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Position paper of the Italian Society of Rheumatology on the Prescription of Biosimilars

The expiry of patent protection leaves the therapeutic field open to medications the so-called "biosimilars", medicines that are similar to the original brand biological drugs, which can be produced by the pharmaceutical industry according to procedures and standards laid down by specific European guidelines and marketed at lower prices with respect to the original products. Biosimilars are biological drugs authorized by the European Medicines Agency (EMA) and are similar to the brand biological product in terms of quality, efficacy and safety.

According to the definition of biologic medicinal products produced by the EMA, "a biological product is one that contains one or more active substances derived from a biological source." **Biological medicinal products**, also known as biotechnological products, that is, obtained with biotechnology, are, therefore, drugs whose active ingredient is represented by a substance produced by or extracted from a biological system (such products are sometimes called biological medicines in the strict sense of the term) or derived from a biological source through procedures of biotechnology, including the technology of recombinant DNA, the controlled expression of protein encoding genes that are biologically active in prokaryotes or in eukaryotes, methods based on hybridoma and monoclonal antibodies (Doc. Ref. EMEA / 74562/2006 Rev1). They belong to the category of biologics products such as hormones and enzymes, blood and immunological products such as serums and vaccines, immunoglobulins and allergens, or monoclonal antibodies. Medicinal products synthesized by means of biotechnology differ from active substances synthesized by traditional medicinal chemistry methods in many aspects, including, for example,

molecular size, structural complexity, the stability of the final product and the possibility of different significant co- and post-transcriptional modifications (*e.g*. glycosylation). Moreover, while traditional drugs consisting of small molecules are produced by chemical synthesis, most biological drugs, given that they are produced by biotechnology that operates on living systems (micro-organisms or animal cells), have numerous aspects of heterogeneity related to the host cell used, the plasmids used to transfect the host cell and, therefore, transfer the gene needed to induce the expression of protein desired, as well as the conditions of growth and fermentation, and the different methods of purification. All of these materials and procedures introduce elements of differentiation and are not readily transferable from one laboratory to another, thus determining the uniqueness of the product. The production process of such drugs is so characteristic that it can be said that "the product is the production process" (1).

The molecular structure and the production process of biologicals play an important role in determining the immunogenic potential of these medicines. In fact, another key feature of biologicals products is their immunogenicity, defined as the ability to induce an immune reaction in the body: these molecules can potentially be recognized as "*non-self*" by the body of the patient and be, in some cases, neutralized in their effect, thus reducing the efficacy of the therapy. In the case of vaccines, the immunogenicity constitutes, on the contrary, the basis of the therapeutic strategy, inducing an immune response aimed at recognizing and combatting the substance the vaccine is directed at. Most unwanted immune responses induced by the immunogenicity of biological products are moderate and do not produce negative effects in the patient. In rare cases, however, immune responses can occur that lead to a serious detriment effects on the health and safety of the patient.

The term "biosimilar" denotes a drug similar to a reference biological product already authorized in the European Union and for which patent protection has expired (2). In particular, the concept of "similar biological medicinal product" was introduced into EU legislation by Directive 2001/83 / EC (3), and subsequently amended in Article 10 (4) which has provided an implicit definition of biosimilar products, then transposed into Italian law by Legislative Decree n.219 / 2006 Article 10 point 7, as follows: "When a biological medicinal product similar to a reference biological product does not meet the conditions of the definition of generic medicinal products due to, in particular,

differences relating to the raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the applicant is required to provide the results of appropriate pre-clinical tests or clinical trials relating to these conditions. *The additional data that needs to be provided fulfill the relevant criteria in the technical annex on the application for marketing authorization (AIC) and the relevant guidelines. It is not necessary to provide the results of other tests and trials contained in the dossier of the reference medicinal product. If the results presented are not considered sufficient to guarantee the equivalence of the biogeneric, or biosimilar to the reference biological product an application must be presented in compliance with all the requirements of Article 8."*(4).

In September 2012 the EMA issued a document providing the following definition:

*"*The term "biosimilar" denotes a drug developed in order to be similar to a biological drug that has already been authorized (the so-called "reference drug"). *The biosimilar medicines, therefore, differ from generic drugs that have simpler chemical structures and are considered identical to their reference drug. The active ingredient of a biosimilar drug and that of its reference drug are in fact the same biological substance, however, they may present minor differences because of their complex nature and to production techniques. As the reference medicine, the biosimilar has a certain degree of natural variability. A biosimilar is approved when it has been demonstrated that this natural variability and any differences there may be with respect to the reference drug do not affect its safety or efficacy.*" (5).

As required by law and in order to provide guidance to the pharmaceutical industries, the European Medicines Agency (EMA) published *Concept Papers* and Guidelines (May 1, 2015), both general ones for biosimilar products, and specific CTD (Common Technical Document) module (concerning specific aspects of the demonstration of biosimilarity in relation to parameters of quality, in clinical trials and pharmacokinetics and pharmacodynamics), and specific to each category of biosimilars (*e.g*. erythropoietin, growth hormone, G-CSF, monoclonal antibodies, etc.). These guidelines are reviewed regularly to take into account the experience acquired through the approval procedures of biosimilar products already registered and in consideration of developments in science and technology (2). The legislation requires that the research and

development program is aimed at demonstrating the "biosimilarity", meaning comparability between a biosimilar and its reference drug, through "**the comparability exercise**", which is a series of gradual comparison procedures (*stepwise*) beginning with quality studies (physicochemical and biological comparability), and then going on to the evaluation of non-clinical comparability (non-comparative clinical studies) and clinical (comparative clinical trials) to evaluate efficacy and safety, including the immunogenicity study. The primary objective of the comparability exercise is the demonstration of similarity ("*similarity throughout"*), through studies designed to identify any possible differences in quality between the biosimilar and the reference drug, and ensure that these do not result in relevant clinical differences between the two products in terms of safety and efficacy. In quality studies, comparability is determined with reference to the molecular structure and it must be proven by a full analytical characterization, studies of receptor binding (if applicable), *biotests* and appropriate studies on animals, all of which must be carried out in a strictly comparative way between the biosimilar and the reference drug. The pre-clinical and clinical comparability exercise is carried out through specific controlled evaluation studies of the toxicological properties, the pharmacokinetic and pharmacodynamic profile, and clinical safety and efficacy. The comparability exercise is therefore based on a sound "head to head" comparison between the biosimilar and the reference drug according to specific standards of quality, safety and efficacy, having defined a priori the differences that are acceptable because they are not clinically relevant.

Biological drugs are often approved for several indications. The extrapolation of indications has been recognized by the EMA, which states that: "*In the case in which the originator drug is approved for more than one indication, the efficacy and safety of the biosimilar must be confirmed or, if necessary, demonstrated separately for each indication. In some cases it may be possible to extrapolate the therapeutic similarity demonstrated in one indication to other indications approved for the reference drug. The justification for the extrapolation should take into account, for example, the clinical experience, the data available in the literature, the mechanism of action and of the receptors involved in the different indications. Any security issues in different subpopulations must also be investigated. In any case, the manufacturer must justify the approach used during*

product development by consulting the EMA for clarification of a scientific and regulatory nature before starting the development program "(EMEA/CHMP/BMWP/42832/2005).

Biosimilars as an alternative to originator products: the question of substitutability

The subject of substitutability, which characterizes the world of generic drugs, is an important aspect for the success of biosimilar drugs. Before dealing with the issue of substitutability in detail it is necessary to clarify the concepts of interchangeability and substitutability. Regarding the concept of **interchangeability** with reference to medical practice, the following definitions are given:

• According to the WHO definition, it is an interchangeable pharmaceutical product: "*a product that is expected to have the same clinical effect as the comparator product and can replace it in clinical practice*" (6).

• Interchangeability refers to the medical practice of replacing one drug with another equivalent one in a given clinical context on the initiative or with the agreement of the prescribing physician (7).

• Interchangeability refers to the medical practice of replacing one drug with another that has the same benefit-risk profile and is expected to have the same clinical effect in a given clinical context on the initiative or with the agreement of the prescribing physician (8).

On the contrary, exclusively in the USA, the terms "interchangeable" or "interchangeability", with reference to a biological product, indicate that "*the biosimilar product may be substituted for the reference product without the intervention of the physician who prescribed the latter*" (9). In this context, the definition of interchangeability of a biosimilar compared to the reference product is established by a committee of the FDA based on the documentation that must be submitted in response to specific criteria defined in advance. Then, once the biosimilar product has been defined interchangeable, a decision on replacement is not required by the physician in the individual case.

Substitutability, on the other hand, refers to the practice of replacing a drug with another drug, often at a lower cost for the Health Service or for the patient, which has the same qualitative and quantitative composition of active substances, the same pharmaceutical form and route of

administration and is bioequivalent to the reference medicine on the basis of appropriate bioavailability studies. **Automatic substitutability** (equivalents) by pharmacists refers to the practice by which the pharmacist may, or must, in accordance with national or local regulations, dispense a drug equivalent and interchangeable instead of the prescribed medicine, without consulting the prescriber. Finally, as regards substitutability, these differences should be noted:

- **primary substitutability** refers to the medical practice of beginning a new treatment with a biosimilar product (or an equivalent) rather than with the originator reference product;

- **secondary substitutability**, on the other hand, refers to the medical practice and / or of the pharmacist of modifying the treatment of a patient already being treated with a biologic drug with its biosimilar.

Regarding the automatic substitution of biosimilars, European legislation has entrusted to the competent national authorities of the different Member States decision-making and legislative autonomy. However, the EMA has stated that the recommendations on the marketing of medicines does not take into consideration whether or not to use a biosimilar medicine interchangeably and that the decision about the choice of prescribing a particular drug to be used, rather than reference biosimilar, must be entrusted to qualified health workers (10). In Italy, the AIFA makes it clear that biological medicines and biosimilars can not be considered purely and simply the same as equivalent products, and thus excludes the mutual automatic substitutive therapy. It is exactly because biological reference medicines and biosimilars are similar, but not identical, that the AIFA has decided not to include biosimilars in the transparency lists that allow for the automatic substitution of equivalent products. Consequently, the choice of treatment with a biological reference drug or with a biosimilar remains a clinical decision entrusted to the specialist prescribing physician. However, the AIFA considers that biosimilars are not only a therapeutic option available to the GP, but are to be preferred, if it entails an economic advantage, in particular for the treatment of the "*naive*" subjects (those who have not had previous therapeutic treatment or for whom the previous treatment is considered by the clinician to have been carried out a sufficiently long time ago).

In conclusion, the AIFA **recommends the use of biosimilars only in patients who are to start a new treatment**. Currently, there is an ongoing public consultation to update the position paper,

but in accordance with the concept of biosimilarity expressed by the EMA, the principle is emphasized of the central role of the prescriber in choosing between a biological originator and the corresponding biosimilar products, confirming what has already been established by the Agency, also in relation to the **non-automatic substitution by the pharmacist**.

The European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) **do not recommend a shift in the course of therapy with biologics**, and the same position has been taken up by the Italian Society of Rheumatology (SIR).

In addition, rheumatologists **recommend particular caution in the use of biosimilars in children**, since children have different risk profiles and comorbidities with respect to adults and may have different side effects and clinical manifestations from adults.

The CHMP document of 27 June 2013 EMA/CHMP/589422/2013 points out for Inflectra CT-P13, biosimilar infliximab, differences with regard to alpha-fucosylation and different antibody-dependent cytotoxicity (ADCC). As regards the production line, the murine myeloma cells used for infliximab are Sp2 / 0, while CT-P13 Sp2 / 0-Ag-14 for Inflectra.

Resolution 450 of April 7, 2015 of the Tuscany Region on the objectives of Prescriptive Appropriateness foresees the following for Biological Drugs: "*limited to internal use of the Regional Health Service, in the presence of the same drug marketed by two or more pharmaceutical companies, ESTAR is to provide the sample collection centers that request it with the product that was adjudicated in the public purchase procedure.*
With regard to these requests for internal use, should the person in charge of the institute of reference of the sample collection unit considers that there are sound reasons to justify the use of a drug not accepted in the public purchase procedure, the same shall make a request for the specific product by completing a special report as required by the authorization procedure of the Health Department".
The subsequent **DETERMINATION OF AREA COORDINATOR # 724 of 06.05.2015** ESTARCC05 SUPPLIER OF CERTAIN ACTIVE INGREDIENTS REQUIRED BY HEALTH CARE SERVICES IN THE

TUSCANY REGION - LARGE AREAS CENTER, NORTH WEST, SOUTH EAST UP TO 10/31/2016, BY DYNAMIC PURCHASING SYSTEM - SDA - IN ACCORDANCE WITH ART. 60 OF LEGISLATIVE DECREE no. 163-2006. ADJUDICATION FOR THE PERIOD 05.06.2015 - 31.10.2016, whose subject is "Assistance interventions for drugs and medical devices for the year 2015", in paragraph 19 (Requirements for Biological Drugs) recalls the obligation of ESTAR to supply to the sample collection centers that request it" the product that was adjudicated in the public purchase procedure", with the provision, however, of processing requests, provided duly substantiated for the supply of drugs other than the one chosen in cases of prescription and/or issue of therapeutic programs.

The Italian Society of Rheumatology in the two position papers published (11-12) declares that the biosimilar infliximab should be used only in the indication for which the drug has been tested in clinical trials (13) of comparability with respect to infliximab and that extension to other diseases such as axial spondyloarthritis, enteropathic and psoriatic arthropathy should be validated by clinical trials.

Moreover, according to EMA / AIFA, the SIR recommends the use of biosimilars in naive patients and agrees to avoid substituting infliximab for biosimilar infliximab and vice versa. In addition, it calls for adequate tracking, evaluation and close monitoring of adverse events and proper monitoring of immunogenicity.

Judicial precedents

The **Tar** (Regional Admistrative Court), in recalling the opinions of the scientific-academic community, and in particular of the National Institute of Health and the AIFA, stated the following principles in sentence no. 817 of 6 July 2011 (for the ruling on appeal, see. Cons. State, **n. 1297 of 7 March 2012**, which, however, merely stated the inadmissibility of the appeal due to lack of current interest):

Therapeutic equivalence of the drug compared to the biosimilar originator is disposed differently depending on whether it is a case of patients already being treated or "new" (drug-naive) patients. While **in the first case is necessary to ensure continuity of care**, in the second hypothesis, the Tar observed how "the scientific-academic world and, with it, the law that dealt with the problem, advocates in an almost univocal way for substantial equivalence when having to treat patients for the first time with the specific therapy". As stated in the aforementioned

sentence, "**in other words, precautions are necessary in the case of drug substitution of biological origin already in use, given the need to safeguard continuity of care**, while no need for specific caution has been found with regard to the first administration of the drug, when the originator drug or biosimilar are on the same level". With regard to the same concept of continuity of care it was also deliberated by the Court of Appeal Criminal Division sentence of 2 March 2011 no. 8254 (the physician must pursue one objective: the care of the sick, without being influenced by needs of a different nature because no one is allowed to give precedence to economic logic over the logic of health care) confirming the same principle.

Essential Bibliography

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8) Definizione EFPIA-EBE/EuropaBIO.

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