BIOPROCESS ONLINE

Guest Column | October 27, 2020

Mapping The Development Of A Biosimilar Candidate: Analytical & Regulatory Decisions

By Mary Lou Zett, Ph.D., Regulatory Affairs, Pharmatech Associates

In Part 1 of this two-part article, we detail the biosimilar development path to identify and evaluate critical quality attributes for both the candidate biosimilar and the reference product, along the regulatory timeline. Part 2 lays out how to approach the FDA to request a meeting, when it is appropriate to do so, and what to prepare. Throughout, we map out the milestones needed for a 351(k) Biologics License Application (BLA).

Step 1 - The Importance Of The Development Plan

Early development documentation must demonstrate traceability of change control history throughout all comparative studies of the reference product and the proposed biosimilar to the proposed clinical material.

The foundation to demonstrating biosimilarity includes not only a comparison of the proposed product and the reference product with respect to analytical bases that include structure and function, but also nonclinical studies, such as animal toxicity, and human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness.

A well-constructed development plan is instrumental to a successful Biosimilar Initial Advisory (BIA) meeting, your first formal transaction with the FDA. It should consist of a description of all planned studies – analytical, nonclinical, and clinical – intended to demonstrate the qualification of the proposed biosimilar for filing a 351(k) BLA.

Supporting the development plan should be preliminary comparative analyses of the developed biosimilar to the reference product. While analytical studies remain the focus, an abbreviated preclinical assessment of the proposed biosimilar is also required. Nonclinical and clinical plans may still be at a high-level view but having outlines of the proposed studies available for discussion gives the opportunity for early advice during this initial contact with the FDA.

By the time you are preparing for the BIA you should have demonstrable evidence of biosimilarity from initial characterization studies. Having initial nonclinical study plans and clinical study designs strengthens the sponsor's position that any "residual concerns" arising from analytical studies will be addressed through nonclinical studies, thus clearing the way for clinical evaluation.

Step 2 – Understand The Molecule And Its Fingerprints

It's important to understand the molecule and how it functions. For example, a molecule may have multiple biological activities and each should be demonstrated to be highly similar between the proposed biosimilar product and the reference product. This shows the importance of the bioassays, and there are thousands of analytical tests to choose from. The team must decide which of them will produce a convincing "fingerprint" for comparing the proposed biosimilar to the reference product.

Orthogonality is key to the fingerprinting concept for comparing overlays of the reference product pattern and the proposed biosimilar. The use of multiple mapping techniques or fingerprinting is the development of a fingerprint-like analysis algorithm that covers a large number of product attributes and their combinations with high sensitivity using orthogonal statistical methods, i.e., attribute vectors are a dot product of vectors. From the pattern formed, you might see undetected structural differences between the products that lead to what we refer to as residual uncertainty regarding biosimilarity. Two products are similar, or orthogonal, in mathematical terms, for example, when $\sin(x), \cos(x)\sin(x)^{f()}, \cos(x)^{f()}$ are orthogonal.

Step 3 – Critical Analytical Considerations

In analytical terms, the higher order structure (HOS) of protein therapeutics, for example, can be evaluated by two-dimensional (2D) nuclear magnetic resonance (NMR) spectroscopy at atomic resolution. Also, 1Hn-15N amide correlated and 1H-13C methyl correlated NMR spectroscopies at natural isotopic abundance have been demonstrated on protein therapeutics as large as monoclonal antibodies and show great promise for use in establishing drug substance structural consistency across manufacturing changes and in comparing a biosimilar to a reference product. Spectral fingerprints from 1Hn-1Hα correlations acquired using 2D homonuclear proton-proton J-

correlated NMR experiments provide a complementary approach for high-resolution assessment of the HOS of lower molecular weight (<25 kDa) protein therapeutics. The evaluation of different pulse sequences (COSY, TOCSY, and TACSY) used to generate proton-proton J-correlated NMR spectral fingerprints may be applied to therapeutic HOS assessment and comparability.[2]

Step 4 – Compare Reference Product and Biosimilar

The basic analytical comparative assessment between the proposed biosimilar and reference product's structure and functional characterization should begin with a comparative assessment of structure and post-translational changes for the reference product and the proposed biosimilar.[3]

Apply various mapping techniques combining analyses to produce a fingerprint for statistical assessment to determine similarity between the reference material and the proposed biosimilar.

An additional factor to consider is that the reference product may vary lot to lot. Differences in areas such as suppliers for cell culture media, new purification methods, or new manufacturing sites can lead to small changes.

When you have enough analytical data on at least one lot of the biosimilar against the reference product (note that lot-to-lot variability is not under review at this time), you are ready to produce a meaningful comparison between the two to the FDA.

To break it down into simple terms: How well do the amino acid sequence and modifications, folding, subunit interactions, heterogeneity (size, aggregates, charge, hydrophobicity), glycosylation, bioactivity, and impurities for the proposed biosimilar and the reference compare?

Proactively, try to identify where the "residual uncertainties" may be as you prepare for that first meeting with the FDA.

At this point you can begin organizing the briefing package for a BIA meeting.

Step 5 – Address "Residual Uncertainty"

In the case of a recombinant protein biosimilar, it would be highly unlikely that the biosimilar would be developed using the same cell line and production platform as the reference product. The biosimilar drug substance is likely to carry small differences compared to the reference product. It is these small differences that create "residual uncertainty" that requires further characterization to ensure those differences do not impact on the pharmacokinetics or efficacy of the biosimilar. It is the residual uncertainty that must be factored away through further in vivo and in vitro studies, as we will describe.

To close the gap on unanswered questions, nonclinical studies are needed. Nonclinical data required fall into the following categories: in-vitro pharmacology and in-vivo efficacy tests; pharmacokinetic (PK) assessment and toxicology studies, including toxicokinetic (TK); and anti-drug antibody (ADA) and local tolerance assessment. Biological characterization studies (bioassays) that form part of the CMC or drug quality package are also included in the nonclinical safety data package.

Research Data From Previous Studies

If the selected reference biologic is older, it may have limited data lacking in sufficient detail to allow identical comparison of study endpoints. For example, cell-based assays may have been used originally, while other methodologies may now be in use for binding information. In some cases there may be little or no TK or ADA information, and animal studies may have been conducted on animal models no longer available, and so developing an animal model can be a time-consuming process. Nevertheless, we must be led to the conclusion that there are no remarkable or important differences in the pharmacological activity, PK behavior, or toxicological or local tolerance profile between the proposed biosimilar and the reference product.

Any published literature on the reference product can serve to guide dose level selection and provide information on expected kinetics, as well as toxicity. So, the need for nonclinical pharmacology and toxicology studies to provide comparative animal studies using both the biosimilar candidate and the reference product becomes paramount. For example, a single dose pharmacokinetic study in rabbits and a four-week repeat dose toxicity study in cynomolgous monkeys can be taken together with the data from the analytical studies to support the totality of the evidence that the proposed biosimilar compares favorably to the reference product.

Before starting any nonclinical testing, map out in full a product development plan that includes all initial plans for both the nonclinical and clinical study designs intended to support the application. Even if nonclinical or clinical plans are not completely crystalized, presenting a high-level view of preliminary plans on how one intends to proceed on nonclinical and clinical studies is valuable dialogue with the FDA, sooner than later.

Clinical Considerations

Clinical pharmacology studies together with comparative analytical studies are used to support a demonstration of biosimilarity. Clinical pharmacology studies include demonstration of the degree of PK similarity and, often, PD endpoints (therapeutic and toxic) and assessment of immunogenicity between the proposed biosimilar product and the reference product. When there may be residual uncertainties that remain after the analytical evaluation, clinical pharmacology studies may help to address those remaining uncertainties. The degree of similarity may be an important factor in a scientific justification that would support extrapolation of PK and PD data to one or more additional conditions of use.

The clinical assessment requirement must be sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed. The selected target population must be the condition for intended use of the biosimilar and for which licensure is sought. However, licensure may be sought for another indication without direct studies of the biosimilar.

The method by which this is justified is called "extrapolation." It is a decision-making process based on all available data and information in the biosimilar application, coupled with the FDA's previous findings of safety and efficacy for other approved indications for the reference product and knowledge and consideration of various scientific factors for each indication. These elements factor into the decision to allow approval of an indication that has not been tested directly. Scientific justification must include knowledge of the mechanism(s) of action, PK, PD, efficacy, safety, and immunogenicity of the reference product in each of its approved indications Here again the integrity of the "fingerprinting" and lot variability play a role in the decision to expand a biosimilar indication without direct clinical studies.

Through clinical studies, any observed minor analytical differences or "residual concerns" can be demonstrated to be clinically inactive. Sponsors should identify which studies are intended to demonstrate that the proposed product is highly similar to its reference product notwithstanding minor differences in clinically inactive components. Demonstrating that no clinically meaningful differences exist between the two products will provide data sufficient to show the safety, purity, and potency of the proposed product. Preliminary clinical study outlines should be developed and ready to include in the FDA Meeting Briefing Package.

Step 6 – Grasp The Totality Of Evidence

When are we ready for a meeting with the FDA? Fortunately, there are several chances to interact with the FDA. First, acquire the reference product and characterize it to define quality attributes. After making the proposed biosimilar, compare the products and collect the totality of evidence. Since no one study is pivotal, it is the sum total of all studies — analytical, nonclinical, and clinical — that comprises what is referred to as the totality of evidence.

In evaluating a sponsor's demonstration of biosimilarity, the FDA will consider the totality of the data and information submitted in the application, which includes structural and functional characterization, nonclinical evaluation, human PK and PD data, clinical immunogenicity data, and comparative clinical study data. The FDA intends to use a risk-based approach to evaluate all available data and information submitted in support of the biosimilarity of the proposed product.

In summation, we have mapped out how to begin the planning process for the development of a biosimilar from an analytical approach supported by nonclinical and clinical comparability studies. In the second part of this article, we will discuss what and when to present research findings and how to prepare for your meetings with the FDA.

Additional Resources:

1. https://purplebooksearch.fda.gov/about
2. Nagel, K. Introduction to Biologic and Biosimilar Product Development and Analysis, AAPS 2018.
3. https://www.gabionline.net/Biosimilars
4. Daller J. Biosimilars: A Consideration of the regulations in the United States and European union. Regul Toxicol Pharmacol. 2016;76:199-208.
5. Mathematics Stack Exchange, https://math.stackexchange.com/questions/1358485/what-does-it-mean-when-two-functions-are-orthogonal-why-is-it-important

About The Author:

Mary Lou Zett, MBA, Ph.D., CQE, is a regulatory affairs professional with experience bringing products from research through to commercialization, encompassing small, large, biotechnology-NME and biosimilars, gene therapy, and medical device (critical, nonclinical, combination products, and in vitro diagnostics). She has prepared responses to regulatory authorities in the U.S., EU, and Canada, including electronic submissions for all types of regulatory applications and reporting, worldwide. She holds a doctorate in immunology from Rutgers University and an MBA from Fairleigh Dickinson University.

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