarida enlightened us about the **centralized market authorization** of advanced therapies and medical products from the EU member states in terms of the GMP provisions, the risk assessments, and post-market surveillance.

She gave us a 2014 status report on the **committee for advanced therapies**, where they were looking at classifications that will be harmonized for these types of products and clarifying data requirements and marketing authorizations across member states.

Margarida talked about the goals to **streamline** the marketing authorization procedures and link certification procedures to the marketing authorization procedures and what incentives there are for academics and non-profits to be able to develop some of these, and also discussed some of the fees for post-market obligations.

Germany

Brigitte Brake talked about BfArM's activities and her activities in the EMA and the BWP as well.

She came in at the end of the session today talking about the comparison of different guidance documents for process validation and the differences in dossier elements vs. inspection practices between FDA and EMA guidances for process validation.

Brake talked about process validation and continuous process verification, which we later learned is causing a tremendous amount of terminology problems in the industry. In fact, she mentioned that we should **harmonize terminology** about these things to facilitate the acceptability of our process validation packages in different regions in the world.

Common Themes: Internal Agency Activities

Even though there were some differences as I just pointed out, there were some common themes that came out from all of the regulators who spoke. There is a set of internal activities that they are all undertaking, and they followed similar themes:

We had outstanding organizational overviews of the regional health authorities.

We heard fantastic details in all of the regulators' slides about: ● what their planned changes to their staff sizes are ● how they are going to arrange their product assignments ● what types of products they approve, and ● how they have changed over the years in the number and type of biotech products and cell products that they have approved. Each of them gave us phenomenal insights into their recent history and future plans.

Each outlined and compared the logistical pathways within their agencies and even between agencies for classifications of our products because they want to be able to have efforts that coordinate, integrate, and streamline those processes. Nobody wants to do any more work than they have to on either side of the table.

Many of them explained the history and gave us the current status and expected near-future elements of their regulations and guidance documents.

Everyone gave us a tremendous list of resources or links or provided us complete citations so that we could follow up after this meeting to get their drafts or guidance documents so that we can understand in great detail the policies and practices that apply to us and apply to them for our types of products.

Common Themes: External Activities

Most of our agency speakers adopted a second hat, like APEC or EMA or CAT, to share with us what their other work has been for regional or global organizations that they and their authorities are participating in.

They gave us a comprehensive view of the structure and function of the working groups that are having a major positive impact on our ability to get our products approved. Each gave us detailed updates on the status of those organizations with key upcoming activities and encouraged participation in discussions and dialogue at meetings such as this to be able to bring information to those agencies and have those thoughts be added to the discussions.

All speakers were acutely aware of the CMC review and inspection scenario that is happening now where we are generating and they are getting an increased number of filings and inspections, which is putting massive pressure on CMC reviews. The clinical timelines for breakthrough products or biosimilar products may be compressed, but the CMC timelines have to remain about the same, because you simply cannot compress things so much. So we end up with a situation where the CMC is on the critical path, and that is a tough thing to do on both sides of the table.

Also discussed were emerging new product classes that are requiring an adaptation of our traditional well-characterized models balanced with the risks and benefits of patient safety and product availability. We do not want to cause problems for patients. But if we do not get products to them, we will never solve those problems, either.

Uniformly the regulatory bodies said that they are looking at staff expansion, assignment flexibility, streamlining and simplifying their internal review and inspection processes, and coordinating and integrating review and inspection activities to reduce redundancies and to maximize their efficiency.

Their external activities are to continue to work with other global health authorities and industries looking for ways to – and these are the same terms I heard over and over again – increase communications, share experiences, align philosophies, harmonize policies, leverage information, etc. We got all of these wonderful concepts. But every one of them said that we have to remember, as industry, that they have to work within the legal constraints of their individual statutory and regional requirements. So while it is a strong desire to want to be as coordinated and convergent as possible, it is very true that each of these agencies has its own constraints that it must honor. And we must be respectful of that.

Breakthrough Products and Accelerated Approval

I am not going to read this slide to you in terms of time (*see box below*).

Regulatory Considerations for Accelerated Approval Pathways

The following are the considerations for breakthrough and accelerated pathway approvals provided by regulators at the CASSS Japan CMC Strategy Forum as summarized by Nadine Ritter :

- Each agency has different designations for accelerated approval based on unmet medical needs, orphan drugs, off-label use or drugs in national interest
- None will compromise quality, safety and efficacy for the sake of expediency; all require a risk assessment/risk mitigation plan (quality parameters should not be on the edge of safety limits)
- Emphasized need to significantly ‘front load’ the CMC studies for process and product characterization to allow detailed evaluation of each dossier sooner than for standard product review
- Cannot make decisions on assumptions; must have data to support conclusions and to review risk assessments and risk mitigation plans
- May exercise discretion in some CMC elements within regulatory/compendial requirements and balancing risks/benefits to patients
- Might place strong emphasis on post approval activities (risk-based decisions on pre vs post approval requirements)
- The quality of the dossier can have a major impact on efficiency of review – if it is poor quality it could trigger more questions from reviewers requiring more data to be submitted which will slow down the review process (and annoy reviewer!)

One thing that I wanted to point out, regardless of whether it was a breakthrough product or a biosimilar product, again and again talked about was the need to front-load the CMC studies. Regulators have to make decisions based on data. And if we do not provide them with the data, they cannot make the decisions that we need for them to make.

We heard a couple of times about the **quality of the dossier** itself: Having the data is important. But if you make it difficult for them to sort through it and review it then you are going to end up with more questions. It is going to slow down the review cycle. And as [FDA Molecular and Developmental Immunology Laboratory Chief Margie Shapiro] once said in a fabulous presentation on pet peeves, ‘a grumpy reviewer is not a benevolent reviewer.’ It can certainly slow down the review to have the information not put in a proper manner that can be reviewed quickly.

From **industry**, we heard the exact same kinds of situations where having CMC on the critical path is now becoming a problem. The good news is that we have these rapid review capabilities. The bad news is that the

CMC is now the gating item. Where we used to be able to hide under the clinical timelines, we are now being pushed to get more data faster and try to get our cases in front of the regulatory bodies as quickly as possible.

We had some terrific **case studies** today on how some companies are implementing this to their maximum efficiency. It did have some surprises. Some things were not so surprising – for example, establishing cross-functional teams. That is a wonderful thing to do anyway.

But the idea of how many people it takes to do things more quickly – we had one report that it could even require quadrupling CMC staff to be able to get the information in a parallel path as quickly as possible.

There were lots of other heads-ups on things like trying to minimize process and test method transfers to minimize disconnects and save time.

There was an idea that if you are going to get a product approval faster it means that the pre-approval inspection will come faster, so it is better to get a parallel system going on to remediate any gaps in the quality systems at the manufacturing and testing facilities. That one is frequently left out. So I was glad to see that one picked up by [Genentech's Earl Dye].

We saw two different approaches to **QbD** from the industry perspective: On the one hand, the thought was that QbD is not going to be all that useful for accelerated products because you do not have the time or the energy or the people to get that really sound process design space data set that you need. However, we did see some examples where a firm did use QbD very successfully. Senior folks put together a QbD package at Roche, and it was a really nice way to approach it. So it is going to probably depend a great deal upon individual companies, their experiences, and their timelines, as to whether QbD will be useful to them in a preapproval mode or in a post-approval mode.

We talked at the end today about **platform analytical methodology** – not just platform process technology. I think we just scratched the surface on that today. Maybe that can be the subject of future discussions, because there is a lot of rich information there that we can continue to discuss, including how to use the data that we get.

Whether it is the regulators or industry, both had the same challenges with limited batches being made for accelerated products, which means that we have a limited amount of information to establish specification ranges or process consistency. Obviously we have limited real-time stability data as is required for biotech products. And then the whole concept of process validation vs. continuous process verification was an issue.

The bottom line is that everybody said **communicate** earlier and more frequently. You do not want to make erroneous CMC assumptions. You do not want to do too much. You do not want to do too little. You want to achieve successful reviews.

Health authorities cannot compromise their responsibilities. I think one of the comments that [BfArM's Brigitte Brake] made was that quality parameters should not be 'on the edge of safety limits.'

Regulators are taking risks for patients. I saw one other slide that said the regulators are the **spokesperson** for the patient population. So respect the regulators' need for the data that they have to have.

I have a comment that came out of the issue we talked about regarding problems with bio-copies and the issues with gene therapy trials a long time ago: We have a lot of quiet successes in biotech. We have done amazing things in the last 30 years that the public really does not appreciate so much. But it only takes one loud product failure – one really spectacular patient population to be hurt – and it can bring parts of our business to a crashing halt.

If you do not know, if you have not seen what happened to the gene therapy trials in the late 90s and early 2000s, gene therapies took a major hit because of one failure. The PRCA issues were causing problems. We

can have a lot of quiet successes, but it only takes one failure for the public to not have any of these products. So we do not want that to happen.

Now in terms of some detailed things, these are the questions *[in bold]* that I pulled out of the panel discussions that I have tried to populate with key answers:

- **In some of the regulatory jurisdictions, evaluation of marketing applications could be streamlined if you have benchmark agencies. If you have breakthrough-type product approaches and accelerated approval, how will their reliance on less well-developed data be accommodated?**

The comments from regulators were that it would be hard to accept benchmark approval if it was highly accelerated because that, by definition, means it may have limited pre-approval CMC data available in the dossier.

But even if the CMC module is OK, a regulatory body could still have questions on the suitability of a product in that particular regional population. It is not a given. It is not going to be a slam dunk necessarily just because you have a good CMC module. There are other considerations, including political experiences with the product in the licensed area versus the patients that are going to be in the new target area.

They could base reviewer expectations on the current CMC guidance for the particular types of products, like the guidance for plant-derived products or other types of products from the benchmark agency. But every health agency retains the right to make the final decisions on a case-by-case basis, which is why they encourage communication early and often so that you can outline the detail of the strategy and get their concurrence.

- **What regulatory frameworks and pathways are available for the potential accelerated new products? What are the advantages and disadvantages?**

We had a really interesting conversation today: Why can't we just treat every product like a breakthrough product where real process and test capabilities are only demonstrated after commercialization? The response from the regulators is pretty clear: They can only work within the framework of the regulations that they have been given to enforce.

But on the other hand, there is nothing stopping industry from planning their programs like they will be breakthrough therapies. In other words, go ahead and add staff and increase your data collection capabilities. And you may even choose to use minimalist approaches for simple formulations or limited shelf-life or a very narrow design space. But in the end, your commercially approved product or process will be constrained by the data you have given them.

How much do you want to get up front versus how much do you want to get in the end? That is a decision that a business has to make for itself. And as Earl Dye pointed out, it is a *Catch-22*, because when you have to do a lot of CMC work up front, you have got to put a lot of investment in it, then the product fails you have lost it all. So that does not benefit anybody.

I think that [Genentech CMC Regulatory Director Kathy Francissen] made a good point about trying to strategically and scientifically understand the molecule, leveraging everything you possibly know about it and its predecessors to get the highest possible chance of success, and then prioritizing those within your company for possible breakthrough status so that if it is successful as a breakthrough product you are ready to go. That is probably the smartest thing to do.

Biosimilars

- **What is the level of current activity and the future landscape for biosimilars?**

Regionally there are highly diverse policies on non-national clinical trial data. Most of it is driven by either statutory constraints and/or population pharmacogenomic questions. That is the clinical side of it.

Actually, we have a lot of **harmonization** on Module 3 CMC requirements, with the exception of which reference drug you choose. Having the information to fill out characterization and process design and reference standards for your own is pretty similar from region to region by following the ICH Module 3 guidance document.

The type and nature and the amount of **analytical comparison** that you have to make to the reference drug can differ pretty widely, as does which reference drugs are legally allowed. We have known that for quite a while.

When you have to use one particular type of drug, frequently **three-way bridging strategies** are possible. We started this discussion. We did not finish it. But I would say to check to see whether your regulatory authority is talking about the three-way bridging strategy as being only analytical head to head, only clinical head to head, or both analytical and clinical head to head. It does vary from region to region. You do not want to make the mistake of doing the wrong study, because it is not an easy study to do.

We also learned that over the last couple of years we have had an increased learning curve, both on the regulatory and on the industry side from global biosimilars, and that this is feeding into both new guidances as well as looking back and updating early guidances for biosimilars based upon experiences.

I thought that the case study that was presented by the Malaysian regulatory authority was really interesting. She listed the typical problems that have been causing non-approvals of biosimilars in Malaysia. I suspect it is very similar to what happens in other health authorities in Asia, which is: ● insufficient data on process ● insufficient characterization of product ● inadequate specifications ● deficient strategy for analytics ● no justification for your choice of the reference product ● poorly designed technical studies ● not assessing immunogenicity adequately enough, and ● prescribing problems and product labeling problems.

That is a laundry list that is probably something you would see similarly in other regulatory bodies as well. I thought it was a nice list to put up here for everybody to benchmark off of.

International Regulatory Convergence

- **What is the state of international regulatory convergence and, in particular, how does the picture for Asia differ from the global picture?**

We saw that regulatory actions vary across global agencies, especially for CMC of new product classes, and also post-approval notification procedures, where you have got to make a change to a method or to a process. The regional requirements for reporting vary quite a lot.

There is no doubt that it would be beneficial on both the industry and regulatory sides to find a process that is within the jurisdictional requirements of each region to make it coordinated as possible for global industries.

We heard that most Asian authorities are heavily involved with key international harmonization and coordination organizations. We did see that it is a challenge to even think that we could get one uniform global guidance for accelerated and breakthrough products, because there are so many things that can happen regionally that can affect it.

Getting a **central approval procedure** for regular products – for example, among the ASEAN countries, which was a question that was asked – would require some kind of mutual recognition process among the countries. But the countries in the ASEAN organization are not legally linked the way they are in the EU. Look

how long it took the EU just to get a harmonized process for clinical trials.

It was thrilling to see that **ICH Q12** has made it to a concept paper now, because that is the document that is going to give us some guidance about product life-cycle. It is going to include things on review and inspections, which is that integrated approach that we were talking about. This is good because we want to drive better global harmonization for post-approval changes and the better use of comparability protocols for post-market changes.

We did hear that many health authorities that we are dealing with are now members of **PIC/S** for globally coordinated GMP practices. Hopefully the ultimate goal is to reduce redundant inspections for commercial products, because regulatory agencies just do not have staff hanging around to go out and inspect. If they can mutually recognize each other's findings against a common set of GMP standards, that is going to make our lives easier as well, because we do not have a bunch of people sitting around just waiting to get inspected.

Cell-Based Products for Regenerative Medicines

• What strategy can be employed for evaluation and control for cell-based products for regenerative medicines? What is the role of specification?

We certainly heard very clearly that the current EU system for regenerative medicine is based on pretty much the same principles as for biotech therapeutics, which starts with characterization of the product and evolves into defining whatever the control strategy is going to be to assure that your defined target product profile is met consistently for each batch of this extraordinarily complex and probably highly labile biological material.

There need to be sufficient and appropriate **analytical tools** to let you molecularly define or cellularly define a regenerative medicine's product profile. It is going to be different from a purified protein, but it still has a profile. From these you would select a subset of release and stability tests that you are going to use for quality control testing of that complex material.

When you make a change, such as getting another set of cells, or generating another stock, then you have to use similar analytical characterization tools to be sure that that change that you have made has not somehow negatively affected or shifted the product quality consistency that you are depending upon that you know has been safe and efficacious with the previous batches of that material.

The real take home message for us is that this is just another type of **heterogeneous material**. We have been dealing with heterogeneous proteins since the beginning of well-characterized biotech products. We are just applying those analytics and those control mechanisms to something that is even more complex.

It is not impossible, you just have to remember what the goal is: You still want to make sure that you have a defined degree of heterogeneity that is controlled and consistent so that you can be sure that you are maintaining safety and not having any contaminations that could possibly negatively affect the patient.

We had a quick overview of what some of the types of regenerative medicine products would be. And this is actually extremely diverse, from skin to cartilage to allogenic and autologous materials, stem cells, and I am sure the list is just going to continue to increase as we go along.

Points to consider for the type of product and its elements: They were risk-based approaches for each of those. But the dossier should contain justifications for decisions that you have made for each of them with the supporting data that justifies your conclusion.

You should be putting this together as a part of an overall risk mitigation plan – that is risk to the patients – for the product type and its intended use, including things like: • the traceability of the source material • the chain of custody of the process material and where it was made and the patient that gets it, and • whatever long-term

safety follow-up there is for post-market surveillance for patients. These products are very limited in their distribution and in their use.

- **For regenerative medicines can we overcome legal differences among countries and regions?**

We had a wonderfully spirited debate about this yesterday. And what we revealed is that there were quite substantial differences in the current status and CMC expectations for regenerative medicines. But the bottom line to me, these are my words – ‘first do no harm.’

One of the comments that was made by Margarida is that if the cell population is supposed to be chondrocytes, and it ends up 50% fibroblasts, you could end up with something that you are not intending, like scar tissue. Depending upon the risk for that particular patient population, scar tissue on a 95% burn victim might not be bad, because there might not be anything else that person has going for them. But if you are using it to repair a highly flexible element, then scar tissue could actually negate the thing it is supposed to fix.

You have to think about: What are the characteristics? What is the control? What is the consistency of the product for its intended use? What is the risk/benefit to the patient population? But again, you do not want a lot of quiet successes to be wiped out by one spectacular failure in the patient populations.

Antibody Engineering

- **What are the biological and structural features characteristic to engineered antibodies? Compared to conventional monoclonal antibodies, are there any additional CMC issues to be considered for their approval?**

We certainly saw the most magnificent presentations about all these molecular entities that can be generated, some wonderfully strategic ways to sort through them, and some very targeted design considerations. This clearly is going to be a class of molecules that we are going to be expanding. I have no doubt about it.

When it comes to their CMC, when they get out of the academic mode and go into development mode, and they go into the clinic, the CMC strategies are pretty conventional. In terms of the structure function relationship characterization for biospecific antibodies, it is pretty much the same strategy and almost the same tools that you would use for a conventional monoclonal antibody.

You apply the **analytics** as appropriate. If you want to look at the stability-indicating capabilities of those methods, you would do certain studies to be sure that they were capable of detecting structural differences as well as functional changes. If the mechanism of action involves two different epitope binding domains, then you have got to assess the ability to measure those two different epitope binding domains.

We did have this wonderful conversation – thank you [Roche Biologics Regulatory Policy Head Thomas Schreitmueller] for bringing it up for us – about whether you define CQAs as something they mean for the product or if they are just something that is just a checkbox or a requirement. I would like to think it is more than a checkbox for a compendial requirement for some of these general characteristics. It was brought up, and I had not thought about it before.

I have to admit that this is a really interesting thing: **Appearance** is the most prominent product characteristic that anybody sees. Literally speaking, no one is going to call in and complain because they have an oxidation, they are going to call because it is yellow. It is not like that it is a trivial parameter.

As was mentioned by one of the regulators, if your specifications say the product can be red, blue, or sparkly, it can be red, or blue or sparkly. But if it says colorless, it had better be colorless.

A question came up: When do you remove product testing for something like a process residual critical quality

attribute? Several different points were made about that. But pretty much universally the answer was when you can show sufficient batch consistency.

I am not sure I got this, Stephanie [Pluschkell], so correct me if I am wrong: I heard you say something about continuous process verification meaning thirty DS [drug substance] batches. And that was not before you removed the spec, I hope. That was a part of the CTD, right? *[Pluschkell]*: Thirty batches before you can truly do statistical process control.

Okay, thank you very much. Because I know that in the A-MAb case study when they talked about relieving some of the specification tests for things like process residuals and host cell proteins, buried in there in a little clause, it said that would be done after 20 or 30 batches are made for consistency. That seemed a little bit much to me, but I was not sure.

In any event, whenever it is that you are allowed to have regulatory relief from some of those process residuals, if you make a process change or something else occurs, then it is very likely that you are going to have to re-introduce those tests until you can show control over the process again.

Process Validation Lifecycle

We had a great discussion today about validation lifecycle. I apologize if I did not do justice to it, because literally as you were speaking, I was writing it. I apologize in advance if I missed a key topic. But this is what I heard at least: That the terminology can have an incredible effect on how we have to plan strategies.

And just listening to discussions – I do not normally get involved in process validation personally – but now I have a major appreciation for what some of the differences are in terms of validation versus verification, continued versus continuous validation, and evaluation. This is not a trivial thing, because it materially affects how much data you collect, when you collect it, what reviewers are expecting to see, and how they are interpreting what you are claiming by the set of data that you are generating for them. That is even complicated by the fact that we have different languages that have different translation subtleties associated with them.

I think Brigitte [Brake's] original comment early on is that we really should be harmonizing this terminology and making it a lot more clear, so that for this extraordinarily expensive and labor intensive activity we know exactly what regulators need to see and when they need to see it, so that we can be sure we generate the set of data that is expected.

We did see that different regulatory bodies are at different stages of adopting the lifecycle approach. And ICH Q12 is going to help that as well.

[Kowid Ho] was very provocative. He threw up a slide postulating where things could go in the Module 3 for process validation and continuous process verification. That was a great slide that stimulated a lot of debate. But the ultimate question would be, how much of the information in the dossier would be legally binding? The conventional interpretation by most people would be 'all of it.'

The caution there was to really give considerations to what that means in terms of what you put in the dossier for continuous process verification. Stephanie pointed out the fact that that is actually kind of an internal process that you are using to your own benefit to be able to understand what is going on with your own process. Any changes outside of the approved ranges would be managed according to your post approval change guidance anyway with appropriate regulatory communication.

The final piece of information I have, and I would certainly plan to look at myself, is the [Industry Group BioPhorum Operations Group (BPOG)] case study, a white paper on the details of how to execute and design continued process verification, which is available online (*link provided above*).

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