

# Roche Position on Similar Biological Medicinal Products

## Similar Biological Medicinal Products - Biosimilars

Innovative biological products (e.g. proteins, antibodies) are starting to go off patent, and a second wave of products claiming to be similar to an innovative product are being placed on the markets.

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 extremely 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, and the term "biogeneric" is absolutely 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. For this reason, they are named as "biosimilars" 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Union (EU) and several biosimilars have been approved based on the new guidelines (other applications were rejected or withdrawn). In the United States, Congress and the FDA have initiated thorough discussions on this topic with a view towards establishing a process for approval. In several other countries, guidelines for the approval of biosimilar products either have already been adopted, or are under discussion.

Roche supports the development of a regulatory framework for introduction of biosimilars in order to 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.

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 quality-related, non-clinical, as well as clinical studies.

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.

## **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 subsequent-entry biological 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 impossible 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*

With biopharmaceuticals, there is a significant potential risk to public health with regards to immune-mediated responses which may be caused by multiple factors. These factors include the drug substance itself, its molecular size, its solubility, its microheterogeneity profile, as well as subtle changes that may affect these properties and which are not detectable by analytical methods. In addition the carriers used in the formulation of the finished drug product, as well as factors that depend on the patient and disease play an important role. Immunogenicity 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 and 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. As for the originator product, 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. Roche does not support extrapolation of similarity shown in one indication to other indications of the reference product for which no data are provided for the biosimilar.

### *The need 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 generic or 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.

### **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 quality, non-clinical and clinical 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 postauthorisation 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 May 12, 2009 and entered into force the same day.*