



## CMC FORUM SERIES

The CMC Strategy Forum series provides a venue for biotechnology and biological product discussion. These meetings focus on relevant chemistry, manufacturing, and controls (CMC) issues throughout the lifecycle of such products and thereby foster collaborative technical and regulatory interaction. The forum committee strives to share information with regulatory agencies to assist them in merging good scientific and regulatory practices. Outcomes of the forum meetings are published in this peer-reviewed journal with the hope that they will help assure that biopharmaceutical products manufactured in a regulated environment will continue to be safe and efficacious. The CMC Strategy Forum is organized by CASSS, an International Separation Science Society (formerly the California Separation Science Society), and is supported by the US Food and Drug Administration (FDA).

The analytical toolbox is of pivotal importance for successful development of a biosimilar. Analytical tools are required for optimizing the manufacturing process and demonstrating a high level of similarity, which affects further clinical stages of development. Therefore, it is important to characterize a product as accurately and deeply as possible. All structural elements of the protein and all modifications should be evaluated using orthogonal and state-of-the-art methods. When choosing an analytical method for characterization of a biosimilar candidate, focus should be on a method's capability to detect differences between the reference and biosimilar products. The following questions may help you evaluate the suitability of the methods in the analytical toolbox:

- Does the method measure sum parameters or individual structural features?
- What are the effects of sample preparation?
- Does the method deliver only qualitative or also quantitative information?
- What is the sensitivity of each method to detect differences?

In this context, for example, the

## MORNING SESSION: THE FIRST BIOSIMILAR PRODUCTS

### Presentations

- "The Current State of the Biosimilar Debate" by Cornelia Ulm (Mylan)
- "Scientific Considerations Impacting FDA's Regulation of Biosimilar Products" by Emily Shacter (CDER, FDA)
- "Well Characterized Biosimilar Proteins: The Role of State of the Art in vitro Assays in Discerning Biosimilarity" by Thomas May (Hospira Inc.)
- "Development and Manufacturing Experience with the First Wave of Biosimilar Products" by Martin Schiestl (Sandoz)

### Workshop Questions

- What can we learn from the first years of biosimilars in highly regulated markets with regard to development and regulation of future products?
- When and how should characterization methods be applied in biosimilar product development?
- How do you justify goalposts for quality attributes in biosimilar development?
- What are the challenges and requirements for global development of biosimilar products, including reference products licensed in different regions?
- What is the way forward in the debate over the use of INNs for biosimilars?

## AFTERNOON SESSION: BIOSIMILAR MABS AND BEYOND

### Presentations

- "Biosimilar MABs: The Challenges Ahead" by Thomas Schreitmüller (F. Hoffmann – La Roche)
- "Requirements for Demonstrating Biosimilarity of Monoclonal Antibodies", by Steffen Gross, Paul-Ehrlich-Institut, Langen, Germany
- "Case Studies for Biosimilar MAB Development: CMC Elements" by Thomas Stangler (Sandoz)
- "Preclinical and Clinical Considerations for Biosimilar Monoclonal Antibodies" by Frank Scappaticci (Genentech, a Member of the Roche Group)

### Workshop Questions

- How do you deal with the multitude of quality attributes in a target-directed development of a biosimilar product?

- What are the opportunities and challenges in using fingerprint-like characterization in analytical evaluation for biosimilarity?
- How do you deal with "changes in quality attributes of the reference product" during biosimilar development?
- To which extent should functional aspects of a biosimilar MAB be compared with its reference product even if some of those may not be considered necessary for mode of action?
- What facilitates/enables extrapolation of safety and efficacy data of a biosimilar MAB in one indication to other indications of the reference product?
- What requirements could enable a claim for interchangeability?
- What is the value of product-product class specific guidance for biosimilar MABs?

variability of a bioassay is sometimes a hurdle that must be overcome if meaningful data are to be generated. Forum participants discussed a fingerprint-like approach as an effort to further improve analytical output beyond current state-of-the-art and gain additional information for biosimilar evaluation. The term *fingerprint* has been used as a concept to describe qualitative evaluation of complex patterns — such as can be gained from spectroscopic methods, for example. However, in an effort to derive more comprehensive testing, the term *fingerprint-like* approach is used for analytical approaches. For

example, measuring more quality attributes or mathematically combining read outs from several methods delivers information not accessible by other means. A topic of discussion remains: what the consequences might be if a company can demonstrate a fingerprint-like degree of similarity between a biosimilar and its reference product.

### ROLE OF NONCLINICAL AND CLINICAL STUDIES

The nonclinical part of development depends on the adequacies of models used. A current trend is to carefully assess the outputs such models can

## GLOBAL STEERING COMMITTEE FOR THESE FORUMS

Siddharth J. Advant (ImClone)  
John Dougherty (Eli Lilly and Company)  
Christopher Joneckis (CBER, FDA)  
Rohin Mhatre (Biogen Idec Inc.)  
Anthony Mire-Sluis (Amgen, Inc.)  
Wassim Nashabeh (Genentech, a  
Member of the Roche Group)  
Anthony Ridgway (Health Canada)  
Nadine Ritter (Biologics Consulting  
Group)  
Mark Schenerman (MedImmune)  
Keith Webber (CDER, FDA)

deliver and consider in vitro alternatives if they provide relevant and more accurate information. The EMA introduced in its MAb biosimilar guideline the concept for using a step-wise, risk-based approach to design an appropriate nonclinical testing program. As a first step, all possibilities for in vitro studies should be exploited. As a second step, the need for in vivo studies should be evaluated. If needed, a third step is to perform those studies in relevant species, with the focus being on additional information that can be gained.

A lot of the nonclinical work depends on the similarity of expression systems used to manufacture biosimilar products. It will also depend on the level of similarity to be analytically demonstrated with reference products.

The clinical part of the biosimilar exercise was discussed very briefly in this forum. All necessary clinical studies should be designed to be as sensitive as possible to detect differences with respect to efficacy, safety, and immunogenicity between a biosimilar and the reference product. Understanding target clinical indications and what sensitive endpoints to look for is key. Based on available justification and the totality-of-the-evidence of similarity, you may or may not be able to extrapolate safety and efficacy data obtained in one indication to other indications established for the reference product. Overall, clinical studies should

demonstrate biosimilarity but not necessarily patient benefit.

### BIOSIMILAR MABs

Some companies are investing strongly in biosimilar MABs development. The EMA has drafted a guideline in light of the increased interest and requests for advice from companies (1). (A final version was adopted in May 2012, after the CMC Strategy Forum).

Presenters provided examples of candidate biosimilar MAB development in which extended characterization methods were applied early on. Such an approach supports the capability to optimize individual manufacturing process steps and make adjustments toward reaching the determined quality attribute ranges of a reference product and designating the follow-on product as “highly similar.”

Special attention is also needed in assessing the biological functions of a MAB. Even for cases in which some functions are not part of the mode of action — e.g., Fc effector functions for a MAB that is designed to work by binding a soluble target only — it is important to demonstrate that the functionality is similar in both biosimilar candidate and reference product.

### GOALPOSTS FOR SIMILARITY AT THE QUALITY LEVEL

An FDA speaker referred to the US statute, which says that a biosimilar product must be “highly similar.”

**((Reference?))** Minor differences are allowed in clinically inactive compounds. No clinically meaningful differences for safety, purity, and potency are allowable. The amino-acid sequence should be identical to that determined for the reference product. Differences in heterogeneity — for example with respect to C-terminal lysine or residual amount of sequence variants — must be assessed as product-related substances and impurities for their clinical impact.

The quality target product profile (QTPP) for a biosimilar product is mainly defined by the properties of the reference product. Industry participants at the forum noted that

biosimilar development is facilitated by extensive surveillance of the reference product to determine the reference product variability early on in development.

A question was raised: “To what degree might a biosimilar developer have access to reference-product batches that also reflect the variability of drug-substance batches? Different drug-product batches can be produced by a single drug-substance batch.” If that is the case, the observed ranges of the reference product might be very tight. In any case, it is up to the biosimilar manufacturer to determine how many batches to analyze. Selection of very few reference-product samples may end up in an accordingly tight QTPP, whereas the characterization of many batches over a few years will provide a more realistic picture of the reference product variability.

In that context, the age of a drug product and the remaining time until the expiration date should be considered because some quality attributes may change during shelf life. Other points to consider are the assay variability and changes to analytical methods and their performance over time. Those can be addressed by proper measures, for example by using controls or head-to-head studies. Overall, observed minimum and maximum ranges of quality attributes for a reference product may set the basis for goalposts for similarity assessment.

Additional information regarding the impact of each quality attribute on clinical properties may be needed, however, especially for cases in which a quality attribute of a biosimilar product is outside the range seen for the reference product. In such cases, it is important to evaluate the attribute and its criticality with respect to safety and efficacy.

Bioassays can provide information about whether an attribute is critical to function and contribute to risk information on that attribute (e.g., with respect to efficacy), whereas impact on safety might be more difficult to obtain. The statistical variance for attribute measurements

on a biosimilar and reference product should be considered. For substantial differences, a discussion with regulators on how to proceed is advisable. Consequently, a manufacturer could potentially justify the difference by increased product understanding (e.g., by elucidation of structure–function relationships). For remaining uncertainties, additional nonclinical and/or clinical data could be meaningful. The worst-case scenario would be the need to leave the biosimilarity route and seek regulatory approval based on “stand-alone” development.

One presenter mentioned reference product data collected over several years that revealed some jumps in certain quality attributes that were believed to reflect manufacturing process changes. An audience member asked: “Shouldn’t the biosimilar manufacturer be allowed to set the goalposts for biosimilarity based on the entire min/max range observed for the reference product?” The answer is most likely yes, because product attributes could drift from the original quality ranges approved in the first license application. Each postapproval change must undergo tiered comparative assessment of the changes, and their potential impact on safety and efficacy, according to ICH Q5E (4). Thus there will have been regulatory scrutiny of data at each step. In the end, the latest form of a product may not look like the original licensed product when compared directly, having gotten there in distinct, approved steps. Regulators will have safety databases gathered over each product’s life cycle as well as during previous clinical assessments.

In addition, and in line with ICH Q5E, the combined effect of multiple postapproval changes on a product is evaluated before approval for whether it is still comparable with the product tested in pivotal clinical trials (4). If there is doubt, a manufacturer must generate additional clinical data or can not implement the change. Therefore, regulatory processes are in place to manage changes in quality attributes of individual products over time. On the other hand, manufacturers of both

the reference product and biosimilar product will independently introduce process changes over time that may lead to jumps in certain quality attributes. So it can be expected that both products will drift apart with respect to certain quality attributes over time.

Regulators also want to be sure not to confuse goalpost ranges for establishing biosimilarity with the manufacturing consistency of a process. For biosimilarity purposes, the range can be as wide as they have been determined by the biosimilar manufacturer for the reference product over time. For process consistency and setting quality control specification, the biosimilar product should demonstrate tighter performance around manufacturing process capabilities. A manufacturer cannot take advantage of a wide field range to absolve poor manufacturing consistency.

Ranges for process-related impurities are determined for a biosimilar process using state-of-the-art methods and requirements. Ranges based on process and method capabilities should be used carefully with regard to host-cell protein issues, process-specific assays, and so forth.

Stability data should be collected according to requirements outlined in ICH Q5C (5). Accelerated and stress studies should also be conducted in comparison with the reference product to better understand product properties of certain stability-indicating quality attributes. It is important to understand stability profiles. But they may differ, for example, if different drug product formulations are used. Of course such differences would have to be justified with respect to a candidate’s safety and efficacy profile of a biosimilar.

Can different expression systems be used in biosimilar development? In essence, that seems possible if it can be adequately justified. The European experience has shown one case in which a biosimilar made in yeast was approved even though the reference product was made in *Escherichia coli*. (include real product names?) But in such circumstances, it may become

more difficult to optimize the manufacturing process to yield a highly similar product. In another example, a biosimilar manufacturer used glyco-engineered *Pichia pastoris*. The resulting product differences were severe enough for regulators to conclude that it was not in accordance with the biosimilar concept of minimized differences to a reference product.

## GLOBAL DEVELOPMENT

Global development with a single, defined reference product is still a matter of debate for legal and technical issues. The US statute set legal framework allowing some flexibility. One forum participant recommended using science and being as rational as possible in designing a global development program. Concern was expressed about using additional animals and human patients for repeated studies with reference products sourced in different regions. That certainly increases time and cost, but it may not provide any scientific value.

Health Canada does not necessarily require a reference product to be sourced in Canada. The agency elected that path for several reasons. Canadian guidance indicates that a biosimilar cannot claim pharmaceutical equivalence and should be considered as “stand-alone” once approved. If a product will not be substituted, then hands-on experience by clinicians and pharmacists with a Canadian reference product is less important than in the case with chemical generics. Also, it shouldn’t really matter whether the reference product comes from Canada. What matters is how much data are publically available for the reference product used as a comparator. Health Canada determined that it could be better for all concerned to have a non-Canadian reference product providing a greater amount of supportive clinical data than a Canadian reference product that perhaps provides limited supportive clinical data.

FDA representatives at the forum pointed out that companies do not



## DISCLAIMER

The content of this manuscript reflects discussions that occurred during the CMC Strategy Forum workshop in addition to personal viewpoints and experiences of the authors. This document does not represent officially sanctioned FDA policy or opinions and should not be used in lieu of published FDA guidance documents, points-to-consider documents, or direct discussions with the agency.

have to wait for the draft or final FDA guidance to be published to learn regulators' thinking on biosimilars. Any company can request a meeting with the agency to obtain direct input on their product development plans. They stressed that they cannot provide information about a theoretical product. It must be based on an actual product with preliminary data — even if the comparison is to a reference product from another region. The agency cannot yet say how much additional or repeated data would be required to bridge those data to a US-sourced reference product.

## PRODUCT NAMING

The clear identification of drug products is an important part of pharmacovigilance (PV). The FDA is looking at adverse events over a wide variety of products that are licensed by product class rather than by product source. The agency has had great difficulty in sorting out PV data. The FDA gets highly variable sets of data with ambiguous identifying information for products used in patients, some containing the International Nonproprietary Names (INN) only. Clearly, the PV systems should be able to track back to individual drug products, strengths, and batch numbers for the industry and regulators to manage problems associated with individual batches.

A forum participant suggested that there are several mechanisms by which source tracking can be done, but not by INN alone (which is not unique to a single product). The European Commission Directive 2010/84/EU4 has defined the following expectation for EU member

states: “ensure that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, in accordance with Article 1(20), and the batch number.” Meanwhile, the United States is promoting use of National Drug Codes (NDC).

The assignment of a nonproprietary name such as the INN or the US Adopted Names (USAN) involves a scientific nomenclature evaluation based on a protein's structural features. That is difficult for glycosylated proteins containing up to hundreds of different molecules. Those with the same amino acid sequence can differ widely in their glycosylation. The INN guideline recommends the assignment of different INNs for molecules with different glycosylation patterns. However, it does not provide the granularity to decide the level of difference in glycosylation a different INN should be assigned to a glycoprotein (*Please clarify previous sentence*). INN decisions also imply a certain degree of transparency, which led to the proposal to think of an “international proprietary name.”

Some participants raised concerns that a different INN (or USAN) could complicate the use of biosimilars: Physicians who are used to the idea that only products with the same INN are (somewhat) comparable may hesitate prescribing a product with a different INN. Another point to consider is the option provided by the US statute ((**Reference?**)) for developing interchangeable biosimilar products; and that certain state laws require the same USAN/INN to execute interchangeability.

Overall, no consensus has been reached on whether the active pharmaceutical ingredient of a biosimilar product should be assigned the same or a different INN as that of the reference product. However, it seems clear that biosimilar products should be uniquely identifiable.

## OUTLOOK

The first biosimilar products have demonstrated suitability of the current regulatory process in the European Union. However, the development and regulation of biosimilar products remains on a learning curve. The EMA is revising its guidelines based on experiences with those first biosimilar products (1), and the FDA is currently finalizing its first biosimilar guidelines (3). New developments can be expected through improved protein characterization. That will allow a focused approach to process manufacturing development and a more detailed assessment of the level of similarity on a quality level.


Whether that deeper level of product knowledge will lead to detection of even more differences when comparing products from different manufacturing processes remains to be seen. It is also uncertain as to whether this will allow a better predictability of safety and efficacy in different patient populations. So a more targeted clinical development program for biosimilars remain to be seen. Although it is becoming clearer regarding how to preserve national requirements while still allowing global development of biosimilars, the scientific debate on how to assess interchangeability of biologics has just begun.

## REFERENCES

- 1 *Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues* (Revision 1), EMA, May 2012.
- 2 *Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics* (SEBs), Health Canada, March 2010.
- 3 *Draft Guidance: Scientific Considerations in Demonstrating Biosimilarity; Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product to a Reference Product; and Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, US FDA, February 2012.
- 4 *ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process*, International Conference on Harmonisation, November 2003.
- 5 *ICH Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological/*

**The following were listed in the article,  
where in the text should be cited?**

ICH S6(R1) Preclinical Safety Evaluation  
of Biotechnology-Derived Pharmaceuticals,  
July 1997; [www.fda.gov/downloads/Drugs/  
GuidanceCompliance  
RegulatoryInformation/Guidances/  
UCM074957.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074957.pdf).

Schiestl M, et al. Acceptable Changes in  
Quality Attributes of Glycosylated  
Biopharmaceuticals. *Nature Biotech.* 29, 2011:  
310–312. 

**Anthony Ridgway**, PhD, is a senior  
regulatory scientist at CERB's Office of the  
Director, part of Health Canada in Ottawa,  
Canada. **Nadine Ritter**, PhD, is senior  
analytical consultant at Biologics  
Consulting Group, Inc. in Germantown, MD.  
**Martin Schiestl**, PhD, is a scientific and  
regulatory advisor for Sandoz GmbH in  
Kundl, Austria. **Thomas Schreitmüller**,  
PhD, is head of technical regulatory policy  
and strategy for biologics at F. Hoffmann-  
La Roche, Ltd. in Basel, Switzerland.

**((Please provide contact information for  
the main corresponding author))**

For electronic or printed reprints, contact  
Rhonda Brown of Foster Printing Service,  
[rhondab@fosterprinting.com](mailto:rhondab@fosterprinting.com), 1-866-879-9144  
x194. Download low-resolution PDFs online at  
[www.bioprocessintl.com](http://www.bioprocessintl.com).