

SUMMARY OF 2016 CASSS CMC STRATEGY FORUM JAPAN

The following is a summary of the presentations and panel discussions at the 2016 CASSS CMC Strategy Forum Japan provided by Global Biotech Experts' Nadine Ritter at the conclusion of the forum. The four sessions at the forum, held in Tokyo on November 9-10, included presentations by industry and regulator experts from Asia, North America and Europe.

- [CLICK HERE](#) for access to the slides from the presentations at the forum and Ritter's summary slides.
- [CLICK HERE](#) 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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SESSION ONE

RECENT TRENDS IN THE REGULATION OF BIOPHARMACEUTICAL PRODUCTS

The first day we were talking about regulatory trends in biopharmaceutical products. We had some wonderful introductory comments from PMDA.

One of the things that struck me is that there are monthly regulatory updates published on the PMDA website in Japanese and English, and it was indicated that PMDA is very actively involved in a lot of important organizations [including APEC, ICH, PIC/S and WHO], and they also have brought in training. And so that is part of what we have been involved in here with the CMC strategy forum.

Japan

We had a further drill down from the first speaker from the PMDA, who reminded us of the five topics that were instituted in 2015 in their International Strategic Plan [training, SAKIGAKE, biosimilars, the Japanese Pharmacopeia, and ICH Q12/EC], and reminded us also of the three pillars of the mission of PMDA [review, safety, rescue], which now includes a fourth pillar of regulatory harmonization. For each of those five topics we got an update.

Under training, we learned that they have indeed executed a series of **training** classes. Three were completed, and there are three upcoming training events. There is a website that has that information, and I can verify that I went to the website, and in fact, the information is there, if you are interested in the next three training classes.

We got an update on **SAGIGAKE**, and we were reminded what the purposes of SAGIGAKE were. The first round is in progress. Six biotechs and five medical devices/tissues have been looked at. There is a second round being offered now. There are 50 applications pending [in the current cycle, Oct-Nov 2016]. SAGIGAKE, though, is not a standard process. It is only open by announcement. So the second announcement is a pretty important window of time for sponsors of products that are interested in that pathway.

We have got an update on **biosimilars**, with a new biosimilar Q&A document that is being issued [in Dec 2016]. They have got tremendous activity consulting with biosimilar products, the majority of which are monoclonal antibodies and fusion proteins for Fc regions, and the rest are other things like hormones, cytokines and enzymes. Interestingly, we have learned that biosimilar topics here are actually beginning to be spoken about in political circles, in the media, due to the impact it could have on healthcare and the pricing of healthcare, as it is in fact being discussed in other parts of the world.

One comment that was made that I think is particularly important, because I am certainly seeing it myself with the projects that I work on, is that there is an increasing challenge to people who are producing biosimilar products to be able to access the amounts of reference licensed drugs that they need from a certain region to be able to do the similarity studies that are necessary. And so there was some comment made in this presentation about the idea that the situation seems to be different in the relationship of the generic drug manufacturers on the chemical side and the biosimilar producers on the biological side about the availability of the reference licensed drug. This wasn't discussed here, but I know that this is being discussed actively in other circles about that issue.

We got an update on the **Japanese Pharmacopeia (JP)**. Congratulations, they are 130 years old now, and JP 17 is out. We have learned that the JP is freely available, including in English, and again I can verify. I was up this morning at 4 a.m, and I did download all the sections of the JP, except the infrared spectra and the ultraviolet spectra, because it doesn't mean anything to biotech products. So thank you very much for allowing us to access that final document.

Gene therapies/cell therapies are out of scope, but vaccines are in scope. Biotherapeutics are in scope for general rules and general methods. As you heard at end of the day today in the analytical discussion, monographs continue to be topic of discussion for biotherapeutic products, and wondering what the purpose is. This is a global discussion not just a regional discussion.

We have also heard about the **post-approval change activities** with ICH Q12. PMDA is quite aware of the global complexity of change control, and that is a part of what they are working on with the ICH committees.

There is a drive to be able have a harmonized established conditions, as we talked about in great detail. Of course, Japan has the model on approved matters. We did hear some interesting statistics: 70% of the discrepancies were found in the application form, versus what is practically in place at the company, although we learned later through discussion that that was mostly typographical errors and minor issues, not major issues, which was good to find out.

Korea

We were happy to have representatives here from Korea to give us an update on the MFDS.

To no surprise MFDS is rapidly growing in **biopharma** – both at the regional level and their interaction with international products of a variety of types [e.g., vaccine/plasma/antitoxin and recombinant/cell culture products]. Korea has the honor of being the first country to grant approval to a stem cell therapy and the first to grant approval to a biosimilar monoclonal antibody product. So they have made their stake in the world very prominently in our biological products.

The **biosimilar legislation**, which was launched in 2009, has established regional definitions for the recombinant protein product, similar biologic product, and the reference biologic product. There have been five approved so far for biosimilars, but there are 21 biosimilar candidates that are currently being processed.

MFDS has issued improved **policies** on a variety of fronts including things like a risk management plan for new or advanced drugs. They have got a Bio IT initiative, where they are looking at collating overseas regulatory information. They have given us the links for that. Again, I have checked that link out and it works wonderfully.

There are additional **initiatives** to streamline biotechnology development – specifically for us, things like: • communal manufacturing facilities and pre-scheduled review inspections • encouraging QbD models • implementing national lot release • and there is certain number of new guidelines out [e.g., for blood products, orphan drugs and exported products]. Also, it was great to hear that MFDS is now a PIC/S and is issuing GMP certifications.

Finally on the APEC side with the Regulatory Harmonization Steering Committee: They are in the middle of their four step plan on developing and providing training. They had a successful pilot program with the Center of Excellence, Northeastern University and the Seoul National University in Korea.

China

We were also very pleased to have for the first time representation from China in this forum. We learned about the Chinese regulatory process and the initiatives that they have going on for biotechnology products.

CDE has strong **alignment with international** guidance documents like WHO and ICH, which was gratifying to hear. They do consider if drugs have been approved in other regions. That is something that they make take on board as a part of their consideration. They do review imported and domestic products, and they do plan to export biotech products of very high quality. So they are very active in the biotechnology product area.

They gave us the **designations** – and I would refer you to the slides on the detailed designations about their biological products – including number of registration categories that crossover. There are special considerations in their regulations for biosimilars and cell therapy products, and there is an appendix on biological and blood products in their GMPs.

They do have a major **focus on QMS**, which is aligned with international guidances. They are concerned about things like ability to perform continuous production, batch consistency, product stability and issues about controlling raw materials and excipients, chain of custody of products, post-marketing surveillance, etc.

They recognize that **post-market changes** are a very complicated system, but they support the use of science-based approaches. They do have annual evaluation reports that are required of each product, for which they get the complete documentation for that year.

In terms of their reform and emerging **initiatives**, they are trying to get a streamlined approves process with unequivocal procedures. They are trying to make sure that things have high transparency and are fair and accurate among regulators, including the possibility of having a re-review of any controversial issues that may come up during your product review cycle. In terms of transparency they are looking at making public information in terms of the three packages that they do review for the products that they get approved, so that there is an opportunity to learn what works, so that other developers would have a chance to succeed as well.

European Union

We heard from the Finnish Medicines Agency. Niklas [Ekman] talked about the ongoing efforts in Europe.

He gave us an update on the **adaptive pathway** – one of the accelerated approval processes. Very importantly, some these have been there long enough now that there is learnings from them. We learned that, of the rejections that occurred, there were some common reasons why, which included: ● products that were already too late in their development phase for the adaptive pathway to have much of an impact, and ● situations where there was not enough information that would support the learnings from that pilot, like no real world data was being planned that was going to be able to give them an assessment of whether that was going to be suitable or not ● or the product actually wasn't filling any unmet medical need.

They did recognize that it is valuable to involve patients and medical personnel earlier in the process. To nobody's surprise, and this is a recurrent theme, CMC could definitely be time limiting when you have an accelerate pathway. The clinic is not normally the limiting factor anymore. We are.

The CMC might need a rolling review, because we used to live in a world where clinical timelines were long and unpredictable, so for CMC we could very comfortably sit back and take our time. Now with accelerated pathways and a variety of other things, the CMC is easily the limiting factor for some of these kind of products. And there might be a possibility of some concurrent activities, depending on what you negotiate with the regulator who is looking at your product.

Niklas also gave us an update on the **PRIME** system. There are two entry points that a product can get into that system. Again the CMC for PRIME is something which is considered to be a potential gating issue, because those critical CMC datasets really need to be in place for reviewers to be able to make a timely decision about the products going forward.

Under **biosimilars**, in Europe of course the target is always to achieve a lower price and affordable healthcare, but also increased access to other markets that wouldn't get access to our products from an innovator side to give patients more options. But he acknowledged that, as we are all seeing, biosimilars tend to put pressure on innovators to renew their continuous improvement strategies for legacy products.

There is quite a strong increase of biosimilars in Europe. It has been a very successful program, no doubt about it, but there have been some criticisms that it has received for having inadequate data-driven scientific advice. So they are looking at possibly more tools, new tools, for accessing quality data, so that they can have the information needed to provide meaningful feedback and scientific advice to biosimilar developers.

And then Niklas told us about a new initiative, open access to clinical reports. I have link here on the slide (<https://clinicaldata.ema.europa.eu>). Currently there are just two chemical drugs listed, but the goal is to publish both submitted and withdrawn studies, so that you could learn from what did not work in the clinic as well as what did.

United States

Sarah [Kennett] gave us an update on the FDA's status. I think that really the strong message that I heard from Sarah was the idea that there are a lot of new things that are possible, but the FDA will never be able to relinquish the oversight of control strategies because their legal responsibility is protecting patient expectations for quality pharmaceutical products – and in fact that is the legal requirement for all regulatory authorities around the world.

They do encourage **new technologies** and they would like dialogue on new approaches like multi-attribute methods (MAMs) if the focus is on assuring product quality consistency.

Also recognized in the comment that she made was that sponsors bear the burden of providing sufficient data on their proposed strategies. Her observation, which was backed up with some examples, was that historical data may not be sufficient to encompass all the potential variables that could occur in the process. So if you are asking for a very large design space or a lot of flexibility, you have to be sure that there is enough data to support everything that you think that might be allowed.

The two key questions whenever a novel control strategy is proposed is: ● number one, are you doing monitoring at the appropriate step in the process, such that no further changes in the attribute can occur after that step has been completed? ● And then secondly, and we talked about this a little bit later, does monitoring mean something does not look good? Or does it mean, if it is outside of a range, that the batch will now fail. She gave very good three examples – and I could not possibly summarize them here but I encourage you to look at her slides – of how the requests for reduced QC testing was really not backed up with an adequate amount of information.

FDA issued a draft guidance for ICH Q12 on **established conditions**. We talked about it quite a bit at the end of the day today. It gives guidance on how much detail is necessary, and what the FDA would consider elements of established conditions. She also presented an example from inspection of a highly atypical process step that should have triggered an internal review and did not. It was a good example to bad example where someone was justifying that reduction of QC testing because their process runs consistently, but their process was not actually running consistently, so that explained the need for the QC testing.

Another new guidance that FDA issued in April [2016] was on comparability and change protocols, which she indicated have been used quite successfully at the FDA except that they have begun identifying some common gaps: ● One, they see lack of data for justifying the comparability acceptance criteria ● two, the comparability acceptance criteria are often the same as the acceptance criteria for release testing, which is not acceptable for especially late phase comparability studies or post-approval comparability studies ● the lack of data plans to monitor stability, and ● inappropriate down-grading of requests based upon a limited comparability study.

On the **biosimilars** front, she remarked, as many others did, that extensive CMC data is required upfront. You have work to do to characterize the referenced license drugs (RLD's). There are four biosimilar BLA's currently approved, but there are many more in pipeline at the FDA.

Breakthrough products, which are of different class but they have the same expedited review schedules, also have issues with CMCs, because it does not change the CMC requirements for product quality, but it may affect the timing of when certain key datasets are required. So the advice to management was start CMC early to avoid it being the gating item for these breakthrough products, because in breakthrough products, by definition, the clinical moves faster than CMC.

Regulatory Panel Discussion

So those were the regulatory presentations that we had yesterday. And these are the panel discussion questions. I have tried to condense them and make them as accurate as I could. They are not in any particular order. I just grouped them as was logical.

- **Is there CFDA testing of clinical trial materials in China?**

And the answer that I thought I heard was: A clinical trial in China is done by document review and not necessarily by testing the clinical trial materials. There is an inspection team available to assess control of clinical trial materials, and imported clinical trial materials will be tested along with the document review.

- **The time to get an IND in China is currently about a year. Is there any possibility of getting a shorter time?**

The answer was that, yes, they have been striving to get faster turn-around times. There is a special team that has been formed, and the goal is to reduce it down to six to twelve months, which is a goal that they have been trying to meet.

- **When would process validation strategy be provided for a breakthrough product or adaptive pathway products?**

The FDA answered that the PDUFA [Prescription Drug User Fee Act] regulation does have limited rules on what the time limit is for agreements. But they do have an option to send you a request for PV strategy in advance of a pre-BLA meeting, because the goal is to get a sanity check. 'Is my process validation strategy going to be suitable before I actually execute it?'

- **What are Japan's CMC expectations for a SAGIGAKE process?**

The answer was that there was no specific impact on the CMC expectations. They would be expected to be filled out the same as any other product. But they do encourage dialogue with PMDA subject matter experts on CMC to learn what would be considered flexible for certain timing aspects.

- **SAGIGAKE details for prior-review rolling submission: Does it have to be on the final CMC or could it be done on a draft ahead of the final clinical data?**

We heard that you can seek prior consultation on draft strategies before final strategy is filed. We did have some comments that were made that rolling submission strategies are not harmonized globally -- some do and some don't. So a global developer that is trying to take advantage of many of these accelerated pathways really has to understand the requirements of each of them in their regions under the separate health authorities.

- **Is SAGIGAKE appropriate for multiple indications?**

The answer was that that becomes a very challenging review, because if there are too many indications rolled into the process, then it makes it very difficult for them to review it. The goal is to be able to have a rapidly addressed unmet medical need for high-risk patients. If you put low risk and high risk indications in the same application project, it kind of conflicts the review and makes it difficult for the reviewers.

- **We did ask questions about the 70% difference in discrepancies [in Japan between the Module 1 application form details vs. what was found in practice.**

The answer that was given was it was typos and minimal errors but the question was how to make sure that does not continue to happen for sponsors in the future.

- **What other strategies are being proposed by industry or are under consideration for improved and more efficient CMC?**

Pay very much attention to what is going in the field. Recognize which data sets are necessary. We heard that EFPIA has a new white paper coming out, and it should be available very soon, but it is not official yet, I believe. We certainly have a plethora of CMC forum white papers and summaries that are freely available on the CASSS website that go into many different CMC issues. I would encourage anybody that would like to know more about that to just go to the website.

There are a lot of organizations that have good strategies out there, and the comment was recommending that you can take advantage of those to compare with what you are thinking about.

- **We had a lot of discussion about training initiatives. It is a very big issue. Do they incorporate internationally harmonized or converging concepts? And if so, is there any consideration for globally harmonized training programs?**

Some of the agencies gave us their opinion. PMDA is just starting their regional training, but in the future, they could potentially have some integrated ICH training. The Europeans indicated that they are doing quite a lot of training as well. Some regulatory training sessions are open for global access. For example, there was a recent biosimilar training, which included Asia and other countries. Individual member states also provide and obtain global training. There is a training network center with a goal of making national training webcasts available. Curricula now being developed to cover those subject matters. FDA's training currently does not include international elements at this time, especially for CMC. But it would be interesting if we allowed reviewers to share their thinking.

I will put a shout out here, for the Center for Biologics Evaluation and Research (CBER) has some webcasts on their site that are free that are from some of the reviewers in the office of gene therapy, where they go in 30-45minute sessions and give their web based presentations on their requirement. So there is something available to the industry, at least from the FDA.

- **What does the panel think are hot topics in training to rapidly increase the understanding of the approval process?**

China said that they feel training must start on the review elements to assure high quality reviewers. After that will look into including international guidances in their training curricula, so that the reviewers have a broadened understanding of global perspectives and common industry practices. Korea indicated that they have provided WHO GMP training for many years, and they have specified training on certain types of products like cell therapies. And they definitely promote global understanding among their reviewers for issues that are in ICH and WHO.

SESSION TWO

SPECIFICATION/POTENCY: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR CELL-BASED PRODUCTS

In the next session on specifications and potency for cell-based products, we had several expert presentations.

Determination of Potency for Cellular and Tissue-based Products (CTP): Considerations and Challenges

We had an overview by the PMDA about the considerations and challenges for these kinds of products. It was clear that cell therapy products have the same objective of process consistency and product quality and stability as other biological products. Because of the nature of the material and the process, they have quite a number of adaptations that may be required technically to achieve those ends. But the principles remain the same, if the practices are slightly different.

The concept that a total quality control strategy is a suitable approach for cell/tissue products is one that is definitely valuable for that class, because you simply can't test enough of the end product. There isn't often enough of it available to do an entire comprehensive slate of final product tests.

We had a great discussion and went into further detail on potency assays. The PMDA's perspective is that the potency assay that you select, or the potency assays that you select, depend on what the cell therapy product actually does. There is a variety of things that different products will do, and that is what should be driving the decision for monitoring potency. There should be some way that the mechanism of action is related to the potency assay. And there should be some relevant measurements of activity, and certainly appropriate system suitability criteria, to achieve results.

There was a comment was that that would certainly need to be validated. ICH Q5 principles may be applicable, but clearly the practices have to be adapted as necessary. For many of these methods for cell therapy products, we talked about them not having an available established reference standard that we can pull out of a freezer and stick into the QC tests. And so that challenges the control and consistency and accuracy of these potency assays.

PMDA had a strong opinion about the role of medical specialists – having an input into the cell therapy products up to the point where they are going to be using them for administration. The product specifications should include considerations of the product, not just in the container as it goes to the clinical site, but actually once it is in the clinical site and how it is used for the patient.

Development of Allogenic Regenerative Medicine, TEMCELL® HS inj: Establishing Test Procedure and Acceptance Criteria, Especially Specifications and Potency Assay

We also heard two truly excellent case studies, probably the most excellent case studies I have seen presented yet on cell therapies. One was on the TEMCELL product. I could barely do justice to either of these, but there was quite a lot of detailed information.

Certainly it is clear that in some cases you can measure multiple attributes of a complex therapy produce and use numerous types of technologies, including flow cytometry, ELISA, PCR and fluorescence microscopy. So I would certainly recommend looking at this in detail and chatting with the presenter about it.

Potency Considerations for a hUTC-derived Therapies

Also, from Janssen we heard about the human umbilical tissue-derived cells. He didn't give as much detail on the specifics of the assays, but certainly there was a great overview of strategies, including some slides that ticked off the advantages and disadvantages of various approaches for the cell therapy product, in alignment with the FDA's guidances.

EU Regulatory Activities and Experience

We heard from Ilona Reischl from Austria on her EU regulatory perspectives. Ilona has been working in this field for a very long time.

She gave a list of all the current guidances that are available on cell therapies. There is a new draft guidance document for investigational advanced therapies that are in progress. She also showed us the new general chapter in the European Pharmacopoeia on raw materials of biological origin for cell and gene therapies. In that, it talked about what was in scope and out of scope.

I think one of the comments that really resonated with me that Ilona had was that, although there were many guidances on these very complex materials, no guideline could ever actually address all specifications for every type of cell therapy product, so the field should not really expect one. They can generate general guidances, but the idea is that each of these is a case-by-case product with case-by-case issues. What you would depend upon are the basic principles that always have been used for product quality – for things like identity, purity, potency, impurities etc.

Her concern was things like making sure that your specifications and control strategy really covered every aspect of the product up to the point of use.

She mentioned that in their region they are talking about two different phrases that might better replace Phase 1,2 and 3 for these products, like ‘exploratory’ versus ‘pivotal’ clinical trials. That is based on sponsors not necessarily understanding what datasets they should have that would represent ‘pivotal.’ Phase 1/2 should not be considered ‘pivotal.’ It should be considered ‘exploratory.’ So maybe a better use of terminology might make that a bit more clear to the industry.

There was quite a presentation that Ilona gave us on specifications, and the idea that every criteria cannot be for information only. There have to be some core criteria that control the material, even when it first goes in human. So, saying that there is no range on the potency assay means that you actually technically allow something with zero potency to be used in the clinic. You have no way of rejecting that material for use in the clinic, and that is not acceptable.

Also, she was quite strident about making sure that producers of cell therapy have mined the scientific literature before they come in, because there is a lot of information that might be out there on a type of product that they are just not aware of.

The conclusion was that just do not submit your product for review unless it is fully characterized unless you have a putative mechanism of action that you identified, that you have got relevant specifications in place to at least control the quality of the product as it goes to the clinic, and that you have got suitable analytical tools.

It is okay to have a strategy to gather more data during clinical trials, but you can’t jeopardize the safety of the patients. which would then jeopardize your clinical trials. So don’t let your CMC be the fatal flaw in your clinical trials for these products. They are very important, and you can’t risk having them fail because of a quality problem.

Discussions

We had very animate panel discussions in this session. Just a few quick ones:

- **Is it hard to measure potency for cell or cartilage generation in vitro?**

The answer was that that is a technical discussion. It is a great example of where something that is case-by-case.

- **Could a surrogate biassay marker serve for potency?**

It is possible, if there is a justified link to the in vivo mechanism of action. Again, another example of where a question cannot be answered without more detail on a case-by-case basis

- **For currently-approved epidermal tissues for skin, how are the specs considered for approval?**

The answer was that it was based on mechanism of action and intended clinical effect. The quality parameters that were defined for the attributes are relevant. It also included how medical practice will use it.

Health Canada indicated that the mechanism of action determination may not be fully elucidated for all products, but did agree to some quantitative measures that correlation to function should be in place. You can't just have everything be qualitative and expect it to be controlling the quality of the product.

And then a comment was made that a full secretome of cell therapy product is not possible to determine in vivo. But it was agreed there could be some metrics that would be derived from what you think you know to model numerous characteristics of a cell therapy product.

- **One of the questions was about control of starting materials versus final product testing as a part of the total control strategy. In that case, could you use non-quantitative attributes?**

any tests are there that make sure the product has the right quality. But for most cell therapy products, some sort of matrix approach is probably appropriate because of the limitations on the material for any given batch. For example, for stability, you may not be able to get 25 time points out of one batch, but you might be able to get selected time points that overlap out of several batches.

But just saying that cells are alive is not enough to assure that there are correct cells with correct attributes. So it was agreed that even homogenous cell preps can vary from lot to lot in quality consistency. So the total control strategy has to take into consideration not just cells that are present or their viability, but a combination of attributes that assure the cellular product is what is supposed to be.

- **How do you do process validation for cell therapy, and how many lots do you use for verification?**

That differs among regions. Japan indicated they expect cumulative CMC data to show process control and product consistency – kind of a CPV (continuous process verification) approach. But the total amount of data depends upon the risk and the medical needs of that material.

In the EU there are numerous pathways as was discussed for early access, and there is conditional approval for really high-need products for a compassionate need and named patient use. But the comment was that they are not going to give full commercial approval to a product that is not fully in control if it exposes the population of patients to unnecessary safety risk simply due to inadequate CMC data. So the CMC data can be commensurate with the product, but it is not going to be an excuse to allow a product to be approved without adequate control of quality.

It was interesting, I had this comment yesterday from the audience: Protein products have more straight-forward quality control testing capabilities. I am going to ask the people in this audience, many of whom were on the original ICH committees for Q5, Q6B. Did you ever think that there would be a time when an audience like this would say, 'oh monoclonals are easy, I wish we had a monoclonal.' I can imagine that people who were involved in that must be thinking, 'oh yea, there was a time when monoclonals were the big hairy monsters that we had to deal for specifications and process control. But I guess by comparison to cell therapy they are just little puppies that we do not worry about anymore. The rules have all been set and if we know what we are doing with monoclonals, right. Thanks guys for all the hard work you did for the last 25 years.

The basic principles that were codified and put together for those purified protein products still remain valuable today, which is that we are trying to get consistent products of suitable quality and make sure that they are safe and efficacious.

ICH Q6B says, we are allowed to have all the heterogeneity that we can manage, monitor and maintain. So if the heterogeneity is isoforms or multiple cellular structures, it is still the same principle – just very different practices.

So the comment was, if you treated a cell therapy like a complete black box, it does not let you design a controlled manufacturing process to produce the designated complex products. One of the comments was made that you should show proof of concept of the product early, even if you don't know the entire mechanism of action for all parameters. But the EU did reiterate that they would not accept a submission where you simply say, 'we will figure out the mechanism of action in phase 3.' You need to know that sooner than phase 3, sooner than your pivotal studies.

The comment was made that you may know that there is a panel of cytokines that your cell therapy product could affect. So just pick up a set of those as a fingerprint and use them as an early way of assessing product consistency.

- **What are some of the good approaches to providing better guidance to new developers of cell therapy products?**

Certainly increasing publications or presentations of case studies. Since these are new classes of products with new CMC guidances, that means that there not many case studies that are out there publically available. So that made the two we did see even more important to us, because there are not that many that are put out yet.

Certainly each regulatory body is producing guidances for cell therapies, because they are a new product class. EU indicated that they are actively engaged in outreach in a variety of venues to bring cell therapy from academic ideas to practical products.

Also, the recommendation was that the sponsors of these products, particularly if you are a naïve sponsor – obviously nobody in this room is a naïve sponsor because you are in this room – but if you know of naïve sponsors, then you would want to encourage them to seek scientific advice as early as possible. Sometimes they may even find that it is less complicated than they anticipated.

PMDA also encourages dialogue for general strategies if the proof of concept is sufficiently developed. Always the focus is on safety. But CMC is very important as clinical starts.

The EU said that they often see academic and small firms lacking good scientific and regulatory input. They have great input on the medical and financial side, but not much input on the actual scientific and regulatory side, and they ought to.

Another comment that really resonated with me that Ilona made was that the trade-off on how much work you do on the CMC, how much characterization you do of your cell therapy product, is really going to be offset by what you need to do if you make a process change. The more you know about the product, the more analytics you have, the less likely that you will miss something that will require you to go to the clinic. The less characterized product you have, we are back to where we used with original biotech products. If you don't know what you don't know, then you have to go back to the clinic to reduce the uncertainty. So there is a great advantage to making sure that you have got a good analytical tool kit. And again, as we saw in the examples, there are some people that are quite successful at it.

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.

SESSION THREE

ICH Q12 UPDATE: ESTABLISHED CONDITIONS IN THE MANUFACTURING PROCESS

Now we are going to do day two, which is the ICH established conditions. Wassim [Nashabeh] gave us some introductory comments and pointed out that we have six members of the ICH committee present here at the meeting. So I think we have got some very good input and had the opportunity for them to hear us as well. So that was a good acquisition for us for this meeting.

Introduction and Update on ICH Q12 Guideline

Frank [Montgomery] gave us an excellent overview of the AstraZeneca approach. He reminded us that the goal of ICH Q12 is just to make our post-approval changes easier and more efficient globally.

Frank indicated that in addition to the US, EU, Japan, Health Canada, Swissmedic, ANVISA [Brazil] and Korea [MFDS] are now **members of the ICH committee**. And then we have observers from WHO, TFDA [Chinese Taipei], and HSA from Singapore. So that body is getting more diverse every week, and it is wonderful that it is expanding.

He gave us an overview of the meeting that they just recently had in Osaka and pointed out some of the topics that were being discussed:

- Change categories: We certainly had a lot of discussion about that. It was really quite a surprise to me several years ago when I learned for the first time that not all regions have the same tier change notification system. I didn't realize that everybody wasn't like a certain set of countries. Then they used the terminology quite often in meetings about the 'tell and do' versus 'do and tell.' They indicated that the revised established conditions chapter would have examples of each.
- They mentioned that the CTD section outline of the EC is similar to the FDA draft guidance document. We talked quite a bit about that today.
- He talked about post-approval change management product documents, product lifecycle, the PQS. The PQS is actually quite important. When ICH Q10 first came out, I thought, 'yeah Ok, it is nice.' I didn't realize it was actually going to become the underpinning of the internal change control that would be carrying the weight for post-approval changes, if it works the way it is supposed to.
- And there was some discussion apparently in Osaka about how legacy products would enter into the ICH Q12 model. I think some draft templates were there for making some changes in methods, which we then talked about later today.

Version 7 of this document was finalized in November. An interim meeting is scheduled for April, because they are expecting quite a lot of comments to come in from this round....

Connection from ICH Q12 (ECs) to Application Form (Approved Matters)

The PMDA gave us a quick overview of the application form for approved matters. It has these three change categories in it, but some challenges still remain: ● the misuse of the mock as a potential template – maybe users don't realise that they should be filling this information with their product specific details ● the discrepancies that we talked about – which of the assignable causes were considered minor ● Some people lose sight of the purpose of the approval form and control the products only per the approval form ● And then sometimes there is not enough detailed discussion of specifications.

There was a really good slide – I do recommend this slide – that showed the overlap between review and inspection responsibilities from the PMDA side. It really gave us a visual illustration of how those things work together, so thank you very much.

Established Conditions for Manufacturing Process – PMDA Perspective

We had another presentation from PMDA about how the previous ICH documents 8, 9, 10 and 11 were targeting CMC development, but 12 is the one designated for post-approval matters, and it uses the CTD format to communicate established conditions versus what we call now the supportive information.

We had lot of discussions about the fact that ECs are legally binding, and today we ended up with a great deal of conversation about that related to methodology.

In the second presentation there was also a tremendous example of manufacturing process established conditions and how that would be affected by different levels of reportable changes.

Case Studies of Established Conditions in the Manufacturing Process

We had a presentation of a practical example from a representative of JPMA as a model of biopharmaceutical manufacturing, launching off of the A-Mab case study. That case study is actually available for free on the CASSS website. I think there is 850 pages of it, but it is excellent.

There was a four-step evaluation approach in the JPMA model, where they describe the assumptions based upon the model of the A-Mab case study for a designated upstream and downstream operation.

They showed in the examples how they prioritized the hypothetical critical quality attributes. They showed in the examples how they assessed and ranked the risks based upon the hypothetical process characterization study and historical manufacturing information. Then they also showed in the examples how they propose to determine those established conditions and their change level. Again, I would refer to the slides of the presenter for that. It was really excellent.

The conclusion was that this was still under discussion within JPMA, but this kind of an approach using an already established hypothetical model with great detail, might be very useful in communicating potential ideas within the committee and across the agencies to see how this might work.

Established Conditions and Enhanced Process Control

Patrick [Swann] gave us a presentation from Biogen. In fact, he made the point that models are very useful because they let us test those higher level policy strategies that are being considered in the working groups.

He also used some examples, using a bioreactor, UF/DF filtration and DS testing model and then a feed forward control strategy, with the concept of just seeing how these would be managed in that established conditions world.

There was a good table in his slides that related business impact versus regulatory affairs impact, and he gave us some examples of where the various elements of established conditions would fall within that matrix.

He also showed a lifecycle management plan. That piece of information was very important, because it provides proof to the regulators that the company is operating in a state of control with respect to their product quality system. It also provides transparency to health authorities and lets them be comfortable about getting agreement on post-approval changes.

I made a note here because it was his example of the DS testing model that we later discussed – about by moving the controls upstream of the process, they actually are controls being passing and failing of those tests and not just alert limits.

Panel Discussion

Our discussions for that session:

- **Could there be some additional review and inspection examples in Q12 on how those reviewers and inspectors work together and avoid duplication?**

The answer was, actually, the goal is to minimize the burden on the reviewers and inspectors by having an increasingly powerful product quality systems to manage the changes.

There is an example in version 7 of the Q12 document. Health authorities noted that it is critical that assessors and inspectors do work together. The comments from the various agencies that were here is that they do expect that reviewers and inspectors do work together, because they have a mutual responsibility for product quality. And it is vital that the assessors and the inspectors understand what the company's product quality system is and come to an agreement that it is suitable to serve to manage internal changes. If it is not a suitable product quality system, then both the reviewers and inspectors will have an issue.

- **One of the comments was, what do companies have to do internally to facilitate the success of ICH Q12?**

The answer was do ICH Q10 really well, because it is the foundation of the trust and the responsibilities that are going to be conferred upon it, if you are go to an established conditions model where you are going to be responsible for adjudicating changes that the regulatory authorities are not going to be doing. So it is a critical base line that must be in place and function properly, so that it can take over responsibilities that ICH Q12 will give to it.

- **Does ICH Q12 have any plans for metrics to be sure the PQS is in fact working successfully?**

The answer was not formally. Currently all approved product changes are managed under the PQS, so it is supposed to be working now. Many of those require regulatory notification anyway, so there is some information as to whether PQS is working okay or not. But the fundamental role of the PQS remains the same, which is to make sure it is responsibly managing the changes within the company.

- **In China, all tests, parameters and specifications are included in documents for biologics. So will CFDA use ICH Q12?**

The reviewers indicated that, while they do definitely focus on advancements in technologies for products in China, they are currently considering what the role is for established conditions in their post-approval change management policies under their current legal system. They encourage advancement, and they are considering what impact this might have, but they are not yet adopting it.

- **It was asked about from the PMDA slides on two options for elements. Is there a preference for one or the other?**

And the answer was that the preference depends on how much data is provided to know which option is the best supported.

- **Also a question was asked about the same thing for the JPMA. With the risk ranking or model process, how much variability could be incorporated?**

The answer is that as much data is supportive of the established conditions on what those ranges would be.

- **Established conditions detail that would be needed could be agreed across each region. But what about harmonization on the level of detail in established conditions across all regions?**

While it was considered by the committee members ideal to get complete consistency across every health authority, it is highly unlikely that is going to occur.

There is a table in Version 7 that is an attempt to converge health authority thinking on these principles. The hope is that future examples would be able to help further discussions with the concepts. But the goal overall is that ICH should provide more clarity across regions. Even if there are some slight differences in practices among different health authorities, it should be much more convergent than it is now.

- **Currently the inherent/implicit established conditions as well as level of communication varies widely across regions. ICH Q12 tries to simplify this. But what if the heterogeneity of the change pathways is greater on the sponsor side than on the regulatory side? It will be a substantial challenge for health authority reviewers.**

The panel feed back that since the level of notification is based on risk approach, there is a potential for different risk rankings. It was acknowledged that there could be some issues with that. If sponsors use the established conditions that are given in the CTD format, it would at least allow consistency on the nature of the changes, but there is no guarantee that that alone will solve the challenges that were brought up by Health Canada.

- **Are biosimilars and their change management covered under ICH Q12?**

The answer was yes in fact they are. There is no distinguishing of the ICH Q12 principles between innovator products or biosimilar products.

- **If transparency and consistency are key elements of fair and balanced regulatory reviews, does the ICH Q12 decision tree facilitate this concept?**

The responses were that the differences in the decision-tree examples presented by the speakers today – some were in there before Version 7 was completed. It was acknowledged that this is a work in progress and that the decision tree examples would come from discussions with industry and regulators, and would be further refined as more information becomes available. The goal of ICH Q12 is to outline the principles on how to define critical process parameters, with an idea to process outputs. The approach to identification of those parameters could be risk ranked by the impact on product quality attributes.

But if the established conditions are mandatory to assure product quality, the question is what process outputs must be controlled to maintain quality and consistency? It was acknowledged that alternative control strategies would be acceptable, but then that alternative would become the established condition for the process and the product. And actually we picked this back up again this afternoon, when we were talking about changes in methods – that alternative methods are acceptable, but they would then become the new established condition.

- **Is it expected that each change category would be well defined in the approved established conditions?**

The answer is yes.

- **But then, once it is captured and approved, how easy or hard is it to change it?**

The answer was, to be determined, we so not know yet.

- **One more comment: performance-based evaluation is the only thing that will make ICH Q12 successful. Parameters-based evaluation seems most logical, but it is more complex to implement for established conditions.**

It is possible that parameter-based evaluation may not be perfect was the answer, but we have to start somewhere to get these concepts in practice. Because until we start walking with baby steps, we will never go any further.

- **Couldn't sponsors simply make a commitment on the product quality attributes for specifications and leave it at that?**

Well, in principle it is true that we are interested in the product quality. But just controlling the final product material has not been suitable for biologically-derived products, because slight changes in the process can impact product characteris-

tics that could be undetected by final testing alone. For reference, look at Sara [Kennett's] examples from the case study that she presented. It was acknowledged that this concept is much easier to do with chemically synthesized drugs that have a different pathway and have different risks associated with their impurities and degradants.

- **JPMA and PMDA are working on ways to adapt the application form to incorporate principles of Q12. What kinds of changes do they envision and when would they be presented?**

JPMA indicated that they showed some examples, but they don't know what is possible yet, in terms of ICH Q12. PMDA indicated that there are cases where established conditions are not solely based on risk assessment strategies. And so, only using risk assessment for defining established conditions may not be acceptable for the application form for every characteristic.

- **As approved matters evolve from the current state to the future, what kind of outreach or education from JPMA or PMDA is being planned to change the mindset and move it into a new direction?**

JPMA indicated that they have a Module 1.2 mock in progress with PMDA now. That may be something that might be suitable to share with the industry for further dialogue and refinement of concepts.

- **How can CDE continue to consider concepts like ICH Q12 and how should China continue engagement and contributions to the knowledge base?**

China indicated that their knowledge and experience could be combined with further interactions with ICH Q12. If China's industries are interested in having them participate, they would do so. Also they would welcome opportunities to get training on initiatives and emerging concepts. They reiterated that their goal is always product safety, so any efforts that allow them to better serve their goal would be welcome.

SESSION FOUR

ICH Q12 UPDATE: ESTABLISHED CONDITIONS FOR SPECIFICATIONS: RELATIONSHIP WITH ANALYTICAL QBD

Established Conditions for the Specification and Analytical Procedure –PMDA Perspective

This was the last session today. We had an overview from the PMDA about the analytical procedures that are in the application procedure in the Japanese Pharmacopoeia, that method would be used for specification testing. Compendial methods contain very detailed instructions so that the method can be reliably conducted. Approval form may refer to the JP methods for the details given there. If not, it would be expected that the details for non-JP methods would be included in the approval form sections. And the goal for the level of the method detail is that another lab technician could easily perform the method as written and achieve successful data.

The PMDA indicated that they can see the issues of the post- approval change system for simple method changes, but they are mindful of the need to assure the quality of the product by understanding in detail how the analysis is going to be conducted for release and stability testing. But they did not rule out the possibility of some elements of ICH Q12 being adapted to the established conditions for methods. However, more discussions will be needed before final decisions could be made about that in relation to the current system in Japan.

An Industry Perspective on Established Conditions in the Analytical Control System

We had two examples that were given. One was from Hoffman-La Roche on how they are looking at QbD for analytical methods. The scenario two that he mentioned was given in Version 7 of ICH Q12.

Case Studies of Established Conditions in Analytical Procedures

The second was another JPMA representation. This is the model they have been looking at.

It was wonderfully detailed set of examples -- the most detailed I have seen yet anywhere about someone giving three levels of detail on an analytical method, as an example for what would be three different level of approaches: ● the current system ● an optimized description, and then ● a description based upon performance expectations. I am going to definitely review that one myself with a great more granularity, because as you probably know by now, I have few opinions on analytical methods.

Panel Discussion

- **How can you avoid conflict of the approved specification if you go to an established condition model with any written compendial procedures?**

The answer that was given rather flippantly was, do not include too much detail and therefore you can't be held to much of a commitment. We know that was done with a smile. We didn't really mean that.

- **How does the goal of analytical QbD in Q12 to allow greater flexibility in making changes to methods line up in requirements in places where compendial methods are mandatory?**

We had a very, very animated discussion about this. The take-home message was that it was clear that most pharmacopoeias do have an understanding of the equivalency of the method. Both Health Canada and PMDA confirmed that alternative methods are allowed with supportable data and suitable validation. But then if you state you are following the compendial as written, then you need to be following the method as written. So you can follow whatever you are claiming to follow, whether it is an alternative method or the compendium method.

- **Would ICH Q12 be suitable for compendial tests to be changed from the written procedure?**

It is allowed to make changes in compendial methods [after approval] with suitable validation data, but any change would require an authorization, at least from the approval form.

- **Would analytical QbD principles allow compendial laboratories, OMCLs, to make changes without notifying the sponsor?**

And the answer seemed to be that, since they use monographs for purposes other than sponsor-based product control and quality, they should follow the procedures as written, and changes would be managed by their relevant pharmacopeia who published it.

- **If you are replacing legacy technologies with new technologies, there were two cautions from the field: ● One is that vendor reagents are not always robust and reproducible, so be careful that you are not jumping from the frying pan into the fire with the new method. ● Also the vendor software for some new technologies is not always validated for GMP-level compliance. How would this be addressed?**

The answer from the panelist was that that they would not expect to introduce a brand new technology directly into a GMP lab – that would be vetted through the analytical development department, and given time to be proving its function before it would be introduced into a full GMP environment for a new methodology.

- **Performance-based established conditions for methods?**

The principle of the method is currently considered as the established condition in ICH Q12, not just the analytical target profile. So any changes to the procedure would be allowed as long as the principle is retained. If you change the principle of the method that is being used, that would trigger a change notification to the regulatory authorities.

- **We had a very long discussion about this question: Is the description in Mod. 3 S.4. sufficient to inform regulators about how methods are being run?**

The FDA said, actually not usually. Most of the time there is not enough information in S.4.Mod 3 to assess if the method validation is suitable or actually to even understand the procedure itself – for example, how system suitability is run, or how the results are calculated. Reviewers and inspectors have to see the complete assay procedure in order to make a determination on the acceptability of a method validation package. So to avoid delay in review times, FDA just often asks for the SOPs, so they wouldn't have to go back and forth with questions and answers and delay the review.

There is a new method guidance validation published by the FDA that gives very clear information on how much detail is expected in the dossier in Mod 3 on method procedures, so they can more effectively review and understand that section.

The ICHQ12 approach envisions providing key elements of the method for the established conditions for commitment. But it was also acknowledged that it intended to provide the complete SOP and method validation package as supportive information for each method. In fact the concept was that maybe if we have an established condition, it would actually take the pressure off of sponsors who would provide the SOP if they did not believe it was being completely adopted as an established condition.

- **We also talked more about the location of information. Where would the EC information on methods be placed in the common technical document?**

The ICH group agreement is that established conditions would be given a separate section which was extracted from other supportive sections, but there is not agreement yet on where that actually would be, because it is different in different regions. For example, Japan already does this. And so, it is still under discussion. What is agreed is that it would be separate. What is not agreed yet is where it would be located.

- **How does just using the analytical target profile (ATP) as the established condition assure control of the product specification?**

The answer was that in fact the ATP was based on a collection of data that supports the specification. It is the culmination of a lot of information, a lot of data, several layers of CQAs and controls. So it is not solo in its value as it might seem to be at top of the pyramid that was presented.

- **How do you handle reference product specifications and methods? Would Q12 allow changes in reference standard?**

The answer was pretty resoundingly, no. The reference standard is a regulatory commitment as established conditions. You can't make changes in your reference standard without regulatory notification and approval.

- **Does industry have to wait for ICH Q12 to be approved to begin to implement and adopt some of the practices?**

The answer from regulators was not necessarily depending on how you want to use it and what its relationship is to the current statutory requirements in each region.

- [CLICK HERE](#) for access to the slides from the presentations at the forum and Ritter's summary slides.
- [CLICK HERE](#) 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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