

Roche Position on Similar Biological Medicinal Products

Similar Biological Medicinal Products - Biosimilars

Innovative biological products (e.g. proteins, antibodies) are losing data protection, and a second wave of products, claiming to be similar to an innovative product, are being developed and commercialized.

While it is relatively easy to copy small molecules produced by chemical synthesis, it is very challenging to copy biological products, as they have complex molecular structures and are obtained in living systems through highly complex manufacturing processes, which are difficult to reproduce. The limitations of analytical methods and pre-clinical testing to fully characterise a biological medicinal product make clinical data mandatory in order to demonstrate similarity of molecular properties as well as safety and efficacy to the reference product.

These 'similar' products cannot be considered as generics, therefore the term "biogeneric" is inappropriate because the testing required to develop these products is more demanding than that of traditional generics for which a limited set of data is accepted by regulatory authorities in most countries. Therefore, based on globally shared scientific understanding as set forth e.g. in WHO guidance on similar biotherapeutic products (see below) they are named differently such as "biosimilars", "similar biotherapeutic products", "subsequent entry biologics" or "follow-on protein products".

The need for a well defined regulatory framework for biosimilars

Due to the complex nature of these diverse products for which the benefit/risk profile must be carefully evaluated and monitored, a well defined and transparent regulatory framework covering development, approval and post-authorisation procedures must be in place.

In the last few years, the first legal basis for this framework has been established by regulatory authorities in the European Union (EU) and several biosimilars have been approved based on the new guidelines (other applications were rejected or withdrawn). Meanwhile the same principles as laid down in EMA guidelines on biosimilar medicinal products have also been adopted by the expert committee on biological standardization of the WHO in their guidelines (Evaluation of similar biotherapeutic products (SBPs)). In the United States, the FDA has initiated thorough discussions on this topic on the basis of

legislation demanding a specific regulatory pathway for biosimilars including provisions under which these products are interchangeable with the originator product. In several other countries, guidelines for the approval of biosimilar products have either already been adopted or are under discussion.

Roche supports the development of these regulatory frameworks for the introduction of biosimilars as they ensure that there is a consistent and high level of protection of public health that applies to biosimilars, on the same basis as it applies to innovator/originator products. In addition, it is our strong belief that biosimilars regulation should not impede, but rather promote, and give incentive for, innovative research towards new medicines as medical progress halts without innovation.

Biopharmaceutical products on the market cover a wide range of molecular complexity, from relatively small, unglycosylated proteins (such as insulin or somatropin) over larger, glycosylated molecules (e.g., epoetin) up to very complex glycoproteins which may possess multiple functions mediated by different parts of the molecule (e.g., monoclonal antibodies), or are involved in several biological pathways (e.g., interferons). In these cases, in addition to analytical characterization – which must include an assessment of the impact of glycosylation differences on the functionality of the molecule - appropriate additional functional testing should be mandatory. Due to these different requirements, the amount of data to be provided for the approval of biosimilar products should be defined case-by-case in specific guidelines.

Approval of biosimilars via an abbreviated regulatory pathway can only be justified when based on the principle of similarity, i.e. comparison with a defined reference product for which extensive analytical and clinical experience is available. The demonstration of similarity has to include head-to-head quality-related, non-clinical, as well as clinical studies.

Any approved product intended to be a copy of an already licensed reference biological product that does not meet EMA or WHO criteria for biosimilars, i.e. has not been demonstrated to be similar with regard to quality, non-clinical properties as well as clinical safety and efficacy in head to head comparative studies should not be called a biosimilar. Unless a manufacturer provides all necessary scientific evidence qualifying its product as a biosimilar the approval of an intended copy should be revoked by the National Health Agency. Manufacturers who bring a biotherapeutic product on the market naming their product a “biosimilar” without being able to provide the necessary scientific evidence, are not acting in a transparent and responsible manner. Roche will

continue to take steps necessary to avoid related misunderstandings and will oppose any misleading claims that are unsubstantiated due to lack of reasonable data.

Comparability and Similarity are two distinct concepts

Comparability testing applies to the evaluation of whether an incremental change to a process established by one manufacturer impacts the quality, safety or efficacy of the post- vs. pre-change drug product delivered to the market. Similarity testing applies to the evaluation of an independently manufactured biosimilar product claiming to be similar to a reference innovator/originator product, already on the market, which is going off patent and for which the data exclusivity period has expired.

Comparability testing cannot be applied to a different manufacturing process where product manufacturing-, quality-, non-clinical- and clinical history does not exist, where a new cell line is used and multiple differences exist as compared to the innovator's process. It is very difficult to understand the impact of these multiple significant process differences to the safety and efficacy profile of a biological medicinal product based on analytical and/or pre-clinical testing data alone. Only data from meaningful and robust clinical trials will link the specific process- and product characteristics with safety and efficacy.

Patient safety as a crucial element when considering biosimilars

The need for appropriate data

Despite the fact that the biosimilar and reference drug can show similar efficacy, the biosimilar may exhibit a different safety profile in terms of nature, seriousness or incidence of adverse reactions. The data from pre-authorisation clinical studies normally are insufficient to identify all potential differences. Safety signals seen with biopharmaceuticals can often be related to their mechanism of action and/or to their high degree of target specificity. In addition, all biotechnology products, including biosimilars have a potential to cause immunogenic events that may sometimes take years to develop, may only occur infrequently, but may have profound clinical consequences. This cannot be predicted using preclinical models, and therefore must be always considered before a biosimilar is placed on the market.

Regulatory authorities and experts agree that non-clinical data and clinical data, including the assessment of the risk of immunogenicity, are needed in order to demonstrate the

safety and efficacy of a biosimilar. This risk must be assessed pre-approval with an adequate number of patients in comparative clinical studies of appropriate duration, as well as by post-authorisation pharmacovigilance and relevant epidemiology data as part of a risk management programme, requiring clear identification of the product used.

Similarity should always be demonstrated for each of the claimed indications unless there is a solid scientific rationale to extrapolate the clinical safety and efficacy data from one indication to a second one. In general, there will be a need to demonstrate that the dose is appropriate and that the safety profile in a second population, which may be more susceptible to immunogenicity, is acceptable. Hence, each indication needs to be duly justified based on scientific evidence.

The need for unique identification of biosimilars

It is essential to identify and trace the product used in case of the occurrence of adverse reactions, particularly immunogenicity, as required for the originator/innovator product. Biosimilars therefore must be branded in order to be able to identify the actual biological product used in clinical practice. For safe prescription and dispensing and effective pharmacovigilance monitoring it is necessary that different products (even if similar) can be identified by a distinct brand and non-proprietary name (INN). Switching patients back and forth between different biopharmaceuticals may pose additional risk to the patients because of potential immunogenicity. This necessitates the understanding that the marketing and utilization of biosimilars (which are similar, but not identical to their reference products) must not imply automatic substitution with a reference product, and/or interchangeability without the consent of a qualified healthcare professional as acceptable practices. Labeling of biosimilars should clearly indicate which clinical safety and efficacy data have been obtained with the biosimilar product and should identify any differences in the safety profile.

The Key Principles

The approval process for a biosimilar must be based on the concept of similarity using a well-defined and transparent regulatory process, as it is the case for innovative biological medicinal products. This concept has to be clearly distinguished from the concept of comparability.

The safety of patients should remain the primary concern when developing, assessing and approving a biosimilar. This requires head-to-head quality-, non-clinical- and clinical-comparative data to demonstrate the safety and efficacy in all the claimed indications.

The amount of data to be provided has to depend on the complexity of the drug substance, as well as on clinical and regulatory experience with the particular drug.

A risk management programme, including immunogenicity testing and post-authorisation pharmacovigilance monitoring, is necessary to ensure that the risk/benefit profile of a biosimilar is properly evaluated. In order to achieve this goal, any biosimilar must be identifiable, i.e. a brand name must be used and a distinct INN should be assigned. Substitution should not be an acceptable medical practice.

This up-dated position paper was proposed by the Corporate Sustainability Committee and adopted by the Corporate Executive Committee on December 14, 2010. It was reviewed in April 2012.