IPQ INTERNATIONAL PHARMACEUTICAL QUALITY
Inside the Global Regulatory Dialogue

Better Glycosylation Understanding Would Further International Biotech Regulatory Convergence Efforts, CMC Strategy Forum Participants Agree

Regulators are highlighting a better understanding of protein glycosylation – its linkage to product safety and efficacy and what constitutes appropriate characterization – as an important element in developing a more internationally-aligned approach to regulating biotech products.

A large number of the proteins in nature are glycosylated – modified with sugar chains – which affects not only their physical properties such as solubility and thermostability, but also their biological properties, including serum half-life and functional protein-protein interactions. Although more knowledge is being gained about the glycan moieties that have been found to be critical to product quality, the biological impact of other glycan structures is still not well-understood, regulators point out.

> **How glycan modifications to therapeutic proteins and antibodies may impact biological action was a central focus at a session of a CASSS CMC Strategy Forum held in Tokyo in December. At the forum, regulatory, industry and academic experts from across Asia, North America and Europe provided their insights on the issues involved.**

Center for Drug Evaluation and Research (CDER) Division of Monoclonal Antibodies (DMA) Deputy Director Patrick Swann commented that "absent that knowledge, all we know is that there are a lot of glycoforms for a product. But we don't know the linkage, so we have to be conservative. I think that provides some motivation for all of us to better understand that linkage."

Amgen Global Analytical Sciences Executive Director Drew Kellner added that "in the absence of this knowledge, there are some risks. Sometimes you can be surprised." In the context of a process change in the manufacture of a glycoslylated protein that seems minor, the follow-up bioequivalence (BE) studies can indicate a major change in how the molecule interacts with the patient – something that has happened to Amgen, he said.

Biogen Idec Biopharmaceutical Development VP Rohin Mhatre, one of the session moderators, commented that "when you have process changes, you will have changes in glycosylation, particularly for more complex molecules, and even for monoclonal antibodies." The challenge is determining what they mean.

> **The characterization and control of protein glycosylation was one of five topic areas addressed at the CASSS international CMC forum in Japan.**

The four other sessions focused on: ● recent trends in the regulation of biopharmaceutical products and practices ● the development of biosimilars ● new technology for the development of monoclonal antibody therapeutics, and ● challenges and opportunities in biologics quality by design (QbD). ***[Editor's Note: A link to a detailed summary of the forum, presented at its conclusion by Biologics Consulting Group's Nadine Ritter, is included below.]***

Presentations were given covering various aspects of each topic, followed by panel discussions during which the presenters and other regulator and industry experts addressed prepared questions and those posed by attendees.

The Japan meeting represented the first of CASSS' CMC Strategy Forums to be held in Asia. The separation science society is anticipating that the Asia meetings will be held on a yearly basis.

The next Asian forum will again be held in Tokyo in December 2013. The Japanese Pharmaceutical Manufacturers Association (JPMA) will again be assisting in the coordination of the meeting.

The Asian meetings are being structured similarly to those now being held on a yearly basis in Europe, which pull together industry and regulators to focus on a handful of biotech topics of international import.

In the US, CMC Strategy Forums are held both in January, in conjunction with CASSS' annual Well-Characterized Biotechnology Product (WCBP) conference, as well as in mid-summer. Each of the US forums drills deeply into one topic area on the regulatory front burner. In conjunction with the January 2013 WCBP conference, parallel one-day forums will focus on the use of expanded change protocols and new paradigms for process validation, respectively. The two-day summer 2012 forum held in Bethesda, Maryland in July, focused on biotech/device combination products.

Discussions Shed Light on Glycan Analysis and Control

The session on glycosylation included presentations by Japan National Institutes of Health Sciences (JNIHS) Nana Kawasaki, Japan National Institute of Natural Sciences' Koichi Kato, and Amgen's Drew Kelner.

They covered the detection and characterization of glycan species spanning academic and industry applications and cited relevant recent publications. Representative results from each technique were provided along with a description of their strengths and weaknesses, including results from among different sources of the same glycoprotein.

In addition, the presenters discussed process analytical technology (PAT) applications of the techniques, examples of structure-function assessments for MAbs, both *in vitro* and *in vivo*, and the potential for method validation and use in setting product specifications.

Kawasaki pointed out that both the USP and EP have general chapters on glycan analysis, but that the JP chapter "fell behind." She noted that her group at JNIHS is putting together a draft for submission to the JP for its glycosylation chapter, and that several options are being considered for putting standardized glycan information in the public domain, including through journals and white papers.

During the panel discussion that followed the presentations, the primary focus was on prepared questions dealing with glycosylation detection and control, regulatory expectations for what analytical data should be included in submissions, and industry implementation of new detection methods.

Amgen's Kellner explained that the selection of analytical technique depends on its intended use – that tools important for R&D process development are different than those used for product characterization and comparability, which may also be different from the QC methods that are needed for supporting specifications for release and stability testing. He noted that high-throughput capability is useful, for example, in the screening of cell lines, but that characterization and comparability should use slower, more robust methods.

FDA's Swann pointed to a paper published in August by Pauline Rudd at Ireland's National Institute for Bioprocessing Research and Training (NIBRT) as a good reference regarding the differences in various analytical applications relative to the nature of glycoprotein methodology. BCG's Ritter characterized Rudd as a "mentor" in this area of research.

Plea Made for Shortening Method Change Timeline

Understanding the differences in glycoforms within a molecule falls under the broad category of microheterogeneity in biopharmaceutical products, covered in ICH Q5E and Q6B.

The ICH guidelines recommend that industry characterize and control the product differences that can result from different glycoforms within clinical trial experience.

"I think there is a general consensus in the public domain, the published literature, about which particular glycoforms are important for particular proteins or antibodies," Swann commented. "As a regulator, it is an expectation that, since these may be critical for your product, you need to have adequate methods to measure and control those particular attributes."

In discussing risk assessment for quality attributes, ICH Q11 points out that since the methods continually improve, the knowledge of what is critical improves as more sensitive and specific structural and functional data are collected on glycoprotein products. Swann stressed that "moving forward, the state of the art is continuously increasing, so that is why it is very important to react and incorporate newer technologies."

> **Genentech's Wassim Nashabeh agreed that "it is always great to change methods and use the latest and best methods." However, he commented, for a global company to change a single method may require "a four-year process" to get the necessary approvals.**

"That has a significant impact on supply chains," he stressed, as approvals are staggered throughout the world and finished product needs to be held awaiting approval. "This is a company trying to improve, to innovate, and [implement] a desired, good change."

Nashabeh asked the regulators in attendance to comment on how that process might be shortened.

FDA's Swann pointed to work being done between the US and EU regarding harmonization of requirements for process changes that he believes could also be applied to analytical method changes.

Q6B says in several places that the most up-to-date methods should be utilized, he said, "which we all see as good. It helps companies innovate. It helps make for better quality products. And we all want to encourage that. I would certainly be open to working with other regulatory colleagues to find ways to make it less than four years. I think we can do that."

> **During the panel discussion, BCG's Ritter pointed to a presentation given at a previous CASSS forum by FDA's Kathleen Clouse that provided some ideas on how new method implementation could be compressed.**

The presentation indicated that "it is possible to compress some of the timeline," she commented, through using "well-designed, thorough bridging studies using a wide variety of product samples – for example, multiple lots and degraded lots."

However, there are still global implementation challenges, especially with the setting of new specifications. "It does require collection of a lot of data to assess whether there is any impact on the specification for a particular attribute."

Ritter noted that from a regulatory perspective, lifecycle management encourages continuous improvement of analytical tools. "So don't be afraid of what you see, because it may have always been there, or there may be

an acceptable set of variations within the clinical range. But until you start measuring it and collecting the data, you will not really know."

CDER Office of Biotech Products Director Steven Kozlowski highlighted two distinct activities that need to be addressed – analyzing any new peaks with archived samples and their risks, and regulatory harmonization.

"Maybe there should be a global forum," he suggested. "Pick one analytical method change that worked – one that has already been done and the company is willing to share with a few other companies – and discuss what was involved in that with a global audience. Then begin to create some scientific agreement about what is appropriate."

Nashabeh commented that the topic is "very important" and could be the basis of a discussion at a future CASSS meeting.

Finnish Medicines Agency Senior Researcher Niklas Ekman and EMA Head of Biologics Peter Richardson provided further insights into what regulatory agencies would like to see in applications regarding glycosylation.

"Definitely the most important piece of this is the link between glycoforms and biological activity and product safety," Ekman commented. "That is what we need to know in order to make sure that the products are safe and stay safe on the market."

Richardson explained that the level of detail in applications is important. "Sometimes there is too much detail," including analysis of every peak in a chromatogram, and agency reviewers are not sure what to do with all the information, he noted.

"The nature of the way technology has evolved is that there is an ability to see a lot, and it is valuable to have that information. But I think it is possibly better to keep some of that at the characterization level and maintain it there as a sort of solid foundation within the product evolution and not be quite so fussy about what is going into the control specifications. Then if something arises there is a good body of information to fall back on."

Regulation Trends Show Convergence Potential

During the session of the forum on regulatory trends, presentations by regulators from the US, EU, Japan, South Korea and Singapore and subsequent discussions indicated some key common threads in their current thinking that could help provide the foundation for further cooperation and harmonization.

These include the desire to make regulatory application and inspection processes reasonable and consistent, to assure that decisions are science and data-based, and to take into account a sponsor's history and demonstration of a sound quality system in making case-by-case decisions.

Also clear was the desire to learn by sharing best practices both inter- and intra-agency, and to harmonize where possible.

FDA's Kozlowski used the term "regulatory convergence," whereby industry groups and agencies work together to head toward common understanding and practices.

He noted that different industry/regulator working groups "want shared expectations for quality for everybody, but based on their unique circumstances they may have a different path or a different way of doing it." He

suggested that having a working group with membership from the various groups with their different viewpoints and approaches, "sort of one level up," would be ideal.

"What may be most important in the idea of convergence is to pick the biggest topics that have the greatest impact that it is worth the work it will take for all of these groups to be on the same page."

Biosimilars Cited as Convergence Target

Participants at the forum pointed to the challenges and benefits that could be derived from regulatory convergence in the biosimilars arena.

> **Of particular concern is the source of the reference product for biosimilar studies.**

Complicating the issue are the legal constraints of the local compliance requirements, reflecting the need to assure the selected originator product has been subjected to the legally-mandated scrutiny of the regional regulatory authority.

Kozlowski pointed out that a biosimilar developer does not know if the same manufacturing plant is supplying different regions of the world, which makes it possible for a reference product purchased, for example, in the EU, to be different from the same product purchased in the US.

> **Participants discussed the possibility of data-driven pathways to allow bridging of non-regional source material to the legally-specified reference source.**

Regulators recommended discussing the design of bridging studies in scientific advice meetings very early in the development process with the designated authority to understand what options are available.

[Editor's Note: The IPQ July/August 2012 Monthly Update contains in-depth coverage of the current dialogue and issues regarding development and registration of biosimilars in the US and EU.]

MAb Technologies Explored

The sessions on new technologies for development of monoclonal antibody therapeutics and on the application of QbD to biologics explored emerging tools and approaches that will enable more targeted and efficient product development and application approaches, respectively.

Kyowa Hakko Kirin's Kazuhisa Uchida discussed process and analytical data used to support development of Chinese Hamster Ovary (CHO) cells – in particular, her company's high antibody-dependent cell-mediated cytotoxicity (ADCC) activity 'Potelligent' cell lines with their Fut8 gene knocked out that produce afucosylated antibodies.

The new cell line, she explained, could be used to produce "enhanced" afucosylated antibodies using her firm's existing production facility, and has been shown to increase ADCC activity ten-fold as compared to a "normal" antibody.

Regulator and industry participants in the session agreed that the large increase in an antibody's ability to neutralize antigens should not present additional safety concerns since the specific activity is much higher. It was noted that the much lower dosing amount likely decreases the risk.

> **Also receiving attention at the MAbs session were: ● their potential for immunogenicity, and ● industry and regulator concerns with the detection and control of subvisible particles.**

Swann commented that FDA is "putting a lot of emphasis on trying to understand subvisible particles – those smaller than ten microns."

He noted that the use of light obscuration may not be "entirely adequate" for detection of the particles, and that there are better ways to characterize, understand and control particulates, including down to the one to two micron range.

> **The CDER official noted that USP is currently developing general chapter <787> that will address particulate measurement for protein products.**

The draft <787> "encourages" characterization of particles smaller than ten microns, Swann explained. The goal, he said, is to generate greater understanding and demonstrate control for that attribute in an application.

USP also plans to publish a subsequent chapter that will describe a variety of methods that may be used for particulate analysis, especially in the one to two micron range, including microflow imaging.

Genentech Has Positive Experience with QbD Pilot

In the final session of the workshop on the application of QbD for biologics, Genentech Regulatory CMC Senior Director Lynne Krummen discussed her company's participation in 2009 in FDA's QbD Biotech Pilot. Two Genentech products were involved – one of these ended up moving forward with the submission of a biologics license application (BLA) and one did not.

Krummen explained that the dossier contained all of the traditional information plus enhanced elements for process and product characterization studies, linkages of critical process parameters (CPPs) to critical quality attributes (CQAs), and change management plans. The design space submitted in the application was not approved, she noted.

The QbD filing was a very intensive exercise, she summarized, but not disproportionally costly or time consuming. The linkage studies added time and cost to the exercise, but they did provide critical information, she said.

Overall, Krummen felt that Genentech developed long-term value from the experience in the form of a powerful new "tool box" to utilize in product development. Even if it did not result in complete regulatory relief for process changes, there were major benefits internally that can be applied to other product development plans.

> **During the panel discussion that followed, FDA's Kozlowski and EMA's Richardson commented that Krummen's presentation was reflective of their experience with QbD applications in the US and the EU.**

Kozlowski suggested that perhaps the best management approach is to break up the elements of risk and to define and manage each one. He characterized this approach as "taking small steps" over time, accumulating experiences with smaller QbD elements that will build confidence in the soundness of the approaches and allow expansion of the various elements.

[A detailed summary of the presentations and panel discussions on the five topic areas presented at the conclusion of the December Japan Strategy Forum by Biologics Consulting Group's Nadine Ritter is available by clicking here.

SUMMARY OF DECEMBER BIOTECH CMC STRATEGY FORUM JAPAN

The following is a summary of the presentations and discussions at the December biotech CMC Strategy Forum in Japan, provided by Biological Consulting Group's Nadine Ritter at the conclusion of the forum. The five sessions of the two-day forum, which included presentations by industry and regulator experts from Asia, North America and Europe, addressed: ● recent trends in the regulation of biopharmaceutical products and practices ● development of biosimilars ● characterization and control of protein glycosylation ● new technology for development of monoclonal antibody therapeutics, and ● challenges and opportunities in biologics QbD.

Session 1: Recent Trends in Regulating Biopharmaceutical Products and Practices

Presentations

We heard, on the first day, information from both current and former regulatory officials on their agencies' past, current and emerging practices regarding how they review and approve biotech and biosimilar products. There were a variety of agencies represented here, which was an amazing accomplishment by the organizers. It was a wonderful thing to hear. [Taking part were representatives from PMDA (Japan), KFDA (South Korea), HSA (Singapore), FDA, EMA, Health Canada and FMEA (Finland).]

Some of the activities highlighted by the key **biopharmaceutical working groups** were also discussed by the regulators and some audience members who participated in the groups ***(see box below)***. The talks endorsed the value of these working groups to continue improvements in the field of biotech products.

Key International Biopharmaceutical Working Groups

- Biologics Working Party (BWP) – EU
- Biosimilar Medicinal Product Working Party (BMWP) – EU
- Implementation Working Group, Quality (IWG, Q) – ICH
- Committee for Human Medicinal Products (CHMP) – EU
- Biologics Technical Working Group of the Pharmaceutical Products Working Group (BTWG, PPWG) – ASEAN

Many of the discussions also acknowledged the value of the contributions of key industry subject matter groups, such as the JPMA and CASSS.

It turns out that among all the regulatory bodies there are very **strong philosophical similarities** for the increased availability of biopharmaceutical products for the medical needs of our patients. These similarities include things like:

● the desire to make their regulatory processes as reasonable and consistent as possible, minimizing redundancies and avoiding inefficiencies in both reviews and inspections. But we have to recognize that they have an obligation to maintain their roles as guardians of public health by balancing the risks and benefits to their patient populations, including for things such as rare diseases and orphan drugs, which we talked about at some great length.

● regulatory assessments that are driven by the body of data presented by the sponsors. In fact, [PMDA's] Tatsuya Kondo made a statement that [Roche/Genentech's] Wassim [Nashebeh] capitalized on, saying that regulatory decisions should 'always be based on sound science.' Wassim agreed and commented that that industry has a burden of presenting sound science in our packages. So it is a mutual understanding that it is a data-driven experience that gives us what we need for product quality and consistency.

● case-by-case regulatory decisions that take into consideration a sponsor's history – a sponsor's demonstration of its sound quality management system. The regulators have to depend on their interpretation and their instincts of how reliable the system is that the sponsor is proposing and has history with to maintain product quality and safety.

[FDA Office of Biotech Products Director] Steve Kozlowski gave us a beautiful example using the game 'Go' illustrating that the goal is not distraction, the goal is 'mutual life.'

I would like to add a little note here that I have seen repeatedly: It can take years to earn a good credible reputation with anybody, especially with regulators, but it just takes minutes to lose it by one boneheaded serious decision that was erroneously made. Just be aware that building up trust with regulators is something that you want to covet, and you want to defend fiercely, because it is a much harder road when they cannot trust what you are telling them. And it should be a much harder road.

In all of the presentations that we had, regulators did promote the concepts of **quality by design** [QbD] and quality risk management [QRM] in product development activities. [European Medicines Agency (EMA) Head of Biologicals] Peter Richardson pointed out on the first day that it is probably not an all-or-none – QbD or not QbD – application, but more likely to be targeted implementation of principles in relative sections. As we just heard, one of the major learnings of the exercises we did was that [it is good to] bite off small chunks and develop history with QbD.

There was a clear emphasis on **increasing communications** among the regulatory authorities, including the observation of best practices across agencies. [Singapore Health Sciences Authority's] Sannie Siaw Foong Chong] explained the Singapore model – benchmarking off the successes of other agencies – and that there is working collaboration between agencies on specific subjects to increase the effectiveness of reviews, and in some cases, even potentially sharing workloads.

Mutual recognition of inspections is one project that is going on now between the US and the EU. The regulatory bodies themselves are working very hard to do the best job they can with the resources they have been given to try to avoid recreating the wheel when good success models are out there.

There is a desire to generate **globally-based regulatory perspectives** to encourage development of high quality biopharmaceutical products and promote data-driven decisions. [Korean KFDA's Kyung Min Baek] talked about the idea of collaboration among experts and leveraging information for patient safety.

It was interesting for me to realize as long as I have been in this business – I am a junkie for regulatory documents, I love to read them – to recognize that development of a guidance document is not a one-time effort. It is an iterative process of refinement. There is no perfect guidance document, although in my humble

opinion I think that ICH Q6B is one of the most perfect guidance documents ever written…. I still use it as an example of an extraordinary explanation of product development and testing.

We learned that the first version of any guidance document is likely to have some unintended consequences, because it is hard to foresee every possible circumstance, especially for challenging new subjects. We expect the need for revisions after a period of regulatory and industry experiences, which are driven by thoughtful feedback and mutual discussions, including in forums like this and many others.

We learned from Peter Richardson that there are some discrepancies in some terminologies, especially in some of the guidance documents for biosimilars. That is probably because there has been rapid expansion of those documents in multiple different areas. With the desire to have this pathway available and an explanation for how to get products reviewed and approved, there could be some disconnects that challenge our understanding of how to align our practices across the regions.

We have a number of **action items** that have come out of this CMC forum, and this is one of them: Many suggested that there is a need to develop a communication link between the terms. Although we did not get into logistically how that could be done, that is one of the things on our plate to consider moving forward on soon.

As a means of increasing global awareness of the critical regulatory thinking in all of the regions, it was brought up that it would be valuable to have access to English versions of some of the draft and final documents – like the ICH model where there is an English version that is placed on the ICH website when they are at a point where they can share it. We did hear that there is an effort at PMDA to do this, but their resources are very highly limited.

Another action item on our plate is to figure out whether we could have other options to suggest – for example, we might have a discussion with JPMA and get their help in getting this done because it benefits the industry….

Where did regulatory authorities significantly differ? And what are the reasons why there are some **differences**? The major reasons for the differences are the needs for specific jurisdictions that they are legally obligated to honor.

We had a tremendous discussion about the choice of reference products and why that has certain limitations. In some cases it is restricted by law.

Sannie Chong mentioned ASEAN requirements for the climate zones that are in her part of the world that have to be looked at for drug products to the point of patient delivery. Even if they are in a controlled-temperature chain of custody, there has to be data to support external excursions.

Also, not surprisingly, there are some differences in internal mechanics of review and approval processes. We had some excellent slides that clearly illustrated the step-by-step logistics of certain agencies for how they conduct biopharmaceutical review. That was really nice to see. The steps that one has to go through in each of the regions were very educational and clearly presented.

There were also some differences – some subtle, some not so subtle – in the studies that are required within the dossiers. There were a couple of presentations, including those by [Hokkaido University and former PMDA official Teruyo Arato] and [PMDA's] Teruhide Yamaguchi, who gave us some slides that compared and contrasted the section elements between the regions that are represented here and also discussed some of the key differences in the selection studies. That was very informative and useful.

Panel Discussion

[The panel of regulators addressed the following questions (*indicated in bold face*):]

● ***Is your agency ready to adopt these new [ICH Q8-11] approaches?*** Most agencies indicated that they are well aware and ready to implement various versions. We heard from FDA that it is looking at its internal approaches to identify best practices.

● ***Do you foresee 'whole-process' design space or multiple, 'unit-operation' design spaces?*** Not all parts of the design space are equally well understood, but a sponsor is free to adapt best principles as appropriate, justify the strategy, and support it with data.

● ***How can the boundaries of individual design spaces be harmonized among regulatory agencies internationally?*** The goal of regulatory relief is based only on lowering the level of reporting category for changes, not lowering the data needed to assess the impact of the change. So you still have to do the science to understand the impact of the change. But what you would get relief from is the amount of administrative work that has to be done to submit that information.

● ***Most biotherapeutics in development are with small companies, with maybe one or a few products. How might this impact the use of quality-by-design approaches?*** Leveraging of CMO platform processes is ok so long as the sponsor has access to the critical information and so long as it is recognized that sponsors always retain responsibility for their own products, even if they are producing them using a CMO that has expertise in that platform.

● ***How do you see the future of international harmonisation? What are the roles for ICH, the Global Regulatory Discussion Group, APEC, and ASEAN in formal, bilateral/multilateral discussions?*** There is great value in inter-organizational communications and global interactions and cluster groups of subject matter experts that generate important positions to facilitate common approaches and minimize discrepancies. A lot of the discussion centered on encouraging further activities to tackle the points that are most challenging but provide the greatest benefit. The term used rather than harmonization was 'convergence' of regulatory expectations.

● ***How and where do you see the role of industry?*** Some elements must be discussed only among regulatory authorities to honor their jurisdictional and legal constraints, but there are many opportunities for industry scientists to engage in meaningful discussions with regulators to promote sound scientific practices and support sound regulatory guidance. That sounds a lot like the mission statement of the CMC Strategy Forums.

● ***How does your agency treat this type of product given the strong patient and family support for approvals and the limited numbers of patients and amounts of clinical data available to support regulatory decisions?*** From the regulatory perspective, we heard that all agencies have some kind of program for rare diseases and orphan products. However, it is true that still not all patient needs can be met. Regulators cannot compromise patient safety and product quality, but several alternative approaches for incentives are being tried. There is a long list of these that I did not include in the summary.

Industry made the point that the CMC burden is very high for biopharmaceutical products relative to chemical products, and in some cases it is hard to justify a considerable investment in such small patient populations. Any incentives that can be provided to lower the regulatory burden even with substantial post-market commitments would be welcome. It was suggested that a possible model for common dossier elements for this very specific set of products would help leverage global data sets,

and would allow a greater total number patients for clinical studies and greater global market after approval through mutual recognition, if that were ever to come to pass.

The following questions were **tabled for future discussion** due to time constraints. [The questions addressed:]

● quality/facility/safety issues related to **multi-partner and contract manufacturing**. What are trends and issues with contract manufacturing of biologic drug substance? How do you manage issues arising from foreign manufacturing sites?

● **comparability and change management protocols**. Does your region support the use of protocols to facilitate future changes? Are there limitations to the types of change that can be achieved using a protocol? What is the current level of regional harmonisation you experience in the use of comparability protocols?

● **submission workload issues**. How can we manage the increasing submission workload for biopharmaceuticals? Many products are under development, and every approval eventually means numerous supplements or other types of submission workload. Is it possible to add more staff, do less in-depth review, or use alternate regulatory approaches – for example, decisions aided by, or based on, prior foreign approvals? Health Canada made a plea for us understanding that there is an increase in the number of products without an increase in reviewing resources....

● **combination products**. How do you approach the evaluation of combination products – for example, chemical-biologic, such as toxin-monoclonal antibody [MAb], and drug-device? Are there classification issues? How to apply necessary/appropriate regulations? Is there intra-agency cooperation?

● **'21st century initiatives.'** What are your agencies approaches to: Personalized medicine? Surrogate markers of clinical efficacy? Adaptive clinical trials? Quicker market access linked to greater post-market monitoring and action?

Session 2: Development of Biosimilars

There was considerable discussion on the source of the **reference product** for biosimilar studies, including legal constraints of the local compliance requirements where the objective is to assure the selected originator product has been subjected to the legally-mandated scrutiny of the regional regulatory authority.

However, there may be data-driven pathways to allow bridging of non-regional source material to the legally-specified reference source. Discuss the design of your plan for bridging studies in scientific advice meetings with the designated authority to understand what you have the option to do.

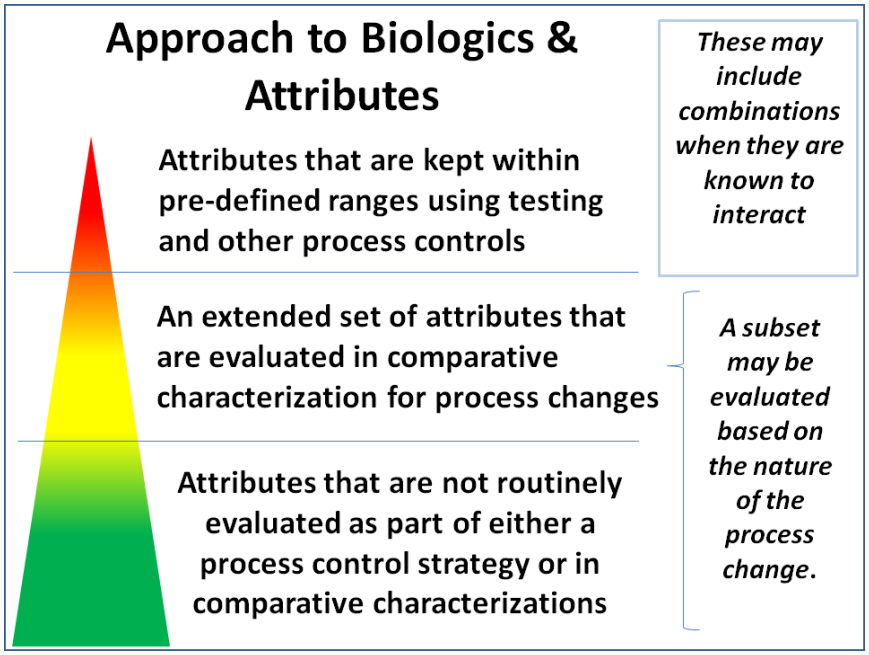
[The following prepared questions (*indicated in bold face*) were addressed:]

● ***What are the challenges and requirements for global development of a biosimilar product including the consideration of the reference product licensed in different regions?*** Do not assume that all sources of a global product have the identical characteristics since each had its own separate data package that was approved by the regional authorities.

● ***To which extent should functional aspects of a biosimilar MAb be compared to its reference product even if some of those may not be considered necessary for the mode of action?*** All aspects of function and structure should be compared between the original and biosimilar product, because the

goal is not just to measure its comparison to the intended mechanism of action. Any function or lack of function should compare between them if the biosimilar is in fact similar. If the originator does or does not have a certain type of effector function, the biosimilar should or should not have it.

● ***What are the opportunities and challenges in using approaches for a fingerprint-like characterization in the analytical evaluation for biosimilarity?*** Steve Kozlowski showed a pyramid with red at the top and green at the bottom to illustrate how using very sensitive fingerprint methods in the 'green zone' – where there is some low-hanging fruit for analysis – can give you a high degree of data-driven confidence in the comparability of elements in the 'red zone' that are critical but perhaps much more challenging to measure from an analytical perspective ***(see box below)***. It allows building of a hierarchy of understanding of the product. The more comparability that you can understand the greater confidence there will be in the product.



● ***How should the immunogenicity of a biosimilar product be investigated in non-clinical and clinical studies?*** There are some slight differences in requirements between regions for non-clinical studies to screen for anti-drug antibodies. All have some requirement for screening of clinical samples for immunogenicity.

One topic that we did not have an opportunity to explore here but that will be the subject of a plenary session and a workshop in January at the WCBP meeting in Washington is anti-host cell protein [HCP] and some of the issues we have seen recently in the US with Inspiration Biopharmaceutical products. Teruyo Arato did point out the Omnitrope HCP issue that occurred during its development, and Martin Scheistl – who is one of the chairs of the program – will be presenting that story and the data from it at the January meeting.

The requirements that could enable a claim for interchangeability were not discussed.

[Celltrion's Ki-Sung Kwon] presented a case study on the development of a biosimilar product, providing a thorough overview of the operational and regulatory elements that a sponsor must manage to achieve development and production of a biosimilar MAb.

Session 3: Characterization and Control of Protein Glycosylation

Presentations

Data-rich presentations on glycosylation analysis technologies were given by [Japan National Institutes of Health Sciences'] Nana Kawasaki, [Japan National Institute of Natural Sciences'] Koichi Kato, and [Amgen's] Drew Kelner – representing a 2-hr crash course on detection and characterization of glycan species that:

- spanned academic and industry applications
- included citations for relevant publications for follow-up
- provided examples of representative results from each technique
- showed comparative data among glycoprotein products, including among different sources of the same glycoprotein
- included discussion of process analytical technology [PAT] applications
- provided examples of structure-function assessments for MAbs, both *in vitro* and *in vivo*
- described the strengths/weaknesses of each technology, and
- discussed the potential for method validation and use in setting product specifications.

Panel Discussion

During the Q&A that followed the presentations, it was noted that both USP and EP have general chapters on this topic, but that the JP chapter has been delayed. Several options are being considered for putting standardized glycan information in the public domain including through journals and white papers.

There was also a discussion regarding whether industry is doing enough to understand the impact of glycans on product quality to assure consistency in safety and efficacy, and whether there is still a gap.

It was noted that the field is gaining more knowledge about which glycan moieties are critical to product quality, but the biological impact of other glycan structures is still not well-demonstrated. These highly complex product characteristics should be subjected to QbD and QRM to justify which elements require control and which are less relevant.

Also pointed out was that there could be highly valuable intersections of academic work with industry applications to further investigate glycans and link modifications of glycans to biological mechanisms. Increased communication between academic and industry scientists was recommended both from the panel and from the floor to generate the key data needed to understand structure and function relationships for glycan moieties.

[The following are the prepared questions (*indicated in bold face*) and key points brought out during their discussion:]

- ***What is the state of the art technology for glycoprotein analysis?*** The point was made that you need to classify the operational applications, because those tools that are important for R&D process development are a little bit different that those used for product characterization and comparability, which may be different from the robust QC methods that are needed for supporting specifications for release and stability testing.

● ***What, if any, limitations exist with the current technology?*** It was mentioned that a paper [published in August, 2012] by Pauline Rudd from NIBRT [National Institute for Bioprocessing Research and Training] is a good reference. She is an excellent glycoprotein mentor. The paper discusses the differences in these applications relative to the nature of glycoprotein methodology.

● ***What high-throughput methods are being used for carbohydrate analysis vs. for detailed carbohydrate characterization?*** It was noted that high-throughput capability alone is not necessarily the only goal. It is useful for some things, such as the screening of cell lines. But there are other things for which a slow, robust method becomes the more important objective – for example, characterizing glycoproteins, comparability of products, or QC specs. It is important to understand the goal of the data that is being generated.

● ***What are the expectations from regulatory bodies for detailed carbohydrate analysis?*** What we can say is that there is an asymptotic expectation. There is an infinite amount of information that regulators could have, but really what they referred us to were the ICH guidelines Q6B and Q5E, which already discuss micro-heterogeneity of biopharm products and what their expectations are. These guidelines recommend that we characterize what they are and we control them within clinical limits regardless of the nature of the micro-heterogeneity.

The point was made that quality should be related to safety and efficacy. But sometimes we only learn about critical features after the product has been on the market for a while, and that may cause us to reassess what we do with the current products to assess process capabilities, process consistency, and the ability to stay within the clinical limits.

ICH Q11 discusses risk assessment for quality attributes, but acknowledges that since the methods continually improve, our knowledge of what is critical improves as more sensitive and specific structural and functional data are collected on glycoprotein products. We had examples of that with Erbitux.

When an adverse event occurs that is linked to a product attribute in one product, then it leads regulators and industry to consider the impact on other, similar product types and determine what the level of risk is to patients if those products do not monitor the same characteristic.

It was also noted that regulators are aware that industry carefully selects what data to submit in dossiers. Anyone who has gone through a PhD dissertation knows that you only provide to your advisors the information that you want to show them. Reviewers may not know how widespread a 'new' molecular characteristic might really be among products – they can only judge the data that is presented to them by sponsors. They have a bit of a handicap in that they can't force industry to turn over a lot of data. So what may be 'new' in the publication field may be something that people in the industry have seen for a while but did not pursue.

● ***How have companies successfully implemented new methods for carbohydrate analysis of commercial products?*** These are implemented pretty much the same way that new methods for any other characteristic are implemented.

From a regulatory perspective, lifecycle management encourages continuous improvement of analytical tools. So don't be afraid of what you see, because it may have always been there, or there may be an acceptable set of variations within the clinical range. But until you start measuring it and collecting the data, you will not really know.

The goal of the regulators is to have sufficient QC testing to assure safe and effective products. But some highly complex tests may be acceptable to keep in the characterization/comparability tool kit and be used only

for those purposes or for investigation of adverse events. It is not that they are asking industry to put everything in the toolkit. The QbD approach presented by [Genentech's] Lynne Krummen supported that concept very well.

[Genentech's] Wassim Nashabeh pointed out that it takes industry about four years to implement a new methodology into a product control system. He asked whether there is any way that regulatory authorities can lower the energy barrier to implement new technologies more quickly.

There are some things that can be done. It is possible to compress some of the timeline with well-designed, thorough bridging studies using a wide variety of product samples – for example, multiple lots and degraded lots. [FDA's] Kathleen Clouse gave a presentation that is still available on the agency's web site on bioassays that provides some examples. However, there are still global implementation challenges, especially with the setting of new specifications. It does require collection of a lot of data to assess whether there is any impact on the specification for a particular attribute.

Another action item that we got was a suggestion from a regulator to convene a discussion group with global regulators and industry subject matter experts, and maybe generate a model case study with example methodology of how this could be implemented and what some of the strategies would be to allow this to be done very efficiently, but still containing the data needed to support the change or the addition.

Session 4: New Technology for Development of Monoclonal Antibody Therapeutics

Presentations

[Kyowa Hakko Kirin's Kazuhisa Uchida] gave a presentation on process and analytical data to support development of CHO cells, in particular his company's high ADCC activity 'Potelligent' cell lines with their Fut8 gene knocked out that produce afucosylated antibodies that have high affinity for FcgRIII. Although I do not think the word was actually used, the data he showed from Rituxin indicated they may be used to produce 'biobetters' due to the ability to get more specific activity.

[National Institute of Advanced Industrial Science and Technology's] Jun Hirabayashi talked about the future of glycoscience. He introduced a term today that I had not heard before, 'cellular glycomics,' which defines the glycome as the complete repertoire of glycans generated at a point in time, space and environment in a cell culture. He showed valuable applications of the lectin microarray analysis using LecChip and GlycoStation technologies.

[Medimmune's] Mark Schenerman talked about a paper that was published as a collaborative effort in Nature Review in 2011. It is an excellent paper that I have used many times. It discusses the classification of MAbs based on Fc effector function as Class I (high), II (medium) or III (low). In the paper are suggested strategies for how to define MAb critical quality attributes (CQAs) based on effector function and how to manage them throughout product lifecycle. Mark made a comment that is worth being mindful of regarding ADCC assays – that one must be certain to design the method procedure properly – for example, the use of correct controls – to ensure valid results. Improper design of the assay can lead to erroneous conclusions….

Panel discussion

There are some remaining **questions or hurdles** for antibody-based pharmaceutical development that were discussed in the panel session following the presentations.

Regarding the possibility of **unique safety questions** for high ADCC MAbs or alternate forms of MAbs, none are expected for ADCCs, especially since specific activity is much higher so the dosing amount is much lower,

and one could argue that the risk is lower simply due to the amount being delivered. Immunogenicity from mutations will require monitoring as with any other MAbs. There was some discussion that MHC binding/T-cell activity may also require assessment for different types of monoclonals.

Future issues that were discussed include Fc gamma receptor polymorphisms in ethnic groups that could drive an enhanced need for personalized medicines in those groups. Also discussed were Fc-linked immune complexes in patients with infectious diseases. Although most MAbs are for therapeutic use, there could be complications that could lead to the formation of these antibody complexes that could be problematic.

[FDA's Patrick Swann] mentioned that there are a number of **next generation products** being looked at, such as bispecific antibodies, antibody drug conjugates, and high ADCC MAbs. He noted that we are constantly learning more about product mechanism of action both *in vitro* and *in vivo*, and the associated range of Fc functions in these products….

We had a great discussion on **companion diagnostics** as another issue that is coming up. Many firms are starting development of companion diagnostics very early in the product lifecycle with the possibility of generating personalized medications. We heard that Japan has policies that promote the development of companion diagnostics to increase personalized and targeted medicines. Their message was that they would like to encourage global approaches for similar strategies for companion diagnostics.

Also discussed was whether there are any **evolving technologies** in sight and eagerly needed that may have significant impact on product development and/or review of dossier.

The ICH Q5 series and ICH Q6B outline the traditional approaches. However, ICH Q11 builds on ICH Q8 which defines enhanced QbD design space and allows for proposing alternative approaches that are justified with data.

A question was asked regarding what incentives there are for sponsors to **adopt new technologies**. Patrick Swann explained that FDA sees a lot of INDs that fail to meet efficacy criteria. One of the incentives for a personalized medicine approach is that it could allow targeting of the patient population that will have a higher likelihood of clinical success for specific therapeutic products.

We had a discussion about promoting the development of more **robust bioassays**, especially to avoid primary cell assays. A question was asked, 'will we ever be allowed to avoid bioassays?' The response was 'probably not' for cell killing assays, since the whole cell is needed, and that very likely it would require an enormous body of corroborative physiochemical and functional data to justify no potency assay in control and monitoring of product quality. But never say never…

We also heard that lectin arrays can map the 'glycome' of a product expression system, which is especially valuable for developing **platform manufacturing** strategies. There is a goal for new technologies to help us develop a reliable means to control the nature and degree of glycosylation at the level of expression systems, that may would allow process development to target a desired set of glycoforms….

In our discussion on platform manufacturing of antibody drug and its application to process development it was noted that ICH Q11 contains a definition of platform processes for manufacturing to expedite product development. It is clear, however, that they will still require validation. It was also noted that requirements for process validation studies have not been globally harmonized.

It was suggested that sponsors could expand the application of platform concepts with justification to the regulators. We heard that the ICH Q11 working group did consider many sources of knowledge of platform elements as valuable supporting information but restricted the definition of 'platform' to a sponsor's own development data for a specific expression system.

Session 5: Challenges and Opportunities in Biologics QbD

Presentation

[Roche's] Lynne Krummen talked about her company's participation in an FDA QbD Biotech Pilot in 2009 with two products. One product ended up moving forward with the submission of a BLA [biologics license application].

She noted that the design space was not approved, but then provided some detailed information about what the dossier did contain, including all of the traditional information plus enhanced elements for process and product characterization studies and linkages of critical process parameters [CPPs] to critical quality attributes [CQAs] and change management plans.

Her conclusion was that it turned out to be a very intensive exercise, but not disproportionally costly or time consuming as everyone assumed it would be. She did indicate that the linkage studies were additive but they did provide critical information.

Overall she felt that Roche developed long-term value from the experience in the form of a powerful new 'tool box' to utilize in product development. Even if it did not result in complete regulatory relief for process changes, there were major benefits internally that could be applied to other product development plans.

Panel Discussion

The regulatory feedback in the panel discussion that followed was that Lynne accurately reflected the issues encountered according to US and EU authorities. From these kinds of experiences, the regulators realized that implementing QbD may best be done in small defined bits rather than with an overly broad approach.

In other words, it is not necessarily 'all-or-none.' It was suggested that perhaps the best management approach is to break up the elements of risk to define and manage each one. Over time, there can be an accumulation of successful mutual experiences with smaller QbD elements that will build confidence in the soundness of the approaches and allow expansion of elements. That is a mutual experience between the industry implementing them and the regulatory reviewers assessing them.

Steve Kozlowski noted that it is important to recognize that QbD is not the same as process design space – it is a tool to incorporate in the quality system for product development.