White Paper | May 2015

Patchwork Regulatory Guidance for Biosimilars: Impact on Biosimilar Development

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Initial Regulatory Steps

The European Medicines Agency (EMA) released the first guidance for biosimilar production in 2005.[1] It facilitated the initial wave of registrations for human growth hormone, epoetin, and filgrastim biosimilars. In the United States, the Biologics Price Competition and Innovation Act of 2009, which became law in 2010, provided an abbreviated biosimilars licensure pathway. It wasn't until 2012, however, that the FDA issued three draft guidelines intended to bridge the gap and enable a biosimilar program across Europe and the U. S. [2-4]

Nevertheless, FDA guidance around the issues of interchangeability (ie, separate trials required?) and substitution (ie, biosimilar can be substituted for originator?) remained elusive. The FDA's 2013 introduction of guidance on formal meetings between the FDA and biosimilar sponsors and an EMA 2014 update of its 2005 guidance resulted in a more harmonized biosimilar development pathway for global biosimilar registration.[5,6] This progress was advanced by the April 2015 finalization of two of the FDA's initial draft guidelines.[2-3] The early success of biosimilars in Europe, coupled with the cost incentive of many profitable drugs scheduled to come off patent, have led Turkey, South Korea, Australia, Mexico, Canada, Japan, Taiwan, Brazil, and India to establish national frameworks for biosimilars.

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Some Considerations for Biosimilar Development

Biosimilar development begins with state-of-the-art analytics to evaluate multiple batches of the originator medicinal product and select the most appropriate batch for biosimilar reference (heterogeneity between batches from the same manufacturing process is common due to biopharmaceutical complexity[3,7]). Any changes to the originator marketing authorization should be reviewed, as product amendments may have altered manufacturing processes and affected product performance.[8] Following the appropriate preclinical and comparability tests, a stepwise approach is usually employed. Numerous factors to be considered in the clinical development of biosimilars include[9]:

- *Selection of healthy volunteers versus patients for Phase I*
- *Choice of indication(s)*
- *Justification for extrapolated indications*
- *Clinical viability based on associated oncology chemotherapy regimens that may have been applicable for the originator study*
- *Standard-of-care restrictions that may limit clinical participation in certain territories*
- *Challenges of producing batch data and/or stability data on schedule despite abridged developmental timeline (versus originator timelines).*

Sponsors should seek scientific advice and consultation from regulators early in the biosimilar product's lifecycle. The timeframe for biosimilar development is shorter than that for originator development because the preclinical program is abbreviated, a Phase II study is not required, and a Phase III study usually need occur only in one representative indication. Therefore, a clear regulatory strategy is paramount from the onset.

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Case Study: A Biosimilar for Rituximab

Choice of Indication

The choice of biosimilar indication is of primary importance. Rituximab (a chimeric anti-CD20 monoclonal antibody) is indicated for non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia, rheumatoid arthritis (RA), and severe granulomatosis with polyangiitis. It might seem logical to develop the biosimilar for the indication that generates the most revenue (ie, NHL). However, the originator studies in NHL were performed with various, evolving chemotherapy treatments. In biosimilar development, current standard of care is a critical consideration. Further, a biosimilar trial for NHL would have required a long treatment period (≤60 months) to demonstrate classic clinical endpoints such as progression-free survival, time-to-progression, and overall response rate.

If the originator's mechanism of action is congruent across authorized indications, then data can be extrapolated. In this case, the data from the anti-CD20 mechanism of action in RA subjects could be extrapolated and applied to the oncology indications. Traditionally, a small-scale study would have to be conducted to test for potential divergence in secondary signaling-mediated effects between the oncology and rheumatology settings. It is now recognized that the indication chosen for regulatory approval of a biosimilar should be the most sensitive and least variable, unless otherwise justified. In this example, rheumatology afforded greater sensitivity than oncology in pharmacokinetic (PK) and pharmacodynamic (PD) measures.

Selection of Population

Close involvement with networking groups such as the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) and a good understanding of the competitive environment were key for successful biosimilar-rituximab development. In some areas, such as the U. S. and Western Europe, a biosimilar trial need not show benefit to subjects beyond standard of care. Therefore, the comparability study was best-served by recruiting from regions with restricted standards of care (eg, Central Eastern Europe and the Commonwealth of Independent States).

Asia was also considered, but to reduce the cost of the overall development program, recruitment was confined to central Europe and surrounding areas. Selection of specific countries and sites depended on an analysis by Worldwide Clinical Trials (**WCT**) of regulatory timeframes, variable approval processes, depth of data scrutiny, and clinical feasibility. Risk-mitigation strategies were formed before study implementation, so that if the data was deficient on initial submission, sites and/or countries could be rapidly added.

Optimization Plan

Most guidelines recommend stepwise biosimilar development, including preclinical testing and comparability studies, quality comparability between the biosimilar and originator, Phase I safety, PK and/or PD study, and Phase III comparability study. A combined Phase I and III protocol is a time-saving regulatory strategy, but compressed developmental timeframes present manufacturing challenges for scale-up, stability data, and procurement of the originator medicinal product. These processes would benefit from the interval between the two Phases. Phase I may conclude faster by recruiting healthy volunteers and administering pared-down therapeutic doses sufficient to resolve a PK/PD profile.

Certain regulators in Western Europe believe that parallel clinical development is possible if a robust comparability and preclinical package using state-of-the-art technologies exists. These regulators may require the adoption of certain safety and monitoring precautions for the first-dosed patients should parallel Phase I and III trials be conducted. Ethics Committees also providing authorization, usually expect to see the Phase I data prior to authorising the Phase III comparability study, and therefore the timing of antecedent studies is a differential.

Parallel clinical development is an emerging and contentious concept. For example, some ethics committees in Western Europe demand Phase II data prior to Phase III biosimilar studies. These committees and other authorities may benefit from additional education about biosimilar developmental requirements and permitted data exclusions, and from principal investigators' input. Investigators could profit from training in this fast-moving field, too. But it is equally important that sponsors clearly present clinical-trial parameters and data similarities

throughout the application process. All stakeholders must work together to facilitate market entry of more cost-effective biological medicines.

Facilitating clinical trial applications

Early, solid input from key opinion leaders (KOLs) and scientific advice from regulators is pivotal to provide insight about deviations from "traditional" clinical endpoints. For example, endpoints are emerging that may reveal greater sensitivity when compared to those used in originator studies. Careful discussion on such surrogate endpoints with national competent authorities (NCAs) can quickly secure lower-cost advice, due to NCA shorter submission and review timeframes, while the sponsor also makes plans to obtain EMA advice and schedules Biosimilar Product Development meetings with the FDA. The EMA and FDA often issue divergent opinions and therefore all of this planning must occur well in advance of the comparability study so that potential problems can be addressed and roadblocks swept aside.

Many biosimilar developers form partnerships. For example, a company that has the biological manufacturing expertise may align with an established top-tier pharmaceutical or generics company that is able to finance clinical development. During partnership negotiations, clauses will be made as to which company will retain marketing rights across different regions of interest. Partners must understand each other's marketing intentions because the biosimilar program may need to include certain countries that require data from their populations for marketing approval (eg, Japan, South Korea, Mexico). Even independent of regulatory requirements, early discussions with KOLs, healthcare providers, and payers can identify countries where presence of data from that country may facilitate uptake.

WCT knowledge of regulatory and biosimilar environments and understanding of marketing objectives allow us to predict study permutations and ensure delivery. For biosimilar-rituximab, Phase I studies in patients had been initiated but recruitment was delayed. Gaining authorization for the Phase III comparability study without provision of the Phase I safety and PK data would be challenging.

When conditional approvals cannot be granted without PK data, your

CRO must be ready with contingency plans for withdrawing applications prior to rejection and subsequent resubmission with the PK data. In certain markets, **WCT** employed the strategy of submitting preliminary PK data from a subset of the required population to provide some safety assurance. These minimal data were insufficient to support submission of Clinical Trial Applications (CTA) in certain Western and Central European regions. Therefore, **WCT** experts applied their knowledge of the biosimilar expectations of regulatory and ethics committees to compose a list of countries that would mostly likely approve the submission with the minimal PK data package. These countries were emerging markets, where specific regulations did not exist and local specialists could influence and navigate biosimilar requirements. The first tier of countries selected did not require the PK data, but could not recruit the entire study population in the required timeframe. A second tier of countries met with more success, and CTAs were both submitted and approved using preliminary PK data. The strategy took into account time needed to address questions by national competent authorities. **WCT's strategy allowed Phase III submissions to occur 2 to 3 months before full PK data were available.**

The strategy included a biosimilar comparability gap analysis in the Investigational Medicinal Product dossier in advance of submissions. **WCT's** country selection and regulatory strategy were successful, and only one of approximately 13 countries raised concerns regarding the lack of PK data. While it is generally acceptable for biosimilars to have fewer stability batches and shorter duration of stability testing, compared to usual chemical or biologic development, not all regulators agree. Unfortunately, despite the robust quality testing and gap analysis, a central European authority raised concerns about the shorter stability timeframe that was submitted as part of the biosimilar CTA application.

Considering quality and supply

One of the greatest challenges is up-scaling manufacturing from Phase I to Phase III. Process optimization can cause changes that introduce undetectable alterations to the protein that could impact safety and efficacy, thus limiting the value of existing studies.

If substantial changes are noted, additional comparability studies, preclinical, and/or human PK/PD studies may be necessary.

Another critical factor relates to the risk-management plan for sourcing the originator and/or blinding in the large scale, Phase III comparability study. Due diligence evaluations into appropriate batches and sourcing constraints may also impact trial commencement. For example, as a barrier to biosimilar development, originator manufacturers can restrict the quantity of batches purchased by biosimilar developers for competitor studies or limit issuance of certificates of analysis required for global biosimilar study importation.

The **WCT** gap analysis in the IMP dossier for biosimilar-rituximab did identify some minor differences in the aggregate profiles of scale-up biosimilar batches when compared to earlier biosimilar batches and the originator product. The disparity also was noted by a Western European authority. A satisfactory justification was provided along with a commitment to further examine the change in some aggregate fractions. Note that every detail of the comparability and impurity tests must be scrutinized, and if any differences are identified, additional analysis may be necessary.

Some Considerations for Expediting Authorization

After consultation with regulators, an abridged surrogate American College of Rheumatology (ACR) endpoint was used for the biosimilar-rituximab Phase III study. The PK/PD endpoint could be realized 18 months faster than the ACR endpoint. **WCT's** strategy to complete a separate PK/PD study in advance of the formal Phase III accounted for the fact that, due to competition, there was a limited number of viable patients. Hence, countries and sites were carefully selected to include optimal centres with confirmed ability to yield results.

This strategy resulted in several overlapping sites, and particular attention was given to ensure sites were adequately trained against the enrolment criteria. The strategy took advantage of the different enrolment periods for the two studies. So once the PK/PD enrolment was completed, then the site could continue on with the Phase III comparability

study. While the PK/PD data was a costly investment and extraneous to the comparability Phase III study, the biosimilar developer received the similarity results well in advance of the conclusion of Phase III. The success of **WCT's** strategy (see table) was in large part due to a strong partnership with the sponsor through protocol development and IMP dossier review. Our combined efforts supported clinical trial authorization in the most expedited manner.

Time for Authorization of Phase III Comparability Study

Region	Countries	Mean Approval Time
Central Eastern Europe	6	3.4 months
Western Europe	5	2.2 months
Commonwealth Independent States	2	2.2 months

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