IPQ INTERNATIONAL PHARMACEUTICAL QUALITY
Inside the Global Regulatory Dialogue

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Increased EMA/Industry Dialogue Needed to Address Upcoming Biopharm Regulatory Challenges, Retiring Quality Director Purves Says

The biopharmaceutical regulatory challenges confronting the EMA over the next decade – from biosimilars, advanced therapies, personalized medicine and transgenics to variations and quality by design – will require close industry/regulator dialogue and new communication channels, recently retired EMA Quality of Medicines Head John Purves stressed at CASSS' European CMC Strategy Forum in Vienna in late May.

The criticality of open scientific dialogue and information sharing to shaping viable regulatory policies and guidance and steering the complex new products through their development, review and manufacturing stages was a central theme in Purves' assessment of the emerging EMA landscape.

Focused on the challenges facing biopharmaceutical development in the next decade, the Vienna forum provided the European regulator a chance to take a broad view of how the EMA will need to evolve to address them. Purves left the UK's MCA 14 years ago to join the newly formed EMEA, where he played a key role in advancing its quality regulatory effort and policies. He retired from the agency at the end of April.

The quality regulator pointed out that the importance of dialogue was inherent in EMA's mission when it was founded 15 years ago to "foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health." The mission, he stressed, includes communication and coordination across the EU network as well as stimulating innovation and research "through the tradition of scientific advice."

Purves noted that over the last few decades, "there have been significant changes in the science, there have been developments in the legislation, and also developments in the way in which the regulators have reviewed dossiers." With the increasing complexity of the agency's core tasks, the scientific communication channels need to be further deepened if the EMA is to fulfill its mission, he maintained.

Scientific Dialogue Central To EMA Roadmap

EMA's facilitation role is underscored in the agency's "Road Map to 2015," in which EMA sets out its vision of how it should develop as a public health agency.

The comment period on the EMA 2015 roadmap ended on April 30. The roadmap will be supported by a companion document, "From Vision to Reality," and its various objectives incorporated in the agency's work plans for the 2011-2015 period.

In general, the EMA roadmap points the way to a harmonized approach to the challenges of regulating innovative therapies, personalized medicines and drug/device combination products. It calls for strengthened measures to increase transparency and communication and to combat counterfeits and monitor GMP/GCP compliance.

The roadmap has four sections focused on: ● further improving the quality, regulatory/scientific consistency and efficiency of the core review process ● facilitating access to medicines ● addressing public health needs, and ● optimizing the use of medicines.

> **Purves stressed that the EMA's role of facilitating access to medicines rests on scientific dialogue through the drug development process.**

Industry and regulators meeting together to discuss the science, he pointed out to the Vienna CMC forum attendees, "is helpful to the regulators because they can identify if there are guidelines that need to be developed, and it is helpful to the industry because it allows you to identify if there are any hurdles that need to be addressed in a different way."

The risk/benefit assessments and communication become "a lot more important now," Purves affirmed, given the need to interact with the Health Technology Assessment (HTA) bodies throughout the product lifecycle. HTAs are national bodies that interface with the EMA like the UK's National Institute for Health and Clinical Excellence. NICE makes recommendations on existing medicines/treatments, sets quality standards, offers scientific advice to industry, and manages a national database.

In turn, the roadmap calls for the EMA to address public health needs by helping fill the gaps in drug development and the emerging science. The regulator support will be "very important" both for advanced therapies and biosimilars, Purves commented, pointing to the response to the influenza pandemic as an example of this regulatory support process successfully at work.

Quality By Design And Personalized Medicine Will Require Collaboration

In his presentation at the Vienna forum, the recently retired quality director explored the challenges the EMA will be facing in addressing biosimilars, quality by design, and personalized medicine, in particular. ***[Editor's Note: The EMA biosimilar developments addressed by Purves are covered in the August 21 "In the News" companion story.]***

> **For QbD, Purves views as key challenges the level of information that needs to be included in an application and the related issue of how to enhance collaboration between assessors and inspectors across the QbD/quality system continuum.**

This nexus of issues has been receiving particular attention in the European discussions on advancing the ICH QbD/Q8-10 paradigm ***(IPQ May 2010 Report)*** and were central to the discussions at the ICH implementation workshop in Tallinn Estonia in early June ***(IPQ "In the News" July 3)***.

The challenge of enhancing the assessor/inspector communication process is even more pronounced in the European context where the preapproval inspection process has not been as fully implemented as in the US and the disconnects of the multistate system come into play.

Purves commented in Vienna that making sure there is sufficient training and dialogue between industry and regulators in this area is critical in introducing "successfully the quality by design concept and practices. So the scientific dialogue between industry and regulators prior to and during submission is encouraged."

> **EMA will also "need to address the new challenges on the horizon relating to nanotechnology, synthetic biology and regenerative and personalized medicine."**

In the personalized medicine arena, the agency will need to build on the current experience with advanced therapies, he said, adding that some centrally authorized products already have personalized indications in the approved product information.

Purves stressed that the scientific/technical and regulatory challenges for these novel approaches "will be quite different." In order to address them, the agency will need to pool its specialized expertise to adapt the regulatory framework.

The area of advanced therapies "is going to be very interesting" over the next decade, Purves predicts, drawing a parallel with "where we were with rDNA products at the beginning of the 1980s." The workload will increase slowly, but there will be "a very progressive and positive increase in the activities between the regulators and the industry."

Recognizing that the review of advanced therapies would require pulling together expertise in various diverse areas such as surgery and medical devices, EMA created a new "Committee for Advanced Therapy Products" (CAT) in January 2009.

There has been a limited amount of activity to date in marketing applications. TiGenix' ChondroCelect (characterized viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins) was authorized in October 2009. Ark Therapeutics' Cerepro (stimagene ceradenovec – adenoviral vector-mediated herpes simplex virus-thymidine kinase gene used with subsequent administration of ganciclovir) received a negative opinion in December 2009 and the company is now looking at further Phase III trails and co-partnering arrangements. The product was granted orphan drug status in both the US and EU.

As of January 2010, 22 products had been classified as advanced therapy medicinal products (ATMP) based on the scientific recommendation of the CAT, and one product was under review for the ATMP designation.

Addressing the guidance needs for the new biologicals, Purves noted that a guideline on the requirements for quality documentation concerning investigational medicinal products is under development.

EMA is also in the process of revising its guidelines on transgenic animals and plants, which were developed back in 1995. The agency did publish a guideline on the quality of biological active substances produced by stable transgene expression in higher plants in 2008.

EMA approved GTC Biotherapeutics' antithrombine alfa product ATryn produced in transgenic goats in mid-2006, which was also approved in the US in early 2009. The company is located in Framingham, Massachusetts. A recombinant C1 inhibitor from transgenic rabbits, Rhucin, from Netherlands-based Pharming Group, received a negative EMA opinion in March 2008, and a resubmission is currently under evaluation. Applications have not yet been submitted to the agency using transgenic plants.

Purves emphasized the enhanced role EMA should take in helping facilitate new approaches to medicinal product development and the need for applying "a more proactive approach to public health threats where medicines are implicated," building on the positive experience gained in the influenza pandemic response.

Along with the new technology products, globalization is another force challenging EMA to evolve its regulatory strategies and broaden cooperation and communication pathways, Purves stressed.

Manufacturing and clinical research is moving away from the classical sites in the EU and US, and "the world is becoming very much a 'supermarket' in pharmaceuticals. So we need to look at things in a globalized

manner. There are changes to the role of regulators, and I think there needs to be a lot more discussion, as there has been over recent years, amongst the regulators – a call for more international harmonization and cooperation." Counterfeiting is also a driver for cooperation, Purves added.

The EMA strategy includes further increasing the interactions with international regulatory partners such as with FDA on "clusters" like vaccines and advanced therapies and on QbD, which, in turn, "stimulates the global approach," Purves commented. The work with ICH and WHO "is also going to further strengthen the globalization of the regulatory approach. So we need to strengthen the partnerships using these tools."

Echoing a recurrent theme among the FDA hierarchy on the global challenges, the former EMA regulator also stressed the importance of recognizing and enhancing "the ability to rely on local regulators to assure the equivalent approach to manufacturing and control of medicines and authorization and supervision of clinical trials" as well as pharmacovigilance. The focus needs to be on "where products are being produced and tested," he said, and support provided for training and capacity building in those regions.

Forum Participants Weigh In

During the discussion period that followed Purves' presentation at the European forum, participants drilled down further on the need for open scientific dialogue to advance the regulatory process and how the need can be addressed.

Abbott Laboratories' Brian Withers, who is the Expert Working Group (EWG) "rapporteur" for the development of the drug substance guideline Q11 ***(IPQ "In the News" July 9)***, pointed out that "the word 'dialogue' – scientific dialogue and dialogue throughout the development cycle" – came up "a lot of times" during Purves' "really interesting" presentation. "Does the EMA have a thought about what that would look like?" Withers asked him.

Withers added that the EMA's procedure for "'scientific advice' is okay if you have specific questions, but the ability to have a dialogue throughout development, particularly on quality-by-design issues," is something industry has been interested in. "Does the EMA have a view on that now?"

> **Purves responded by sharing his experience on the important role that scientific dialogue has played in allowing the regulatory process to keep pace with new technologies.**

While at UK's Medicines Control Agency (now MHRA), his "initial experience regarding dialogue was back in the 1980s when we had the first rDNA application for human sequence insulin in the UK. At that stage, I think the industry and the regulators were both wondering how do we take things forward. And what we did at that stage was sit around the table and actually talk about the scientific issues, and we came to an agreement on what would be a reasonable submission from the regulators' point of view and based on the science that the company had provided."

Subsequent to that, Purves continued, "the experience in the late 80s and the early 90s showed quite clearly that repeated scientific advice was helpful in identifying potential hurdles before the submission of applications."

> **Turning to the current dialogue around QbD and the changing variations regulations, Purves noted that this is a new area for both the regulators and the industry, potentially requiring new communication channels.**

"The regulators are probably more curious about the company's strategy for taking the product forward. What do you want to do? I think if a request was put forward to the agency to have that dialogue before some of the

variations were submitted in relationship to, say, quality by design, I am sure that that would be agreed to. The mechanism of how that is going to be done, I think, needs a little bit more thought."

Recognizing Withers' comment on the limited scope of the current scientific advice procedure, Purves added that "there is also the opportunity for the industry going to the agency to discuss some new issues…. If the industry takes that initiative and puts in requests, I am sure they are going to be honored in some way. But probably one needs to think of a more formal way of doing it. That will come out from the initial discussions between the industry and the regulators."

Sharing Science Drives Toward Harmonization

The participants in the dialogue at the Vienna CMC forum pointed to the power that the sharing of science has in driving toward harmonization.

Purves reflected that in the mid-80s when the 12 EU member states began to come together to review dossiers through the consultation procedure, their reports "were really quite disparate with respect to comments." However, as scientific information was shared and guideline discussions pursued, the member states began aligning. The international discussions in the ICH and WHO contexts fostered further consensus building.

Advance therapies present a ripe area for regulators and industry to dialogue as "was quite evident" at the workshop EMA held in May on stem cells, Purves maintained. While it is early in the regulatory curve and there are many open questions, "the debate that was had at that meeting helped take things forward."

In general, in approaching new technology areas such as advanced therapies and biosimilars, Europe needs to take a more holistic view, he asserted, with the national competent authorities, the EMA and the HTA bodies and the other stakeholders working together to share the information on safety, efficacy and quality as early as possible.

Former FDA biotech regulator Kenneth Seamon, currently a professor at the University of Cambridge, commented on the need for post-marketing feedback from physicians and practitioners to help fill in the gaps left by the small patient population studies conducted for approval. "I think that is an area where we would benefit from further world alignment," he said. Seamon was cofacilitator of the influential A-MAb case study illustrating a biotech QbD development process ***(IPQ May 2010 Report)***.

> **The question was posed whether industry's ultimate goal of a single global application and clearance process was achievable.**

CDER Office of Biotechnology Products (OBP) Director Steven Kozlowski commented that "it is a long path to trust completely the review of an application by another group," and a complicated one both scientifically and politically.

"On the other hand," Kozlowski said, "I think the more the science is transparent and shared, the more the requirements become the same. As John [Purves] said, when groups talk together, usually we end up coming to the same conclusion. So I think the more we share the science…the more the requirements will tend to harmonize of themselves.

"Trusting another group to do an inspection for you, to actually review all of the data, I think those are challenges." However, the CDER official maintained, "if you can come to agreement that the science principles are the same, you are at least a large step in that direction and save industry a lot of effort too, even if they need multiple applications.

"So I think that over time, we move closer together. When there will be a global marketing application reviewed by one local regional group – that is an attractive idea, but a little bit off in the future."

Seamon commented that "mutual recognition is a holy grail, but it is still going to be…many years."

The former FDAer emphasized the importance of sharing ongoing post-approval inspectional data as well as the development science, questioning whether "there are strong enough opportunities for transparent discussions" on the post-approval side.

> **Kozlowski concluded the session discussions on the benefits of scientific information sharing to evolving the regulatory process by pointing to the need for industry to understand that these benefits far outweigh the risks.**

The regulatory agencies, the OBP official said, can establish bilateral sharing agreements, but sharing more broadly becomes an industry decision. "We can't force you to share data you don't want to share…. It needs to be industry viewing that the value of sharing is greater than the risk of sharing."

He pointed to treating biotech science as proprietary out of concern for biosimilars as a case in point.

"The way technology advances, your lawyers may worry about protecting some piece of data or some analytical test [but] that will probably be irrelevant by the time that product is challenged."

Kozlowski urged the industry participants to "think long term – that sharing the science is much less risky than you think…. It is worth thinking about the true risk and value of sharing a lot of this information."

LINK:

EMA Road Map to 2015