IPQ INTERNATIONAL PHARMACEUTICAL QUALITY
Inside the Global Regulatory Dialogue

EMA's KEY BIOTECH QUALITY INITIATIVES IN FOCUS AT CASSS' 2012 CMC STRATEGY FORUM EUROPE

INTRODUCTION:

The EMA is continuing to refine and harmonize the European CMC expectations for clearing drug and biotech products for marketing.

European regulators provided updates on the key initiatives and dialogued with industry about them at the CASSS' 2012 CMC Strategy Forum Europe, held in Berlin in late April. The following is a three part review of the initiatives that received attention at the biotech forum. The review was prepared by International Pharmaceutical Quality and included in the IPQ May Monthly Update. IPQ is a media partner with CASSS for the European forums and shares its reports on the forums with CASSS members on the society's website.

The three parts focus on the discussions of:

- EMA's release of the draft process validation guideline
- the finalized guideline on the quality documentation requirements for obtaining clinical trial approval for biological products in Europe
- EMA's effort to revise its biosimilars guidelines and other key EMA biotech CMC initiatives, including the cooperative application review effort with FDA.

Leading the discussion of the EMA process validation draft was AFFSAPS biotech products assessor Kowid Ho, who is a member of EMA's Biologics Working Party.

Ho explained that the basic intent of the draft is to identify what assessors want to see in the MAA regarding process validation and that it is not prescriptive regarding how to conduct the validation.

Noting that the quality system information not requested in the dossier will be covered during inspections, the BWP member emphasized that EMA is looking for industry input through the comment process to help find a good compromise on what should be in the filing and what should be handled within the site. Included is a comparison of the EMA guideline with FDA's – relating, in particular, to the use of small scale studies, lifecycle stages, and statistical models.

While EMA considers the general principles in the new process validation draft as applicable to biological products, the agency is working on a separate guidance that will address PV issues specific to biotech products, which is expected to be released soon.

The finalized guideline on the quality filing expectations for biological IMPs is the result of extensive EMA vetting with stakeholders and should help bring some harmony across Europe to what has been a disparate process. The story includes the insights provided at the CMC strategy forum by EMA Biological Section Head Peter Richardson on the changes made to the guideline as a result of the industry feedback.

Richardson also discussed other key EMA CMC initiatives, including those on biosimilars and variations – the focus of the third part of the story. Addressed, in particular, are the agency's efforts to revise its biosimilar guidelines, including Richardson's insights on how the agency's experience and stakeholder input are impacting those revisions.

At the end of May, EMA released the new draft of its biosimilars quality guideline. In previewing the release at the strategy forum, Richardson commented on the agency's thinking regarding some of the key changes it made to the earlier 2006 version. The comment period on the new draft runs through November.

Also addressed in this third section of the story are the interactions that EMA has had with FDA regarding biosimilars, and a discussion of the EMA/FDA joint biotech product review initiative at the forum, including some thought-provoking insights from Richardson and from CDER Office of Biotechnology's Jeffrey Baker.

PART I: EMA Process Validation Draft Targets Filing Requirements and Assessor Needs

The European Medicines Agency (EMA) has released a draft process validation (PV) guideline that mirrors FDA's PV guide in principle, but is aimed more at the content and assessment of marketing authorization applications rather than the execution of validation in a manufacturing facility.

The 11-page draft covers process validation for drug products for both human and veterinary medicines, excluding legacy products, and is out for comment until the end of October.

The draft guide explains that its fundamental principles "are applicable to biological products," but that "these should be considered on a case-by-case basis in view of the complex nature and inherent variability of the biological substance." EMA is working on a separate guidance that will address process validation issues specific to biotech products, which is expected to be released soon.

FDA states in its process validation guidance that it does encompass biotech products, and the agency is not working on a separate biotech-specific document.

> **At the CASSS European CMC Strategy Forum in Berlin, Germany in late April, Kowid Ho, a biotech products assessor for AFSSAPS and a member of EMA's Biologics Working Party (BWP), explained that a primary intent of the draft is to identify what assessors want to see in the MAA regarding process validation and that it is not prescriptive regarding how to conduct the validation.**

"We are trying to provide some clarification on the data expected in the dossier," he commented. "This is something that helps you understand what we need to see in the filing. It is not to tell you how to validate it."

As a reviewer, he explained, "I will certainly not tell you how you should validate it, particularly when I see how different companies' approaches to process validation are different. I will not tell you what is the right or wrong approach. I prefer to tell you what I want to see in a dossier to make me confident that your process is in a validated state."

> **In addition to describing what EMA would like to see in an MAA, the draft also gives a general indication of what is not requested – namely the GMP aspects of process validation handled by the firm's quality system.**

"What is not requested in the dossier will become something that will be covered by the quality system and verified on-site during inspections," Ho commented.

Through the comment process, EMA is looking for industry input to help "find a good compromise on what should be in the filing and what should be handled within the site."

Any changes to the guideline, Ho reminded the CASSS meeting attendees, need to be aligned with other current EU guidance as well as relevant US guidance and GMPs, or at least "not in contradiction. So you see that we have a lot of constraints involved in the way we can move in these documents."

Small Scale Studies Addressed

Like the FDA guidance, the EMA draft allows some aspects of process validation to be addressed by studies done at less than manufacturing scale.

EMA notes that the process validation batches should be representative of the commercial-scale process. "Representative is a very important word here," Ho stressed, "because this is something that will also need to be demonstrated afterward. The applicant will have to provide data to the regulators to convince us that the small scale work is relevant to the final commercial process."

The PV draft states that "some process validation studies may be conducted on pilot scale batches if the process has not yet been scaled up to production scale." It instructs that the pilot batch size "should correspond to at least 10% of the production scale batch."

> **Biotech and other biological products, aseptic processes, and processes in which "non-standard" manufacturing or sterilization techniques are used, however, may not be eligible for the pilot scale validation option.**

EMA explains that in these cases, pilot scale data "may not be predictive of production scale," and production scale validation data is requested for the MAA.

Where non-standard sterilization methods or aseptic processing are employed, the agency asks that data be provided on a number of consecutive batches at production scale. A minimum of three batches should be used, with the total number based on the variability of the process, the complexity of the process/product and the experience of the manufacturer.

EMA Echoes FDA on PV Lifecycle and QbD

The concept of a lifecycle approach and traditional versus "enhanced" QbD approaches are treated similarly by EMA and FDA. However, the definition of process validation and the timing regarding when it should take place differ somewhat between the two agencies.

> **Both agencies recognize that validation is not a one-time event and that a lifecycle approach needs to be taken.**

In the FDA PV guidance – finalized in early 2011 – the concept of a lifecycle approach and the resulting three stages of a validation continuum is a central focus ***(IPQ "The News in Depth" February 23, 2011)***.

EMA's guide also gives a nod to the three-stage model but does not make it the central theme as FDA does in its guidance, reflecting the latter's focus on validation implementation.

The EMA and FDA guidelines both address traditional process validation and continuous process verification and the use of a hybrid approach.

According to AFSSAPS' Ho, the intent of the EMA guide is to "show the topics we want to be covered in your validation studies" – whether a traditional or enhanced development approach or a combination is used.

FDA and EMA Definitions Vary in Emphasis

FDA's definition emphasizes the lifecycle aspect, which in turn impacts the way FDA framed its expectations for application approval and marketing.

The EMA draft states that process validation is comprised of "the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes."

FDA's guide defines PV as "the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products."

With its greater emphasis on the three stages of the validation process extending through continuous verification, FDA's guidance shies away from calling a process validated at a particular point in its lifecycle – for example, prior to marketing.

The EMA draft states that "the manufacturing process should be validated before the product is placed on the market. In exceptional circumstances, concurrent validation may be accepted."

The FDA guidance states that "before any batch from the process is commercially distributed for use by consumers, a manufacturer should have gained a high degree of assurance in the performance of the manufacturing process."

The relative focus on statistics also varies between the two guidances.

While the FDA guidance places a significant emphasis on the use of statistical tools and provides insight into when and where they are applicable, EMA's only mentions that "any statistical models or tools used should be described."

LINKS:

EMA PV draft

FDA PV guidance

EMA concept paper on PV for biotech products

<u>PART II:</u> EMA's Finalized Biological IMP Quality Guideline Furthers European Clinical and Biotech Review Harmonization

EMA's finalized guideline on "the requirements for quality documentation concerning biological investigational medicinal products in clinical trials" reflects significant changes made to the draft resulting from extensive industry/regulator dialogue and marks an important step in the agency's efforts to harmonize requirements in the clinical and biotech arenas across Europe.

One important change made in the final version as a result of the dialogue is the ability for sponsors to extrapolate shelf life of the investigational product beyond the period covered by long term, real-time stability studies, provided that the extension is supported by relevant data, including accelerated stability studies.

The guideline applies to proteins and polypeptides, their derivatives, and products of which they are components (e.g. conjugates), produced from recombinant or non-recombinant cell culture expression systems. The principles may also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids.

> **Responsibility for the approval of a clinical trial application (CTA) in Europe resides at the state level. Each of the EU's 27 member states is responsible to approve applications for trials in its own country.**

Varying experience levels of both sponsors and competent authorities with biotech products, and differing requirements across the member states, have made registration of trials for biologics problematic. The new guideline attempts to address these discrepancies by serving as a common reference for the evaluation of the quality of a biological CT material.

A concept paper on the topic, published in 2008, was discussed in several industry/regulator forums, including a CASSS Europe CMC Strategy Forum in Spring 2009 in Lisbon, Portugal. A draft for public consultation was released in February 2010 with a six-month comment period. During that time, the document's rapporteur, BfArM's Brigitte Brake, presented the key points for feedback and discussion at the 2010 CASSS meeting in Vienna, Austria. Nearly 200 pages of comments were received on the draft.

In June 2011, a face-to-face workshop between industry associations and EMA's Biologics Working Party (BWP) was held in London, where the controversial issues of shelf-life determination and filter sterilization were a focal point. The guide was finalized and came into effect in April.

> **At the CASSS Europe CMC Strategy Forum, EMA Biological Section Head Peter Richardson discussed the changes made to the just-released guideline as a result of the industry feedback. He also provided updates on other key EMA initiatives, including those on biosimilars and variations *(see Part III)*.**

"Harmonization has always been an issue for clinical trials, and I think it is an ongoing task that we need to keep pushing on," Richardson commented. "It is difficult to see whether a single assessment of a CTA will come under the umbrella of the EMA. It is very much a national member state competence and I think it will stay that way, so we need to work with that in mind to keep the harmonization ongoing."

Industry Comments Shape Final Draft

Richardson reviewed the more influential industry comments and how they were reflected in the final draft. Key concerns included: ● splitting out early versus late-phase requirements ● control of starting materials ● the use of prior knowledge, and ● specifications and bioassays.

A request to broaden the scope of the guideline to cover other product types was not taken. As the guideline pertains to "recombinant products that are well-characterized," he commented, "I think we want to keep it reasonably tight."

A suggestion to split the discussion of requirements for early phase and late phase into two distinct chapters was "taken on board." Although the requirements were not moved into separate chapters, how they differ is addressed in the guideline.

> **Comments on the control of starting materials and the level of characterization originally requested for early stage materials was recognized as "maybe being burdensome," and the final guideline contains somewhat relaxed requirements, accordingly.**

Prior knowledge and how it could be used in the investigational product file was a topic of discussion by the BWP in response to comments in that regard. "I think some of those aspects can be brought in," Richardson commented. However, he characterized it as "something which is relatively new and needs to be done with some consultation with the member states."

Regarding justification for specifications and how they are detailed, the main emphasis in the final guide is on Phase III, and there is some relaxation of the expectation in early-on clinical development.

> **The original draft included a mandatory requirement for a bioassay. "I think in some certain cases it could be relaxed," the EMA official said. "It is not something that we would like to see relaxed very far, but there is an opportunity in some cases."**

Several other changes were made following the consultation, Richardson explained:

- the introduction was shortened and linked with CT-1 [the overarching CT guideline]
- information on comparators was removed
- the evolution of quality and level of detail through CT phases is recognized
- mainly editorial clarification was made on comparability
- additional flexibility on controls and specifications was provided – for example, regarding a test for bioactivity
- references to other guidance was substantially reduced, and
- substantial amendments linked to CT-1.

LINK:

EMA IMP final quality guideline

<u>PART III:</u> EMA's Biotech CMC Focal Points Include Biosimilar Guideline Revisions and Joint Reviews with FDA

EMA is nearing release of revised drafts of its biosimilars guidelines to reflect experience gained and stakeholder input and is refining its cooperative application review process with FDA – two of the European agency's focal points in the biotech CMC arena.

> **EMA biotech initiatives were addressed at the CASSS Europe CMC Strategy Forum by biologics regulator Peter Richardson and were explored further in a panel session following his presentation, which included FDA Office of Biotech Products Deputy Director Jeffrey Baker.**

Richardson provided updates specifically on the various European biosimilar guidelines under development, including an overarching guideline and its guides addressing quality and clinical/non-clinical aspects of biosimilars. He also addressed EMA's efforts with FDA to share information and facilitate mutual understanding regarding biosimilars.

The biologics official's discussion encompassed a recently-released final guidance on the requirements for quality documentation for biological investigational medicinal products in clinical trials. Also explored was an initiative the EU Commission is undertaking regarding EMA's variations regulations.

> **A revision to EMA's 2005 overarching "guideline on similar biological medicinal products" was proposed in a concept paper in November 2011 with a three-month comment period.**

EMA's Biosimilar Medicinal Products Working Party (BMWP) and it Biologics Working Party (BWP) are using the comments received to produce a draft for public consultation, expected in Q3 2012.

Comments on Concept Paper on Revising Biosimilar Overarching Guide

The following are some of the key comments made by stakeholders on the concept paper that EMA released on revising its existing biosimilar overarching guide, followed by remarks at the recent Europe CMC Strategy forum by EMA biotech official Peter Richardson on the comments. He noted the positive reception that the concept paper received and that terminology was also clarified in response to the stakeholder input.

- **Use EMA's website as a tool to get access to the guidelines rather than the guideline itself containing the references** – EMA agreed and will proceed in this way.
- **Safety and efficacy aspects are better covered by the general and product-specific clinical and non-clinical guidelines** – "I think there is a move to use that where possible."
- **The 'generic approach' for a biological is not appropriate and not necessary; sufficient flexibility is provided in article 10(4)** – In general the agency agrees, although "there may be situations where that may be possible."
- **Pharmaceutical form, strength and route of administration should normally be the same as for the reference product, although liquid versus lyophilized formulation should be acceptable** – "I think this may be one of the more common issues with biosimilars recently, because territories like Europe were requiring a reference product for comparison from that territory."
- **Include a discussion on global development and follow the same approach as FDA** – The requirement for the reference product to be batch-released in the same territory where the biosimilar is to be marketed has been "commonly questioned from a scientific perspective" and ethical concerns about repeating clinical trials have been raised.

The guideline revision was proposed to: ● provide updates reflecting the experience gained since its publication ● provide clarification on biosimilar principles and terminology ● discuss whether in exceptional cases a product could be authorized based on bioequivalence studies with comparability exercises ● include discussion of safety and efficacy aspects ● provide clarification on whether differences in form, strength and route of administration are possible, and ● remove detailed references to other guidelines.

Richardson commented that the provision regarding possible authorization on the basis of bioequivalence "raised a lot of eyebrows."

"The point was that option could be a basis for certain molecules that are extensively characterized or very simple," he commented. "I think that it is unlikely that we would get to that for most of the biosimilar cases that we see. In fact, that it is something which has been possible in the legislation since the start of all this."

The desire for global harmonization of biosimilar registration requirements has been gaining momentum as illustrated by the outcome from a recent meeting between the European Generics Association (EGA) and the European Commission (EC).

"EGA met with the EU Commission and gave quite an upbeat presentation on this topic, and the EC was positive about moving forward to modify the thinking such that there could be a global development of biosimilars," Richardson commented.

"I think that is quite an important development because it will alleviate the need to repeat studies in the different territories. We are hoping that by further talking with FDA, etc., to look at the scientific mechanisms to put that in place that will allow for a much more global assessment, which is certainly what we have been talking about over the years. I am pleased to tell you that it is moving closer to reality."

Comments on Clinical/Non-clinical Revision Concept Paper Also Under Review

A revision to EMA's 2006 guideline on non-clinical and clinical aspects of biosimilars was proposed in a concept paper in September 2011 with a three-month comment period. EMA's BMWP is using the comments received to produce a draft for public consultation, expected in Q3 2012.

The primary intent of the revision is to incorporate experience gained since the publication of the original guideline.

On the non-clinical front, Richardson commented that the EU guideline, "in line with the guidance from FDA," will move to restrict the use of animal testing wherever possible. Animal tests should only be used when they produce "data that is relevant and that provides useful information. Where the quality data package is sufficiently robust, you can reduce the non-clinical data requirements."

On the clinical side, an emphasis is being placed on pharmacodynamic (PD) markers. The EMA official commented that "we have already seen some applications that have been authorized more on a PD approach than on a clinical end point."

Also incorporated regarding comparability trials is a discussion of whether acceptance should be based on non-inferiority versus equivalence. "I think in some cases that non-inferiority can be useful," Richardson commented. "However, the equivalence two-sided test is the more appropriate."

Regarding extrapolation of the indication, the justification "needs to include clarifications on the factors to be considered to support the extrapolation. It will become a more debated area."

Quality Guideline Revision Also Advancing

A revision to EMA's 2006 biosimilars quality guideline was proposed in a concept paper in February 2011 with a three-month comment period.

EMA's BMWP is using the comments received to produce a draft for public consultation, expected to be released by mid-year for a six-month consultation.

> **The main changes to the guideline address opening up the possibility of a global development approach, use of the quality target product profile (QTPP) of the reference product when developing a biosimilar, and how to handle comparability considering changes that occur over time to the reference product.**

"The focus on comparability is shifting more towards the finished product," Richardson commented. "Similarity is what is important to the patient, so a little bit less emphasis in terms of what is happening with the active substance. I don't think it changes the scientific data requirements really, it just changes the emphasis."

He noted that the guideline has a section on immunochemical properties introduced to cover the additional testing expected for monoclonal antibodies. "It discusses the possibility of different expression systems. I think that we have gotten to the point that the more you change it the more differences are possible and the higher the risk of failure. It is not something that we say outright that you can't do, but the more you change, be wary that you may find yourself in a situation where there are unacceptable changes."

EMA and FDA Interacting Regularly

Richardson reported on the interactions that EMA has had with FDA regarding biosimilars and the progress made, which he characterized as "significant."

With regard to EMA and FDA sharing information to facilitate mutual understanding, he explained that EMA is liaising "regularly" with FDA.

The EMA-FDA "biosimilar cluster" was launched in July 2011. Cluster meetings occur three times a year in conjunction with the Biosimilar Medicinal Product Working Party meetings.

Richardson noted that one of his colleagues at EMA is working at FDA on a fellowship, and that the agencies have been "working closely with regards to global development," emphasizing that "I think we have good agreement that is positive for global development."

> **Another important component of the CMC agenda in Europe is the continued refinement of its policy regarding variations.**

A "public consultation paper" on the EC review of its 2008 variations regulation (1234/2008) was issued by the Commission in September ***(IPQ "The News in Depth" October 19, 2011)***. The consultation period extended a month to October 22, 2011.

As a result of the consultation, questions are being addressed concerning: ● changes to stability protocols ● frequent questions to competent authorities on how to classify novel excipients ● inconsistencies between the active ingredient and the product, and areas where that consistency was missing in the quality-by-design fields, including design space detectability ● what is critical and non-critical, and ● submission of variations for updating viral safety data in the file.

Richardson explained that the EC is taking steps to get the regulation to the member states for national authorizations. "It was discussed at the standing committee at the end of March and there was generally positive reaction, I think. So that is moving forward."

Q&A Focuses on FDA/EMA Joint Application Reviews

In the Q&A after Richardson's talk, a primary focus was on the EMA/FDA joint biotech product review initiative and how it is progressing.

Richardson responded that the review timelines have been challenging in some cases, and "need to be managed a little bit. We are managing it, though, I think, and there has been some good discussion."

He also noted that the agencies have "different styles" in terms of the way reviews are done.

"I think the way FDA corresponds with the applicant and raises questions through the early phase development is different than us," he explained, commenting that EMA is considering being "more reactive."

The EMA official further commented that "more broadly speaking, we have got a lot of similar thinking. There are some differences I think in terms of experiences that we've had. Hopefully it will continue and grow."

Also commenting on the joint review, FDA's Office of Biotech Products Deputy Director Jeffrey Baker agreed with Richardson's assessment and explained that the success of the pilot depends on what goals are being assessed. Baker joined OPB this last year after an extended biotech career at Eli Lilly.

"If the purpose of the exercise is to streamline efficient, effective, joint reviews between the FDA and the EMA, there have been some teething problems," he commented.

However, if the purpose of the exercise is "to develop a shared understanding of expectations and process and try to lessen divergence of advice and direction, I venture that a lot of progress has been made and continues to be made. And that can be foundational to a lot of stuff."

Baker admitted that there have been a number of operational and execution challenges. He emphasized, however, that "there are outstanding, honest, open and forthright discussions – not only about what we are each doing but also on 'what do you think about this' and 'where do you see things going?' I think that the better harmonization of advice and counsel and direction that we provide to industry helps lessen surprises. By that standard, I think there has been enormous progress. We need to work on the other two."

Another meeting attendee asked the panel to comment on the legal status of information provided in a product registration and what becomes legally binding.

Baker commented that "managing that ambiguity really changes the risk equation. How do we relieve that ambiguity? One way is to hire a bunch of very highly-paid attorneys. One is for the agencies to issue lots and lots of rules. Another way is for the sponsor to come in and to describe their actions in response to certain situations and how they would view it and how they would handle it."

The FDA official believes "there is an additional opportunity to remove the ambiguity by saying, 'should we see thus and such an event, here is how we would respond to it,' and then let that be part of the record with the company owning that themselves. But again, there are a lot of different approaches."

Richardson approached the question by focusing on the amount of information provided in a dossier and how much the agency really needs to see.

He noted that some firms feel – especially with QbD applications – that providing more information is better.

"There is a lot of information being provided to gain understanding, but I think also we need to be judicious about being very clear about what we will say. It has to be carefully constructed and made crisp and simple and understandable." He noted that the more information provided the more complex the application review becomes and "we find it hard to reach a decision on exactly what it is that you are trying to do."

The EMA official commented that there may be times "when some of the development data work their way up into the control strategy and they may be more important. But I think it is more a question of submitting development reports as part of the dossier and they won't change" but will serve to support the line of thinking that went into the decisions made and will not be part of an ongoing lifecycle module. "So I am hopeful that it doesn't become that burdensome."

Another meeting attendee asked if the US is considering producing product-specific guidances for biosimilar products as EMA has done.

Baker replied that "principle drives practice. The current guidelines that are out there now are foundational and are establishing the principles that are still open for comment. We need to get those out there and locked down first before we go into additional granularity."

LINKS:

Biosimilar guideline revision concept paper

Clinical and non-clinical aspects of biosimilars concept paper

Biosimilars quality concept paper