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OPINION

Biosimilars for Healthcare Professionals

Biosimilarity is not a transitive property: implication for interchangeability, naming and pharmacovigilance

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Current regulations do not require a given biosimilar to remain similar to its reference biological over time. However, two products that were initially deemed biosimilar or interchangeable could each undergo unique patterns of drift and evolution in their manufacturing processes (divergence), ultimately resulting in two products that would be no longer biosimilar. In cases where divergence in potency, safety and immunogenicity may be present, care should be taken with multiple switches between reference and biosimilar products: each time a switch occurs, the difference between products could be greater. Taking into account that post-marketing comparative biosimilarity validation is not required, drift, evolution and divergence may present greater challenges when assessing biosimilar. In a marketplace with multiple biosimilars of a given reference product and in the context of interchangeability with drift and divergence, pharmacovigilance systems should be strengthened.

Keywords: Divergence, drift, evolution, interchangeability, pharmacovigilance, variability

Background

Currently, regulatory agencies in most of the world have established the requirements to achieve biosimilarity between two biological products. However, there is no mandatory legal obligation to perform quality or clinical studies that directly compare the biosimilar versus originator products in the post-approval period. Loss of biosimilarity over time could have important implications for the way in which regulators and healthcare providers handle safety surveillance, product naming, interchangeability, and medical records. Thus, biosimilars introduce new challenges because two products that were initially deemed biosimilar (or interchangeable) could each undergo unique patterns of variation resulting in two products that are no longer biosimilar (nor interchangeable). In this context, it would be essential that regulatory agencies adopt measures to minimize the risk of possible adverse events or lack of efficacy of treatments with biologicals, such as to determine extended biosimilarity and interchangeability standards and to strengthen pharmacovigilance systems.

Changes in the production process: comparability concept

During manufacturing process, the cell culture and fermentation processes are particularly critical and sensitive in terms of defining the identity, purity and potency of the approved biological. Modifications of parameters in any of these steps may impact cell culture performance, leading to variability in the quality of the recombinant protein [1].

Throughout the product life cycle of an approved biological molecule, a manufacturer may implement process changes to incorporate technological advances or efficiencies. Regulatory agencies evaluate these changes carefully and use scientific comparability criteria to determine whether there is a potential impact on the safety or efficacy that underlies its approval. The evolution of the changes introduced by the manufacturer follows a comparability exercise between the pre- and post-change product; and depending on the nature and extent of the manufacturing change, routine control measures and analytical tests may not be sufficient to assess the impact of the change on a product's quality, safety and efficacy; this may necessitate non-clinical and clinical evaluations [2].

Until the mid-1990s, manufacturers of innovative biological products faced significant regulatory hurdles in making changes to their own manufacturing processes. But, in 1996, the US Food and Drug Administration (FDA) changed the paradigm for conducting comparability assessments of biological products in order to facilitate this approach. The agency's justification for an increase in regulatory flexibility was based on recognition of the advances in analytical methodology and, perhaps more important, on the reasoning that 'knowledge of the process involved in the manufacture of the product is an integral component in determining the design of an appropriate comparability assessment program' [3].

The evolution of the regulations in Europe was certainly different from those of FDA. In 2001, the European Medicines Agency (EMA) established a comparability approach with the adoption of the Committee for Proprietary Medicinal Products (CPMP) by the 'Guideline on comparability of medicinal products containing biotechnology-derived protein as active substances' [4]. This guidance focused on comparability in the context of a change in the manufacturing process of a given product, but also, at the same time, on 'comparability exercise' that would need to be conducted to support an application for a product claimed to be similar to an already marketed product, with the recommendation that, in this latter case, additional preclinical and clinical studies (potentially a full data package) would be required. However, no 'essentially similar' product was approved based on this guidance, until, in 2005, a new independent pathway for the approval of 'biosimilars medicinal products' was introduced [5].

Later, other regulatory bodies provided analogous guidelines, culminating in the International Conference on Harmonization Comparability Guidance ICH Q5E, which acknowledges that

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'the demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product'. Currently, the principles of the comparability exercise established on ICH Q5E are recognized by regulatory authorities throughout the world [6].

In addition to the changes that manufacturers usually implement in manufacturing processes of an approved biological for a variety of reasons (including the need to comply with regulatory commitments, improve product quality and yield, and improve manufacturing efficiency and reliability), the technology transfer between different manufacturers is considered another potential scenario where comparability exercise would be performed. In this scenario, the company that developed the innovator product transfers the know-how and the full history of the manufacturing process to another manufacturer, similar to when a company opens its own second manufacturing site. All the information regarding critical quality attributes (CQAs), raw material, excipient suppliers, purification, formulation studies, containers, stability data, analytical methods, and product packaging would be available for consideration by the other manufacturer. Access to the full range of innovator manufacturing information fundamentally distinguishes this comparability approach from the situation facing the biosimilar product manufacturer [7].

Comparability versus biosimilarity

A biosimilar is a biopharmaceutical that has demonstrated similar CQAs, biological function, clinical efficacy and safety to that of an already licensed biological reference product. Then, biosimilarity must first be proved in an extensive analytical comparability exercise, systematically evaluating the quality and similarity of the biosimilar product and the originator product across dozens of physicochemical, biological and pharmacological CQAs, before establishing equivalence in clinical efficacy and safety [8].

Therefore, the scientific principles to establish the impact of a change in manufacturing process of a biological product (comparability) and those necessary to the generation of a biosimilar taking an innovator biological as a reference product (biosimilarity) are not the same. The potential for differences between an innovator biological and a biosimilar is greater than that between a biological before and after a manufacturing change [9].

The comparability practice as described within ICH Q5E applies to a single product before and after process changes within a single manufacturer. ICH Q5E would not sufficiently cover differences in the manufacturing process of the biosimilar compared to that of the reference product including expression system, recombinant DNA plasmid, fermentation system, control strategy, and purification process, process-related and product-related, formulation, container-closures system, drug product manufacturing and storage [10, 11].

The regulatory agency that most appropriately establishes the differences between biosimilarity and comparability is FDA in the 'Scientific considerations in demonstrating biosimilarity to a reference protein product; Guidance for industry', which states that: 'Demonstrating that a proposed product is biosimilar to a reference product typically will be more complex than assessing the comparability of a product before and after manufacturing changes made by the same manufacturer. Even though some of the scientific principles described in ICH Q5E may also apply in the demonstration of biosimilarity, in general, FDA anticipates that more data and information will be needed to establish biosimilarity than would be needed to establish that a manufacturer's post-manufacturing change product is comparable to the pre-manufacturing change product' [12].

By contrast, from 2003, EMA uses the term comparability when evaluating both inter- as well as intra-manufacturing changes and as the explicit basis for biosimilars development [4]. More recently, EMA has used the expression 'biosimilar comparability' to clarify the context but not to change the concept as a scientific matter. Furthermore, EMA considers that, with the extensive experience of regulators and sponsors in highly regulated markets, comparability is the universal standard for judging interchangeability of pre- and post-manufacturing changes of any biological. With the development of the biosimilar approval pathway, the scientific approach underlying interchangeability can be broadly applied to an originator product undergoing a manufacturing change or a biosimilar at initial approval or a biosimilar undergoing a manufacturing change [13].

On interchangeability, the US legislation is much stricter and more specific, and differs substantially from EMA's position. In 2019, FDA issued the guideline 'Considerations in demonstrating interchangeability with a reference product; Guidance for industry', in which it established that a biosimilar is not interchangeable with the innovative biological until the sponsor provides scientific and clinical evidence that supports such property of the biosimilar. In this guideline, FDA states that the term interchangeable or interchangeability means that the biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product. In this way, interchangeability is directly related to automatic substitution at the pharmacy level [14].

The interchangeability between innovator biological and biosimilar is not regulated in other countries of the world. However, it is an important scientific issue that is under constant debate.

Impact of drift, evolution and divergence on biosimilarity and interchangeability

Currently, one important question under debate is how to manage the oversight of a biosimilar if its reference product undergoes a change in its quality profile (or vice versa, if a biosimilar undergoes a change). In other words, is a biosimilar a 'biosimilar forever' or just a 'biosimilar for licensing purposes' that has a life cycle of its own after approval?

Biological product quality changes resulting from process variation may be unintended or intended. Unintended process

variation may occur owing to the impact of uncontrolled variables and can result in gradual changes over time or in a sudden shift in a quality attribute, a process called manufacturing drift. The source of the change may not be well understood and may be an unintended result of changes outside of the manufacturer's control [15].

As mentioned in the previous section, additional changes in product quality may be the result of intentional changes made by the manufacturers of biological medicines to the manufacturing process and can range from changes in manufacturing sites to changes in suppliers or cell culture media. Also, changes to a manufacturing process are sometimes made to introduce new technologies that can improve productivity. This type of change in the manufacturing process, called evolution, has been observed in most, if not all, approved biologicals on the market today since their initial approval [16].

Put together, normal variability, drift and evolution may present greater challenges when assessing biosimilars, and much more when they are evaluated as possible interchangeable products. Two products that were initially deemed biosimilar or interchangeable could each undergo unique patterns of drift and evolution, ultimately resulting in two products that are no longer biosimilar nor interchangeable. This process is defined as divergence [17].

Divergence is not just a hypothetical phenomenon. In some cases, divergence can occur for biologicals transferred between licensing partners, where the partners retain some right of reference to the originator's development data, and also divergence can certainly occur and is arguably more likely with completely independent entities that have no right of reference to proprietary information collected during development, such as biosimilars manufacturers.

The case of epoetin alfa is an example of both types of divergence. Epoetin alfa is manufactured by separate entities for the US, Japan and Europe. Subcutaneous administration of Eprex® (epoetin alfa) in patients with chronic kidney disease (CKD) was banned in Europe between 2002 and 2006 after increasing reports of anti-erythropoietin (EPO) antibody-mediated pure red cell aplasia (PRCA) [18]. An investigation revealed that the transient increase of anti-EPO antibody mediated PRCA was associated with a change in the formulation/composition of the product. More precisely, the excipient of the formulation, human serum albumin, was replaced with polysorbate-80. This route of administration was subsequently restored after the sponsor addressed the manufacturing issue. Meanwhile, the corresponding US product did not implement the formulation change and retained the original route of administration on its label. The reason for the increase in PRCA observed with Eprex® has been associated with safety issues become apparent only in the post-marketing setting when larger numbers of patients are being treated [19].

Currently, a wider group of innovator, biosimilar and second-generation epoetin products are available across different markets [20]. Epoetins are heavily glycosylated proteins. Glycosylation profile is a CQA of epoetins, as it has a crucial influence upon *in vivo* biological and clinical activity [21]. Marketing authorization of biosimilar epoetin alfa products, e.g. Binocrit® and Silapo®, by EMA was based upon detailed biosimilarity exercises with the innovator product, Eprex®. In a recent study, the glycosylation profiles of Eprex® and the two approved biosimilars Binocrit® and Silapo® were characterized and compared. The products exhibit notable differences in N- and O-glycosylation, including attributes, such as sialic acid occupation, O-acetylation, N-acetyllactosamine extended antennae and sulphated/penta-sialylated N-glycans, which have the potential to cause divergency. The study highlights the need for continued monitoring of epoetin glycosylation, ideally allied to pharmacological data, in order to ensure consistency and therapeutic equivalence between products over time. In a marketplace where multiple epoetins are available, there exists the potential for divergence of glycosylation profiles, and therefore therapeutic potencies. It was evidenced that, post-authorization product surveillance and life-cycle management of epoetin alfa biosimilars, which may involve process manufacturing changes, can occur independently of Eprex® and to produce divergence in their clinical performance [22].

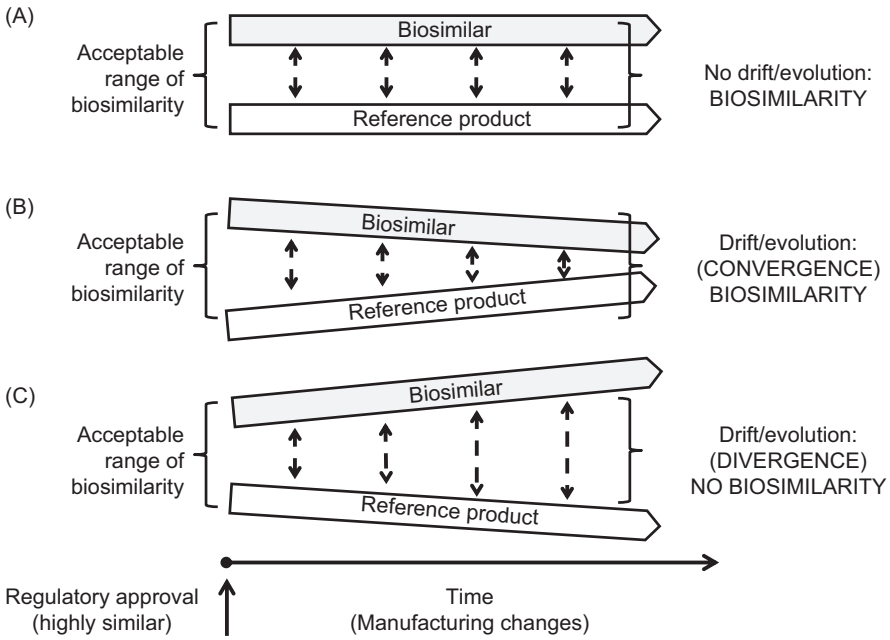
Regulatory controls are in place to ensure comparability of stand-alone biologicals before and after manufacturing changes. However, manufacturing changes to the biosimilar will not trigger repeated biosimilarity testing with the innovator; therefore, a standard of biosimilarity that is achieved at the time of approval of the biosimilar may not be maintained over time. Taking into account the possibility that divergence occurs, the similarity assessment should be an ongoing exercise that requires the biosimilar candidate to be assessed throughout the life cycle of the product. In addition to continuous biosimilarity, one important challenge for regulatory agencies is to demonstrate whether interchangeability is maintained in the longer term, particularly following changes to either the originator or (multiple) biosimilar product versions, see Figure 1 [6].

Biosimilarity is not a transitive property

The relationship between a given biosimilar product and its reference product is unique and not transitive to other biosimilars. This is a consequence of the fact that biosimilars are not structurally identical to their reference biological products or to each other. Although differences between a biosimilar and its reference product are evaluated for equivalent clinical effects during biosimilarity assessment, it is unlikely that potential differences between any two indirectly related biosimilars will be formally evaluated. Indeed, there is no regulatory requirement to ensure that all biosimilars of a particular reference biological differ in a similar qualitative manner or to the same extent. Furthermore, biosimilar pathways permit variations in pharmaceutical attributes, clinical development approaches, and regulatory outcomes, resulting in further diversity of attributes among approved biosimilars [23].

The more important implication of this diversity is that biosimilars should not be used in practice in the same manner as multiple-source generic drugs. By definition, a generic medicine is interchangeable. A prescriber need not select any particular version, i.e. they are prescribed by the International Nonproprietary Name (INN) or generic name, and substitution

Figure 1: Biosimilarity should not be forever



At the time of regulatory approval, a biosimilar and its reference product will be highly similar (otherwise approval would not be granted). Over time, independent manufacturing changes can occur (evolution or drift) in one or both manufacturing processes, with different consequences. In the hypothetical case that no change or drift in the manufacturing process has been verified (A) or they are convergent (B), the initial biosimilarity would not be affected. On the contrary, when these changes are divergent (C), the biosimilarity could be lost throughout the life cycle of the products. This last situation would have a direct impact on the efficacy and safety of the treatments, and an unpredictable outcome if these products are interchanged during a chronic treatment (dash arrows). As there are no requirements for comparative tests to be carried out after approval, this is difficult to measure or monitor.

among generic equivalents is commonly practiced at the pharmacy level without prescriber involvement [24]. Because biosimilars may vary across the ranges of structural and functional acceptance criteria, they should not be treated like multisource drugs and then none of the generic drug practices are advisable for biosimilars. Rather, once approved, they should be considered as individual therapeutic alternatives, stand-alone products, with all of the associated regulatory requirements. In practice, and in the context of multiple biosimilar versions of a single biological reference product, this means that biosimilars should be prescribed and tracked in medical records by a unique name, and clinicians should be involved in decisions to switch patients from one biological to another, particularly when a given biosimilar has not been qualified as interchangeable with the prescribed biological.

As was described above, uncorrected manufacturing process drift and/or evolution of one or both products, originator and biosimilar, could result in product divergence, and this divergence can occur between an originator and a biosimilar and between multiple biosimilar products. Divergence should not lead to a change in the safety or efficacy of each single product, originator and biosimilar(s), but could potentially result in clinically meaningful differences, e.g. potency, safety, or immunogenicity profile, during a chronic treatment interchanging biological. In cases where divergence may be present, care should be taken with multiple switches: each time a switch occurs, the difference between products will be greater. The most relevant cases may be divergence in potency (although both approved products are still effective, switching between them could cause a disruption in dosing), and divergence in immunogenicity profile (a patient could be exposed to one less immunogenic product and then be switched to the more immunogenic product) [25].

Concluding remarks

Three dynamic actions could be taken by regulatory agencies in order to control, at least partially, the clinical impact of divergence between innovator biologicals and biosimilars:

(1) Strengthen pharmacovigilance systems

Pharmacovigilance is especially important for biologicals because of their susceptibility to changes in the manufacturing process and the possibility that drift, evolution, or divergence may have adverse consequences for patients. A robust, product-specific pharmacovigilance system for biologicals may require special policy measures such as mandatory use of distinguishable names for prescribing.

(2) Determine interchangeability standards

Currently, only FDA has established the scientific basis to determine if a biosimilar should be deemed interchangeable with an innovator biological [14]. However, no regulatory mechanisms are currently in place to ensure continued interchangeability in the event of product drift, evolution or divergence. Thus, products that were interchangeable at the time of approval might continue to be considered interchangeable by regulators even though the quality attributes of the originator and biosimilar products have diverged.

(3) Establish the differences between comparability and biosimilarity

The impact of a particular change and any product evolution can be readily evaluated by comparability exercise. To the contrary, in biosimilar development, almost every aspect of the manufacturing process may have changed, and the only point of reference is the reference drug product. As biological manufacturers do not have access to the originator manufacturing process as a point of reference, comparing the biosimilar product to the reference product (biosimilarity) is necessarily a more complex process.

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