Regulatory Considerations for the Development of Biosimilar Products

Biosimilar products (biosimilars) have emerged as one of the fastest growing and rapidly changing areas in the biopharmaceutical industry. Biosimilars are biological products that are developed to be similar to an existing approved biological medicine (biologic). They should not be mistaken as generic drugs which have simple structures and are produced to be exact copies of an already approved drug. A biologic contains one or more active substances made or derived from a biological source. The active substance(s) of a biologic is larger and more complex than those of non-biologic or synthetic drug. There is a degree of variability in the molecule(s) for the active substance within one batch and from batch to batch.

A biosimilar is a biological product that is developed to be similar to an existing biologic (reference product), with the same biological substance but has minor differences due to their complex nature and manufacturing methods. A biosimilar should have no clinically meaningful differences from the reference medicine. Regulatory agencies evaluate biosimilars based on their level of similarity to the reference medicine and although not expected to be identical, their analytical characterization is carefully assessed and a stringent criteria is applied comparing structure, analytical properties and biological activity.

The regulatory landscape has been rapidly changing since the US Congress approved the Biologics Price Competition and Innovation (BPCI) Act in 2009 as part of the Patient Protection and Affordable Care Act. The intent of the Act was to create an abbreviated approval pathway for biological products shown to be biosimilar to, or interchangeable with an FDA licensed reference biological product. The objectives of the BPCI Act are conceptually similar to those of the "Hatch-Waxman" Act of 1984. FDA is to permit appropriate reliance on what is already known about the biologic, to reduce time/cost of development including unnecessary duplication of animal and/or human testing.

1. Although excessive data requirements may dissuade some sponsors from pursuing the 351(k) route and to consider a new Biologics License Application (BLA), the 351(k) route is considered by FDA as an abbreviated pathway for approval of "Biosimilar" and "Interchangeable Biosimilar" products under the Act.

2. FDA considers the 351(k) route to offer a significant reduction in time and cost for development of "Biosimilar" and "Interchangeable Biosimilar" products due to the reduced need for extensive nonclinical, clinical pharmacology, safety pharmacology and clinical data supporting "Biosimilar" approval.

3. Since "Biosimilar" and "Interchangeable Biosimilar" products are similar and not identical (as for generic pharmaceutical products) conduct of clinical studies to characterize PK/PD, immunogenicity, safety/ efficacy and interchangeability are not considered unethical or/an unnecessary duplication of trials in humans as considered in the context of the "Declaration of Helsinki."

Since 2009, the FDA and EMA have developed a number of guidances that set out general principles for demonstration of comparability. Collectively, the guidances recommend a risk-based approach based on data derived from analytical studies, animal studies and a clinical study or studies, including immunogenicity, pharmacokinetic and pharmacodynamics assessments, unless it is determined that certain studies are unnecessary to be performed. These agencies will consider the totality of the data and information submitted. They recommend that data be collected in a stepwise manner and to plan to have discussions along the way to assess the need for additional studies based on the degree of residual uncertainty that remains after each step.

The World Health Organization (WHO) has also been active in the biosimilars space with the intent of ensuring better access to safe and effective biosimilar products [Similar Biotherapeutic Products (SBP)] globally by fostering the harmonization of development guidelines. The views expressed in their 2009 guideline and also discussed at a 2010 joint WHO and Korean Food & Drug Administration (KFDA) workshop, are reflected in the current FDA and EMA guidelines. The workshop was attended by 13 different countries in Asia, Europe, Middle East, North America and South America.

Reference Product – In recent 2014 draft guidances from both FDA and EMA, a reference product is defined as a product authorized in their area of authority based on a complete application review of quality, efficacy and safety. Both agencies indicate that a single reference product should be used as the comparator throughout the development of the biosimilar. With the intent to support global development of biosimilars and to minimize the number of nonclinical and clinical studies that need to be conducted, both FDA and EMA do allow the use of a non-local licensed comparator product in certain studies to support a demonstration that the proposed biological product is biosimilar to a local reference product. It remains the sponsor's responsibility to demonstrate that the comparator authorized elsewhere is representative of the reference product authorized locally with an appropriate bridging study including data from analytical tests that directly compare all three products.

Confirmatory Clinical Trial – In certain circumstances, a confirmatory clinical trial may not be required by FDA or EMA. This requires that similar efficacy and safety can be clearly demonstrated by the similarity of the physiochemical characteristics, biological activity/potency, and PK and/or PD profiles of the biosimilar and reference product. It also requires the impurity profile and nature of the excipients do not give rise for concern. Dialog with these agencies is recommended.

Extrapolation – FDA and EMA indicate that if the reference product has more than one indication then these can be extrapolated provided that the efficacy and safety of the biosimilar is justified based on the overall evidence of comparability provided and adequate justification. In the EU, EMA has accepted extrapolation of indications for monoclonal antibodies based on the assumption that the mechanism of action of the product is similar in all the indications together with the criteria listed above.

Clinical pharmacology data are an important component of the scientific justification supporting extrapolation of clinical data or additional conditions of use. In May 2014, FDA released a draft guidance clarifying the clinical pharmacology data required to support a demonstration of biosimilarity to a reference product.

Current Limitations with Harmonization

Although the regulatory expectations by EMA and FDA have become more harmonized over time, especially most recently, there are still several differences.

Interchangeability – For biological products intended for repeat administration to patients, the risk assessment of alternating and/or change-over between the reference biological product to an approved biosimilar product, without prescriber input, presents unique and special challenges related to the safe use of therapy. FDA 2012 guidance, Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, states that it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability and the sequential nature of that assessment. FDA has still not issued specific guidelines on how they plan to implement granting an indication of interchangeability. EMA 2012 document, questions and answers on biosimilar medicines (similar biological medicinal products), states that EMA evaluates biosimilar medicines for authorization purposes and don't include recommendations on whether a biosimilar should be used interchangeably with its reference medicine. Patients should consult their doctor or pharmacist. Sponsors may need to conduct post approval Phase IIIb/IV studies to evaluate interchangeability to support pricing and reimbursement considerations especially in the EU.

Similarity – FDA and EMA have harmonized the risk-based approach for generating data and the type of studies needed in order to demonstrate similarity. However, views on how to specifically demonstrate similarity with regard to equivalence margins for non-inferiority trials and specific endpoints have not quite aligned yet. These differences lead to different study designs and possibly unnecessary clinical trials and patient exposure. It is important to communicate with these agencies to align expectations and streamline the global development plan.

FDA Meetings – The Biological Product Development (BDP) meeting concept was introduced as part of the FDA legislation (FDASIA) in 2012. FDA released a new guidance in March 2013, Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants, outlining the structured approach to providing advice and ongoing consult for biosimilar products. As stipulated by statute, for sponsors to be eligible for a BPD meeting, they must pay an initial BDP development fee (~$200,000) and continue to pay the annual per product fee to remain in the program. The development fee, due at the time and Investigational New Drug (IND) application is submitted or within five calendar days after FDA grants a sponsor's request for a meeting. If development is suspended, annual fees can be suspended and reactivated (with an associated fee) by formal request. Sponsors can also have a Biosimilar Initial Advisory Meeting without an associated fee.

Participating in the FDA's BPD program provides the applicant access to FDA meetings

- **Biosimilar Initial Advisory Meeting** – Initial assessment limited to general discussion regarding whether licensure under section 351(k) may be feasible for a particular product and general advice on the expected content of the development program.

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- **BPD Type 1 Meeting** – Necessary for an otherwise stalled program to proceed. At such a meeting, there could be discussions about clinical hold, special protocol assessment, important safety issues, dispute resolution.
- **BPD Type 2 Meeting** - A meeting to discuss a specific issue (e.g. study design, endpoints, etc.) or questions where FDA will provide targeted advice regarding an ongoing program. Includes review of summary data but not full study reports.
- **BPD Type 3 Meeting** – An in depth data review and advice meeting. Includes substantive review of full study reports and FDA advice regarding the similarity between the biosimilar and reference product along with possible additional studies needed.
- **BPD Type 4 Meeting** – A meeting to discuss format and content of a biosimilar biological product application or supplement to be submitted under section 351(k) of the PHS Act.

Global Biosimilar Development

Many agencies have developed biosimilar guidelines. Since the EU was a leader in this regard, many countries have largely adopted the EMA guidance. These include Canada, Singapore, South Korea, India and Australia. China has just recently released their own biosimilar draft guideline which also largely follows the EMA guidance. Latin America, Mexico, Brazil and Argentina all have their own guidelines for biosimilar development but refer to these products as, "biocomparable biotech drugs," "similar biotherapeutic products" and "similar products" respectively. All these countries state that the reference product needs to be sourced locally. Now that the FDA and EMA have recently agreed to allow non-local reference products to be used with appropriate comparative bridging data, it can be expected that these countries will also move in this direction in the near future.

Some additional specific issues per country are shown below.

Canada - The principles within the existing regulatory frameworks for biologic, pharmaceutical and generic pharmaceutical drugs shall be the basis for the regulatory framework for Subsequent Entry Biologics (SEBs). Where appropriate, the regulatory principles and practices for the regulation of generic pharmaceuticals shall be applicable to SEBs, such as;

- SEBs should be eligible to apply for indication(s) within those granted to the reference biologic product and any claims made by the SEB shall be supported by suitable scientific data.
- The pharmaceutical form, strength, route of administration of the SEB shall be the same as that of the reference biologic product.
- The chosen reference biologic product should be a product approved and marketed in Canada. Use of a reference biologic product with market experience in other jurisdictions may be considered on request of the Minister or on recommendation by the Minister. Biologic products approved by regulatory agencies which have Memoranda of Understanding (MOUs) and information sharing agreements with HPFB have a better chance of being approved as suitable reference biologic products. Consultation with BGTD is required for use of a non-Canadian approved reference biologic product.

- Approval of a product through the SEB pathway is not an indication that the SEB may be automatically substituted with its reference biologic product. Substitutability with the reference biologic product may be granted separate from and/or subsequent to market authorization of a SEB. The decision for substitutability with the reference biologic product shall be based on science.

Australia – Has similar requirements as the EU and will accept the EU biosimilar authorization application.

Japan – The reference medicinal product selected has to be approved and marketed in Japan. A well-defined manufacturing process and extensive characterization studies demonstrating a high-degree of similarity in quality attributes with the reference medicinal product. Data from nonclinical and clinical studies in addition to the data of quality characteristics are required. Clinical studies should be designed based on the data from quality characterizations, nonclinical studies and comparability studies. No indication in the guidelines if bridging to a non-local reference product is acceptable.

South Korea - Although the extent of testing of the similar biological product is likely to be less than is normally required for an innovator product (new biological entity), it is essential that the testing of the similar biological product be sufficient to ensure that the product meets acceptable levels of quality, safety and efficacy to ensure public health. Generally, a reduction in data requirements is possible for nonclinical and/or clinical parts of the development program by guaranteeing quality of product, which may vary depending on the characteristics of the already approved reference product. Extrapolation is a possibility provided scientific data supports this. The reference product should already be licensed in Korea and the same reference product should be used throughout the development of the biosimilar product. No indication in the guidelines if bridging to a non-local reference product is acceptable. Korea does not have market exclusivity for biosimilars.

Taiwan – Has regulatory guidelines for registration of a biosimilar and are open to waiving clinical trial requirements if science is supportive for PK and safety/toxicity findings.

India – Equivalence must be demonstrated in clinical trial subjects in randomized double-blind studies with placebo, reference product licensed in India and new biosimilar product. India requires local patient exposure of approximately 100 patients in a Phase III trial. Permits the use of a reference product not licensed in India as long as the product has been approved and marketed for at least four years and has significant safety and efficacy data. A post-marketing Risk Management Plan is required upon approval.

Russia – There are no guidance documents specific for biosimilars. All products should be manufactured locally for marketing approval and must have a local trial in Russian subjects/ patients for registration.

Brazil – There are three available guidance documents by ANVISA that govern the registration, changes, renewal and modifications of biosimilars in Brazil. There is no specific definition of a biosimilar and that term is not used locally. As mentioned above, Brazil refers to these products as “comparable biological products,” The reference product should be a product already approved by ANVISA and assessed in a non-inferiority Phase III trial. Dialog with ANVISA would be recommended.

Mexico – In Mexico, general guidelines for biocomparable biotech drugs or biosimilars have been established. Local exposure of Mexican subjects in a global development plan may be required by the Mexican Agency (COFERRIS) so communication with them would be recommended.

REFERENCE:

World Health Organization

1. Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)
   http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf
2. WHO guidelines on biosimilars: case studies and discussion highlights 2012
   http://www.gabionline.net/Reports/WHO-guidelines-on-biosimilars-case-studies-and-discussion-highlights

European Medicines Agency (EMA)

3. Guideline on Similar Biological Medicinal Products, London, 30 Oct 2005. CHMP/437/04
   http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf
4. Guideline on Similar Biological Products containing Biotechnology derived proteins as active substance: Quality Issues, EMEA/CHMP/BWP/49348/2005.
   http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003953.pdf
5. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1), EMA/CHMP/BWP/247713/2012
   http://www.ebe-biopharma.eu/uploads/Modules/Newsroom/ema:chmp:bwp:247713:2012.pdf
6. Guideline on similar biological medicinal products, CHMP/437/04 Rev 1
   http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500142978.pdf

Food and Drug Administration (FDA)

7. FDA issues draft guidance on biosimilar product development.
   http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm291232.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=biosimilar&utm_content=5
8. FDA draft guidance on biosimilar product development. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. 2012
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf
9. FDA draft guidance on biosimilar product development. Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product. 2012
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf
10. FDA draft guidance on biosimilar product development. Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009. 2012
    http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf
11. FDA draft guidance on Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants. 2013
    http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm345649.pdf
12. FDA draft guidance on Clinical Pharmacology Data to Support a Demonatration of Biosimilarity to a Reference Product. 2014
    http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm397017.pdf
13. Biosimilar User Fee Act (BsUFA) of 2012. http://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/default.htm

Health Canada

14. Draft Guidance for Sponsors: Information and Submission requirements for Subsequent Entry Biologics (SEBs) 2008.
    http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/brgtherap/003-2008-seb-pbu-eng.pdf

Pharmaceuticals Medical Devices Agency (PMDA)

15. PMDA Guideline of Quality, Safety and Efficacy of the Biosimilar Product, 4-Mar-2009.
    http://www.pmda.go.jp/english/service/pdf/notifications/PFSB-ELD-0304007.pdf

Ministry of Food and Drug Safety (MFDS)

16. Evaluation Guideline for Biosimilars – KFDA. July 2009.
    http://www.nifds.go.kr/en/research/bio.jsp

Central Drugs Standard Control Organization (CDSCO)

17. Biosimilars jumpstart biotech in India, accelerated growth expected in next decade. Genetic Engineering and Biotechnology news, Apr 15 2007, 27(8).
    http://www.genengnews.com/gen-articles/biosimilars-jumpstart-biotech-in-india/2099/
18. CDSCO Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India
    http://www.cdsco.nic.in/forms/list.aspx?lid=1812&Id=1

Chinese Food and Drug Administration (CFDA)

19. CFDA Draft Guidelines for R&D and Evaluation Techniques of Biosimilars 2014.
    http://www.biocentury.com/Data/NewsCenter2/Multimedia/elearningdownloads/WhitepaperFiles/China_Biosimilar_Draft_Guidelines_EN.pdf

The National Health Surveillance Agency (in Portuguese, Agência Nacional de Vigilância Sanitária (ANVISA))

20. Castanheira LG, et al. Current development in regulation of similar biotherapeutic products in Brazil. Biologicals 2011;39(5):308-11
    http://gabionline.net/Guidelines/Brazilian-guidelines-for-follow-on-biological-products

Mexican Health Authority (in Spanish, Comisión Federal para la Protección contra Riesgos Sanitario (COFEPRIS))

21. COFEPRIS published guidance for 'biocomparables' in the Mexican Government's official journal, Diaro Oficial de la Federación, on 19 October 2011. These guidelines came into force on 20 April 2012.
    http://www.gabionline.net/Guidelines/Mexican-guidelines-for-biocomparables

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