IPQ INTERNATIONAL PHARMACEUTICAL QUALITY
Inside the Global Regulatory Dialogue

Accelerated Development and Review Initiatives in Focus at 2016 CASSS CMC Strategy Forum Europe

The accelerated development and review initiatives in the US, Europe and Japan, and their implications for lifecycle quality management and regulation of biotech products, were in the forefront of the discussions at the 2016 CASSS CMC Strategy Europe held in Paris in May.

> **The dialogue started at the traditional "satellite session" sponsored by the European Biopharmaceutical Enterprises (EBE) during the morning before the forum itself began. The EBE session focused specifically on the adaptations to the traditional approaches to development and manufacturing that need to be made to allow CMC to keep pace when early access timelines are in play.**

Roche EU GMP Regulatory Policy Lead Markus Goese began the session with a review of the recent EBE BioManufacturing Working Group activities and initiatives.

Goese highlighted the late-October 2015 workshop that EBE co-sponsored with EMA on lifecycle management at the agency's London headquarters, which provided a forum for further industry input into the Q12 development process ***(IPQ December 31, 2015)***. Issues receiving attention at the EMA workshop included established conditions, post-approval management plans/protocols, and the role of the quality system – issues which were further addressed at the Paris CMC forum in the context of accelerated reviews.

With encouraging global convergence of regulatory standards a major EBE goal, Goese commented, engagement with ICH Q12 is "certainly a very important activity."

Following Goese's introduction, presentations were given by Genentech Staff Scientist Fred Jacobson on antibody drug conjugates, and by Sanofi R&D Global Regulatory Affairs Group Leader Serge Mathonet on learnings from the cross-industry information session EBE held on developing and licensing biologic/device combination products.

> **The satellite session then focused directly on EBE's initiative on the accelerated development CMC challenges.**

Janssen Biologics BV Global Regulatory Affairs Senior Director Ronald Imhoff explained the range of CMC issues the initiative is involved with. Imhoff is co-founder and vice-chair of the EBE BioManufacturing Working Group, a member of the EFPIA Technical Development Expert Group, and a member of the EFPIA/EBE ICH Q12 support team.

Presentations followed on the related topic of using prior knowledge to facilitate the development process. These encompassed the use of prior knowledge in: ● applications, by Sweden Medical Products Agency Pharmaceutical Assessor Mats Welin ● drug substance process validation, by Genentech CMC Regulatory Policy Director Earl Dye ● establishing the control strategy, by IPSEN Biopharm novel pharmaceutical CMC development leader Alistair Kippen, and ● drug product modeling in scale up and transfer of lyophilization processes, by Chiesi Pharmaceutici Drug Product Development and GMP Manufacturing Head Ciro Cottini.

Goese commented in his introduction that a "key objective" for the EBE has been expanding its relationship with the EMA's Biotech Working Party (BWP), including co-developing one or two day workshops in key areas, such as the use of prior knowledge for biotech products.

The Roche official noted that the "whole topic" of accelerated development has been one on which EBE has been in active dialogue with its EFPIA colleagues. A joint EBE/EFPIA whitepaper has been produced on the CMC challenges and opportunities for these accelerated programs, which has been submitted to EMA for feedback.

Regulators Probe CMC Implications

The dialogue on the CMC challenges for fast-tracked biotech products continued at the plenary international regulator panel that traditionally leads off the CMC strategy forums.

Biotech product CMC regulatory updates were provided: ● on the EU, by Ireland Health Products Regulatory Authority (HPRA) reviewer Sean Barry ● on Japan, by Pharmaceuticals and Medical Devices Agency (PMDA) Office of Cellular and Tissue-based Products Principal Reviewer Yasuhiro Kishioka, and ● on the US, by CDER Office of Biotechnology Products Review Chief Sarah Kennett.

Joining the presenters on the panel during the engaging discussions that followed were CBER Division of Viral Products Deputy Director Robin Levis, Health Canada Center for Evaluation of Radiopharmaceuticals and Biotherapeutics Regulatory Scientist Anthony Ridgway, and EMA Quality of Medicines Principal Scientist Pascal Venneugues.

Breakout sessions were then held over the course of the forum to hone in on: ● leveraging continuous process verification to facilitate the faster patient access ● the Q12 dialogue on established conditions ● the evolution of post-approval change protocols in biopharmaceutical lifecycle management ● the regulatory and scientific challenges of combination product development, and ● innovative approaches, tools and techniques to streamline the manufacturing and control development process.

At the forum, Roche Policy and International Operations VP Wassim Nashabeh, who chairs the CMC Strategy Forum Steering Committee, provided the CASSS welcome and introductory remarks. Roche Pharma Technical Regulatory Policy expert Kowid Ho, a former biotech regulator and policy setter for France's AFFSAPS, addressed the implementation of established condition principles. Genentech's Dieter Schmalzing probed into the challenging considerations for control strategies for mAb/mAb combination therapies.

CMC Challenges, Solutions, and Key Questions Raised

The regulator panel discussions at the international CASSS CMC Strategy Forums have been fertile ground for bringing the most pressing issues across the biotech product regulatory spectrum to the fore.

In beginning her remarks, Kennett stressed the "informative" nature of the discussions that take place. "I think the discussions at all of these CMC forums," she commented, "are really important to regulators and industry to keep pace with each other and understand what is going on and help each other learn different things."

In his opening presentation at the session, HPRA's Barry reviewed: ● EMA's PRIME and adaptive pathways approaches ● the CMC challenges presented by these accelerated development approaches ● the implications of EMA's recently published guideline on process validation for biotechnology-derived active substances, and ● recent trends in CMC questions from EU regulators.

In going through the CMC considerations for the PRIME scheme, Barry acknowledged that they represented his "own opinion, as we have not gone through applications yet – it is still in the very early stage."

Using the regular scientific advice procedures, he pointed out, PRIME offers an opportunity for the applicants: ● to discuss plans for process validation, scale up, and stability "quite early on" ● to get "continuous feedback on pharm development and process validation activities," which is important since "there may not be very many batches to work with," and ● generally "to engage with regulators on areas which are challenging" both for the applicants and regulators. "Because we have this longer lead-in time with scientific advice, we can…come to an understanding of how best to deal with…these difficult questions before filing, so hopefully all these issues are ironed out."

The Irish regulator also explored the CMC challenges, solutions and outstanding questions that have surfaced in the adaptive pathways context.

Key questions posed by Barry, most of which were explored in the regulatory panel discussion session that followed, include:

- Where does the balance lie with the limited data that you are going to have versus regulators acceptance of risk?
- Can specifications and control strategy be reassessed post-approval, and how will that look with the site and the post-approval change management protocol? What tests are going to be done? What studies will be carried out? But then when that data is brought back up, what specifications will change?
- How will the control strategy change?
- Is there flexibility to adjust the control strategy and the specifications once the validation is complete?
- How will we deal with post approval extension of shelf life?
- How will the recently published process validation guideline help in terms of post-approval process validation?

Protein Sequence Variants of More Concern

The HPRA biotech reviewer concluded his talk by an insightful look at the trends in the current questions that regulators are asking in reviewing monoclonal and recombinant protein dossiers, based on his own analysis of 20 dossiers that went through the EMA review process during the past year.

Major objections were cited for about 15% of monoclonal dossiers and 30% of recombinants. The average number of questions overall was 60 for monoclonals and 80 for recombinants in the cohort.

Barry reviewed the issues that "keep popping up" in three leading problem areas: process development, specification setting, and one that "we are seeing more and more of" – protein sequence variants.

He commented that the onus is on regulators to explain more clearly to industry what they want when the same issues continually resurface.

"A lot of times," the Irish regulator advised, the solution is "just to tell a story. It is just an explanation and does not even rely on a lot of extra data. It is just an understanding and the dialogue so we are both on the same page."

FDA's Kennett Echoes Communication Theme

As in the presentations by Barry and PMDA's Kishioka, a central theme reverberating through the presentation by FDA OBP's Kennett at the opening international regulatory panel session was that, while advancing biotech product and process knowledge has created the foundation for regulatory changes, close communication and coordination between manufacturers and regulatory agencies will be necessary to realize those changes while ensuring and advancing product quality.

Kennett offered a nuanced view of the regulatory opportunities, on the one side, and the challenges that have to be addressed in realizing them, on the other.

"I think we are in a time period now where we really have a potential to see a lot of change," she affirmed – "thanks in part to a lot of the advancements that have been made by industry over the last few years. At the same time, I think that we have to have some good communications and coordination between manufacturers and the regulatory agencies to get some of these changes implemented."

The three presenters addressed a similar range of front-burner CMC issues for biotech products, including problems in recent applications, their respective agency's accelerated development programs, and the shifting approaches and expectations for lifecycle management.

[An in-depth review of Kennett's presentation is provided in IPQ's August/September 2016 Monthly Update. The IPQ issue also includes the full remarks by Barry at the session.]

Panel Q&A Probes Analytical Issues in CMC Acceleration

The analytical method component of the CMC challenge in the accelerated program context emerged into relief during the regulatory panel discussions that followed the three presentations. Also drawing attention were the possibilities for further leveraging of regulator knowledge and for more inter-agency coordination in the biotech review arena.

Joining Barry, Kennett and Kishioka on the panel for the discussions were CBER Division of Viral Products Deputy Director Robin Levis, Health Canada Center for Evaluation and Radiopharmaceuticals and Biotherapeutics Regulatory Scientist Anthony Ridgway, and EMA Quality of Medicines Principal Scientist Pascal Venneugues.

The discussions began with consideration of whether and how prior knowledge and the experience gained could be better leveraged across different products, reviewers, agencies, and companies.

CBER's Levis commented that the agencies have been building on the success of the tri-lateral conference calls between FDA, Health Canada and EMA prompted by the need to respond quickly to the H1N1 epidemic and the experience gained in collaborating internationally on the Ebola crisis.

EMA's Venneques pointed to the high number of interactions EMA has with FDA in particular now through which information is shared on a confidential basis, and the impact it has had on reducing GCP inspections in particular.

Pointing to the "cluster" conferences that now take place between EMA, FDA, Health Canada and PMDA, HC's Ridgway suggested that there may be room for "a greater amount of 'work sharing' between agencies in various ways – perhaps in drafting guidance documents and other work-type activities.

Collaboration will stop short of mutual acceptance of approval decisions for "quite a while yet," due to the need for internal accountability, Ridgway said. However, what may be possible to improve efficiency is a shared first review followed by a rapid second review at the individual agency level to confirm agreement and tailor labeling, etc.

Highlighting the need for getting company buy in on information sharing, FDA's Kennett noted that when draft reviews have been shared between the FDA and EMA, "the similarities were striking."

Criticality Justifications Remain at Issue

The conversation then turned to industry/regulator risk communications, particularly around criticality justifications for process parameters and quality attributes (CPPs and CQAs).

> **GSK Vaccine's Simone Gallo asked about using extra characterization to avoid a clinical study for master seed changes – an issue that he views as "having a dramatic input on the supply of vaccine biological drugs."**

Levis responded that "it is going to depend a lot on the level of characterization of your product and what we know technically about this product before and after you implement the change in the seed as to whether or not a clinical trial would be required." However, she stressed, "we understand that a clinical trial is a huge deal at this point, especially when you are licensed and you have distribution and it is a critical compound or drug or a vaccine and needs to get to the market."

What the agency would want to see to obviate the clinical testing is that "the basic level of characterization in that product is sufficient and strong enough that once you have implemented that change" the re-characterization can show that technically they are identical and that "the data will be strong enough to ensure that the clinical behavior will be similar. That goes back to whether you have well-defined the critical attributes and whether they match after the change."

In general, the challenge, HPRA's Barry said, is "really a matter of trying to explain your risk assessment and why things are considered a certain risk or not, [which] can seem a little bit random if it is not well-described."

> **Merck's Scott Tobler pointed to the discussion by Kishioka of the expectations for application submissions in Japan regarding critical and non-critical parameters and the implications regarding established conditions and post-approval changes.**

For a lot of companies, the CPP is defined as something that has been studied over a certain relevant range and has an impact of some practical significance. However, Tobler pointed out, "sometimes that is not always all of the parameters that the PMDA or other agencies would like to see in an established condition or commitment to your process."

He asked the PMDA reviewer to "comment a little bit more on what type of body of evidence or conclusion from a process evaluation might support not having the parameter in the application form," and what would be "the distinguishing body of evidence to make it" a partial change application (PCA) vs. a minor chance notification (MCN) when adjustments are made post approval?

> **Kishioka acknowledged that how the criticality assessment should be determined and the CPP described in the application is an open-ended question.**

"Through the characterization study, many companies have their proven acceptable range," which can then be described in the application form, and "changes made within the PAR would not need post-approval regulatory action," he explained.

As per ICH Q8, the CPP, in turn, is the essential element to ensure pharmaceutical quality and can be managed under the company's pharmaceutical quality system, allowing the regulator to better focus on the critical elements and changes.

Danish Medicines Agency biotech product lead assessor Nanna Kruse commented that the issue has been under discussion for "a very long time" and the focus of several workshops, and "we still have not found a solution." Kruse currently serves as vice-chair of Europe's Biologics Working Party (BWP) and is its representative on the Q12 EWG.

The problem, she said, is that companies can put a narrow range on a process parameter so that it **"**will not have any relevant impact on the CQA and therefore is not 'critical.' In the end you will end up having nothing being 'critical.'"

However, this becomes "difficult for regulators to swallow," creating "a little bit of dancing around the tree on what to do." As a "kind of trade off," the company may decide to designate some CPPs to "make the regulator happy."

Netherlands Medicines Evaluation Board (MEB) biological products assessor Martijn van der Plas admitted that the issue has been a "hotly debated" one and a solution still not agreed upon. He suggested that "one of the ways out of this dilemma and one of the things that we implicitly seem to do" is looking for redundancy as an approach to scientifically assessing criticality and classifying process parameters.

"If there is a critical process parameter and it has an impact on the CQA, but if the CQA is controlled several times during the process at later steps or in the form of release testing, then for all practical consequences it does not matter whether or not a certain parameter is a CPP, because any deviations will be picked up later. But if it is the only place where the quality is really controlled – and this is especially true for impurity removal or viral removal – then suddenly this CPP becomes, so to say, a single point of failure. If it fails, there is no other place where you are going to detect it."

Janssen's Kris Barnhouse focused the conversation on the role of the quality system in adjusting the post-approval regulatory paradigm under ICH Q12 and assessing its strength to play that role.

Ridgway, who serves on the Q12 Expert Working Group, explained that the EWG has moved away from trying to grade the quality system on a sliding scale in determining what regulatory flexibility can be applied post-approval, deciding that the more feasible approach is for the inspectors to go in and decide if the PQS is functional or not.

Kennett commented that FDA sends both reviewers and inspectors on pre-approval inspections and that evaluating the quality system based on how deviations are being managed is a focal point.

Alignment is High on Industry Wish List

Genentech's Earl Dye pointed to the similarities between the FDA breakthrough therapy and EMA PRIME programs, which both involve working with sponsors "to look for the most efficient path forward to bring those medicines to patients." With the same sponsors likely to be interested in both programs, Dye noted the potential advantage of discussions between the two agencies so these sponsors "do not get started down" different paths.

EMA's Venneques concurred on the mutual eligibility for the two programs, adding that FDA and EMA are discussing ways to interact and share information for these products.

CBER official Levis also pointed to the "very extensive dialogue" now going on between the regulators.

"I think the regulators have finally gotten the message, mainly from meetings like this and other gatherings, that convergence of our advice is something that manufacturers would love more than almost anything else. I think we are finally hearing that message and that there really is an extensive dialogue at the product level. Again with the caveat that you get all of the appropriate legal permissions to do so, there really are some very granular discussions going on about how to regulate products and the best way forward."

Biogen's Diane Wilkinson queried on the potential for harmonizing the CMC expectations from EMA, FDA and PMDA for accelerated development and review programs – for example, regarding process validation.

Levis responded by noting the "tremendous amount of crosstalk" on how to bring the vaccines for Ebola through manufacturing, testing and distribution for use in the outbreak situation, and that the communication was now "ramping up" around the Zika virus.

Kruse pointed out that there is a different approach between the EU and US "in relation to which part of the process validation is looked at by the assessors and what is looked at by inspectors," making harmonization more difficult.

However, she stressed that the new EU process validation guideline for biotech products has brought the two approaches more in alignment. "It might be that it is not the same information that you have to provide to the specific parties, the assessors or the inspectors, but at least we have tried to get closer to FDA, I would say, then the chemical guideline."

A question by Genentech's Kathy Franciscan on the use of the Japanese system as a model for established conditions (ECs), led Ridgway to comment on the considerations before the ICH Q12 in developing an approach to ECs that would be viable for other regions.

Impact of Accelerated Pathways Further Explored

Biotech industry consultant Nadine Ritter then moved the conversation into a more extended review of the "stress that is placed on the analytical method toolbox by having these accelerated programs" and what regulatory agencies are looking for, prior to full method validation, "to support the regulatory relief that sponsors are asking for" – for example, in "leveraging prior knowledge for setting specifications."

In general, the regulators on the panel saw "no easy answers" and advocated the need for early attention by sponsors on methods development and their qualification and up front communications with the agencies.

More dialogue followed at the end of the regulatory panel session on the impact of the accelerated pathways.

Receiving attention was the potential for accelerated pathway approaches in regions outside the US, Europe and Japan.

A hurdle, Ridgway commented, is the labor intensity involved and the lack of available resources smaller agencies like Health Canada have beyond their regulator workload. The potential, he suggested, may lie more in their piggybacking off the clearances done by the major regulators.

Lilly's John Dougherty shifted the conversation onto the relationship between CMC and the broader risk/benefit analysis involved in breakthrough designations.

The panelists explained the pressure they are under as CMC reviewers to facilitate the ironing out of the CMC issues with the sponsors so they do not impede breakthrough product clearance. A "culture shift" is also needed by industry to deal with the CMC exigencies in the "very short timeframes" they are facing in the accelerated review context and make the early resource investment involved, Kennett commented.

At issue is the extent of "uncertainty" and its reduction through tools like post-approval change protocols and not the acceptance of lesser quality, HPRA's Barry summarized.

[Editor's Note: More on the regulatory panel discussions is provided in IPQ's October/November 2016 Monthly Update.]

EU Combination Product Regulatory Situation Explored

The breakout session on the "regulatory and scientific challenges of combination product development," held on the second day of the conference, reflected the identification of the topic at previous CMC forums as one in need of more attention in Europe. An initial, introductory session was held at the 2015 Europe forum in Copenhagen to gauge interest, and a full session was scheduled in Paris based on the input.

> **At the session, then UK Medicines and Healthcare Products Regulatory Agency (MHRA) Pharmaceutical Assessor Janine Jamieson discussed the different regulatory systems for medical devices compared to medicinal products in the EU. She then explored the challenges the differences create in working towards the goal of a "proportionate, appropriate, and very much risk-based regulation of these drug/device combination products that can span a whole range of different types of devices."**

[Editor's Note: Jamieson left MHRA in mid-2016 and has joined IPQ's editorial staff in Europe. She is helping IPQ expand the depth and breadth of its coverage of the global industry/regulator dialogue on combination products.]

Based on her considerable experience in CMC review that has included a focus over the past decade on ancillary medicinal substance components of medical devices, Jamieson highlighted the need to look at combination product regulation from the perspectives of the overall product as a unique entity as well as from that of two individual components.

She highlighted the challenges faced by both regulators and industry on drug/device combination and "borderline" products that have been surfacing at the various conferences and scientific advice meetings in which she has participated. She pointed out that there are some "current, very positive initiatives" in the EU to try to address these challenges, provide clarity, "and work, if not towards global harmonization, towards a more consistent approach internationally."

AZ, Sanofi and Genentech Experts Provide Industry View

Providing industry views of the CMC challenges for combination products at the session were Astra Zeneca (AZ) CMC Regulatory Affairs Device Capability Lead Tim Chesworth and Sanofi global regulatory affairs group leader Serge Mathonet.

Chesworth took a wider vantage point, offering insights on: ● achieving a consistent approach to combination products in "an inconsistent and changing world" ● the review of new drug/device combinations that are becoming increasingly complex ● experiences of industry and regulatory agency collaboration, including the role of the Combination Products Coalition (CPC), and ● future challenges and opportunities.

Filling in for his Sanofi device regulatory affairs colleague, Debbie Thomas, who had prepared the talk, Mathonet narrowed down onto the issues around the development and licensing of high concentration mAB solutions in pre-filled solutions and pens.

Mathonet had also presented during the pre-conference European Biopharmaceutical Enterprises workshop on the initiative EBE has launched on helping clarify and advance the development and submission of CMC information for combination product applications.

> **A fourth presenter at the forum session was Genentech Director Dieter Schmalzing, who shifted the focus onto control strategy issues for mAb/mAb combination therapies.**

The industry presenters offered complementary insights on the range of current CMC issues faced in developing and improving the delivery of high volume, highly viscous and high cost biotech injectable products. It was noted that the development of available technology is fast outstripping regulatory guidance in this area, underscoring the importance of the current dialogue.

> **The lack of consistency of the regulatory approach for combination products, and the difficulty industry has in determining what needs to be filed and where, were recurrent themes in the four presentations and in the panel discussion that followed.**

The discussions focused in particular on: ● the CMC issues raised by Schmalzing regarding Mab/Mab combination therapies ● the stability evaluation considerations in shifting from prefilled syringes to pens ● what is expected in medicine dossiers regarding the device components, and the impact of the CE mark ● the drift in expectations for risk profiling ● the communication between the drug and device manufacturers – for example, regarding changes ● the need and potential for driving clear regulatory expectations and harmonization, and ● the impact of regulator resource constraints in addressing the regulatory challenges.

[Editor's Note: In-depth coverage of the combination product session of the 2016 European CMC Strategy Forum is provided in IPQ's December 2016 Monthly Update.]