Jordan FDA Issues a Guideline for the Registration of Biosimilars

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Recently, the Jordan Food and Drug Administration (JFDA) issued a guideline regarding the registration of biosimilars. Much of the information used to develop the guideline was adopted from the European Medicines Agency (EMA) guidelines.

Definitions

The guideline defines “reference product” and “biosimilar product” as follows:

“Reference product” refers to an innovator biological medicinal product already approved/registered in the reference countries in the European Union (via the centralized procedure), U.S.A., Australia, Canada and/or Jordan based on complete dossier (containing full quality, safety and efficacy information). The reference product is used in demonstrating the comparability of a biosimilar product through
“Biosimilar product” or “similar biological medicinal product” refers to a biological medicinal product that is similar to the reference product in terms of its quality, safety and efficacy, and contains a version of the active substance that is similar, in molecular and biological terms, to the active substance. The posology and route of administration of the biosimilar product must be the same as those of the reference medicinal product. Any deviations from the reference product in terms of strength, pharmaceutical form, formulation excipients or presentation require justification. If needed, additional data should be provided. Any difference between the biosimilar product and the reference product should not compromise safety.

**Scope and application**

As in other jurisdictions, the guideline makes clear that the aim of the biosimilar approach in Jordan is to demonstrate close similarity of a biosimilar product in terms of quality, safety and efficacy to a reference product. The guideline states that the information requirements outlined for demonstrating similarity apply to biologic drugs that contain, as active substances, *well characterized proteins* derived through modern biotechnological methods, such as recombinant DNA, in microbial or eukaryotic cell culture. The guideline further states that the “biosimilar approach” is often more difficult to apply to other types of biologics that are more complex, more difficult to characterize and for which little clinical regulatory experience has been obtained thus far. Therefore, the guidelines do not cover “complex” biologics such as blood-derived products, vaccines, immunologicals/allergens and tissue, gene and cell therapy products.

In Jordan, as in other jurisdictions, a biosimilar manufacturer is required to conduct a direct and extensive comparability exercise between the biosimilar product and the reference product in order to demonstrate that the two products have a similar profile in terms of quality, safety and efficacy. Only one reference product can be used during a comparability exercise and a biosimilar product cannot be used as a reference product. Additionally, eligibility for a biosimilar pathway hinges on the ability to demonstrate similarity to a reference product. Biosimilar products that employ clearly different approaches of manufacturing compared to the reference product (such as, for example, the use of transgenic organisms versus cell culture), will only be eligible for approval if justified. Additionally, approval of a biosimilar product is not an indication that the product can be automatically substituted for the reference product.

The guideline provides non-clinical and clinical requirements for biosimilar products that demonstrate similarity to a reference product based on the results from comparability exercises from chemistry, manufacturing and control (CMC) perspectives. When similarity of a potential biosimilar product cannot be adequately established, the applicant should submit the product as a stand-alone biotechnological product with a dossier containing complete non-clinical and clinical data.

The non-clinical and clinical issues with respect to specific products are further provided in the product-class specific guidelines. According to the guidance, if the comparability exercise is supported by state-of-the-art analytical systems, the
quality level may allow for a reduction of the non-clinical and clinical data requirements compared to a full dossier. Nonetheless, the guidance makes clear that a case-by-case approach will be used depending on the level of clinical experiences with the substance class. Additionally, in principal, extrapolation from one indication to another is possible, but would need to be scientifically justified.

Finally, the guideline recommends that biosimilar applicants seek advice from the JFDA before submitting their biosimilar application.

Specific information regarding the comparability exercise

According to the guideline, the following should be considered by a biosimilar applicant during a comparability exercise:

1. The comparative quality, non-clinical and clinical studies need to substantiate the similarity of the structure/composition, quality, efficacy and safety as well as the immunogenicity of the biosimilar and the reference product.

2. The pharmaceutical form, strength, dosage and route of administration of the biosimilar product should be the same as that of the reference product. Any differences between the two should be justified by appropriate studies made on a case-by-case basis.

3. Comparability of a chosen reference product should be addressed for both the active substance and the drug product.

4. It is not expected that the quality attributes of the biosimilar product and the reference product will be identical. Minor structural differences in the active substances such as variability in post-translation modifications may be acceptable provided that such variability is justified and supportive information is provided demonstrating that such differences will not affect the clinical safety, efficacy and immunogenicity should be provided.

5. Quality differences may impact the amount of non-clinical and clinical data needed (which will be assessed on a case-by-case basis).

6. The purpose of the comparability exercise is to demonstrate that the biosimilar product and the reference product are similar at the level of the finished product.

7. If, for some analytical techniques, a direct or side-by-side analysis of the biosimilar and reference medicinal product is not feasible or gives limited information (such as due to the low concentration of the active substance and/or the presence of interfering excipients such as albumin), samples could be prepared from the finished product. In such instances, the techniques used to prepare the samples should be outlined, and their impact on the samples should be appropriate documented and discussed (namely, a comparison of the active substances before and after formulation preparation).

8. A representative number of batches produced according to a manufacturing process with proven consistency for intended commercial use should be used in all comparability studies.
Quality standards

The guideline states that a biosimilar product derived from a separate and independent master cell bank using an independent manufacturing and control methods must meet the same quality standards as an innovator product. As a result, a fully quality dossier will always be required. Additionally, a biosimilar manufacturer will be required to submit extensive data focused on the similarity, including comprehensive side-by-side physicochemical and biological characterization of the biosimilar and the reference product. Moreover, due to the limitations of analytical techniques and the unpredictable nature of the clinical consequences of any structural or biophysical differences, it was not possible for the JFDA to define the exact degree of biophysical similarity that will be considered “sufficiently similar” for a product to be regarded as biosimilar. As a result, comparative non-clinical and clinical data must be submitted. The clinical data to be submitted will be determined independently for each product.

Regarding manufacturing, the biosimilar product must have its own specific manufacturing process for both the active substance and drug product. The process should be developed and optimized taking into account state-of-the-art science and technology. Additionally, the manufacturer of a biosimilar product (both the active substance and drug product) should be approved by the JFDA according to the drug manufacturer accreditation criteria.

Regarding the analytical procedures, extensive, sensitive state-of-the-art analytical methods should be applied to maximize the potential for detecting small differences in all relevant quality attributes. If available, standards and internal reference materials (such as from the European Pharmacopeia and the WHO) should be used for qualification and validation.

Non-clinical requirements

Biosimilar products must undergo appropriate non-clinical testing (in vitro and in vivo studies) to justify conducting clinical studies. These studies should also be comparative with the reference product with the aim of detecting differences between the biosimilar product and the reference product. According to the JFDA, ongoing consideration should be given to the use of emerging technologies (such as real-time binding assays (for in vitro testing) and genomic/proteomic microarray science (for in vivo testing) to detect minor changes in biological response to pharmacologically active substances. In vitro studies should include receptor binding or cell-based assay studies. In vivo studies should include animal pharmacodynamics studies, at least one repeat-dose toxicity study and relevant safety observations. Other toxicological studies are not required unless warranted by the results from the repeated toxicological studies and/or based on the known properties of the reference product.

Clinical Studies

Comparative pharmacokinetic studies should be conducted to demonstrate the similarities in the pharmacokinetic (PK) characteristics between the biosimilar and the reference product. Healthy volunteers can be used for such comparative PK studies. The choice of design of these studies must be justified and should consider
factors such as clearance and terminal half-life, linearity of PK parameters, the endogenous level and diurnal variations of the protein under study (when applicable), production of neutralizing antibodies, the conditions and the disease to be treated as well as the route of administration. Additionally, based on the biosimilar product and its half-life, an appropriate pharmacokinetic design should be set. The acceptance range/equivalence margin to conclude clinical PK comparability should be defined prior to initiating a study, taking into consideration known PK parameters and their variations, assay methodologies, safety and efficacy of the reference product.

Pharmacodynamic (PD) studies should also be comparative in nature. The parameters studied should be clinical relevant or employ a clinically validated surrogate marker. The PD study may be combined with the PK study and the PK/PD relationship characterized.

Additionally, comparative PK/PD studies may be sufficient to demonstrate comparable clinical efficacy if the following are met:

1. The PK and PK properties of the reference product are well characterized.
2. Sufficient information regarding the PD parameters is available.
3. At least one PD marker is accepted as a surrogate marker for efficacy.
4. Dose response is sufficiently characterized.
5. The equivalence margin is pre-defined and appropriately justified.
6. The most sensitive population, dose and route of administration has been used.

Clinical efficacy trials

Comparative clinical trials are required to demonstrate the similarity in efficacy and safety profiles between the biosimilar and the reference product. The study population used should be representative of the approved therapeutic indication for the reference product and is sensitive to detect potential differences between the biosimilar and reference products. Equivalent, rather than non-inferior efficacy, should be demonstrated in order for the biosimilar product to adopt the posology of the reference product and to open the possibility of extrapolation to other indications, which may include different dosages.

The safety of a biosimilar should be demonstrated to be similar to that of the reference product in terms of the nature, seriousness and frequency of adverse events. Therefore, data from a sufficient number of patients and study duration with sufficient statistical power to detect major safety differences is required. A written rationale on the strategy for testing immunogenicity should be provided and state-of-the-art methods should be used.

Post-marketing risk management and pharmacovigilance plan and periodic safety update reports

A post-marketing risk management plan (RMP) is required and must include detailed
information of a systematic testing plan for monitoring the immunogenicity of the biosimilar post-approval. The RMP must be maintained throughout the entire lifecycle of a product and include:

1. Risk identification and characterization (for example, case definitions, antibody assays).
2. Risk monitoring (for example, it must include a specific framework to associate risk with a biosimilar product).
3. Risk minimization and mitigation strategies.
4. Risk communication (for example, it should include mitigation messages for patients and physicians).
5. Monitoring activities to ensure the effectiveness of risk minimization.
6. Detailed information of a systemic evaluation of the immunogenicity of a biosimilar product.
7. A discussion about methods to distinguish adverse event reports from those for other licensed products, including the reference product.

A pharmacovigilance plan must also be designed and implemented. The pharmacovigilance plan should be designed to monitor and detect both known inherent safety concerns as well as any unknown safety concerns that might result from the impurity profiles of a biosimilar product or may not have been detected in the pre-market testing or otherwise not expected. Additionally, the pharmacovigilance plan should be able to distinguish between the biosimilar and reference product and track different products and manufacturers in the same class. The purpose of this requirement is to help ensure that adverse events are properly attributed to the relevant medical product.

A periodic safety update report (PSUR) of a biosimilar product must also be submitted. This report must evaluate the benefit/risk of a biosimilar product post-marketing.

Interchangeability and substitution

The guideline makes clear that the decision to treat a new patient with either a biosimilar or reference product, or to switch a patient already being treated with a reference product to a biosimilar product, should only be done by a qualified health care professional. Moreover, the guideline states that automatic substitution of biologics with biosimilar products is not permitted.

Naming

The guideline states that all biosimilar products should be distinguishable by name. Specifically, each biosimilar product should have a brand name that is not suggestive of the originator’s name or other biosimilar products. Thus, every medicine will have either a trade name or the name of the active substance (such as the International Non-proprietary Name (INN)) together with a company
name/trademark. According to the guideline, the approved name, batch number, country of origin and manufacturer will be important for clear identification of biological products in Jordan.

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