FACT SHEET 4

BIOSIMILARS AND THE IMPORTANCE OF ADHERENCE TO INTERNATIONAL REGULATORY STANDARDS

International Alliance of Patients' Organizations

CAN Mezzanine
49-51 East Road London
N1 6AH
United Kingdom

International Federation of Pharmaceutical Manufacturers & Associations

Chemin des Mines 9
P.O. BOX 195
1211 Geneva 20
Switzerland

SOURCES

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BIOSIMILARS & THE IMPORTANCE OF ADHERENCE TO INTERNATIONAL REGULATORY STANDARDS

Appropriately balanced regulatory guidelines are not a hindrance to access; they are a prerequisite to assuring patients benefit from safe and effective medicines.

For all medicines, and especially biologics, it is critical to adhere to high regulatory standards during development manufacturing and distribution to ensure they are effective and safe in use. To that end, patients, physicians, pharmacists, regulatory agencies, and industry all need to be aware and engaged in the implementation of these regulatory standards, to ensure each stakeholder fulfils its own obligations and each holds all others accountable to implement best practices across the entire health care system.

Some critics have argued that stringent (WHO) regulatory standards may limit or delay access to biologics for some patients. This concern has been raised specifically with respect to low-and-middle-income countries (LMICs), where biosimilars have been highly anticipated as offering opportunities to patients to access treatment at a potentially lower cost.[1] However, patients are among the most vocal stakeholders in these settings who stress that **efficacy and safety cannot be compromised for lower cost.**[1]

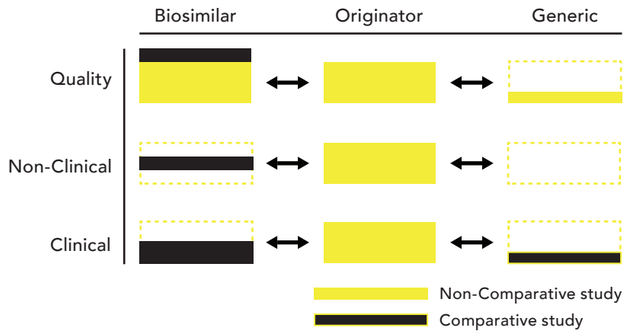
A comparison between requirements for approval for new molecules, generics and biosimilars can be seen on **Fig. 1.**

Whereas generics (usually) require no non-clinical data studies, biosimilars must provide be compared head to head with the originator in all parameters. The most striking difference though is in terms of quality: Whereas generics require only a small amount of quality data, biosimilars require the same amount of quality data as the originator, in addition to comparative data, in order for it to be approved as a biosimilar.

GENERAL REQUIREMENTS FOR DRUG APPROVAL APPLIED BY MOST STRINGENT NRAS

Figure 1.

This graphic shows how qualitatively and quantitatively different are the studies required for biosimilars and generics in contrast to originator medicines.



Source: Ministry of Food and Drug Safety of the Republic of Korea

Two cases are cited here to demonstrate exposure to risk and potential harm of not adhering to appropriate regulatory standards in the development and approval of biosimilars. The first discusses the case of erythropoietin in Thailand (**Case study 1**) and the second focuses on interferon beta in Latin America (**Case study 2**).

Lack of WHO-level regulatory guidelines in some countries meant sub-standard "non-comparable" biologics were approved, resulting in lack of benefit, exposure to risk, and patient harm.

CASE STUDY 1 / Non-comparable human erythropoietin products (EPO) with high immunogenicity

Erythropoietin (EPO) is a biologic medicine used to stimulate red blood cell production in a number of conditions, including kidney disease and cancer. Since the expiration of the patent for innovator EPO, a number of manufacturers have developed EPO biosimilars. In Europe, these are evaluated by the European Medicines Agency (EMA) using biosimilar regulatory guidelines, and there has been little challenge as to their safety and efficacy since the first approval in 2006. The situation is quite different in Thailand where EPO "copies" were approved using their generics regulatory pathway. [2]

Unfortunately, numerous serious adverse effects can be linked to these products. There have been reports of immunogenic reactions in cancer patients, further suppressing red blood cell production as well as cases of pure red cell aplasia (PRCA), whereby the body shuts down production of all red blood cells. [3]

In 2011, EPO products approved through the generics pathway were linked to unusually high instances of PRCA.[4] In 2014, a nationwide investigation using six state-of-art analytic methods was conducted to compare the manufacturing quality of non-comparable biologics available for purchase in the Thai market to the originator product. Significant molecular differences among the non-comparable EPO products were found, including one product with an endotoxin level well above the FDA accepted limit.[2] In response, Thailand has implemented a national biosimilars regulatory pathway.

CASE STUDY 2 / Non-comparable interferon-beta products with low efficacy

Without standardized regulatory guidelines, non-comparable biosimilars with lower efficacy than the reference biologics have been approved.

Interferon-beta is a biologic medicine used to treat multiple sclerosis (MS). One study compared the biologic potency of four "non-comparable" interferon beta products from Latin America and Iran with two originator interferon betas. The test products were found to vary in biologic potency and had significant batch-to-batch variability.[5] In another case in Mexico, there were suspicions that a biologic approved as an interferon-beta biosimilar did not seem to be achieving therapeutic goals when used with MS patients in clinical settings. To study these concerns, a direct comparison to the reference biologic was undertaken in a clinical trial involving MS patients from Mexico and Colombia. It was found that the approved non-comparable biologic caused minimal adverse reactions, but these data also seem to suggest that the non-comparable biologic had reduced bioavailability when compared to the original biologic.

These cases demonstrating low efficacy or immunogenicity among real-world patients demonstrate the importance of systematic plan of development for biosimilars, including not only in vitro ("test tubes") studies but also non-clinical and clinical evaluations to assure equivalent efficacy and no greater risk of adverse effects.[5 6]