Biosimilar Products

Scientific Principles, Challenges, and Opportunities

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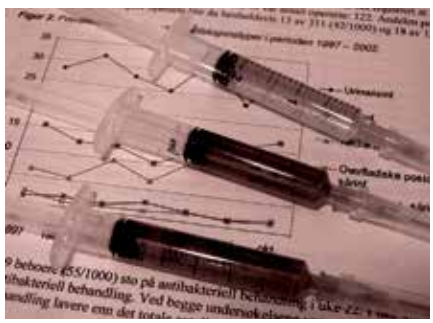
The Chemistry, Manufacturing, and Controls (CMC) Strategy Forum held on 22 January 2012 in San Francisco, CA, focused on selected scientific and regulatory aspects in the development of biosimilar products. Such products are an increasingly important area of interest for both the biopharmaceutical industry and its regulatory agencies. Biosimilars are highly complex, so scientists have been unable to demonstrate identity to a level typically possible for small molecules. Consequently, specific scientific and regulatory approaches are required to ensure the high degree of similarity sufficient to reflect the safety and efficacy of reference products.

The purposes of this forum were to highlight scientific and regulatory challenges for developing and assessing biosimilar products and to discuss industry opportunities. Presentations included case studies of experiences gained with the first biosimilar products (e.g., in Europe and Canada), examples addressing recent efforts in developing biosimilar monoclonal antibody (MAb) products, and specific regulatory guidance (presentations are provided on the CASS website: www.casss.org/displaycommon.cfm?an=1&subarticlenbr=674).

Participants discussed development and regulatory expectations associated with the biosimilar approaches for those cases. Discussions focused on analytical characterization of biosimilars and reference products,



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preclinical and clinical aspects of biosimilarity evaluation, development of biosimilar MAbs, naming, goalposts for similarity at the quality level, and global development specific to biosimilars.

Regulatory Status

Biosimilar product development is a stepwise process. It consists of an independently developed manufacturing process and a thorough comparison of a biosimilar candidate with one reference product at the quality level, nonclinically and clinically. Demonstrating a high level of analytical similarity is the foundation for targeted, comparative, nonclinical and clinical development studies.

In essence, we can see a high level of agreement of that concept, implemented in the regulatory guidelines of the European Union (**1**), World Health Organization (WHO), Health Canada (**2**), PMDA (Japan), and an increasing number of other organizations in many countries. The US FDA draft guidances that were published soon after this CMC strategy forum reflect the same basic principle (**3**). However, when looking in detail at the biosimilar pathways of the different agencies, we can also see some differences with regard to the granularity of the advice given and some differences in topics such as for those related to global development, use of nonclinical data, and analytical characterization.

The first biosimilar products following the abovementioned approach were approved in Europe in 2006 (somatropin), 2007 (erythropoietin), and 2008 (filgrastim). The experience is evolving overall, and biosimilar manufacturers are now moving toward more complex proteins such as MAbs following the loss of exclusivity of first-generation products. The European Medicines Agency (EMA) is currently revising some guidelines in light of the experiences it has gained so far with biosimilar products. Many US sponsors — independent of guideline finalization — are pursuing biosimilar development programs. FDA had 21 preinvestigational new drug (IND) meetings for biosimilar studies at the time of this January 2012 forum.

Because the level of similarity demonstrated by analytical data affects the preclinical and clinical parts of development, we advise a stepwise approach toward successful development. Such a strategy is also indicated because of the substantial effort and costs required by a biosimilar development program.

The First Biosimilar Products

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?

Biosimilar MAbs and Beyond

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?

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).

Analytical Characterization and Fingerprint-Like Analysis

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 enables 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. In the choice of 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 in evaluating 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 variability of a bioassay is sometimes an obstacle 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 achieve more comprehensive testing, the term *fingerprint-like* approach is used for analytical approaches that deliver additional information not accessible by other means. For example, measuring more quality attributes or mathematically combining read outs from several methods that deliver additional information inaccessible by other means (e.g., measuring more quality attributes or mathematically combining read outs from several methods). 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 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 stepwise, 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 gaining additional information.

The extent of the nonclinical work will depend on the similarity of expression system used to manufacture the biosimilar products and the level of similarity to be analytically demonstrated with the reference product.

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 its 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, one 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 need to demonstrate biosimilarity but not reestablish overall patient benefit.

Biosimilar MAbs

Some companies are investing strongly in biosimilar MAb 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 to deliver a highly similar product."

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." 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 that product's variability early 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. They can contribute to risk information about 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

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step. In the end, the latest quality profile of a product may not look like the original licensed product when compared directly, having gotten there in distinct, approved steps. To justify the approval of these changes, regulators will refer to characterization and 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 before it can 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 a biosimilar manufacturer has determined for the reference product over time. For process consistency and setting quality control specification, the biosimilar product should demonstrate tight 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 for better understanding of 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 biosimilar candidate's safety and efficacy profile.

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*. 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 a 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, and it may not provide any scientific value.

Health Canada does not necessarily require a reference product to be sourced in Canada. The agency chose 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 publicly 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 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 its product development plans. The regulators stressed that they cannot provide information about a theoretical product. Information 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 receives highly variable data sets 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 source tracking can be done using several mechanisms, but not by INN alone (because it is not unique to a single product). The European Commission Directive 2010/84/EU4 defines the following expectation, advising EU member states to "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 Namtes (USAN) involves a scientific nomenclature evaluation based on a protein's structural features. This is difficult for glycosylated protein products, potentially containing hundreds of different molecules, which despite having the same amino acid sequence can differ widely in their glycosylation. The INN guideline recommends assigning different INNs for molecules with different glycosylation patterns. However, it does not provide a threshold for the magnitude of a difference in glycosylation, which should trigger a different INN. Differences in glycosylation pattern are already detectable from batch to batch and also after manufacturing process changes. This is important considering that differences in glycosylation patterns are detectable after a manufacturing process change and even from batch to batch.

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 comparable may hesitate prescribing a product with a different INN. Another point to consider is the option provided by the US statute 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 its 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. These may allow a more focused approach to process manufacturing development and a more detailed assessment of the level of similarity on a quality level.

How this improved product characterization will lead to a more targeted clinical development program for biosimilars remains to be seen. Whereas it is becoming clearer about 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*; 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/ Biological Products.* International Conference on Harmonisation, July 1996.

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