The constrained prescription, interchangeability and substitution of biosimilars

To the editor:

The requirement for a Marketing Authorization of a biosimilar medicinal product includes demonstration of its similar nature to the originator product in terms of quality, efficacy and safety[1]. Biosimilarity is demonstrated through an in-depth comparison of physical chemical and *in vitro* biological characteristics and comparative non-clinical and clinical studies, which together are named the 'comparability exercise'[2,3].

Weak points of this approach are the debatable potency of comparability studies and the lack of a scientific and robust approach to set the equivalence margins[4]. This uncertainty is reinforced by the manufacturing changes made by makers of originators and biosimilars during development and approval of the medicinal product. This result is an evolving quality profile that makes the conclusions of a comparability exercise only valid for a given time, whereas the goal should be to show similarity for the whole life cycle of the product. As a consequence, the issue of therapeutic equivalence is not easily addressed, and possibly should not end with the marketing authorization but should, rather, be managed for the entire life cycle of the medicinal product[5,6].

The assessment of therapeutical equivalence carries important consequences for how a medicinal product is managed, particularly concerning the choice of the prescribing physician and the possibility of intervention by pharmacists at the dispensing level. The management of medicinal products depends on global and local policies on interchangeability and substitution. The clear distinction between these two concepts is necessary, as tasks and responsibilities fall to different authorities.

Interchangeability is a scientific concept, which follows from therapeutic equivalence and is related to intrinsic drug characteristics. As such, its assessment requires the scientific knowledge that, at the institutional level, only agencies granting marketing authorization have.

Section 351 of the US Public Health Service (PHS) Act, as amended by the Biologics Price Competition and Innovation (BPCI) Act of 2009, explicitly addresses the issue of interchangeability (for proteins and peptides over 40 amino acids), stating that the conditions for a biological product to be interchangeable with the originator are that the product is shown to be biosimilar to the reference product, and that it can be expected to produce the same clinical result as the reference product in any given patient. Moreover, the BPCI Act requires that "for a biological product that is

administered more than once to an individual the risk, in terms of safety or diminished efficacy, of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch"[7]. Even though the US Food and Drug Administration (FDA) considers the possibility of demonstrating interchangeability between biological products, establishing interchangeability in a 351(k) application is difficult from a scientific viewpoint[8].

In Europe, biotechnological medicinal products are regulated by Regulation EC No. 726/2004, issued by the European Parliament in 2004[9]. The legal basis for biosimilars was established by an EU directive, which lays down the requirements for the marketing authorization applications on the basis of the demonstration of the similar nature of two biological medicinal products. The authorization process for biosimilars of polypeptide-based and protein-based products is the same and it differs from the route of generics. Regulatory policy for biosimilars is governed mainly by the European Medicines Agency (EMA), through general guidelines addressing quality, nonclinical and clinical issues as well as additional product class-specific guidelines[10]. Unlike the situation in the United States, where the FDA provides guidance on interchangeability, the EMA leaves the decision about interchangeability to individual member states.

The term 'substitution' requires further explanation, as it has different meanings in different contexts. We use it here to indicate automatic substitution at the dispensing level, without the physician's explicit prior consent. In the case of generics, automatic substitution is generally accepted. In the case of biological medicinal products, however, substitution is a debatable practice because it may lead to difficulties in traceability and may compromise pharmacovigilance. The term substitution is also used to indicate the prescription of a biosimilar to drug-naive patients (called primary substitution), or every switch between two medicinal products (called secondary substitution) by the prescribing physician. Because the prescriber's choice in these two cases is not limited to interchangeable products, we feel that the use of the term substitution should not be used even when, owning to the payer's policies, physicians may be forced to prescribe a biosimilar instead of the innovator product.

Automatic substitution can be introduced by local authorities on the basis of interchangeability and is based on administrative procedures implemented differently in different jurisdictions. In addition to addressing the issue of interchangeability, the FDA has considered "means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product"[11] if the products are designated as interchangeable in accordance with the PHS Act definition of interchangeability. In

the European Union, many countries do not allow automatic substitution at the dispensing level. In France and Spain it is explicitly prohibited[12].

Having clarified the distinction between interchangeability and substitution, and the different responsibilities of central regulatory agencies and local authorities, we feel that EMA, whose mission is to provide the "Member States and the institutions of the EU the best-possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products"[13], is the only European institution to bring together the scientific competence needed in the assessment of interchangeability of biotechnological medicinal products.

In the United States, the FDA considers the issue of interchangeability. In Europe, EMA should do the same. Only after the regulatory agencies have assessed interchangeability should individual member states allow substitution with the aim of cost saving. If local health authorities choose to adopt this practice, they should also have to guarantee traceability of the administered medicinal product and allow physicians to monitor which medicinal product has been dispensed to their patients. In our view, when the prescription of a biosimilar arises from payer's policies, it is not substitution in the proper sense, and, if it constitutes an administrative limit to the prescriber's freedom, it should have a different name, such as a 'constrained prescription'.

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