IPQ INTERNATIONAL PHARMACEUTICAL QUALITY
Inside the Global Regulatory Dialogue

CMC Priorities of EFPIA's European Biopharmaceutical Enterprises Include ADCs, Drug/Device Combos and Statistics

Drug device combinations (DDCs), antibody drug conjugates (ADCs), and the use of statistics in comparability assessments are among the current focal points of the European Biopharmaceutical Enterprises (EBE) in its efforts to identify and build consensus around the most pressing issues on the global regulatory agenda for biotech manufacturing and control.

A specialized group within the European Federation of Pharmaceutical Industries and Associations (EFPIA), EBE plays an important role in the biopharmaceutical regulatory discussions in Europe and in interfacing with EMA's Committee for Human Medicinal Products (CHMP) Biologics Working Party (BWP) on industry's priorities and concerns.

In the wake of EMA's February 2017 proposal for a DDC quality guideline, EBE released a broad-based "reflection paper" in January 2018 providing "an industry perspective on the EU marketing application technical requirements, regulatory review process and post-approval device-related change assessment" for medicinal products incorporating a drug delivery device component. ***[See IPQ May 10, 2018 for more on the DDC regulatory developments in Europe.]***

EBE is currently finalizing a "position paper" focused more specifically on the impact of Article 117, which is amending the Medicinal Products Directive to require a notified body (NB) opinion on these combination products. The group is also leading a cross-industry letter to European Commission (EC) outlining its concerns about how Article 117 is going to be implemented in practice.

Also under development is a position paper scheduled for release this year on developing an efficient lifecycle control strategy for DDCs to give flesh to the outline in the EBE reflection paper of the challenges involved.

> **The EBE/EMA dialogue on the DDC issues, as well as on other of the pressing biotech manufacturing topics EBE is engaged with, continued at EMA Biologics Working Party (BWP) "interested parties" meeting held in London in the later part of June.**

The BWP indicated that an EFPIA/EBE letter on its DDC questions and concerns should be addressed to the European Commission (EC), and the industry group is working to send the letter by the end of July.

There was also an understanding reached that: ● there should be a transition period in implementing Article 117 during which the absence of an NB conformity opinion would not forestall an MAA filing, and ● a requirement for an NB opinion during clinical trials would not be added.

The BWP indicated that a workshop on DDC products would probably not be scheduled during 2019. The EFPIA/EBE request for the upcoming BWP/QWP guideline to include a risk-based approach to device variations was acknowledged by the BWP, although the recommendation for a pilot program on the NB involvement was not addressed.

> **Building clarity and consensus around the regulatory challenges that antibody drug conjugates (ADC) present is another effort on the group's agenda.**

Targeted is the release of a position paper in the latter half of 2018 that will provide an industry view on what regulators should expect for ADC analysis, control, and dossier filing.

Analytical Statistical Comparisons Also on EBE Radar Screen

Similarly to the drug device combination situation, a March 2017 EMA "draft reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development" resulted in EBE's Biomanufacturing Working Group (BWG) forming a topic group to explore the issues raised in the paper and to offer an industry perspective on them.

EMA issued its reflection paper with a 12-month consultation phase, in recognition of the need for further consideration and dialogue with industry – in particular, on "the opportunities and limitations related to inferential statistical methodology applied on quality attributes data in the exploration of similarity of two drug products." Rather than providing explicit guidance on which statistical approaches are most suitable, the paper describes its intent as establishing "a framework and a common language to facilitate future discussions among stakeholders."

> **The EBE topic group began its work on the statistical paper in June 2017, and at EMA's behest, submitted high-level comments to EMA, which was starting to plan for a workshop to further the dialogue, as committed to in the reflection paper.**

In anticipation of the EMA workshop, the EBE topic group put together six case study proposals. These included a case study from Vaccines Europe with whom they were in consultation. The group also consolidated the comments it had been collecting on the EMA reflection paper into a 62-page report that went to the agency. The workshop followed in early May.

The EBE/EMA dialogue on the statistics paper, as well as the ADC continued at the June BWP "interested parties" meeting.

FDA Draft Guideline Fuels Statistics Dialogue

Heightening the discourse on the statistical comparison issues was the release by FDA in September 2017 of a draft guidance for industry on "statistical approaches to evaluate analytical similarity."

Unlike the broader-based EMA guidance, the FDA draft was explicitly focused on providing advice on the evaluation of analytical similarity by biosimilar product sponsors in demonstrating that their product is "highly similar" to the reference product.

> **The comments that came into FDA on the draft during the Fall 2017 comment period – as well as the attention it has received at public forums such as those sponsored by CASSS since it was issued – indicate the challenging nature of bringing statistics to bear on the quality regulatory process.**

Comments were submitted by 17 different companies and organizations. Companies submitting included: Novartis/Sandoz, Boehringer-Ingelheim, Amgen, Genentech, Pfizer, Sanofi, Momenta, and Shire. Well-informed and substantive comments also were submitted by five influential trade associations: the Biotech Innovation Organization (BIO), the Biosimilar Forum, AAPS through its Biosimilars Focus Group, the Association for Accessible Medicines (AAM), and the International Generics & Biosimilar medicines Association (IGBA).

> **The comments provide valuable insights on the challenges of trying to create statistically-based regulatory expectations as well as where the opportunities lie.**

Among key areas of concern about the draft guideline voiced in the comments were: ● the shift of the mean of a reference product's quality attributes over time, limiting the applicability of the proposed equivalence test for "Tier 1" attributes, and ● the number of lots of the reference product needed and the concern expressed about sourcing of the reference product from outside the U.S. ***[A link to docket No. FDA-2017-D-5525 with the comments is provided below.]***

In the wake of the comments and the discussions, in late June FDA announced its decision to withdraw the draft guidance while giving "further consideration to the scientific and regulatory issues involved" *(see FDA's explanation below)*.

The announcement explains that the comments "addressed a range of issues that could impact the cost and efficiency of biosimilar development, including the number of reference product lots the draft guidance would recommend biosimilar developers sample in their evaluation of high similarity and the statistical methods for this evaluation."

FDA WITHDRAWAL OF DRAFT GUIDANCE ON EVALUATING ANALYTICAL BIOSIMILARITY

On June 21, FDA announced the withdrawal of its draft guidance for industry entitled "Statistical Approaches to Evaluate Analytical Similarity," issued in September 2017. The following is the agency's explanation of its decision and next steps.

The draft guidance, if finalized as written, was intended to provide advice for sponsors developing biosimilar products regarding the evaluation of analytical similarity between a proposed biosimilar product and the reference product. After considering public comments that the agency received about the draft guidance, the FDA determined it would withdraw the draft guidance as it gives further consideration to the scientific and regulatory issues involved. Comments submitted to the docket addressed a range of issues that could impact the cost and efficiency of biosimilar development, including the number of reference product lots the draft guidance would recommend biosimilar developers sample in their evaluation of high similarity and the statistical methods for this evaluation. The FDA believes that in better addressing these issues in the future, the agency can advance principles that can promote a more efficient pathway for the development of biosimilar products.

The agency intends to issue future draft guidance that will reflect state-of-the-art techniques in the evaluation of analytical data to support a demonstration that a proposed biosimilar product is highly similar to a reference product. The goal is for future draft guidance to address potential challenges faced by biosimilar sponsors in designing studies that are intended to demonstrate that a proposed biosimilar product is highly similar to a reference product, including consideration of appropriate methods to analyze analytical data to account for potential lot-to-lot variability of the reference product. Future draft guidance also will focus on providing appropriate flexibility for sponsors in order to help spur the efficient development of biosimilars without compromising the agency's rigorous scientific standards for evaluating marketing applications for biosimilars.

The FDA continues to encourage sponsors of proposed biosimilar products to discuss product development plans with the agency, including the evaluation of analytical data intended to support a demonstration that the proposed biosimilar product is highly similar to a reference product. The FDA will continue to provide development-stage advice to sponsors of proposed biosimilar products or proposed interchangeable products through several types of formal meetings, which are described in more detail in FDA's guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products*. More information about this and other FDA guidance documents related to biosimilar products and interchangeable products, as well as contact information for FDA, is available at http://www.fda.gov/biosimilars.

The FDA will communicate publicly when new draft guidance is issued in relation to the evaluation of analytical data between a proposed biosimilar product and a reference product.

ICH Q12, Accelerated Development, Continuous Manufacturing Also In Focus

Also emerging from the EBE consensus-building pipeline this year will be position papers on risk-based approaches to ID sampling of biologic drug substances and to setting sterile filtration bioburden limits. The latter builds on and updates an October 2016 concept paper in the wake of EMA's release of a redraft of Annex 1.

> **Reflective of its focus on global convergence, EBE is actively engaged in the dialogue on the lifecycle management concepts being worked through in the ICH Q12 context.**

The guideline emerged in November from ICH's Expert Working Group (EWG) as a step 2b draft for public comment ***(IPQ July 3, 2018)***. EBE, in conjunction with EFPIA, has put a support team in place on Q12. The team is consolidating comments to feed back to EMA.

EBE has also been helping inform the global dialogue on the regulatory issues involved in advancing continuous manufacturing in the biotech arena. EBE made the case to ICH that biopharmaceutical manufacturing should be included in the scope of a CM guideline effort. At its June meeting, the ICH management committee agreed in approving continuous manufacturing as a guideline topic.

> **Helping work through the quality implications of the expanded offering of accelerated development programs by the key regulatory agencies globally is another EBE priority.**

EBE and EFPIA together produced an influential white paper addressing the "challenges and opportunities" in the expedited CMC development when accelerated approval is in play. The highly substantive paper was released in November 2017 and is helping facilitate the industry/regulator communications around the issues it covers.

> **EBE has also been closely monitoring the evolving CMC regulatory situation in Europe regarding advanced therapies. A position statement was issued jointly with EFPIA in October just prior to a European Parliament meeting on "exploring solutions for innovative treatments" *(link provided below)*.**

In the effort "to boost patient safety and increase access to much needed therapies in Europe," EBE/EFPIA advocated the need for the EU Commission and member states to improve transparency and consistency on hospital exemptions (HE) for advanced therapies.

Divergence across the member states, the group points out, "has created parallel paths to market access for ATMPs, resulting in uncertainty, barriers to patient access, lack of transparency on available therapies, and reduced incentives for developing ATMPs in the EU." EBE/EFPIA urges the EC to develop a "best practice guide" and work with the national competent authorities to develop a registry of ATMPs made available under the hospital exemptions.

Prior Knowledge Issues Get CASSS Airing Globally

EBE and EFPIA are also strong participants in the discussions that have heated up around prior knowledge in the face of the accelerated development/approval timelines and the product and process complexities now in play.

> **The combined industry group played a key role in an EMA stakeholder workshop on the topic organized by the agency's biologics and quality working parties (BWP/QWP) in London in November 2017. EMA provides a full video recording of the workshop on its website, and a report on the workshop was released by the agency in April *(link provided below)*.**

Through a combination of presentations, industry case studies, and panel discussions, the BWP/QWP workshop brought regulators and industry experts together to reach a clearer consensus on: ● what prior knowledge entails ● how it can be used to support product development, manufacturing and control strategies, and ● how it should be used, justified, and presented in dossiers.

In these discussions, EBE is building on the work it has done in helping refine the approach to the use of platform manufacturing in biopharmaceuticals and in clarifying the regulatory implications involved. A concept paper on "putting accumulated data and experience to work" was released on the topic in 2013.

> **EBE has been engaged with CASSS in a year-long effort to intensify the regulatory dialogue globally on "the use of prior knowledge to support biopharmaceutical CMC in conventional and expedited settings." A similar international airing was made by CASSS last year at its various international forums on lifecycle management, in the effort to help inform the ICH Q12 development process.**

The CASSS prior knowledge conversations began at its CMC strategy forum in Tokyo in December 2017. The final session at the Japan forum included presentations on making use of prior knowledge in regulatory files from an assessor and an industry perspective.

Providing the assessor's view was Sweden Medical Products Agency (MPA) quality assessor Mats Welin, while Roche EU CMC Regulatory Policy Lead Markus Goese shared the EBE/industry view. Welin is a Swedish delegate on the Biologics Working Party and a member of the EMA PAT team. Goese is the current chair of EBE's Biomanufacturing working group and the EFPIA topic lead for ICH Q12.

The prior knowledge dialogue continued at a one-day CMC strategy forum subtitled "Learning from our Successes and Failures to Improve Product Development and Manufacturing," which was held in conjunction with the CASSS 2018 WCBP conference in Washington, D.C. At the forum, Welin and Goese teamed up to present a summary of the 2017 EMA prior knowledge workshop discussions.

> **The two offered an updated review of the EMA workshop and the ensuing discussions from the industry and agency perspectives during the prior knowledge session at the 2018 CASSS CMC Strategy Forum Europe, held in Noordwijk, Netherlands in mid-May. At the Europe forum they had the advantage of referencing EMA's report.**

A concluding session in the CASSS prior knowledge series will take place at the 2018 Japan forum being held in Tokyo in December.

WHY PRIOR KNOWLEDGE IS A CURRENT FOCUS IN CASSS CMC STRATEGY FORUMS

The following is an explanation provided in the CMC Strategy Europe 2018 program of why the use of prior knowledge in CMC submissions is an important and timely topic for international industry/regulator dialogue, and what the session at the forum would be addressing.

Prior knowledge has great potential to impact many aspects of CMC development, but to date has been relatively underutilized in regulatory filings. It is well accepted that CMC can represent a bottleneck for the submission and timely approval of products undergoing accelerated development through PRIME in the EU and Breakthrough in the US. In such cases prior knowledge can be successfully leveraged to overcome the need for certain product-specific studies, facilitating a tailored approach that can ultimately lead to faster approvals and earlier access for patients.

For both accelerated and standard approvals it is important to strike a balance between product-specific data and the application of regulatory flexibility where appropriate. The areas in which prior knowledge can be exploited are wide in scope and include, for example, CQA and process parameter risk assessments, defining the criticality and proven acceptable ranges for process parameters, and justification of specifications. Moreover, a combination of product-specific data and prior knowledge can be used to underpin the control strategy.

One of the key challenges for industry and regulators is how to demonstrate that such knowledge gained during the development of similar products is fully relevant for the product under review. This session will therefore explore a common understanding of prior knowledge and discuss the most effective way to present it in regulatory submissions. Discussions will also focus on how uncertainties arising from the use of prior knowledge can be addressed post approval. Finally, this session will share industry and regulators' experience of prior knowledge and build on the recent productive discussions and conclusions of the EMA Prior Knowledge workshop.

EBE Explores Its Processes, Accomplishments, and Goals at CASSS Europe Forum

The traditional satellite session sponsored by EBE as the kickoff for the CASSS CMC Strategy Forum Europe prompted EBE to do an internal assessment of its processes, accomplishments and goals. The assessment was, in turn, shared by key working group members at the forum and discussed by the participants.

> **As the current EBE BWG chair, Goese led off the EBE session with a review of the group's achievements during the past year and its ongoing initiatives. Two basic activities of the group, he explained, are: ● raising awareness of the biotech manufacturing technical quality areas, and ● promoting consistent application of technical/regulatory standards.**

He pointed to the key EBE objectives, citing examples of its current engagement with them. These are: ● global convergence of regulatory standards through contributing to efforts such as ICH Q12 ● further strengthening of the relationship with EMA's BWP in developing appropriate regulatory guidance, and ● supporting manufacturing standards for accelerated development and regulatory approvals.

Goese then outlined the agenda for the session. Included were presentations and a panel discussion on the EBE papers under development, followed by a "workshop" in the later part of the morning on the challenges of regulating, manufacturing and assessing CAR-T and other cellular therapies. ***[A link to Goese's remarks at the session are included below.]***

> **Goese was followed by GlaxoSmithKline (GSK) CMC Advocacy Strategy and Policy Director Saroj Ramdas, who gave an intriguing view of her engagement with EBE and what she and others are gaining from the experience.**

Ramdas offered definitions of the "concept," "position," and "reflection" papers EBE produces, and then took the audience through how they are produced – from the IDing of a "hot-trending" topic, to a team being formed, through internal and external review of the papers, including broader industry and regulatory input and feedback, such as through the CASSS forums.

She reviewed the papers EBE has published and their significance. She then commented on the results of a survey EBE conducted, which shed a lot of light on: ● the advantages of being part of the EBE team ● the challenges in time and effort involved in the consensus building process, and ● how the various papers are being used strategically – both within the companies and in their communications with regulators.

> **Generally, the papers are being used to progress risk-based approaches and best practices within industry, Ramdas summarized. They are also being "referenced in regulatory submissions and to support industry responses to regulatory queries within our member companies." Their development, she stressed, is "a process for us to leverage and document prior and platform knowledge across industry."**

Ramdas ended by inviting the session participants to access the papers on the EBE website and make use of them "as much as members have done" and to join with EBE and its sub-teams on its consensus-building journey. ***[A link to Ramdas' remarks at the session are included below.]***

EBE Engagement with Drug Device Combinations, ADCs Reviewed

Sanofi Global Regulatory Affairs Group Leader Serge Mathonet – a member of EBE's BWG and the leader of its visible particle and biologics/device combination product topic group – then provided an overview of EBE's advocacy work on combination products.

Mathonet reviewed the impact of the new EU Medical Device Regulation (MDR) on drug device combinations (DDCs) and the concerns manufacturers have about implementing the extra notified body review requirements ***(see IPQ May 10, 2018).*** He then reviewed the broad reflection paper EBE published on the DDC regulatory situation in Europe in January as well as its work on the DDC position papers on the impact of MDR article 117 and on an "end to end" control strategy.

> **Following Mathonet to the podium was Novartis Biologics Technical Development & Manufacturing Pharmaceutics Senior Strategy & Technology Leader Karoline Bechtold-Peters. She reviewed the history of antibody drug conjugate regulation and the discussions that have been going on in the Biomanufacturing Working Group in developing a position paper on quality and regulatory aspects of antibody drug conjugates.**

She began with an explanation of the perspective and scope that the paper will take. It will recognize the greater complexity of ADCs and their manufacturing process, and that there is additional characterization required. However, Bechtold-Peters stressed, redundant analysis, specifications, or comparability studies "should be avoided."

The requirements for market authorization "should be based on scientific understanding and consider "the huge progress we have made regarding the conjugation procedures in the last ten to fifteen years." In turn, the extent of comparability studies after process or manufacturer changes for ADCs should be assessed based on the changes and not just required by default."

Noting the different expectation that regulators have on where to place information in dossiers, she explained that the position paper will strive to convey more clarity on these expectations, and drive "a risk-based approach." ADCs, she stressed, "are not necessarily high-risk products as we know today."

> **Bechtold-Peters then reviewed the progress industry has made in the last ten to fifteen years in understanding and controlling ADCs, to the point where the processes are now well understood and consistent. The better understanding of unique quality attributes and their criticalities for ADCs means that "it is now time to risk-adjust the controls," she affirmed.**

She also reviewed the team's perspective on the extent of comparability studies needed after process changes are made and how ADC filings can best be handled. ***[A link to Bechthold-Peters' remarks at the session is included below.]***

EMA Holds Workshop to Further Statistics Discussions

Biogen Idec EBE BWG member Richard Keane followed with a discussion of how the group has been responding to EMA's March 2017 draft reflection paper on "statistical methodology for the comparative assessment of quality attributes in drug development."

The group ended up submitting high-level comments at EMA's request in November to help the agency in planning a workshop where the issues raised in the reflection paper could be further discussed with stakeholders. This was followed by the submission of 62 pages of more detailed comments to EMA and the development by the BWG of six case study proposals for discussion at the workshop, which followed in early May just prior to the CASSS Europe forum.

Keane then provided some comments on the workshop discussions and the main points that emerged from them.

The discussions, he said, centered around the need to define the target of the exercise, whether it is biosimilarity or comparability, and then what the most appropriate statistical methodologies are in that context.

Important points made at the workshop, Keane summarized, included that: "● statistical approaches are an important tool ● decision making does require CMC expertise ● decisions do need to be made on the totality of the data, and ● statistics alone cannot just be a pass/fail criterion for the comparability exercise."

[A link to Keane's remarks at the session are included below.]

EBE Session Q&A Opens with ADC Queries

The Q&A that followed the four concept paper presentations at the EBE satellite session probed further into some of the more challenging issues raised by the presenters and where EBE could make a further contribution in addressing them.

Amgen's Andrew Lennard asked Bechtold-Peters if any of the recommendations EBE was putting together on ADCs were considered to be particularly challenging or controversial.

She suggested that the "most discussion" will be on the free drug related impurities (FDRI), because of the mindset change involved.

"We considered some 10 or 15 years ago everything related to the drug as being super toxic, and also, I have to admit because I had my first ADC in hand in 2002 or so, at that point in time it really fell off the drug. But now we have improved the linker technology so much that it is rock stable." This change in mindset, she said, is the biggest hurdle.

"We have also gained so many clinical and pre-clinical results regarding this theoretical concern we had 10 or 15 years ago. We have a lot of data that show it is not as toxic as thought."

Paul Ehrlich Institute's (PEI's) Steffen Gross commented that the concept of a drug master file that Bechtold-Peters had mentioned in her talk is attractive in reducing the burden to both agencies and industry. However, "currently we are not there yet, because the legal framework does not allow for such a drug master file for ADCs, as they are only allowed for well-characterized drug substances."

She responded by expressing appreciation that Gross had recognized the suggestion. "We would really love to see the advancements going on," she affirmed, to cut down on the repetition of information having to be reviewed and filed.

Staying with the ADC focus, HPRA's Sean Barry recognized the desire to avoid repeat testing on the drug substance and conjugated antibody in the context of charge variants not changing and low levels of conjugation. Noting that "a lot of that requires significant process knowledge," Barry asked if companies would have that at the time of approval.

An alternative that would apply to any type of product, he suggested, would be getting approval with a more standard set of specifications, accompanied by a post approval change management protocol to indicate how more process knowledge would be generated over the next couple of years, and the specifications removed. "You may have process knowledge. But if you don't, you could still get agreement up front to remove those specifications, if you can show after a while that there is no change."

Barry asked Bechtold-Peters to comment on what the considerations would be around how much knowledge it would take at the time of approval to justify that approach.

"It depends on how much knowledge a company has already acquired," she responded. "If a company has just started, they cannot claim a lot of process knowledge. But if you go to companies like Seattle Genetics or Roche/Genentech they can provide you with so much data that, in this case, this prior knowledge and this platform can be easily used. I would say, show the data, show the history, and then, depending on that, our proposal is to get more or less of this relief. So case by case."

What Should Go Into the DDC Dossier?

PEI's Gross turned the discussion to DDCs and the reference made by Sanofi's Mathonet on the experience that notified bodies and competent authorities have with evaluations in regard to the EU's Medical Device Directive.

"How do you decide what goes into the dossier, and what not," asked Gross – "because I can imagine you will be asked by certain agencies to introduce ISO norms into the dossier?"

> **Mathonet explained that EBE is working on the question of what device information should be provided in Module 3 for DDCs – for example, in the P section of the dossier regarding compliance with Annex 1 of the MDR – and has put forth a "reflection" from the industry.**

Understanding that the regulators are not always accessing all the ISO guidelines, it is important to have EMA working on drafting a guideline, he said, recognizing that aligning the device and CMC perspective is not easy. He pointed to the case study EBE has made available for the public and the drafting group to consider. As proposed, EBE would like to continue discussion on this topic in a workshop, he added.

In engaging with notified bodies, Mathonet pointed out, "we have made some progress through this questionnaire we sent to key notified bodies to understand their perception of what they would want to review for DDCs in the context of the new Medical Device Regulation."

"Obviously, we would like to avoid these overlaps in the assessments. But also we would like to avoid sequential assessments" for which there are "a lot of issues" – taking the time during development to have to go through a notified body assessment and then submitting and MAA. "We are pushing for an integrated review process – or at a minimum, that EMA can consider, for example, receiving an assessment report during the MA review process. It is much better if it is a coordinated effort like, for example, the ATMPs, which would benefit the need of the industry. Otherwise it seems very difficult."

The Challenges of Applying Statistics

Roche's Thomas Schreitmuller turned attention onto the presentation by Biogen's Keane on the statistical methodology for assessing comparability, during which he mentioned EMA's conclusions from its May workshop.

> **Schreitmuller asked if industry's assessment matched up or if EBE would include something in addition. He also inquired as to EBE's assessment of the FDA guideline on the topic.**

Keane suggested that it would be "presumptuous of me to give a conclusion of the workshop," except to say that "it was a very useful workshop."

The topic is under development, he said, inserting his "personal opinion that a draft reflection paper at this stage would be very good from a level-setting perspective. There certainly are differences of opinion within the industry and within the various groups as to what that paper should look like. Perhaps in five or ten years' time, we will have more detailed papers on some of the specific aspects of biosimilarity, quality changes, small molecules – whatever type of flavor of a statistical approach that you might have. But we have to start somewhere, and that is a key part of it."

On the FDA query, he commented that there was FDA participation at the workshop, "which was fantastic." The thought was expressed at the workshop that "there needs to more put into, perhaps, the harmonization between the agencies in their approach, because of the recognition of the importance of this topic."

Noting the additional session held among regulators at the conclusion of the workshop, Keane invited comment from those in the audience.

> **Netherlands Medicines Evaluation Board (MEB) biologics reviewer Martijn van der Plas, who participated in the workshop as part of the EMA organizing committee, expressed gratitude to EBE for "giving us a lot to chew on. We are still digesting" and it will take some more time to reflect on the issues.**

"Often you see at this stage a clear way forward on how to proceed." However, "I think it is not immediately clear what is the best way to proceed…and the options are on the table."

The EMA reflection paper, Van der Plas pointed out, "has a very broad scope. It will apply to all products and product classes, including small molecules." However, most of the contributions at the workshop were on biologicals, and it "would be good" if this biologics emphasis were reflected in any further update.

Cross-Referencing Dossiers Recommended When Feasible

HPRA's Barry followed up on the earlier comment by PEI's Gross on use of drug master files. The issue was touched on in the QWP/BWP prior knowledge workshop, where it was pointed out, he said, that "although we don't have drug master files, we are open to cross-referring to previous dossiers, when you submit and you clearly state, 'this drug substance is approved in X product.'"

Although it is not a formal master file approach, Barry point out that "you are very unlikely to get questions" if the assessor sees that "this is all approved, and the control strategy is the same as the other one," and he encouraged doing this kind of cross-referencing.

Sweden Medical Products Agency (MPA) regulator Mats Welin suggested that, although you may need to again submit the data, an explanation that this is the same as was approved for another product "would really help us, because then we don't need to go into detail. We can refer to that, and you would have a harmonized outcome," and avoid redundant assessment. Otherwise there is danger, depending on the drug, that you may have different requirements.

> **Bechtold-Peters commented that it can be a problem referring to previous submissions, adding that with ADCs, "it is rarely the case that all is in one hand."**

At Novartis, she noted, "we make it predominantly ourselves, which I think is a unique situation. But typically you are taking different CMOs and providers. They have a platform, so it would be great if they had a DMF. I think there is no other choice than going that route" in order to avoid having repetitive content and review.

PEI's Gross agreed on the benefit that having a DMF system to share confidential information would provide.

Notified Body Pilot Program Idea Draws Attention During Q&A

At the conclusion of the panel, Lilly moderator Fionnuala O'Driscoll invited the panel members to ask the regulators participating in the dialogue any questions they might have related to the content they presented.

> **Sanofi's Mathonet asked if the EU regulators in the room had any comments on the proposal for a pilot program between EMA and notified bodies. He observed that there would be a session of the forum the following afternoon on DDC issues, at which the discussion could continue in this regard.**

UK MHRA combination product regulator Liz Baker emphasized that these collaborations between the interested parties "are really important." She recognized the amount of liaison EBE's DDC working group has with EMA and its working groups.

However, she suggested, "it is also important to bear in mind that there are many more products in combinations that are not going through the centralized route involving EMA. There are many more varied products going through national and decentralized authorization routes. So it is important that whatever the pathway is, it is applicable not just to the much more controlled processes of the EMA, but that it is adaptable for all of the regulatory routes."

Austrian Agency for Health and Food Safety (AGES) Clinical Trials Head Ilona Reischl expressed her personal feeling that before talking about pilot procedures, "we have to find a common language and we have to identify who we really need to talk to. Because I don't think we have notified bodies approved according to the future regulations. So until we have that, who are we really talking to? I have the feeling that in a couple of situations…we don't yet sufficiently understand the work of the other party to be sure we are talking about the same thing."

Before solving that, Reischl suggested, a pilot procedure might "not make much sense. There is a lot of up front effort to understand each other that is needed [beforehand] to avoid losing a lot of time once we have the pilot procedures."

EBE Session Concerns Explored Further in CASSS Forum

The CAR-T cell therapy workshop that followed at the EBE session provided an opportunity for Netherlands Medicines Evaluation Board Biopharmaceuticals Senior Assessor Marcel Hoefnagel to review the regulatory aspects. BioNTech Business Development Manager Andrea Schilz then discussed CAR-T manufacturing challenges, and Amgen CAR-T Cell Therapy Operations Leader Sam Yaghmour presented more generally on those involving autologous cell therapy.

The last speaker before the panel discussion was Novartis New and Enabling Technologies Head, Cell & Gene Therapy, Erik Rutjens, who provided insights on the potency assessment of his company's Kymriah CAR-T cell therapy product – the first in class to be approved by FDA, with approval coming in August 2017.

> **The issues at the forefront of current EBE attention that were in focus during EBE's satellite session were also prominent in the presentations and discussions that followed over the next two days at the CASSS forum.**

Following the forum model, it began with regulatory updates from around the world, at which key regulators from US, Europe, Japan, Brazil and Peru had a chance to explain their respective agency's engagement with the prominent issues now on the biopharmaceutical regulatory agenda, including the handling of accelerated reviews, biosimilars, advanced therapies, and lifecycle management.

Breakout sessions followed on the challenges and developments around: ● drug device combination products ● the clinical relevance of specifications ● the current and future approaches to enhancing development and quality by design, and ● prior knowledge in CMC submissions.

[CLICK HERE for the full remarks by Goese, Ramdas, Mathonet, Bechthold-Peters, and Keane at the CASSS forum.]

LINKS:

- List of EBE Papers
- EBE/EFPIA Press Release on Advanced Therapies and Hospital Exemptions
- EMA Prior Knowledge Workshop Materials
- EMA Report on Nov. 2017 Prior Knowledge Workshop
- EMA Draft Reflection Paper on Statistical Methodology
- Workshop Announcement
- Comment Docket on FDA Draft Guidance on Statistical Approaches to Evaluate Analytical Similarity
- ICH Q12 Step 2b

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