



IFPMA Position on Follow-on Biological/Biotechnological Products

Biological/biotechnological products have become an integral and valuable part of modern medicine. Many biotechnology products have been developed and licensed to treat serious illnesses, including cancer, heart disease, multiple sclerosis, anemia and rheumatoid arthritis. Notwithstanding the different legal and regulatory systems in each country, the design of a new pathway for approval of follow-on biologicals¹ raises important questions relating to patient safety, science, incentives for innovation, and patient access to medicines. IFPMA believes that any regulatory process for the approval of follow-on biologicals must be shaped by three cardinal principles:

- a) The primary concerns are the health and safety of patients and patient confidence in their medicines.
- b) The approval process for any biologicals should recognize the ownership and value of the innovator's intellectual property, including data submitted for regulatory approval/licensure.
- c) All aspects of the regulatory framework should be supported by sound science of the same rigor as was used in the approval of earlier products.

1. Introduction

Generic drugs are chemical medicinal products which have the same qualitative composition in terms of drug substance(s), the same pharmaceutical form and which are bioequivalent to an approved originator product. Generic drugs are approved with reference to the toxicological and clinical data submitted by the innovator and marketed after the patent/data protection of the originator's product has expired. Because there is no requirement to conduct studies establishing the safety and efficacy of a generic product, the development costs amount only to a fraction of the on average US\$ 800 Million² which it costs to bring to market a drug containing a new active ingredient. Therefore generic products can be much lower-priced than new innovative drugs. Generic drugs have become an accepted and integral part of the drug market. They help stimulate innovation and competition.

Interest has been expressed in some countries to extend the generic approach to biological/biotechnological products and to create an abbreviated application process for follow-on products that would, subject to patent and data protection, rely in part on the safety and efficacy data generated and filed by the innovator for similar products which had been approved. However, because of the unique characteristics of biologicals compared to small molecule drugs, as explained below, it is not appropriate to apply the generic drug paradigm to follow-on biologicals.

¹ Recognizing that definitions vary between regions, throughout this paper we use the terms "Follow-on Biologicals" or "Biosimilars" to mean follow-on versions of biologics, including therapeutic proteins, produced either through recombinant technologies or from natural sources, developed and manufactured by a company unrelated to the innovator and using an abbreviated approval pathway, which in some way relies on the prior approval of the innovator product.

² DiMasi, JA, Hansen, RW, and Grabowski, HG. 2003. The price of innovation: new estimates of drug development costs. *Journal of Health Economics* 22:151-85.

2. Patient Safety Must Come First

Unlike typical small-molecule drugs, biological/biotechnological products raise unique concerns due to their complexity and the close relationship between a biological's manufacturing process and its clinical attributes. Any regulatory approach to follow-on biologics must address these concerns from a sound scientific perspective to ensure that the high standards of safety and efficacy now applied are not compromised. These concerns for biotechnology products are not merely theoretical ones but are substantiated by practical experience. Given this experience any approach to follow-on biologics should be based on sound science to ensure that there are sufficient data to demonstrate safety and efficacy of each individual product. Based on the current state of scientific knowledge, all follow-on biological applications should be supported by appropriate clinical studies using the investigational follow-on product. The study requirements applicable to different products can be expected to vary based on relevant therapeutic, manufacturing and other concerns as evaluated based on evolving science. While these considerations may permit the approval of follow-on biologics based on scientifically-justified data sets different from the dossier of the original innovator product, each follow-on product should be supported by data generated from appropriate preclinical work, clinical safety and effectiveness trials, and a full quality part of the dossier. Post-marketing surveillance should also be required under the same guidelines as for innovator products.

3. Innovation

Strong intellectual property protections are critical to promoting innovation that results in advanced therapies to meet patient needs. These protections—including rights in patents, confidential information, and trade secrets—are well established and must be respected. IFPMA supports competition among safe and effective products that do not violate intellectual property rights, such as where patents have expired and trade secrets are respected.

4. Special Considerations for Biological/Biotechnological Products

The terms “follow-on biological” and “biosimilar” imply abbreviated approval requirements for the follow-on, or similar, product predicated on the similarity of the product to a reference innovator product. However, there are significant analytical challenges to achieving adequate characterization of biological/biotechnological products to establish the similarity of the manufactured products. These challenges reflect to a large extent the significant physico-chemical differences between biological/biotechnological and small molecule drug products. The analytical capability to demonstrate similarity between innovator and follow-on biologics is currently limited at best.

The manufacturing process for each biological/biotechnological molecule, or complex mixture of molecules, defines to a significant extent, the quality, safety and efficacy of the product. This is because these processes are based upon living cells or organisms, which are inherently variable. Unlike chemical drugs, individual batches of biological/biotechnological products are heterogeneous at the molecular level, as a result of the random variability of the living process by which they were made, even if manufactured by a single manufacturer. By virtue of this inherent heterogeneity it is not always possible to analyse and specify products made by different manufacturers with sufficient precision to support the conclusion that they have identical clinical properties, even if they are indistinguishable by *in vitro* tests.

Methods to detect and quantify impurities, particularly for those that are process dependent, have to be more sensitively monitored and identified than for chemical drugs, as even small

molecular differences can have a clinical impact by affecting, for example, the product's immunogenicity or pharmacokinetic and / or pharmacodynamic profile.

A follow-on or biosimilar product manufacturer must have a comprehensive database of every step of its own manufacturing process, including cell banks, key intermediates and established in-process controls and reference standards. However, this manufacturer does not have access to the innovator's manufacturing data, cell construct, cell bank, key intermediates, reference standards and reagents and complex or unique validated methods (e.g. bioassays). Without these data, it is difficult to make a direct and meaningful comparison between innovator and biosimilar manufacturing processes or between the innovator and biosimilar products using solely physico-chemical analyses.

Manufacture and clinical testing of biological/biotechnological products must include additional safety control measures beyond those used for small molecule drugs. Safety concerns related to a biological can involve a wide array of effects on multiple target organs, including sub- or superpotency, altered biodistribution, toxicity, neoactivity, altered therapeutic index, and immunogenicity. Assessment of immunogenicity is a key component for determining safety of biologicals. There are some examples of biologicals that have resulted in problematic immune responses in patients. It is well established that the immune system is exquisitely sensitive to and capable of responding to subtle characteristics of a biological that may not be detectable by analytical methods.

Thus, it would not be scientifically justifiable simply to expect that a product of a follow-on or biosimilar manufacturer would share the clinical properties of the innovator product. The only way to characterise the clinical properties of a product of a second manufacturer is to evaluate them in clinical studies adequately designed to demonstrate the product's safety and efficacy followed by a post-marketing surveillance program, including assessments of immunogenicity.

Therefore, due to the complexity of biological/biotechnology products, the generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) as normally applied to chemically derived medicinal products, is scientifically not appropriate for biological/biotechnology products. Furthermore, so that patients and physicians are better informed about the products being prescribed and to support pharmacovigilance, all biological products should be clearly and uniquely identified by name.