The biosimilar medicines **decalogue**

BioSim

Spanish Biosimilar Medicines Association

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1 Biosimilar

A biosimilar medicine (or similar biological medicine) is a biological medicine that contains a version of the active substance of an original biological product (reference product) for which equivalence has been demonstrated. The biosimilar medicine is approved for all, or some of the indications of the reference product, and its posology and route of administration must be the same. Equivalence with the reference product must be established by means of an exhaustive "comparability exercise". The object of this exercise is to demonstrate that the slight physicochemical differences that exist between the two products have no significant impact on the quality, efficacy and safety of the biosimilar, implying that the active substance of both medicinal products is essentially the same. A physicochemical variability with no therapeutic impact is inherent to biologically sourced products, and is identifiable occasionally between batches of medicines subject to manufacturing changes, whether originators or not.

2 Biological medicine / Biotech medicine

A biosimilar medicine is a biological medicine (or biomedicine); i.e. a medicine that contains an active substance of biological origin. As such, it is produced in a living organism by a procedure equivalent to that of any biological product, and with the same quality criteria. Its biological origin, and consequently, its structural and functional complexity, distinguishes it from medicines obtained by means of chemical synthesis (or "small molecules"). When a prior manipulation of the biological source (typically a genetic modification) is applied in the manufacture of a biological medicine, it is a medicinal product derived from a biotechnological process, or a biotech medicine.

3 Comparability exercise

A Comparability exercise refers to the studies needed to ascertain the equivalence between biological medicines; whether these are batches of a given biological medicine, or a biosimilar candidate versus an original product. The biosimilar development requires an extensive and stringent head-to-head comparison to verify the equivalence between the biosimilar candidate and the reference medicine. This exercise generally encompasses from an exhaustive evaluation of the degree of structural and functional analogy as the fundamental support for biosimilarity to confirmatory clinical trials in patients.

4 EMA guarantee

The European Medicines Agency (EMA), the agency responsible for issuing a report as regards the simultaneous marketing authorisation in all countries of the European Economic Area (EEA), paved the way in creating a regulatory framework for the development of biosimilars. The criteria of this framework were later reproduced almost literally by the World Health Organisation (WHO), and adopted by reference regulatory agencies (the United States' FDA, and the Canadian, Japanese and Australian agencies). The EMA experts that evaluate the dossiers of original biological medicinal products also assess biosimilar candidates, and apply the same criteria with respect to the level of risk-to-benefit balance considered acceptable.

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5 Extrapolation

The European Medicines Agency (EMA) and the other reference regulatory agencies, on occasion, and according to strict scientific criteria, extend the safety and efficacy data to a disease, or a patient population, different from that, or those, studied during clinical development. This principle, called extrapolation, has been applied to original biological products; for example in cases where an application for an innovative formulation has been evaluated by means of comparative studies. This is equally applicable to biosimilar medicines. These may thus be authorised with an equivalent guarantee for certain indications of the original, based on the "Totality of Evidence", which includes; (1) the result of the quality, pre-clinical and pharmacokinetic comparability exercise, (2) the accumulated knowledge of the risk-to-benefit balance, and the pharmacological characteristics of the original reference product with which it is compared, and (3) the extrapolation of equivalence in efficacy and/or safety demonstrated in the studied disease, or diseases.

6 Therapeutic interchange

Prescribing physicians on occasion change a biological treatment in a given patient for an analogous treatment, for clinical or other reasons. This practice, known as interchange, is frequently applied to original biological products, without any specific harmful effects having been identified. It is therefore considered that the reciprocal interchange between two products that have been shown to be comparable under a stringent exercise, such as a biosimilar and its corresponding original reference product, should not be associated with a significant clinical risk. Nonetheless, it is the prescribing physician who, in the light of the evidence, should decide whether to interchange, or not, both products.

7 Substitution / "Non-substitution" policy

Substitution is understood as the practice whereby the pharmacist dispenses a medicinal product different from that prescribed by the physician without his/her knowledge. In Spain, in retail (community) pharmacies, the law does not permit the substitution of a medicinal product of biological origin for another, no matter which one is prescribed, the original or the biosimilar.

8 Immunogenicity

Immunogenicity refers to the immunogenic property of a medicine; that is, the tendency of a medicine to induce an immune response against itself. Except in the case of vaccines, this is an unwanted phenomenon, fundamentally attributed to biological medicines. The immune response against a medicinal product may or may not have clinical implications. Consequently, the European Medicines Agency (EMA) requests that pharmaceutical companies that develop biological products, whether original or biosimilar, conduct extensive immunogenicity studies during product development. Furthermore, the marketing authorisation holder (MAH) must incorporate an explicit proposal in the Risk Management Plan for the vigilance and evaluation of possible immunogenicity and its consequences once the product has been marketed.

9 Traceability and experience

Prescription by brand name, and the recording of the same and of the batch number in the pharmaceutical dispensing, are sufficient to guarantee the traceability of the biological medicine administered at any time to any given patient. Spain, and in general all countries within the jurisdiction of the European Medicines Agency (EMA), has implemented a rigorous pharmacovigilance plan. Accordingly, it can be stated that since the first biosimilar was launched in 2006, no increase in side effects or clinical consequences relating to immunogenicity has been reported. In other words, there is no medical evidence of any particular therapeutic risk attributable to biosimilars.

10 Patient accessibility and sustainability

The incorporation of biosimilar medicinal products into healthcare systems means that a greater number of patients can benefit from biological treatments. In certain cases this has also facilitated the optimisation of therapeutic protocols. By promoting competition in the pharmaceutical market, biosimilar medicines contribute to the economic sustainability of national healthcare systems, and provide an incentive to research into new products. Both facts reinforce the guarantee of quality healthcare coverage for future generations of patients.

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