IPQ INTERNATIONAL PHARMACEUTICAL QUALITY Inside the Global Regulatory Dialogue

Post-Approval Change Regulatory Burden Draws Heat at Japan Biotech CMC Strategy Forum

Industry associations have been meeting with Japanese regulators to highlight the problems they are experiencing in Japan's process for regulating post-approval manufacturing changes, including a lack of flexibility around biotech product changes that results in most requiring prior approval as well as meetings with the agency to resolve unclear expectations.

The Japan Pharmaceutical Manufacturers Association (JPMA) met with Japan's Pharmaceutical and Medical Device Agency (PMDA) and Ministry of Health, Labor and Welfare (MHLW) in the latter part of 2012 to highlight concerns its membership had raised regarding post-approval changes. Of primary concern were the requirements for reconfirming shelf life and the disparity between Japan's requirements and those in the U.S. and EU.

A 2013 meeting also brought in the Pharmaceutical Research and Manufacturers of America (PhRMA) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) to provide perspectives from outside of Japan.

The post-approval change regulatory process in Japan and how it compares to approaches in the rest of the world was a key focal point of a CASSS "CMC Strategy Forum Japan," held in December in Tokyo, at which Japanese industry and regulators were well-represented. Also in attendance were regulators and industry representatives from Asia as well as from Europe and the U.S.

The first of CASSS' Japan CMC Strategy Forums was held in Tokyo in December, 2012 (*IPO, January 16, 2013*). A third in the series will be held in December of 2014, also in Tokyo.

CASSS also hosts a strategy forum in Europe in the spring supported by European regulators, along with the strategy forums it holds in the U.S. in January and July. The Europe forum this spring will take place May 5-7 in Sorrento, Italy.

Changes are a Japanese and Global Problem

The session on biopharmaceutical post-approval changes at the 2013 Japan meeting included: • a detailed look by PMDA's Futaba Honda at Japan's regulations regarding submissions and changes • JPMA's perspectives on the current post-approval change requirements, presented by Takeda's Takao Kojima • the difficulties and challenges faced by industry when making post-approval changes in multiple markets by Amgen's Toshiko Mori-Bajwa, and • Genentech's Lynne Krummen on managing post-approval changes using risk-based comparability concepts.

[Editor's Note: Honda's, Kojima's and Mori-Bajwa's complete remarks are included below].

PMDA's Honda explained that most post-approval changes in Japan for biopharmaceuticals need to be filed using a "partial change application" (PCA), which requires approval prior to implementation, takes one year to approve, and includes an on-site GMP compliance check.

Specified lower-risk changes under the two-tiered Japanese system can be implemented at the time a "minor change notification" (MCN) is filed. PMDA assesses the MCN at the time a subsequent PCA is filed or during the next GMP inspection, whichever comes first.

Honda explained that biological product changes typically require a PCA because biological syntheses are less defined than chemical ones, produce less homogeneity in the molecular structure, and require a multidimensional analysis when changes are made to ensure that safety and quality are not impacted.

Takeda's Kojima also reviewed PMDA's change categories en route to discussing JPMA's concerns.

Kojima's remarks encompassed: • the results of a survey of JPMA's member companies concerns with how changes are administered • the association's meetings with PMDA to voice the concerns and present alternatives • Japanese requirements vs. those in the U.S. and EU, which shows that, in general, Japan's requirements are more onerous, and • the case for international harmonization.

JPMA's survey revealed that, of 48 post-approval changes that needed regulatory notifications in Japan, the U.S. and the EU, there were some that could be filed in the U.S. as an annual report and handled in the EU as Type 1A variation, but in Japan required pre-clearance through a PCA.

Amgen's Mori-Bajwa provided a broader view of the problems international firms face when trying to make changes in multiple markets.

She presented a revealing case study showing how a single manufacturing change applied across global markets can take as long as five years to complete and require 100 or more separate supply chain strategies to ensure market supply while the changes are being approved.

Mori-Bajwa explained that Amgen's model for filing in multiple countries includes three "waves:" • The first wave of filings are in reference countries with approval cycle timelines which can take between six and twelve months. • The second wave of filing goes to countries that do not require approval from a reference country filing, with approval times between nine and 24 months. • In the third wave are countries that require reference country approval prior to filing, further extending the global clearance process.

The Amgen exec pointed to a variety of reasons that prompt changes during the lifecycle of a product. She highlighted the difficulties of managing approvals in multiple countries, and the increased work load that multiple variations cause for regulators. "They have limited resources to support all the changes that we are filing," she noted. "Sometimes this can lead to delays in approval."

The last presenter in the post-approval change session – Genentech VP Krummen – provided further insights on strategies to manage global changes, emphasizing the importance of risk management in post-approval change filings and approvals.

Krummen made a case for: \bullet continued dialogue regarding the realities of global manufacturing and supply \bullet embracing and implementing risk-based approaches for product development and life-cycle management with an emphasis on enhanced product and process knowledge and patient risk/benefit, and \bullet continuing to strive towards regulatory convergence and facilitating risk-based requirements and implementation timelines.

Post-approval changes were also a front-burner issue at the CASSS/FDA WCBP Symposium in late January in Washington, D.C. A plenary session was held at the conclusion of the conference, which provided a wealth of additional insights into the post-approval regulatory quagmire in which global companies are currently immersed. (An in-depth review of the WCPB discussions on post-approval changes and the implications for the current CMC review paradigm will be provided in IPQ during February.)

Other Key Biopharma Topics Explored

In addition to the session on post-approval changes, the Japan CMC Strategy Forum included four other sessions on key topics with which the international biotech community is actively engaged.

Setting the stage at the opening session were presentations on the "recent trends in the regulation of biopharmaceutical products" and how various stakeholder collaborations are impacting them.

The current regulatory landscape in the various regions was explored from the perspective of: • PMDA by Office of Cellular and Tissue-based Products Director Jun Sakamoto • FDA by Office of Biotech Products Director Steven Kozlowski • EMA by Head of Quality Peter Richardson • India by Indian Institute of Technology Department of Chemical Engineering Professor Anurag Rathore, and • the Asia Partnership Conference on Pharmaceutical Associations (APAC) by JPMA's Kozo Akasaka.

Biosimilarity was among the regulatory topics addressed in the updates. Receiving attention was the first EU approval a few months earlier of two monoclonal antibodies (MAbs) – Celltrion's Remsima and Hospira's Inflectra – both determined to be biosimilar to Janssen's Remicade (infliximab). Remicade was originally approved in the U.S. in 1999 for the treatment of rheumatoid arthritis and inflammatory bowel disease. The EU approval process was highlighted as an important step that can provide a template for other agency evaluations of biosimilarity for monoclonals.

The second session explored control strategies for aggregates and particles in biopharmaceuticals, including the challenges of identification and quantitation.

Esai's Yasushi Shikata presented an overview of the issues. Discussions followed by Kyoto University's Takayuki Yoshimori and Biogen Idec's Robert Simler regarding recent advancements in technology used for aggregate and particle characterization.

Simler focused on the 0.1-1 micron size area that has proven the most challenging to characterize. He provided examples of both new applications of proven techniques and novel analytical methods, such as resonant mass spec and nanoparticle tracking analysis, which "allow for an ever increasing characterization of the aggregate/particle populations of protein solutions."

On the second day, following the discussion of post-approval changes, a session was held to explore how quality by design (QbD) is advancing in Japan and internationally.

The PMDA perspective was provided by Office of Cellular and Tissue-based Products Reviewer Yasuhiro Kishioka. Chugai Pharma's Mikio Suzuki then provided "lessons learned" from a QbD biologics application in Japan for breast cancer therapy Perjeta (pertuzumab). Chugai is licensed to distribute Roche's Perjeta in Japan – the first cancer drug approved to treat breast cancer pre-surgery.

The CMC section of the Perjeta application has received considerable international attention, having undergone a joint review through the FDA and EU QbD parallel assessment pilot program. While the joint review was resource-intensive for the agency, it proved highly informative on highlighting some differences between the two regions and has led to important discussions around how to further harmonize and standardize the biotech, CMC, and QbD approaches.

FDA granted Perjeta priority review status and approved the drug in 2012, along with Switzerland and Mexico. Approvals were granted in 2013 in the EU, Russia, Canada, Australia, Brazil, Korea, Taiwan, Japan, New Zealand, and South Africa.

The concluding presentation at the session was given jointly by two former top biotech regulators now working in industry – Kowid Ho and Patrick Swann. Ho left the French agency AFSSAPS to join Roche in the latter part of 2013, and Swann left FDA mid-year to join Biogen Idec. The two provided their perspectives on the evolution of QbD for biotherapeutic products.

Ho focused on the learnings to date from the FDA/EMA parallel assessment process. Among them is that: • The agencies do not support the use of the term "key process parameter" (KPP) since it is not an ICH term and may be used differently by companies • All parameters that have an impact on a critical quality attribute (CQA) should be classified as critical; and that • A risk judged to be "critical" remains critical even if it is mitigated.

The final session examined new technologies in MAb engineering and the scientific, structural, and regulatory complexities of antibody-drug conjugates (ADCs).

It was noted that the promise of ADCs to increase the effectiveness of the antibodies while decreasing adverse reactions, such as in chemotherapy, has gone beyond proof-of-concept and into commercialization – with more than 30 products approved and over 200 under development.

Receiving attention were the challenges of developing appropriate analytical methods. It was noted that the methods used for antibodies may not be generally reliable for ADCs – for example, charge-based methods will give different results depending on the linker – and often need to be modified to be effective.

Tokyo University Institute of Medical Sciences School of Engineering's Kouhei Tsumoto provided an overview of new technologies that are being developed to analyze antibodies and ADCs. Further input on characterization of and control strategies for ADCs, with Genentech Protein Analytical Chemist Fred Jacobson addressing lysine-linked products and Seattle Genetics Quality VP Charles Smith focusing on cysteine-linked ADCs.

At the conclusion of the CASSS CMC Strategy Forum Japan in December in Tokyo, Roche Biologics Regulatory Policy Head Thomas Schreitmueller provided a summary of each of the five meeting sessions *(see box below)*.

SUMMARY OF 2013 JAPAN CMC STRATEGY FORUM

At the conclusion of CASSS' biopharmaceutical CMC Strategy Forum Japan in December in Tokyo, Roche Biologics Regulatory Policy Head Thomas Schreitmueller provided a summary of the five forum sessions, which covered: • trends in regulation • control strategies for aggregates and particles • post-approval changes • how QbD is advancing in Japan and internationally, and • new technologies for antibody engineering and ADCs.

Trends in the Regulation of Biopharmaceutical Products

The first topic we discussed was recent trends in the regulation of biopharmaceutical products. I was happy to see the remarks and slides from [JPMA Executive Director Hideo Utsumi] regarding his definition of pharmaceutical regulation – that it is a collaboration between industry, academia, and regulators. Really, I could not agree more with this. In fact, this is what we discussed over the last two days. This was, to a certain extent, setting the stage.

We then heard what is going on in the agencies. There is a lot of activity, whether you look at Japan, the U.S., or Europe. This is necessary to cope with all the things that are going on in new product development, QbD, tighter review timelines, and so on.

What we also learned is that there are new guidances and new approval systems underway – for example, exchanges with academia are taking place more and more. Special groups are being implemented in agencies to cope with QbD and other challenges.

With respect to **biosimilars**, we saw that the number of consultations is really increasing. Eventually it might be good if there were more exchanges between the agencies, especially on a global level, to ensure proper implementation of the respective guidelines. This is especially true when we look at emerging markets.

QbD, like in every conference, was an important topic. I found [FDA Office of Biological Products Director Steve Kozlowski's] elaboration very interesting in starting critical discussions and collaboration about critical attributes.

Also important are the activities which we have seen in **APAC** [Asia Partnership Conference of Pharmaceutical Associations]. This is an example of ongoing harmonization efforts that is recognized in other parts of the world.

We had quite an extensive discussion regarding QbD. There is still limited experience on the biotech side, but we are moving along. What regulators criticized is that a risk-based approach is often not very developed by companies, and immunogenicity is seen as a very critical thing.

Like always, when we discuss QbD, this is still evolving. If you ask five different people about a certain term, previously, you would get five different answers. Now you will get two or three. There is still room for improvement.

We heard today that QbD is progressing in the analytical areas as well.

Biosimilars were quite extensively discussed, focusing on changes in new regulation with respect to sourcing of the reference material. It was also recognized that the monoclonal antibody guideline in the EU is really setting the stage with respect to biosimilar concepts.

We discussed that the link to reference products is getting weaker over time, with new guidelines now clearly saying that the biosimilar will have its own life-cycle. What does this mean for interchangeability, for example?

In the context of emerging markets, clearly, I think, leading agencies should take more responsibility with respect to education of other agencies.

The regulatory framework regarding **cellular therapy products** was also discussed. I think the common-sense view was that a risk-based approach is key for these kinds of products. It is a fast-moving field, and therefore quite challenging with respect to guidance development.

Harmonization was also mentioned with respect to **orphan drug designation**, which might be something to consider. Regulatory convergence in Asia, as pointed out before, we think is really a good thing and should be taken further. I have to say I was extremely impressed looking at the improvement of the review timelines that were presented by PMDA over the time.

Control Strategies for Aggregates and Particles in Biopharmaceutical Products

We then discussed aggregates and particles and their importance for biopharmaceuticals. Clearly, we have methods in place, but they are interpreted in many different ways. The measurement itself, especially if you think about visible particles, is something that is highly subjective. We get more and more methods these days that allow more accurate detection of aggregates and particles, and even further characterization. What we also can say is that we really have made a lot of progress with respect to composition analysis of these mixtures. We can ask more questions, but are these academic questions? Or do they really add value with respect to product development?

With respect to **immunogenicity**, I think there is no clear evidence for the relationship to particles. We have certain hints that there might be something behind it, but we always have to keep in mind that there is not a very straightforward study that would show us that it is actually related.

Independent of this, aggregates have to be controlled as an impurity. I think we have a handle on this as well. The question now seems to be where and how to control the process and what method to apply.

Post-Approval Variations for Biopharmaceuticals

We had very interesting discussions around post-approval variation of pharmaceuticals. PMDA explained that a new API, strength, dosage form or brand name requires a new application. A partial change application [PCA] will be followed by a one-year compliance check. Process change categories are to be specified by the applicant. Details regarding how these compare to the U.S. and EU were discussed.

Then we also had a very interesting **survey by JPMA**, which I think is quite a solid piece of work, given the numbers of companies and variations that they examined. What was interesting was that most of the variations really related to the manufacturing process and analytical methods or specifications. The vast majority, of course, were handled as partial change applications. JPMA hopes that eventually there might be some relief with respect to that burden.

Most critical of these was how shelf-life is established after variations. There have been proposals developed by JPMA concerning this.

One proposal is that a more risk-based approach might be appropriate in cases where comparability has been demonstrated – that good comparability of the drug substance change should not impact the shelf-life of the drug product. Continuous dialogue between local and global stakeholders is helpful and essential....

We also saw some presentations concerning the **global post-approval change** situation, including some case studies where it became clear that for certain changes you actually need five years until you can have global implementation. I think it is clear to everybody that this is not an acceptable situation and we clearly have to work on this to improve the situation. The key is convergent harmonization. From my personal experience knowing many of these agencies, I have to say the way forward has to be mutual recognition and collaboration between the agencies in order to improve the situation.

We had a nice presentation on **comparability** and what we should do there. I think it became clear that this requires a risk-based approach. But it is not just doing an analytical comparison on the results and deciding what else to do. It is clear that you need to decide right away on the proper strategy of what you should really do. Again the message came out that in fact these different regulations that we have all over the world, rather than helping, eventually are putting more risk on the supply chain.

We do a lot of things at manufacturing sites, and we heard comments from the agencies that they are not aware of all the data that we have. There certainly is a bit of mistrust, on both sides, which then also may lead to delays. But the key is once they go in the direction of global harmonization, then they really may be able to solve this.

The important role **ICH** members have was discussed because they are setting the stage. I think the whole world is looking at these ICH requirements and how the countries are implementing these regulations. I think the closer we work together, the closer we interpret things, the more impact this will have for all the other countries.

There was an interesting discussion talking about variation in **guideline generation**. Should they be more prescriptive? Should there be a lot of examples? Would this add clarity? I really did not sense the opinion going clearly in one direction or the other. And it is clear that there are advantages and disadvantages of both. You lose a lot of flexibility the more examples you put in, but then you also have clarity at the end, and you can plan for it.

QbD Case Study

Regarding QbD, I am still dizzy with respect to critical quality attributes, CQAs, CPPs, and I do not know how many other abbreviations have been used during this discussion. We still have open questions and there is still learning going on. This was, for me, the key message of the discussion. We have made a tremendous amount of progress over the last years. In fact, this resulted in the first approval of a QbD application including design space in the US for a biotech product.

Whether we like it or we do not like it, it will set the stage. It will set the development stage for the future, because people have recognized that this systematic approach really will lead to rational designs of control systems and so on. This is why, eventually even for orphan drugs or breakthrough products, there were will be no way around using the principles here.

As pointed out before, in using **QbD for analytics**, regulators are open for discussion. I think this was the key message. So let's take this opportunity, and during the next forum have a session on this topic.

New Technologies for Antibody Engineering

Concerning **ADCs** [antibody drug conjugates], what was interesting to me is that there are now thirty-four ADCs in development – I was not thinking there were already that many. It is really great that that much work has been done. I think there are lots of challenges. We heard during the presentation and also during the discussions the challenges related to the formulation, the linker, stability issues, manufacturing changes, and so on. I think it is a challenge to make these ADCs. I think that was made very clear during the presentation.

The good news is that we have a lot of analytical methods, which we are using for characterization, and also for establishing a control system. The orthogonal method, for the complexity we are dealing with, is highly critical.

QbD principles might be applicable for individual components. It still might be difficult for the whole product, but eventually could be used for small molecules and for antibodies.

We also had discussions around **starting materials** for intermediates. The message here was that all these intermediates are practically treated as an individual API at the moment.

PRESENTATIONS FROM POST-APPROVAL CHANGE SESSION

The following are the complete remarks made by PMDA's Futaba Honda, Takeda's Takao Kojima, and Amgen's Toshiko Mori-Bajwa at the post-approval change session of the Japan CMC Strategy forum. Honda, a biopharmaceutical reviewer for PMDA, provided a detailed look at Japan's post-approval change requirements and procedures. Kojima focused on JPMA's concerns with the current approach in Japan and how the requirements differ from those in the U.S. and EU. Amgen CMC Regulatory Affairs Director Mori-Bajwa provided a broader view of the problems international firms face when trying to make changes in multiple markets, including a revealing case study on the complexities and timelines for making the changes, and a "wave" model used by Amgen. [Editor's Note: Honda and Kojima delivered their presentations in Japanese. Provided below are the translations done simultaneously at the session.]

PMDA'S FUTABA HONDA ON REGULATIONS IN JAPAN

I am from the office of in charge of review of biopharmaceuticals at PMDA [Pharmaceuticals and Medical Devices Agency].... I would like to talk about the post-approval change regulations in Japan regarding the partial change applications in Japan, and what regulations apply here in Japan.

This is the agenda for today – there are four points:

- Number one is that in Japan within the application forms there is a part related to manufacturing methods and partial change applications.
- There are procedures to make the submissions, and the associated standard review periods and procedures for that.
- There are two types of change procedures here in Japan: There is a partial change approval application and a minor change notification.
- And number four is about making partial change applications and what sort of data would be expected from the regulatory authorities.

I will be using these abbreviations: PCA, for partial change approval applications; and MCN for minor change notifications.

This is the CTD structure that is agreed upon within ICH *(see box below)*. Under M1, we have administrative and prescribing information related to manufacturing methods, the summary of which is given in M2.3, Quality Overall Summary, or QOS. M3 gives the manufacturing method information.



There is an application form for marketing approval. And within that, the items written there, include the brand name, ingredients and quantity, annex specifications, and manufacturing procedures. It also includes dosage administration, indications, storage conditions, periods of validity, spec and test methods, and manufacturing sites.

Within the application document are the requirements for the appropriate change procedures. It will be a PCA or an MCN.

So number one, under M3, as you may be aware, are the manufacturing methods, and the manufacturing siterelated information for the drug substance [DS] and drug product [DP]. They will be put into the respective chapters in accordance to the ICH guideline.

In M2, the overview for development strategies will be provided based on the information in M3. In the application forms, there will be different items specified under which the essence of the critical information will be given. In Japan, information in the application form is what is approved. If there is a change applied, then you need to take up some procedures related to change regarding M3 and M2 when making the original submissions. If there is a PCA, it will need to be submitted, but they will not always require exhaustive change procedures.

For PCA and MCN, these are the standard periods and procedures (see box below).



After the **PCA** submission is made, one year is the standard review period, during which, of course, a review will be taking place. Within the review period there will be a GMP compliance check as well. This is not PMDA – the quality control office will be in charge of that GMP compliance check.

The check will probably happen six months before the expected approval time. You need to make an application for that GMP compliance check. Therefore, after the initial submission for change, within this period, you have to verify the application information. According to the information, the reviewers will also be preparing for GMP inspections. The approval will be expected at about one year's time. After that, you will be able to ship the products with the changes.

In Japan, after the **MCN** change is applied – for example, if there is a change in manufacturing methods – the shipment of that first product with the change will be that day. And within thirty days of that you have to notify the regulatory authorities. The content of the notifications will not be subject to review right away. But if there is a new PCA, or if there is a periodic GMP inspection, the inspector will be reviewing or checking the contents of the MCN.

Comparing the change categories between the EU, US, and Japan MCNs: Between the EU and Japan, there are two major categories for applications and notifications, and in EU there is Type IA and Type IB. In the U.S., on top of that you have an annual report as well.

Regarding notifications in the EU, you have the notification before a change, and after a while, if there is no response, then you can affect the change. But in Japan, notification will happen only after the change is applied. So there are different categories by market regarding which one you should be applying. If it is critical, you need a PCA. If it is minor, then you can use the MCN.

As already mentioned regarding the MCN, there is no review happening right after that. It would happen only during the next GMP inspection or PCA submission. During the next periodic GMP inspection, if the MCN content was reviewed and it was found that it should have been a PCA, then the MCN will be invalidated. Once it has been invalidated, if the change was applied to the product and it was shipped, then according to the regulations there may be some administrative actions taken depending on the risks that such a change may have posed.

I would like to explain what sort of classifications there are regarding the general principles for deciding whether the change is a PCA or MCN.

Changes Requiring a PCA in Japan

- Deletions or changes of specifications and test methods
- Change of the manufacturing processes regarding inactivation or elimination of pathogens
- Additions , changes, or deletion of dosage, administration, and indications
- Any other change that may affect quality, efficacy or safety of the final product

Regarding MCNs, the scope of an MCN are those other than specified here. This is very conceptual, by the way. If it does not fall under these definitions, you can use the MCN.

For biological products, according to the notifications issued in 2009, changes to items under manufacturing methods will require a PCA, in principle.

The reason for that is that biologics, unlike chemicals that are manufactured based on chemical synthesis, will utilize a biological synthesis process in biological bodies. Due to the mechanisms, there may be some inhomogeneity in the molecular structure. There are limitations to the physical chemical analysis. By changing the manufacturing method, the assessment to impact on quality and efficacy will require a multi-dimensional analysis. Therefore, there are many features, unlike the chemical synthesis products. That is the reason for the PCA.

Another aspect is that biological products consist of various kinds of materials such as proteins, glycoproteins, polypeptides and their derivatives, and there are extracts from biological bodies as well. Therefore, they require different controls. So unilaterally, we cannot specify what changes could use an MCN. So we think these changes require PCAs rather than MCNs.

The change of manufacturing site requires an adequate change control system. Therefore a PCA is required, because changing a biologics manufacturing method may impact quality. Changes related to facilities for inspection and testing would only require an MCN. Therefore, even if it was the same manufacturing method,

once the manufacturing site changes, the impact needs to be assessed and reviewed by the regulatory authorities. When you submit the PCA, the process validation data at the new manufacturing site and the lot analysis results will be required to be submitted.

Regarding spec and test methods, this should be addressed, in principle, by PCAs, just like for a chemical synthesis product. However, if the acceptance criteria changes to become stricter, then such a change may be addressed in the MCN.

Regarding the expiration dating for biologics: In principle, you need to address it by means of PCA. When making submissions, you need long-term storage testing based on the real storage conditions.

Now I will talk about manufacturing methods, which is the main part of my talk. I will cover which changes will be a partial change, and which will be a minor change.

You need to include certain descriptions in the manufacturing method column in the application form. The processes required to ensure the quality of the drug shall be described. The control items should be clearly stated, and by doing that, GMP compliance can be verified. It is necessary to clarify all of the process operations and the manufacturing methods, including targets or set values, protocols and SOPs, and how they are controlled according to GMPs.

In actual production, if there are outliers, they should be handled as a deviation in terms of GMP compliance, and there are some considerations for the description and how you prepare the document. Where there is a change in a manufacturing method, whether that change will fall into a PCA category or not should be determined by the applicant and mentioned in the document.

The items should cover the flow of the manufacturing process – for example, raw materials, or cell banks, in the case bio-genetically modified protein products. Cell bank management should be described, including when they are updated and what procedures are to be followed. Also include the established criteria for proper process control and the sources of the biological materials.

Regarding process parameters, what should be PCA and what should be MCN? If there is almost no impact on the product, it is MCN and no additional data would be needed. In other cases, applicants need to use their judgment to decide what to include in the PCA or MCN – for example, validation data, equipment operation procedures, risk-management, design of experiment results, or prior knowledge. Those pieces of information will be included in the M2 or M3 document.

An allowable range for the target value or set value must be established in the product master formula or SOPs.

However, if these parameters are set for parametric release – for example, for homogeneity – or if the parameters can affect the quality significantly, it is necessary to specify an allowable range on the approval application form rather than a target value or set value.

In the event it is evident that there is an extremely low possibility of the change having an adverse impact on the quality or safety of the final product, an MCN may be applicable. For those cases, the applicant may make such a proposal when submitting an approval application. The proposal will be judged during the review as to whether it can be accepted. As an example of an applicable case – the allowable range for process parameters at the same manufacturing site – that is proposed at the time of application and may be changed during the review for approval or on the occasion of the actual production results.

Regarding changes in manufacturing method, regardless of the impact you would need adequate validation and change control, either for a PCA or an MCN, regardless of the magnitude of the impact of quality. You have to submit the changes based on Q5A and Q5E.

Regarding the documents that need to be prepared, you can have a simplified consultation with PMDA, and you can use that opportunity to decide if the protocol is adequate or not, and the agency judgment on whether there is an impact to quality and other items can be consulted through that formal process.

TAKEDA'S TAKAO KOJIMA ON JPMA'S PERSPECTIVE

The main topic of my presentation is a review of the current regulations in Japan regarding quality and our vision for the regulations.

In the biopharmaceutical committee, we discuss change management at the post-marketing stage. We have participation from each of our member companies. We talk about and research the issues and conduct questionnaires.

Today, based on the results of the questionnaires, I would like to present four topics:

- The first topic is the current status of administrative regulatory procedures. In the previous session, Ms. Honda explained the procedures in detail, so I would just like to briefly touch on this topic.
- The second one is a proposal on the administrative regulatory procedures based on the questionnaire results: I would like to cover the requests we gathered from the respective pharmaceutical companies.
- Number three is an overview of discussions on post-approval changes between JPMA, PMDA and EFPIA and what we have submitted to the authority.
- Last, for the biopharmaceuticals product development, to be able to facilitate product development, I would like to introduce what we are doing as a committee and our vision.

First of all, I would like to cover the current status of administrative regulatory procedures. *[Kojima briefly reiterates Japan's regulatory procedures, which Ms. Honda explained in detail above].*

This does not incorporate all the items, but here are some examples of the items which are applicable for PCA and MCN for biotechnology products and synthetic products.

Examples of Japan Change Filing Categories: Biotech vs. Synthetic

Biotechnology products:			
Partial Change Application (PCA)	Minor Change Notification (MCN)		
Package form change/addition	Testing site change/addition		
Site change/addition (DS, DP, packaging, storage)	Manufacturing process change identified in the application form and justified in the CTD		
Ingredient changes			
Manufacturing process change			
Testing method change			
Synthetic products:			
Partial Change Application (PCA)	Minor Change Notification (MCN)		
Package form change/addition	Site elimination (one of several sites)		
Site change/addition (DS, DP)	Site addition (storage, packaging, testing)		
Ingredient changes	Manufacturing process change identified in the application form and justified in the CTD		
Manufacturing process change	Tighten specs		
Testing method change			

These are just some examples. For biopharmaceuticals compared to synthetic products, only limited changes are within the scope of minor change notifications....

As Ms. Honda explained, for the parameters within the scope of MCN, it is possible to use those marks listed here, and the legitimacy would be determined in the reviewing process. Compared to synthetic products, for bio-pharmaceuticals it is very limited.

Survey of Changes Shows Disparities

I would like to give some examples we collected as a result of the questionnaires. Here is the purpose or objective of this questionnaire: In the biopharmaceutical committee, we identified what kinds of administrative and regulatory procedures we have as challenges. That was the overarching objective – to list those challenges. We have listed some actual cases of those change variation cases and we have made a proposal to the authority.

This questionnaire took place from May to June of 2011, and involved 36 pharmaceutical companies, which are the members of the biopharmaceutical committee of JPMA. We received responses from 32 companies out of 36, so it was an 89% response rate. We had 21 Japanese companies and 11 non-Japanese companies respond.

For the change cases, we have gathered over two-hundred cases. Further analysis was based on 99 variations and 43 proposals, with detailed information provided by 18 companies.

Here is the breakdown of the products of those variations: • mammalian cell culture products make up thirtyeight cases • recombinant microorganisms thirty-five cases • fourteen cases for recombinant vaccines, and • twelve cases for animal cell products that were not recombinant.

Here is the graph of the number of cases by the types of changes *(see box below)*. Here are the actual changes that took place by ingredients and contents, manufacturing process, specification of API and drug product, storage and shelf life, manufacturing sites, and others. The parts in blue are handled as PCA, and the green represents the minor change notifications or MCNs.



The number of changes related to the manufacturing process is over fifty, so that was the most. Next were the changes related to specification and testing methods. What the MCN and PCA ratio tells us is that most of the cases you see are blue, so there are more cases that needed to be handled as PCA.

I would like to talk about what kind of specific cases we had within the MCN scope. For the minor change notification cases, there were seventeen cases. To give a breakdown, the changes related to the manufacturing process were seven, the specification and testing method was one, manufacturing sites had six, and the 'other' category three....

Here are some overseas cases. I have made some comparisons between Japan and overseas. In overseas markets, there were forty-eight cases reported for changes taking places. Out of those forty-eight cases, the sorts of changes that took place in the US are listed here on the top. Here is the number of actual cases listed next to it, and in the EU as well.

Post-Approval Change Requirements in the U.S., EU, and Japan The following is data representing 48 change proposals reported to JPMA from its members and the corresponding classification requirements in the U.S., EU, and Japan.				
		РСА	MCN	
Annual Report	4	3	1	
CBE	2	2	0	
CBE-30	5	4	1	
PAS	18	17	1	
No answer	19	18	0	
EU		Japan		
		РСА	MCN	
Type IA	2	1	0	
Туре ІВ	3	2	1	
Type II	26	25	1	
Extension Application	0	0	0	
No answer	17	16	1	

In Japan, it lists what kind of change procedures are needed to take place, either partial change or minor change. Comparing Japan and overseas, the measurable gap was observed in annual reports. In the US, some could be handled in the other parts of the annual report, but in Japan we needed to file a partial change. Those are the three cases. In the EU, it was handled as a Type 1A. But in Japan, we needed to file a partial change application for one case.

JPMA Members Request Simplification and Clarification

Now I would like to move on to the second topic of my presentation. We have done these surveys, and as a result we have identified requests that were expressed by the member companies. Altogether, forty-three proposals were identified in the questionnaire.

This is the breakdown of the requests: • There were twelve proposals about the setting of shelf-life • a simplification of administrative procedures had twelve proposals • there were eight on clarification of administrative procedures requests; and • eleven other requests.

Because of the limitation of time, I would like to focus on setting of shelf life and simplification of administrative procedures.

Regarding requests for the **setting of shelf-life** when changes are made to the production method, comparability needs to be established. There is a possibility of a reduced shelf life. For example, if three years was the shelf life with an older drug, and the manufacturing process changed, because of time limitation you may only have data for one or two years for stability. So the original shelf-life was three years, but was reduced to two years because the data submitted only covered two years. Approval is only given for the data which is available at the time of the submission.

With this as a background, member companies have made requests. The basic assumption is that before and after the change, if product comparability needs to be established, a high level of comparability should be established. If system comparability is established, based upon the experiences and achievements in the previous years, and if it was determined that the change never had impact on the product after the change, and if the comparability can be demonstrated in terms of the safety and efficacy, instead of establishing a new shelf-life, the shelf life pre-change of the product should be able to be used for the product after the change.

Setting Shelf Life

This is the first request which we have identified from the questionnaire. Stability data will be gathered and it will be used for the internal purposes, but should not be required to be submitted to the health authority.

The second request that we identified has to do with when quality and efficacy and safety are not impacted as a result of the change. If you do not have enough experience with the performance of the previous site to demonstrate comparability, and if there is a need to gather long-term data to ensure comparability, then the shelf-life should be established based on product data at the new site. During the course of the review, we will commit to the authority that we will gather safety data, based upon the protocol, and when the long-term safety data is obtained, then we will go through the MCN instead of the PCA. Currently, this kind of approach is not accepted, but our expectation is that in such a case only a minor change notification will be required.

For the purpose of extension of the shelf life, these are the approaches taken by the rest of the world.

In the case of the United States, based on the approved safety protocol when the shelf life is expected to be extended, the annual report is enough. Likewise, in Europe, a Type IB will be required. However, here in Japan, based on the safety protocol, the safety study needs to be done, and when the shelf-life is to be extended, the PCA procedure has to take place. The review period will be twelve months.

Given this background, member companies asked us to request changes in how shelf-life is set.

Likewise, similar requests were expressed about site changes. If the sites are highly similar, the shelf life of the product produced at the new site should be the same as that for the product produced at the old site. Stability data would be used only for in-house purposes and would not be submitted.

Simplification of Administrative Procedures

The next request is about the simplification of administrative procedures. As was mentioned before, when there is a change made to the manufacturing method for biopharmaceuticals, the basic principle is to apply the PCA – the partial change application procedure. Even with appropriate change management and control, unlike the case of a chemical synthesis, we have to go through the partial change application. If the change has little impact to the biopharmaceutical, then we think it should be handled just like for chemically synthesized products.

There are differences between the procedures followed in Japan and the rest of the world. In Japan, a PCA is required for most of the cases. Currently, here in Japan, we only have two approaches – one is PCA, and the other is MCN. In the United States and Europe, there are CBE-30 or Type 1B approaches. And also in the

United States, if the comparability protocol is submitted prior to the change, and if it is approved, then there is a possibility of reducing the level of the requirement. These are the main differences between Japan and the rest of the world in terms of the procedures to be followed.

The third topic stems from requests that we looked into on the biopharmaceutical committee. When it comes to the administrative procedures associated with the changes for biopharmaceuticals, unlike the chemically synthesized product's administrative procedures, there is not a very clear description of what we have to do, so a case-by-case approach has to be taken. As a result, we have to talk with the health authority every time we have to go through those changes.

Nowadays, the development of biopharmaceuticals has been advanced. As a result, the health authority has accumulated lots of experience reviewing biopharmaceutical products and changes. Based upon on those accumulated experiences, we would like to request to the authority to simplify and improve the administrative procedures. That is why we have decided to compile our requests and ask for an opinion exchange with the health authority.

We have had discussions with the health authority. The first meeting was with MHLW, PMDA, and JPMA's Biopharmaceutical Committee and Regulatory Affairs Committee. That took place last year. When the second meeting took place, PMDA, JPMA, PhRMA, and EFPIA participated. The contents of the meetings cannot be described here in this room, because of limited time, but I would like to tell you that these meetings were very fruitful and productive....

Summary

In summary, we would like to further promote the development of pharmaceutical products. We have identified some of the issues and challenges. As far as biopharmaceutical products are concerned, unlike for chemically synthesized products, we have limited knowledge and experience. So what we have to do is promote collaboration between industry, academia, and the health authorities.

The first thing we have to do is to create an environment that will allow for collaboration among these three parties for the development of biopharmaceutical products. As an expert committee here in Japan, we would like to make a proposal to the health authorities and ask for the clarification, if possible. We would like to approach the health authority and have very fruitful and productive discussions with them at this CASSS CMC forum. We appreciate this kind of opportunity to discuss the improvement of procedures with the regulatory authorities.

AMGEN'S MORI-BAJWA ON THE GLOBAL PROBLEMS

Today I am going to go over some of the difficulties and challenges facing industry as we globalize and commercialize.

First I would like to review some of the types of changes that we make. As you know, there is a spectrum of changes, and some of them are minor in nature – such as changing a filter supplier – and carry very low risk.

And the analytical data package supporting process studies that go with that, because they are lower risk, are essentially minimal.



But as we move up the spectrum into more complex changes that carry moderate risks, such as moving to a new production facility, the data package increases and the studies supporting that change also increase. As we move up the spectrum to the higher end – for example, when we introduce new cell lines or major formulation changes – we also need to have clinical studies to support those changes. All the changes that we make are typically governed by the fundamental basis of Q5E.

So why do we make changes? We make changes for a number of reasons throughout the development of the product. We make changes during the clinical phase of the product, and once we commercialize we make changes to the process, facility, and scale. We have new manufacturing technology. We may introduce a new media heat treatment platform to inactivate viruses that may be in our raw materials to prevent drug substance contamination as a risk mitigation program. We may introduce isolator filling technology to prevent drug product contamination.

We may also have new testing technologies.... We may introduce NMR to check for adulterated raw materials, or mass spec to do multi-attribute testing. We also have regulatory agency expectations – for example, serialization. Serialization is a new requirement that has been implemented across many countries and health authorities, and not all of the guidelines and regulations for serialization are the same.

Also, we need to add second sites for facility risk-mitigation. Or we need to add second sourcing for critical components or raw materials.

We make these changes throughout the development of a product. We make them during clinical development. And then we make changes during the post-approval phase.

We can make changes for a number of reasons that I have already mentioned. During development, we typically transfer the process from the clinical site to the commercial site. And we also introduce scale changes along the way to accommodate the market demands as we get prepared for launch.

All of the changes that we implement are governed by the quality system for change control. For each change that we have to make, we have to make an assessment whether it is reportable or not reportable. And if it is reportable, we need to know what kinds of restrictions will be placed on the product. For each and every application that we have in clinical trials, or in a marketing application, we have to make an individual assessment. It can be a complex process. Depending on your program, you can have hundreds of individual assessments that you have to make for one particular change.

Herein lies the problem. We make changes. We are going to continue to make changes. And as we make more changes throughout the development of our products, we increase the complexity in our supply planning. Where we have to manage the approvals in multiple countries, it creates a big burden on our supply chain management.

We also are increasing the burden on our regulators. We are making multiple changes, submitting multiple variations, and it increases their workload. They have limited resources to support all the changes that we are filing. Sometimes this can lead to delays in approval.

While we can increase inventory to cover the gap between approvals, it is not always an easy thing to do. It often creates increased costs, and there can be supply scrap risks where we have countries or products with limited stability to cover that gap in time. So when we start planning for changes, we ultimately have to decide how we are going to file in many countries that we are going to file a change in, and what emerges is that there are three distinct waves.

The first wave is our core country or our reference country. And that is the first filing wave that we make. After we prepare the submissions, those approval cycle timelines can take between six and twelve months.

The second wave that emerges is for the non-reference countries. These are countries that do not require approval from a referenced core country before we start filing. But those data packages have country-specific requirements. They might have different formats. So it takes time to make those submissions. And those approval cycles for that second wave tend to be longer – between nine and 24 months.

That third wave that we encounter are the countries that require reference country approval. So we cannot even begin filing until we have approval in the core countries. That creates a bigger gap in time to implement a change. The wave three countries can be even longer in their approval cycles. Over time, you get an additive effect of increasing the time it takes to implement a single change.

Now I am going to test your math skills. We do not only make a single change, per year, per product – we make multiple changes for a product per year. This is a little bit of an extreme case, but I think it is a good example to show you how complex the process can be.

I talked about the waves. In wave one, say we have five jurisdictions. We are making four changes per year, and that jurisdiction's review cycle is one year. That can lead to up to 10-20 different supply chain strategies for one product per SKU for one presentation.

Then we move into the wave two countries, and those can be up to 50 jurisdictions with a cycle time of two years. Doing the math, we see eight versions per jurisdiction, which can lead to 200-400 different supply chain strategies on top of the ones that we have from wave one.

In wave three, there is usually a smaller number of jurisdictions. But as I mentioned before, they have a longer cycle time. So we can end up with 12 versions per jurisdiction, and this is for CMC changes only. This calculates to around 108-216 different supply change strategies.

While this is an extreme example, you can see that our supply chain is completely maxed out and complicated by the number of changes that we are making, and by the review cycles and cycle times across the global regulatory environment.

Now I am going to give you an example of a real case study where we transferred the drug substance manufacturing site. This process took over five years. We went into 96 countries beginning in 2009 with this particular manufacturing site change.

One of the key challenges that we had to plan for when we were implementing this change and planning how we were going to file the change in the different waves was that the changes were not all equal in classification across countries. For some, it was only a minor change. For some, it may be a new registration. For others, it may be a prior approval.

I mentioned that the approval timelines across the regions are quite different and they add to the complexity. So we had to manage the approval times, and be able to manufacture the product with the original process, and create enough supply to cover the gap in time across the approval timelines.

We also had to keep in mind those countries requiring a certificate of pharmaceutical product. I mentioned that we have core countries that need to be approved prior to being able to file in those wave three markets. We also have to be cognizant of specific country requirements where, in some countries, for a drug substance change, we have to have twelve months of real-time stability data. Complicating that, there are countries where we also have to manufacture that drug substance into drug product, and we have to have an additional twelve months stability data on that drug product before we can even file.

Each country has different reporting requirements and specific content requirements. Some of them require executed batch records. Certificates of analysis are pretty typical across regions. Some require actual raw data, where we have to go back to the release results and copy all of the original analytical chromatograms and submit all of that. It creates very complex files that we have to manage for each individual country.

And then there is the matter of declarations, where there are statements from the company indicating stability, that the product is the same, that the quality of the product is the same, or regarding TSE [transmissible spongiform encephalopathy]. It just depends on the country what types of declarations we have to include in the package.

At the end of the day, in the major markets, the approval time lengths span over five years. When we begin to dispatch our wave one countries, there are gaps in the ability to file, as I mentioned, depending on the countries' specific requirements.



You can see Brazil is one of our longest lead countries because it requires twelve months of drug substance and twelve months of drug product stability data, so we cannot file until we have all of that data available. There are also translations involved for different countries. So the whole process adds up to over five years....

And then by the time we dispatch in the Latin American, Asia-Pacific and Middle East countries, we are dispatching those regions and those submissions along with the major markets. But you can see again, the point is that we are really taking over five years to implement one single drug substance site change.

One of the key messages that we have from this example is that adding a manufacturing site submission takes over five years in some cases to get global approval. The regulatory environments are often dynamic and sometimes unpredictable and they may change in their expectations throughout this process. There may be different types of questions that we have to respond to, based on those different expectations from the health authorities.

On a positive note, most countries are accepting dual sourcing from drug substance sites. That is a good thing, where years ago dual sourcing was not allowed.

Harmonization Options

Given all these challenges that we have when we make a global change, are there ways that we can harmonize across the regions to make this process more efficient so we can facilitate world-wide drug availability?

For example, in the U.S. and the EU, we have the ability to have pre-approved comparability protocols, which allow us to shorten our review cycles and implementation of changes. Do we have an opportunity for those reference countries in the wave three markets to accept a CPP from a major market under mutual recognition? And can we leverage some of our organizations across WHO, ICH, ASEAN, and APEC to accept more a risk-based variation management plan? And is there potential to align those reporting categories across regions to align approval timelines and the notifications for prior approval in some cases?

And finally, where we have to implement a change immediately because there may be a safety risk or quality risk, is there a possibility we can have certain exceptions, where we submit the notification, we wait a certain period, and then we can implement because there is a high need due to risk to implement that change?

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