# IPQ INTERNATIONAL PHARMACEUTICAL QUALITY Inside the Global Regulatory Dialogue

## SUMMARY OF NOVEMBER 2015 CASSS BIOTECH CMC STRATEGY FORUM JAPAN

The following is a summary of the presentations and panel discussions at the 2015 CASSS CMC Strategy Forum Japan provided by Global Biotech Experts' Nadine Ritter at the conclusion of the forum. The four half-day workshop sessions at the forum, held in Tokyo on November 9-10, included presentations by industry and regulator experts from Asia, North America and Europe.

• <u>CLICK HERE</u> for access to the slides from the presentations at the forum and Ritter's summary slides.

• <u>CLICK HERE</u> for access to the forum program, which includes an agenda with the names and affiliations of the moderators, speakers, and panelists for the sessions and more information on the forum and its content.

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## **INTRODUCTION**

We started the program with Dr. Tetsuo Nagano [Pharmaceuticals and Medical Devices Agency (PMDA)] indicating that Japan is one of the few countries that develops innovative drugs in the world, and that it is a growing industry.

He reminded us how the three main goals of the PMDA are in alignment with what we were talking about at this forum:

- supporting availability of products, including novel products and biosimilars, with swift scientifically sound product reviews
- working closely with other health authorities to promote convergence of policies to maximize the efficiency of regulatory processes for globally-produced products, and
- leveraging knowledge and experience for the ability to build capacity among regulatory regions and collaborations among regulators, industry, and academia.

These are guiding principles that we saw over and over again in the summaries of the individual health authorities over the last two days.

#### **SESSION ONE**

### **RECENT TRENDS IN THE REGULATION OF BIOPHARMACEUTICAL PRODUCTS**

#### <u>Japan</u>

In the sessions moderated by Dr. Futaba Honda [PMDA] and Dr. Anthony Ridgway [Health Canada], Dr. Daisaku Sato [PMDA] talked about the initiatives in Japan. There was a really interesting slide that was presented on the median review times for a nine-year period in the US, EU, Japan, Canada, Australia, and Switzerland, which all show trends of reduction, with more review time consistency among them now than 10 years ago.

There was a great slide on the comparison of the early access programs that are available in the US, EU, and Japan, and it indicated about Japan's own policies where there is priority review for a number of products.

Of interest was the approval pathway for regenerative medicine products. There were two new cell therapy products approved in September [2015]. One was via the conditional and time limited path with the five-year review. The question came up in the discussion later, what affected that decision? And the answer was provided: positive exploratory clinical data. And the conditional and time-limited pathway is a case-by-case basis depending upon the sponsor, the product and the data set.

There was more information about the 'Forerunner Review,' the SAKIGAKE process, that we learned about last time. Just two weeks ago, six pharma products out of 51 applications were assigned to this program, and two of those were biological products. That is very hopeful progress.

Also, there was an update on Japan's approach to biosimilars:

- Seven biosimilars were approved. Currently, more than 25 are under review, and they are expecting 30 more in the next five years. This is in line with what other regulatory agencies are seeing.
- There is a new update coming out soon for using non-Japan reference products in the similarity studies compared to the proposed biosimilar products.
- We had an illustration of the Japanese accepted naming [JAN] rules, establishing identification for traceability of biosimilar products that are approved in Japan.
- There is not yet a decision on interchangeability, but extrapolations of indications would be possible when data support it, pending regulatory review.

Under the product lifecycle **ICH Q12 guidance initiative:** It is important to PMDA because they want to be able to have post-market review efficiency and effectiveness. But there is also a very specific set of rules right now, legislation, on approved matters for Japan, which we have heard a lot about today and will go into in more detail later.

And then an update on **International Collaboration and Cooperation Strategy** that was launched in 2015. Review summaries from PMDA are now going to be available in English for global transparency. Thank you very much from those of us who are not fortunate enough to be able to speak Japanese.

There is a new regulatory training center that is being discussed with partner countries. They remain highly engaged, and have always been, in regional and global regulatory cooperative harmonization organizations, and we have certainly heard a lot about that in the last two days. So that was the update from the Japan health authority.

#### **United States**

The update from the US Heath Authority was from Dr. Susan Kirshner from CDER. We heard later from Dr. Ingrid Markovic from CBER.

Update on **biosimilars:** Susan provided a list of the biopharmaceutical products that have been approved or in progress, along with a very comprehensive list of the applicable guidance documents for FDA.

She gave a very good case study of the Neupogen biosimilar three-way bridge that was used to utilize a non-US reference product for clinical data. She showed that it is important to not only bridge the biosimilar to the US reference and the biosimilar to the European reference, but to bridge the European reference to the US reference in the analytical bridge, because you cannot assume that any two licensed reference products are similar to each other. You have to generate the data package yourself to be able to demonstrate that, if you are trying to bridge to clinical data using a different licensed product.

There was a lot of debate around the guidance document that was just issued on the statistical tiered approaches to establishing analytical similarity studies with the three different tiers of statistical approaches: • starting from the highest risk quality attributes, which was expected to be around two to four common features that might be shared among all of the biosimilar candidates for a particular molecule – that was discussed later as well [Tier 1] • then the statistical ranges around the moderate risk ones, which would provide for mean standard deviations around the data sets for the reference product and the biosimilar [Tier 2] • and then the lower risk ones, which are raw data or qualitative comparisons for low risk attributes [Tier 3].

It is still the case in the US that interchangeability is not yet being discussed, but extrapolation of indications is possible with appropriate data. It is expected that a guidance might be coming out soon, which is why they can't discuss it at this point.

There were very nice set of discussions on lessons learned within the agency on what their experiences have been with advisory committees reviewing biosimilar products. The take home message was that it was very heavily driven by clinicians. It seemed like there are some opportunities to perhaps help them understand more about how the analytical data impact the uncertainty on safety and efficacy with biosimilar products, because it is the analytical data package that essentially informs the design that is needed to be able to establish the pre-clinical and clinical data sets that remove the residual uncertainty from whatever is left in the analytical package.

On the update for the **CMC lifecycle:** I am not going to go over much of that here because much more was covered in the ICH Q12 session. There is a new guidance document that drew a lot of comments about established conditions for commercial products – i.e., legally binding vs. the supportive information. Regardless of whether it is established or not, you still have to use post-approval change notifications that are given in the statutory requirements and manage control internally via the quality system. That was the subject of a lot of debate as you just heard today.

Under the **expedited priority review program** update: There is still fast track, accelerated, and breakthrough capabilities with the FDA. But all of them, as we saw with the other regulatory authorities, put pressure on the CMC data packages to be more front-loaded than they are for traditional review cycles. So it is really incumbent upon sponsors to prioritize the critical path, highest risk CMC items, and even consider strategies that minimize changes in the pre-approval phase, so that you can get the data sets needed to be able to support the initial approval. But you need to still balance that with the potential impact of the clinical scale processes on commercial supply. The good news is that you could be approved, but the bad news is that you can't give it to anybody because you only have two bottles of it left. So that is a concern.

The **take home message** was 'communicate early, often, and with sufficient relevant data to the FDA.' But as was said with other regulatory agencies, this is a very resource intensive pathway. So it is as critical for patients, but it does take a lot of energy and effort on the industry side, of course – but definitely from the regulatory side, with the amount of hands-on work they have to do with sponsors to get that pathway.

#### <u>Indonesia</u>

We heard some wonderful updates from Indonesia. Dr. Roy Sparringa [National Agency of Drug and Food Control (NADFC)] gave us a great overview of what is going on in that country.

They are in the process of reorganizing to meet the needs in this major region [ASEAN]. He made it very clear to us how important Indonesia was in this area, which has 40% of the population and GDP, and the fastest growing middle class – so the demand on biopharma is increasing.

The update on the **regulations** is that they have a very similar review process using the ICH common technical document quality, safety, and efficacy sections. And they have similar post-market inspection policies in place. But their desire is to switch from what they are currently, which is a 'watchdog' agency reacting to inspection observations, more to a prospective risk management agency, where they are trying to proactively prevent risks by implementing appropriate quality systems and quality issues.

Under the **biosimilars** update: They had three biosimilars currently in progress via tech transfer procedures, and one biosimilar being internally developed. They currently align with WHO and other global guidances for review of biosimilars, and they follow the ICDRA 2014 recommendations, as illustrated in his talk.

There are three options for selecting the reference product, including one where the reference material is no longer being produced, which was dependent upon additional data. The question was, 'what if the reference product is not approved in Indonesia – can you do a bridging study like we would do for other regions?' The answer is, that is under discussion now within that country.

The **CMC** lifecycle update: They use risk-based approaches to change management with a focus on the impact to quality, safety and efficacy. They do follow ICH Q5E for therapeutics, and then WHO for vaccines. They showed details of two case studies. There are three levels of change. There is a tiered approach for change notification in this country, as we were talking about at the end of the day today.

In terms of the **international** update: Indonesia is highly engaged in the regional groups. They are in the process of adopting the ASEAN common technical document. They are now a member of PIC/S.

One of the questions was: How would the agency use the PIC/S scheme? The answer was potentially as a benchmark to improve quality and consistency of their own inspections of the numerous cGMP facilities in the country and manufacturing facilities outside Indonesia. I may have gotten this wrong, but I got the impression that there may be over 200 pharmaceutical entities within Indonesia. That is a lot for that country to harmonize their inspections. So that is great.

They strongly support ongoing collaborative interactions with other regional and global regulatory authorities, and they were certainly quite involved in the discussions we had. So it was great.

#### <u>Thailand</u>

The update from Thailand was by Dr. Piyanan Boonprasirt [Bureau of Drug Control, ThaiFDA].

The **regulatory** update was an excellent overview of the processes and guidances required for the Thai regulatory agency, and I will refer you to the slides, because they were quite descriptive and clear. They listed the local regional and global regulatory guidances that applied to the biotech products and biosimilars that they review.

They do utilize the ASEAN common technical dossier and the common technical requirement, and they have a new submission process with online appointments. I was really impressed personally by the state of electronics going on in Thailand. It is quite a leadership role they are playing there for electronic communications with sponsors. They are piloting the use of the electronic CTD – the first ASEAN country to do this – which is designed to shorten the review times. They hope to have full implementation of electronic systems by 2016/2017 for all the products that they are dealing with. So very forward-thinking systems there in Thailand.

**Biosimilars** guidelines there: They have a general guideline that includes five parts, which is very similar to the ICH common technical document. They also have specific guidances now on four individual biosimilar products [somatropin, interferon alpha, Mabs, GCSF].

One of the questions was about conventional biological products. The question from the field was: How do they define it? The answer was that a conventional biologic is a product with which they already have regulatory experience, including things like legacy products like plasma derivatives or vaccines.

Another question from the audience was: Are there specific requirements for the selection of reference products for biosimilar studies? The answer was that actually at this point it varies, depending upon the type of biosimilar product and what the sponsor is trying to do with it. So there are no hard and fast rules yet about whether it has to be licensed there or not.

And then finally, are there any efforts underway to generate an ASEAN-specific biosimilar guidance? And the answer was: Yes, that is actually under way right now in committee discussions.

It is very clear that Thailand is a very active and engaged member of this region, and is leading the way in some of the initiatives going on.

#### <u>Korea</u>

We also had an update remotely from Dr. Jeewon Joung from Korea [Ministry of Food and Drug Safety (MFDS)].

The regulatory update was that there is a new regulatory approach based on the pilot of the risk management plan. They have seven products now running under that system, and there is a new guidance on that approach. She had a great slide that compared the risk management plans of the US, Europe, Japan, and Korea. So I would refer you to that slide for the details.

They have included patent and exclusivity rules now into the drug approval process. Products will be listed on a green list. She indicated it was similar to FDA's Orange list. That list has over a thousand products on it -146 are biological products, of which 129 are recombinantly expressed. So that is a pretty big number of products on the green list that would be protected by this.

She gave an update on the harmonization of comparability data from the APEC workshop on process changes and stability data that would be needed. Previously, any DS changes always required supportive amounts of real time stability data for a drug product. That has been changed now. It is not just blanket mandatory that you need DP stability data for every DS change. It is a case-by-case basis. It is not mandatory. Stability data as a gating item came up later in the discussions.

Majungmool, which is a very elegant word meaning priming water for wells or pumps, was started in 2014. That is a fast track assistance with enhanced support for regional academic and small-scale organizations who are not particularly familiar with the existing pharmaceutical regulatory system. It represents a strong outreach of the Korean regulatory authority to their local sources for new product development. So that is a nice system.

And then an update on the **biosimilars:** To date there are 26 that are currently in IND phase -17 of these are locally originating, and nine are foreign originating - and five that are approved. Four of the approved biosimilars originated in Korea, and one tech transfer originated from a foreign entity.

Wearing a different hat, she also provided an update from the APEC 2015 Biotherapeutics Workshop. That is actually a step 2 of the four-step road map that was initiated in 2013, which is at the point now where they are looking at the actual implementation and design of training programs. She outlined the concepts and logistics for these Centers of Excellence for regulatory training on biotech products.

She added three categories of training that are part of pilot programs: • basic, which is the general orientation to processes for biotech/biosimilar products And then two specific ones • on comparability, which is intra-product [biotech/biosimilar product] lifecycle process changes per ICH Q5E • and biosimilarity – comparing a reference product to a potential biosimilar, and focusing particularly on training associated with the unique aspects for biological products for the analytical similarity study.

They are launching two pilot programs right now: one of which will be a face to face, and another which could be potentially on line. They already have agreements in place with several national universities – for example, Northeastern University in the US. She did indicate that there is a possibility to discuss relationships with CASSS that support this effort, which would be nice if there is a role to play.

The question was asked from the field: 'Is there a committee in place now for this educational initiative?' The answer was that it is being finalized now.

Another question from the field was: 'What would be the source of general case studies?' One of the things that they really want to do is not just include training on general issues, but include specific case studies or model examples that they can use for illustration. The answer was that the case studies would hopefully come from practical experiences, but that is going to be determined by the committee in the ultimate decision. So that is a nice initiative that is going on.

#### **Discussion Session**

## Theme 1: Innovative regulatory strategies for enabling rapid development and the potential for early marketing approval of highly promising new biotherapeutic products, the associated challenges, and progress being made

These are the bullet points that I took from those discussions: Health authorities do have accelerated review pathways for designated products. But the challenge is that those pathways consume a tremendous amount of time and attention of the most senior reviewers in communications and assessments with the sponsors. There are benefits to the patients, but it is not without some cost to the regulatory authorities themselves.

Quality elements are still critical, regardless of what you tell them in your program that you got. CMC is more front loaded. In fact in some of those programs, CMC can become rate limiting. So the suggestions were:

• Make minimal changes pre-approval – for example, to scales, sites, and formulations – to get the biggest data set you can for the initial assessment.

• Because biotechs need real-time stability data to support shelf life, one of the suggestions was to lock into an initial formulation and container closure to allow approval of an adequate shelf-life to support commercial supplies. Don't make a bunch of changes that will then reset the clock on your stability shelf life, because you might be able to discuss leveraging stability data from other similar products in the same formulation, same container closure, if the risks are low. But otherwise the changes that you make are going to reset the clock on stability because the risk will be too high.

• You must also determine if your clinical scale production can support supply needs once approved, so that you are not going to have a shortage. But there is a tradeoff with time and materials needed for making scale-up changes. The best recommendation was to discuss those logistics and those options with your health authorities, and plan immediate post-approval changes together with them.

Regional Health Authorities indicated they share the goal of rapid approval of products, but they really still have to have data to make an appropriate scientific review. They can not make a decision on a deficient dossier.

It was recommended that regardless of what region of the world you are in, because there are some commonalities and some differences, please be sure that you are thoroughly familiar with all the guidance documents, and communicate with the health authorities where you are seeking approval for what they need and when they need it.

ASEAN health authorities are making great progress in reviewing biotech and biosimilar products, but they still have to honor legal jurisdictional constraints. The comment was made that they really don't have any interest in reinventing the wheel for product review strategies, but they are sometimes constrained by their jurisdictional requirements. The thought was that perhaps the emerging ASEAN CTD format may greatly facilitate even potentially mutual review processes.

One of the questions that came from the audience was: Does a SAKIGAKE product have to originate in Japan? The answer was actually no. It could have originated internationally, so long as it is marketed first in Japan. So, that is an interesting part of the definition.

## Theme 2: Evolving approaches to ensuring product quality (e.g., validation, post-approval changes, and facility inspections) and updates on relevant guidelines, new or planned

Concepts are being discussed including how you divide roles between reviewers/assessors and inspectors. This does require consideration of the impacts on the existing PIC/S GMP inspection harmonization program. So it is all to be determined pending outcome of the discussion of ICH Q12, and we had a lot of discussion on this later as I will go into. I won't go into that here.

#### Theme 3: Regulatory updates on cell and gene therapies and biosimilars

Just a quick snapshot from each regulatory entity:

- FDA said CBER indicated that cell and gene therapies might possibly be breakthrough products. They have one currently in progress. But it is very case by case. Some CMC elements can't be postponed for these products to post approval because of the risks of the nature of the product.
- In Europe, currently there are six approved advanced therapy products including two gene therapy products. 300 ATPs have been studied in trials during years 2011-2014. Three guidances are in progress now one revision to a current guidance, plus guidance on quality aspects of advanced therapies for IND submissions and GMPs for ATPs.
- In Japan, there are several regenerative medicine products approved, and more are expected.
- And in ASEAN, the discussions on cell and gene therapies are just starting. The Indonesian government has approved a few hospitals to manage some of these cell and gene therapy trials.

There is so much information that came from the presentations and discussions and I will refer you to the slides for details. A lot of the discussion was around specific questions related to selected points, so I did not capture all that for the purpose of this summary.

One of the questions that came up was, what if a biosimilar product yields a better product quality profile then the reference product? And this has come up in other discussions. All the health authorities agreed that you cannot have a biosimilar AND a biobetter at the same time. It is okay to have fewer process impurities – like host cell proteins or DNA - or to have more stable formulation. You are going to generate your own shelf life anyway. But you cannot claim 'better quality' or 'more pure,' especially if that is possibly going to be used for marketing against the original product. That is not acceptable.

Another question was: Are costs factored into the health authority decisions when it comes to biosimilar products? The answers were no -- that the health authorities have a separate scientific decision-making process from decisions on marketing and product pricing. Some of those are subjected to regional medical reimbursement schemes. So that is a different process entirely for what the cost is going to be versus what the scientific advice is for whether the product is safe, effective, etc.

## Theme 4: Efforts being made at international or regional harmonization, regulatory convergence and work sharing between health authorities.

From the ASEAN entities: The working groups are very active. The thought was that if you can remove the trade barriers, then they can possibly establish mutual recognition agreements and memorandums of understandings for things like GMP inspections. ASEAN guidelines are considered very valuable to those regional health authorities, they reported.

APEC is not a mandatory collaboration group, but it is very important to be engaged in it for shared understanding of issues, shared challenges, and possibly coming up with solutions together. Capacity building is a big effort. Regulatory training programs are a high priority in this region and other regions. They expect greater collaboration among industry, academics, and regulators for the science and compliance aspects of these complex products.

Japan indicated that international collaboration is already built into its five-year plan. They have confidentiality agreements in place now with the EU, US and Canada for internal information sharing, but not yet in place with ASEAN countries. Those are under discussion though.

And the EU is also highly engaged with other agencies, including WHO. They strongly support dialogue, including things like CMC forums, to build trust and understanding with industry. Thank you very much. We agree.

#### **SESSION TWO**

### **DEVELOPMENT OF BIOSIMILARS: TECHNICAL ASPECTS**

In terms of the development of biosimilars, technical aspects, that session was moderated by Dr. Teruyo Arato [Hokkaido University] and Dr. Kazuhisa Uchida [Kyowa Hakko Kirin Co.].

#### Development of Infliximab Biosimilar in Japan

We had a presentation that was given by Dr. Masatoshi Yamada [Nippon Kayaku, Japan]. *[Editor's Note: The slides were not provided for distribution.]* He gave the details on the case study of the CT-P13 biosimilar product that was co-developed by Celltrion, which was approved in 2012 in Korea, 2013 in Europe, and 2014 in Japan.

He went into great detail on some of the issues they faced, which included a thorough analytical structural and functional characterization. But the outcome was that they did see some differences in some of the structural elements and one of the functional elements. So the discussion was how you deal with that – what factors into the review and acceptance of that. He talked about some of the issues. He gave examples of what data they used to support that this was not going to be a significant impact on the product's quality, safety, or efficacy.

It turns out that their data supported a conclusion from PMDA and EMA that these physiochemical properties had no impact in view of efficacy. They did an appropriate analytical bridge of the EU Remicade and Japan Remicade and demonstrated comparability. So they were allowed to bridge the pre-clinical and clinical data to the Japan Remicade to allow regional switching of the product once it was approved.

#### **Critical Considerations for Analytical Similarity Assessment**

Dr. Jennifer Liu from Amgen gave another case study. She did distribute the slides, so you can see all the nitty-gritty details that she has in her overview.

She talked about some of the challenges that you face when dealing with the biosimilar reference product for the analytical studies.

One of them is that the tier 1 critical quality attributes that are associated with the most rigorous statistical review could vary for different sponsors, even among the same biosimilar products. That would challenge consistency of reviews from product to product. Also, it requires a statistically relevant number of lots for both the biosimilar and reference product. She has a graph that indicated greater than 10. That came up later in discussion. Of course, it is very difficult to know what the true variability is in the reference product because of the relationship of the age or number of DS batches to DP, and potential post-approval changes that occur to DS that you are not aware of. Also, analytical variability is included in the ranges.

She also gave a good discussion of what the difference between the fingerprint-like similarity and fingerprint-like methodology, and gave a very good overview, with a lot of detail, on the comparisons of what fingerprint-like methods would be appropriate, and some of the issues associated with them. So I would refer you to her.

#### **Biosimilars in the EU: Regulatory Update with a Focus on CMC**

Dr. Niklas Ekman from the Finnish Medicines Agency indicated that there were recent updates of several guidance documents, including one on insulin biosimilar. Please see the slides for the presentation. For the European side, they don't have any degrees of similarity. There is not a fingerprint concept. However, the clinical data alone can't justify substantial differences in the analytical characteristics between the biosimilar product and the reference product.

They also do not have specified statistical requirements. The sponsor is free to propose and justify relevant models, if they chose to use them. The same basic principles apply to a biosimilar as to a reference product in terms of quality. The expectation is you are going to make a similar version of a known API that is safe and effective. The approach would be to establish the quality target product profile based on full characterization of the reference product, and then design a manufacturing process for the biosimilar to generate something which is similar in those characteristics, and then examine the risks of any observed differences.

He presented the example of Remsima/Inflectra, where those differences occurred in glycosylation and FC gamma receptor binding, and how the preponderance of the evidence indicated that there should be no risk to the clinical approval of that. In fact, he even made a speculation that at some point there might be a possibility in certain cases of looking at difference preclinical study approaches if the analytical data are strongly convincing and sufficient.

#### **Discussion Session**

In the panel discussion for that session, in terms of the draft guidances, what is highly similar with fingerprint-like similarity?

In the EU, it is all the same. It is similar or not similar. But the FDA actually has a statutory definition of 'highly similar' that they have to work within.

The real discussions came from the issues for interchangeability and whether the outcome of that legal decision could impact the degrees of similarity required to qualify for that kind of classification. We had a long discussion in that session about interchangeability and substitutability, because they have different definitions in different regions, and a single global approach may not be possible for these issues.

Health Canada indicated that they are not ready to allow interchangeable or substitutions due to manufacturing and indication changes between the referenced licensed drug and the biosimilar product, which, after they are approved, can change separately, because that designation of interchangeability or substitutability would presuppose a lifetime link between the referenced licensed product and the biosimilar product.

The question was: Once a biosimilar gets approved, are you then obligated to continue comparisons to the referenced licensed drug?

The answer was no, that is the point. You are going to be free to make changes, and so will they. So there is no way of assuring that there is connectivity in quality between the two products in the changes they are allowed to make post-approval.

The EU indicated that EMA is only responsible for approval of biosimilars. They are not taking any positions on this yet. However, member states have their own policies for their states. What happens to those products after approval? Niklas indicated that FIMEA did a retrospective review, and there is a paper on this, and it found no adverse events for switching products in that region.

Some of the questions were, was the detection of adverse events sensitive enough? Since the body is very sensitive and has immune memory, it could trigger problems later.

Amgen indicated they did see neutralizing antibodies in some patients that could be highly severe. The root cause was investigated by traceability but they did not see anything that was not expected. The EU indicated that it seems to be more of a theoretical risk than actually observed for the current products in their region at least.

One of the questions was, what if the analytical data shows the biosimilar is not adequately similar to the reference standard for this product?

The EU indicated that if there are substantial differences early on, they would notify the sponsor that those differences are significant enough to possibly jeopardize approval.

What if the process that is being used to produce the biosimilar is different from the originator?

Well that actually is very likely. Health authorities do not expect the processes to be exactly similar. They focus on the product characteristics, not the process that generated it. In fact if the process really was the product, then biosimilars would not be possible theoretically at all. Health authorities do the process review as a stand-alone issue. So whether you are original or biosimilar, your process has to be supported on its own. The comparison of the two products is based upon the product characteristics.

There was a question on what was the FDA's rationale for the ranges that are given in the statistical guidance document? In other words, why is it 1.5 instead of 1.48 versus 1.52?

The answer was this really is just a starting point guide for sponsors. They can justify other ranges if reasonable. However, be aware of the fact that if ranges are very wide it leaves open too great a degree of uncertainty on the comparison of the biosimilar to the reference product. So it is kind-of a double edged sword. You can have wide ranges, but then you are going to lose the ability to reduce the uncertainty that the study is designed to do.

How does assay variability factor into equivalence testing approach, since very imprecise assays reward equivalence? It is easier to show equivalence with an imprecise assay than with a precise assay.

The answer was that Amgen actually struggled with this, and concluded that the comparison data should be robust and reliable so long as each assay is – and I took detailed notes on this so bear with me: • adequately qualified for intended use • has acceptable intermediate precision • has good system suitability to assure each run is valid • uses a statistically relevant number of sample replicates and assay runs • uses a meaningful number of product lots for both the biosimilar and reference products.

The FDA said that they wouldn't let you get by with a bad method, even if the equivalence tests pass any mathematical ranges. So, the burden on the analytics is pretty high. There are some things you can do to help minimize the impact of imprecise methods, but this is obviously a very rigorous consideration and rigorous study design.

PMDA said that, regardless of whether statistics are used or not, analytical quality comparison design is quite critical to their consideration of the data sets. They are focusing very closely on the nature of the data, the amount of data, and the methodology.

EU also added that, since not all attributes can be measured analytically, in the end you still have to have some degree of clinical trials to confirm things that cannot be analytically measured – for example, immunogenicity is not something you can measure in vitro with any analytical method. So that is something that is always going to be an uncertainty from the analytical comparison studies.

What if you can't make enough lots of the biosimilar product, or can't get enough lots of the reference product?

Well that is a real issue for a variety of reasons – for access to it, and also for costs. The answer was definitely it is going to challenge the analytical study design and its conclusions. If you have fewer lots of either, then you are left with a higher uncertainty for what true variability is for both products. On the one hand, it impacts the conclusions of what the reference product characteristics are that you could peg yourself to. Plus it challenges your ability to set specs on your own process control and product consistency for your biosimilar. So fewer lots represents a more challenging study design and challenging conclusions. There is no doubt about that.

#### **SESSION THREE**

## ICH Q12 OVERVIEW: ESTABLISHED CONDITIONS/APPROVED MATTERS

#### **Introduction**

Then we head to the ICH day, and we had a great introduction. The moderators were Dr. Yasuhiro Kishioka of PMDA and Dr. Wassim Nashabeh of Roche.

Wassim gave us an indication that ICH Q12 had three major gaps that it is trying to close: • one, it was the only ICH guideline specifically for commercial products • two, it was hopefully going to be harmonizing different interpretations of what the regulatory binding information was • and also, unfortunately as of today, ICH Q8 and 11 have not seemed to achieve the full expected benefits of QBD. So Q12 was hopefully going to be able to address some of these things for the industry and for regulatory.

#### ICH Q12 – Pharmaceutical Product Lifecycle Management: Current Status and Future Perspectives

We had a great drill down overview by Dr. Kishioka of the current status and future perspective of the committee now.

He went through the concept paper which is available for review and gave us the main points from it, and then went through the discussions topics, including:  $\bullet$  the established conditions  $\bullet$  the ICH CTD format – whether it can be used to support the regional requirements or not  $\bullet$  the role of the product quality system, Q10, in managing post-approval changes.

There were very different views among industry and agencies. But they agree that the product quality system must be robust in any case, regardless of what ends up happening with Q12, and that the post-approval change management protocol, which we talked about at the end of the day today, would have the benefit hopefully of lowering reporting categories, with faster review times.

But there were lots and lots of questions, as you saw today. I would refer you to the slide on the product lifecycle process draft. It is just a draft, but it was good to look at because it really does link the roles of industry and regulatory for assessment and inspection.

The ideal was for this guidance document to be a self-contained, harmonized global guidance that is both pragmatic and forward-looking. I think you saw in the discussions today that is still hotly debated as to how that can happen. But it is certainly interesting.

#### <u>New Drug Application of Biotechnology Products in Japan: Approval Contents/Legal Binding Related to CMC</u> <u>Part</u>

We also had a presentation from JPMA, by Dr. Takao Kojima. He went through the J-CTD Module 2 as the primary review unit. That is the one that is required to be in Japanese. It has more detail in it than the typical US or EU quality overall summary.

Then he went into great detail on the J-M1.2 application form contents about legally binding matters and the different levels of change control notification that is embedded within it.

#### J-Module 1 Preparation (CMC): Model Document for Manufacturing Process Description

We also heard a discussion by Dr. Kei Nishimura, JPMA. They are in the process of generating a model mock-up for a biotech monoclonal antibody for drug substance for discussion.

That drew a lot of interest. In fact, the question at the end of the day was, is it going to be possible for the [ICH Q12] committee to at least consider looking at a presentation of it in their discussions coming up in December [2015]. It was based on a 2006 study on the impact of the J-M 1.2 module for biotech products, plus the experience of the approved monoclonals. They included Q8, Q9 and Q10 concepts in their consideration for the model, and they grouped it into upstream and downstream elements and things that would potentially be included or excluded in that approved conditions.

The proposal was that things that were included would be controlled by the PCA process. And things that were excluded might be controlled by GMP and product quality systems management. There were some examples that were given of that. This came into the discussions later after this presentation.

#### Japanese Application Form: PMDA's Perspective on Manufacturing Process

Then we had a presentation by Dr. Reiko Yanagihara of PMDA and talked about the projects that are going forward. Please see the slides on that. He indicated that since the mock up was not available prior to the discussion here, that the comments are not the final PMDA comments, but just thoughts from the presenter.

He indicated that the current J-M 1.2 document is a good regulatory tool. It provides clear, transparent communication on legal commitments. The details are given in the 2005 notification document, which includes an appendix specifically for biotech products. That is now available in English on the PMDA website for global distribution. You can denote upfront whether you have a PCA or MCN parameter, and justify those designations based on your own product development, prior knowledge and data sets. CMC review focuses on elements that maintain control of the process and product quality.

He gave excellent examples of how the current form can be used for post-approval change flexibility. He indicated that the 2010 notice does discuss acceptable ranges for process controls. It is not specific for biopharm processes, but it was postulated that perhaps you could use it for them, and also agreed that having a mock up for discussions would be a useful thing, but they can't make the public comments yet.

#### **Discussion Session**

The discussions from this were varied, enriched and heated, which is exactly what we like to see in a CMC forum for this purpose.

There were a wide range of regional approaches to some of the concepts that are in ICH Q12, and I can see why the committee is so engaged in the discussions. I think the goal that was clear from the discussions was that it could definitely add value to the industry for submitting, and for Health Authorities for reviewing, fewer complicated notifications on changes. But it also could result in inconsistent expectations across products and among reviewers.

One of the questions was how would it impact a level playing field for all products and sponsors if some of these concepts were implemented? And that is definitely a question that is still not answered.

Some of the main points from the discussions that we had included:

It didn't seem to me that the issues were if post-approval changes (PAC) for biotech products have to be done under any control system. They do have to be done under some control system, but the question seemed to be whether it was an internal review, product quality system, or whether it was going to be a regulatory review level, and how much flexibility is associated with whether it is an ask and then do vs a do and then document approach. There is so many different levels of this that I can see where the debates are just challenging.

Some regions actually have already tiered post-approval change notification systems, which include annual reports, but others don't. So it is not easy to develop a system that is going to allow all regions to be able to have the same levels of reviews. One of the concerns was if you suddenly change some of the levels that you would drop from what was originally a higher reporting category – something that was sort of an 'after the fact' reporting category. And that was a concern for risk.

There is a WHO guidance on post-approval changes for vaccines. One for therapeutics is in the works. That could be very useful in establishing consistency in regional notifications – more of a tactical approach – whereas ICH Q12 was designed as a more strategic approach, because it sort of assumes that the tiered systems would be in place already.

And then there were questions on how the established conditions and approved matters would be presented, and format issues – whether it would be a list form or a CTD grouping like in the current FDA guidance document.

One of the health authority concerns from the audience was that if you are allowed to make a lot of changes in the Module 3s that were not considered established conditions. What would be the risk of suddenly having the filed dossier losing accuracy for what is really being done in the site where the product is being made? That was a concern that was reiterated. It is possible as I mentioned that tiered-risk changes could be replaced with very simple inspectional controls after the fact, and that would drop down reporting categories with one fell swoop.

Some of the format questions ended up with the conclusion that at least the committee is looking at the established conditions to maybe be a stand-alone section, such as the Module 2 quality overall system. But that is still to be determined as a part of the discussions, because there are regional differences, like with the J-M 1.2.

The question was what would happen to the FDA guidance document if changes were made to the format? The answer was that it is a draft, so it could either be updated to align with the final Q12 decisions, or it could even be rescinded. They have the flexibility to do that, depending upon what happens.

One of the questions that came up in the discussions was who decides what elements must be established for every process or product? The answer was that it is still based on the same approach as of total control, based upon your defining your critical process points, etc., and that Q12 established conditions would simply enhance this and require just as much justification and rationale for those points of control that will be included or excluded.

One of the questions was, would the established controls be different for existing legacy products versus new products with less history? The answer was, yea, very likely, because it is a data different strategy and legacy products would have more data for process and product control than new products would. But it is possible that the established conditions could start quite constrained for new products, and then decrease as data and experience grows as the product life-cycle continues.

This was where JPMA was asked if they could prepare a mock-up presentation for the December meeting because they thought it would be very useful as part of the discussions and they were considering it.

#### **SESSION FOUR**

## ICH Q12 OVERVIEW: POST-APPROVAL CHANGE MANAGEMENT PROTOCOL

#### <u>Regulatory Perspective on Comparability Protocols in Biologics: A Tool to Effectively Manage Post-approval</u> <u>Changes</u>

In terms of the last session, the regulatory perspectives from CBER on the post-approval change, Dr. Ingrid Markovic gave a very comprehensive overview of the current requirements for FDA, EMA and ICH guidance documents.

She provided a breakdown of the types of change protocols that the FDA received from 2004 - 2014. She referenced the CMC forum paper on comparability that has some of the concepts in it, and I would point you toward the CASSS website. That copy is available if you want to get it.

Her conclusions were that she found that the success of the change protocol implementation was directly proportional to the amount of product and process knowledge, risk assessment, and effectiveness of the total control strategy for the process. She mentioned that the biggest challenge seemed to be setting meaningful prospective acceptance criteria to allow you to conclude comparability when you did make those changes. Choosing what the changes were and what the tests would be were important, but the actual criteria for acceptance prospectively can challenge the sponsors.

She also concluded that the CP may enable greater predictability regarding expectations and timing of implementation, including expedited product distribution, and that they may offer an opportunity for reduction of regulatory oversite. The experiences at FDA show that CPs might actually be underutilized as a regulatory tool – indicating that about 12% of CMC supplements are submitted as a change protocol. So there might be some opportunity there for sponsors, even before ICH Q12 gets finalized.

#### Post-approval Change Management Protocols - Current Status and Next Steps on the Way towards a Global Tool

Dr. Kowid Ho replaced Dr. Markus Goese from Roche, talking about their experiences with post-approval change management protocols.

He also gave an overview of the contents of the EMA PACMP 2010 guidance, including the question and answer document that is associated with that guidance. He noted that most biotech variations are Type II, and gave examples of these in the slides.

He also gave an overview of the FDA's guidance documents, with a note on the potential 2015 update on that document, and said that essentially the US and Europe have similar strategies for tiered notifications, but noted that other regions have very different notification strategies.

He talked about expanded change protocols, for which there was a forum in 2009. I will just point you to the CASSS website, because again, the ECP forum paper is published and available for free on the website if you want to drill down into the ECP concepts.

And then he gave an update on the FDA pilot QbD program, and again I refer you to the slides.

The final note that he had was that ICH Q12 is intended to incorporate post approval change management protocols (PACMP) as a part of the overall product lifecycle strategies, but the details as we saw are still be discussed in the EWG committee, so it is not anywhere near finalization yet.

#### **Industry Perspective: Current Status of Global Change Control**

Dr. Tetsuya Kawakami from Chugai gave their example of their change control management program. It was a wonderful case study with a great deal of detail on the communications that were used, the subject matter experts that were involved, and how they manage the change control process globally for multiple products in multiple regions.

The conclusions from their experiences were that: • they could successfully introduce a change control system with strong emphasis on good communications among all experts that were involved in all sites • for regulatory compliance, it is necessary to have a good change control system that functions efficiently and effectively, or it will turn into a mess very quickly, and • different regulatory actions based on different binding information may definitely burden the management system, because you are juggling many parallel changes in different sites around the world. The hope or the expectation would be that globally unified established conditions could really simplify regulatory actions for companies to have better regulatory compliance.

#### **Discussion Session**

We ended up with recognition that there are highly diverse health authority systems, legal requirements, policies and practices – they are so diverse. I am amazed that this committee can even think straight with all the differences they have to juggle. It is very challenging at this point to find common strategies, but the dialogue is going on. That is what dialogue is for. The thought was that we just simply have to try to find ways, if we are going to make progress, of thinking outside the historical box on post-approval change options.

One of the questions was how does the ICH Q12 work with the QbD approach? In other words, how does established conditions impact the QbD design space?

I think what I heard, because I was writing quickly, was that that should be independent of the nature of the development strategy. You can use any development strategy that you want - QbD or conventional approach - but the change protocol would be for changes that are outside of your quality-by-design conditions or established conditions.

Is a post-approval change management protocol applicable to accelerated products? The hope is that it would be equally applicable to large and small companies, new and legacy products, because the basic premise is that when sufficient knowledge exists to prospectively specify the acceptance criteria, you could then make prospective plans for those changes. It is important to note that you would be allowed to file a change protocol after the initial approval for any post-market changes. So if you have an accelerated product approval, you are not compelled to submit a post-approval change management protocol at that time. You can submit it any time later in the lifecycle of the product.

Because different regions have different notification levels that are legally codified, it is challenging with what ICH can do with Q12, because it can't superceded the actual legislation in some regions. But as Health Canada indicated, there are some possibilities that there are policies that are not legislative, but are policies that could support implementation of some of the post-approval change elements. It was considered valuable for transparency and consistency of data requirements.

Even if it is not legally binding, it has concepts that would provide for better transparency and better consistency for data for post approval changes. But the hope would still be to not lose sight of the goals, which is actually having a legal impact and downgrading and minimizing regulatory burdens, both on the review and inspection side prior to implementation of what we be defined as low-risk types of changes.

At the very end, we had a discussion on how to leverage mutual reviews. We had proposals by Health Canada – those wily Canadians – on bench-marking health authority approvals that would be mutually recognized by others, or, as came from Europe, even sharing health authority decisions with other health authorities, so that the individual regions could factor that into consideration for their approvals of your post-approval change management protocols.

The last question that we had right at the very end was what about multi-products and multi-facility post-approval changes? FDA indicated that they had experience with trans-BLAs, which is a single change across multiple products. Some parts of that, their successes, could be incorporated in Q12, but the elements related to multiple changes across multiple products in a single post-approval change management protocol does come with a lot of risks. In other words, if one change fails one product, there is a possibility they could fail everybody together. So you succeed together or you fail together. So there is a risk there.

That was my conclusion of the last two days. Apologies if I got anything incorrect. The summary slides will not be distributed publicly until individuals have had the chance to make any corrections that I indvertently made a mistake on. However, they will be available soon on the CASSS website. I would say that look at your handouts, and look at the slides, and look at the reference papers because they were quite useful in these discussions.

• <u>CLICK HERE</u> for access to the slides from the presentations at the forum and Ritter's summary slides.

• <u>CLICK HERE</u> for access to the forum program, which includes an agenda with the names and affiliations of the moderators, speakers, and panelists for the sessions and more information on the forum and its content.



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