

## **Roche Position on Similar Biological Medicinal Products**

(Approved by the CEC March 15, 2005)

### **Similar Biological Medicinal Products or Follow-on Biologics (FOB)**

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

If it is relatively easy to copy small chemical molecules, it is very challenging to copy biological product, as they are obtained through extremely complex manufacturing processes, which are difficult to reproduce.

These second wave products or second-entry biologics 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 a traditional generic for which a limited set of data is accepted by regulatory authorities in Europe or in the USA. For this reason, these authorities are naming them “similar biological medicinal products” or “biosimilars” (Europe), and follow-on biologics/proteins (USA).

### **The need for a well defined regulatory framework for Biosimilars/Follow-on Biologics**

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 two years, the first legal basis for this framework has been established by regulatory authorities in the European Union. In the United States, the FDA are initiating thorough discussions on this topic.

Roche supports the development of this framework in order to ensure that there is a consistent and high level of protection of public health that applies to biosimilars/follow-on biologics, on the same basis as it applies to innovator/originator products.

## **Comparability and Similarity are two distinct concepts**

Comparability testing applies to the evaluation of identifiable incremental changes to one single product and one process by one manufacturer, whereas Similarity testing applies to the evaluation of a second-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 totally new manufacturing process where product manufacturing, quality, non-clinical and clinical history does not exist, where a new cell line is used and multiple changes are made to the process. The ability to understand the impact of these multiple significant changes to the safety and efficacy profile of a biological medicinal product based on analytical testing data alone is significantly diminished where there is no access to this product history.

There are complementary requirements that must be met before comparability testing results can be considered adequate enough to assess the impact of manufacturing changes for a single manufacturer of an approved biological medicinal product without the need for further preclinical and clinical data to be generated.

The complementary requirements are:

- the process flow (including starting materials and cell bank), its data and its history and
- pre-clinical, clinical and post-authorisation data

Both the above are intimately related and correspond to significant technical and scientific knowledge and experience, which is not available to a biosimilar/FOB manufacturer.

The absence of essential elements such as reference materials, batch history for active pharmaceutical ingredient (API) and no access to in-process control (IPC) data would make it impossible to accurately compare processes. There is also limited published data on validated analytical methods and data correlated to development.

There is significantly greater complexity of biotechnology-derived proteins compared to small chemical molecules due to the heterogeneity of the proteins. There are limitations to the ability of analytical methods and functionality testing to fully characterise a biological medicinal product and there is a need for non-clinical and clinical data to demonstrate similarity of quality, safety and efficacy to the reference product.

## **Patient safety as a crucial element when considering biosimilars/FOBs**

### ***The need for appropriate data***

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, and its properties, as well as subtle changes that may affect these properties, and which are not detectable by analytical methods, the carriers used in the formulation of the finished drug product, or factors that

depends upon the patient. Immunogenicity cannot be predicted using preclinical models, and therefore must be always considered before a biosimilar/FOB 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/FOB. This risk must be assessed with an adequate number of patients and clinical studies of appropriate duration, as well as post-authorisation pharmacovigilance and relevant epidemiology data as part of a risk management programme.

### ***The need for identification of Biosimilars/Follow-on Biologics***

Biosimilars/FOBs must be branded in order to be able to identify the actual biological product used in clinical practice for pharmacovigilance purposes. 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. For effective pharmacovigilance monitoring it is necessary for prescriptions and dispensing to be by brand and not a common generic name (INN). This necessitates the understanding that the marketing and utilization of a biosimilar/FOB does not imply that generic substitution is acceptable, i.e. there is an alternative branded product available with its own clinical safety and efficacy data represented in the label.

### **The Key Principles**

**The approval process for a biosimilar/FOB must be based on the concept of Similarity, a well-defined and transparent regulatory process, as it is the case for innovative biological medicinal products. This concept is independent of the concept of Comparability.**

**The safety of patients should remain the primary concern when developing, assessing and approving a biosimilar/FOB. This requires to adequately generate the quality, non-clinical and clinical data, which will demonstrate the safety and efficacy in all the claim indications.**

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