

**AIFA POSITION PAPER**

**BIOSIMILAR MEDICINAL PRODUCTS**

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# Premises

In view of the importance of biological medicinal products, including biosimilar products, for the treatment of numerous serious and potentially lethal pathologies, and for many of which no effective therapeutic treatment was hitherto available, the Agenzia Italiana del Farmaco (AIFA) [Medicines and Healthcare Products Regulatory Agency] considers it essential to release this document in order to promote the knowledge and use of biosimilar medicinal products and hence provide health operators and citizens with clear, transparent, sound, objective and authoritative information on the following questions:

* Definition and principal characterizing criteria of biological and biosimilar medicinal products;
* Classification of regulatory laws in force in the EU on biosimilar medicinal products;
* Role played by biosimilar medicinal products in the NHS's economic sustainability

# Introduction

Biotechnological techniques have made it possible to develop therapies for a large number of clinically and epidemiologically serious diseases, which now represent fundamental solutions for the population's increasing health demand. At present, millions of patients worldwide are benefitting from biological medicinal products approved for the treatment or prevention of many illnesses such as, for example, cancer or inflammatory, autoimmune, neurological and degenerative diseases.

Biotechnologically derived therapies are the product of enormous investments and effort at all stages of their development, from the initial research phases to sophisticated production processes, market entry and dispensing cures. However, such costs pose a significant problem in terms of economic sustainability as concerns the identification and definition of the best allocation of available resources. However, if on the one hand, there are a large number of biotechnological medicinal products in phase of clinical development, on the other, the first generation of biological medicinal products has already reached or is reaching patent expiration. In fact, the loss of patent protection allows the so-called **"biosimilar products"** to enter the therapeutic stage: i.e. products that are similar to expired-patent innovator biological products and that can be produced by pharmaceutical industries on the basis of procedures and rules laid down by specific European guidelines and marketed at prices lower than their reference biological products. Therefore, biosimilar are biological medicinal products authorized by the *European Medicines Agency* – EMA, and similar in terms of quality, effectiveness and safety to the reference biological product. The availability of biosimilars represents an important factor for maintaining the economic sustainability of healthcare services in the near future.

# Biologically derived medicinal products

According to the definition of biological medicinal products produced by EMA, "a biological medicinal product contains one or more active principles derived from a biological source. Some of these active principles may already be present in the human organism, for example proteins such as insulin, the growth hormone and erythropoietin. Biological medicinal products are also larger and more complex molecules than non-biological medicinal products. Only living organisms are capable of reproducing such complexity” (EMA/837505/2011).

**Biological medicinal products**, also including biotechnological products i.e. products obtained through biotechnologies, are, therefore, medicines whose active principle is represented by a substance produced or extracted from a biological system (such products are, in their turn, defined as biological medicinal products, in the strict sense of the term) or a substance derived from a biological source through biotechnological procedures including recombinant DNA technologies, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes, hybridoma and monoclonal antibody methods (or biotechnological products) [Document Ref. EMEA/74562/2006 Rev. 1]. Products such as hormones and enzymes, blood derived products and immunological medicines such as serums and vaccines, immunoglobulins and allergens or monoclonal antibody belong to the category of biological medicinal products.

Medicinal products synthesized by biotechnological methods differ in many respects from active principles synthesized by traditional chemical pharmaceutical methods: i.e. molecular size, structural complexity, the stability of the final product and the possibility of various significant co- and post-translational modifications (for example, in the glycosylation profile). In addition, while traditional medicinal products, characterized by having small molecules, are produced through chemical synthesis, the greater part of biological medicinal products, because produced using biotechnologies that operate on living systems (micro organisms or animal cells) acquire very heterogeneous features as a consequence of the host cell used, the plasmids deployed for transfecting the host cell and transferring the gene needed to produce the protein required, as well as growth and fermentation conditions and different purification methods. All these materials and procedures introduce elements of differentiation, and as they are not immediately transferable from one laboratory to another they contribute towards the determination of the product’s uniqueness. The production process of these medicinal products is so highly distinctive that it can be said that "the product is the production process" (Karson KL., Nature Biotecnol, 2005).

The molecular structure and the production process of biological products play an important role in determining their immunogenetic potential. In point of fact, an additional and fundamental characteristic of biological products is their immunogenicity, defined as the capacity to induce an immune response in an organism. These molecules possess the potentiality of being recognized as “*non-self*” by the patient's organism and, in some cases, can be neutralized by their own effect, thereby diminishing a therapy’s effectiveness. In the case, for example, of vaccines immunogenicity, on the contrary, represents the basis of the therapeutic strategy by inducing an immune response in order to recognize and combat the substance for which the vaccine is designed. The larger part of undesired immune responses induced by the immunogenicity of biological products are moderate and do not produce negative effects in patients. In rare cases, however, immune responses may lead to serious noxious effects detrimental to a patient's health and safety.

The foregoing clearly illustrates that biological medicinal products, on account of the intrinsic variability of the molecule and the complexity of the production techniques, are extremely difficult to characterize and reproduce. So much so, in fact, that some differences may exist as between the various batches of the same product, especially if changes take place in production conditions. Therefore, for their characterization as also for the quality and safety controls upon them, the regulatory authorities require not only biological physical and chemical examinations but also specific data on the production process and the immunogenetic potential and safety problems that may derive from it. In addition, they also carry out rigorous controls to guarantee that every process of the production and distribution phase of these medicinal products is carried out in compliance with specific and mandatory guidelines.

# Biosimilar Medicinal Products

The term "biosimilar" is used to indicate a medicinal product similar to a reference biological product whose use is already authorized within the European Union and for which patents have already been taken out.

In particular, the concept of a "similar biological medicinal product" was introduced into the European Union's legislation by directive 2001/83/EC and successive amendments[[1]](#footnote-1). The implicit definition of a biosimilar product given under article 10 (4) of the foregoing directive was successively implemented into Italian law with legislative decree no 219/2006; under article 10 subparagraph 7, which reads as follows: "*Whenever a biological medicinal product similar to a reference biological medicinal product is unable to satisfy the conditions by which a generic medicinal product is defined on account, in particular, of differences referring to raw materials or differences in the production process of the biological medicinal product and reference biological product, the applicant is required to submit the results of appropriate preclinical tests or clinical trials regarding such conditions. The supplementary data to be provided must satisfy the pertinent criteria stated in the technical annex attached to the marketing authorization application and the relative guidelines. It is not necessary to provide the results of other tests and trials contained in the dossier on the reference medicinal product. If the results presented are not deemed sufficient to guarantee the equivalence of the biogeneric or biosimilar product with respect to the reference biological medicinal product, an application is submitted in compliance with all the requisites required by article 8.*”[[2]](#footnote-2)

In September 2012 EMA issued a document containing the following definition: *"A biosimilar medicinal product shall be understood to be a medicinal product developed in such a manner as to be similar to a biological medicinal product that has already been authorized (the so-called "reference medicinal product"). Biosimilar medicinal products, therefore, differ from generic medicinal products insofar as the latter have simpler chemical structures and may be deemed identical to their reference medicinal products. The active principles of a biosimilar and those of its reference medicinal product are made from the same biological substance but minor differences may also be present due to the complex nature of such active principles and the production techniques involved. As with the reference medicinal product a biosimilar is also characterized by a certain degree of natural variability. A biosimilar is approved whenever it can be demonstrated that this natural variability and any differences with respect to the reference medicinal product do not impact on its safety or effectiveness." (Questions and Answers on biosimilar medicines EMA/837805/2011 27 September 2012).* A biosimilar and its reference product as a result of being produced with different production arrangements are not identical but rather essentially similar in terms of quality, safety and effectiveness.

In conclusion, it should also be mentioned that in some cases a biosimilar may be derived from more innovative production processes with respect to those used for the reference product, and, consequently, the biosimilar may acquire properties in terms of quality, (for example in terms of impurities), that are actually better than the reference product.

# Current EU law on biosimilar medicinal products

European law provides the first example of the legal regulation of the biosimilar authorizing process. Thus, the World Health Organization (WHO ) and many countries throughout the world including the USA, Canada, Australia and Japan have based their own regulatory law upon EU law. All applications for marketing authorization in respect of biological medicinal products, including biosimilar applications, within the European Union are examined by EMA through a centralized procedure. Consequently, a marketing authorization issued by EMA is valid for all member states of the European Union. However, this procedure, first and foremost, requires that the reference product to which the marketing authorization application for a biosimilar refers be a medicinal product holding a marketing authorization issued by the European Union based on a complete registration dossier, pursuant to the provisions of article 8 of Directive 2001/83/EC.

As required by law and also for the purpose of providing guidelines to manufacturing industries, EMA published a Concept Paper together with a set of guidelines: general ones for biosimilar products, specific ones for the CTD (Common Technical Document) form (referring to specific aspects demonstrating biosimilarity with respect to parameters of quality, clinical and nonclinical studies), and additional specific guidelines for individual categories of biosimilar medicinal products (e.g. erythropoietins, growth hormones, G-CSF, monoclonal antibodies, etc. ). The guidelines are regularly updated in order to incorporate the experience acquired with the authorization procedures of biosimilar products already registered or undergoing registration, and to take account of developments in science and technology.

The various guidelines can be consulted on the specific page of the EMA's site at the following link: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\_content\_0004 08.jsp&mid=WC0b01ac058002958c&jsenabled=true

As the active principle of the biosimilar medicinal product is essentially similar but not identical to that of the reference biological medicinal product, the registration procedure for a biosimilar product is very different from that adopted for equivalent products of non-biological medicines, and for which it is generally sufficient to submit the results of bioequivalent studies (Directive 2003/63/EC, Ann I, P.II).

The law requires that the R&D program is designed to demonstrate "biosimilarity" understood as the comparability between a biosimilar and its reference product, through a "**comparability operation**", namely a set of stepwise procedures commencing from quality studies (physical, chemical and biological compatibility and continuing with the evaluation of nonclinical (comparative nonclinical studies) and clinical (comparative clinical trials) comparability in order to evaluate the effectiveness and safety of the product, including immunogenicity studies. The primary objective of the comparability operation is to demonstrate similarity through studies designed to identify any quality differences between the biosimilar and the reference product, and ensure that such differences do not translate into significant clinical differences in either safety or effectiveness as between the two products.

In product quality studies, comparability is established with reference to the molecular structure and must be demonstrated by a complete analytical characterization, receptor binding studies (if applicable), biotests and adequate studies on animals, which must be performed in a rigorously comparative manner between the biosimilar and the reference product. The preclinical and clinical comparability operation is carried out through specific control studies to evaluate toxicological properties, pharmacokinetic and pharmodynamic profiles, safety and clinical effectiveness.

Therefore, the comparability operation is based upon a robust head-to-head comparison between the biosimilar and the reference medicinal product according to specific standards of quality, safety and effectiveness and by having defined, a priori, differences that can be deemed acceptable insofar as not clinically relevant.

# Denomination and identification of biological medicinal products, including biosimilar products

In compliance with European law, all medicinal products holding marketing authorizations must bear a commercial denomination represented by an invented name, a brand, or by the denomination of the active principle[[3]](#footnote-3) followed by a brand name or by the name of the company holding the marketing authorization. Therefore, every biological medicinal product, including biosimilars, can be clearly identified by a unique denomination formally approved by EMA as part of the authorization process. The approved commercial denomination, together with the batch number, is important if the medicinal product is to be clearly identified for monitoring adverse reactions and collecting information on the product and hence guaranteeing traceability.

# Safety of biosimilar products

Biosimilar medicinal products must be produced according to the same qualitative standards as those required for other medicinal products (e.g. the products of reference chemical and biological synthesis). The manufacturers of biological and biosimilar medicinal products must, in compliance with law, put in place a pharmacovigilance system to monitor a product's safety. The pharmacovigilance system for such products, as for all medicinal products, is supervised by regulatory authorities that carry out periodic inspections on the product, the production facilities and the monitoring system at both the pre-marketing and post-marketing authorization phases. Each company is also required to submit a risk management plan when filing an application for marketing authorization (EU-RMP). This system must illustrate the risk management system in detail by describing the product's safety profile, taking due account of the safety profile known for the corresponding reference medicinal product, and set out the arrangements for the ongoing monitoring of the medicinal product’s safety and effectiveness by the manufacturer and the measures that the holders of the marketing authorization intent to introduce in order to prevent or minimize any possible risks during the medicinal product's use, including the measurement of effectiveness in clinical practice. Thus the EU-RMP of a biosimilar medicinal product is a specific risk management program that must be approved by the competent authorities prior to the marketing of the medicinal product. Every biosimilar product on the market has implemented an EU-RMP of which a summary is published in the European Public Assessment Report (EPAR).

The new law on pharmacovigilance (*Directive 2010/84/EU*) requires all medicinal products to use standardized wording in the product-characteristics summary and the package leaflet with which health operators and patients are urged to report any suspected adverse reaction *Adverse Drug Reaction* - ADR) in compliance with national systems for spontaneous reporting. As clear identification of the medicinal product is especially important in communicating ADRs on biological products, including biosimilars, European legislation requires the approved denomination of the product, and the batch number, be included in every ADR report.

Furthermore, the foregoing directive 2010/84/EU classifies biological and biosimilar medicinal products as "priorities" of pharmacomvigilance and requires them to be included in a special list of products subject to supplementary monitoring. In this sense, AIFA’s National Pharmacovigilance Network represents an essential tool for implementing recent European legislation as it increases transparency, and communication on the correct use of biological and biosimilar medicinal products and enhances trust between the institutions and the citizens.

In conclusion, Directive 2010/84/EU lays down that the release of a marketing authorization is conditional upon the performance of post-authorization safety (PASS) and/or effectiveness (PAES) studies. PASS studies set out to identify, characterize and quantify a safety risk or confirm a medicinal product's safety profile, or, alternatively, measure the effectiveness of risk management measures during the marketing of a medicinal product (immunogenicity phenomena are of special importance in this context as they represent an essential safety problem for any biological medicinal product and, as such, they are mandatorily managed in the EU-RMP). PAES studies, instead, are concerned with effectiveness evaluation whenever uncertainties exist with respect to some aspects of the product's effectiveness and which only can be clarified after marketing.

Directive 2010/84/EU can be consulted on the EMA's site at the following link: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\_listing/document\_li sting\_000199.jsp&mid=WC0b01ac05800250b3

# The extrapolation of therapeutic indications

Biological medicinal products are often authorized to be used for a number of therapeutic indications and the practice of extrapolating such indications has been accepted by EMA, which states that: "*In the event that a reference biological medicinal product is authorized for more than one indication, the effectiveness and safety of the biosimilar product must be confirmed or, if necessary, demonstrated separately for each single indication. In these cases it may be possible to extrapolate the therapeutic similarity demonstrated in an indication to other indications authorized for the reference medicinal product. The justification for extrapolation should take due account, for example, of clinical experience, data available in the literature, mechanisms of action and the receptors involved in the various indications. Any problems that emerge in different sub populations must also be investigated. In any case, the manufacturing company must justify the approach used during the development of the product by consulting EMA for any scientific and regulatory clarifications prior to the commencement of the development programme"*(EMEA/CHMP/BMWP/42832/2005).

The possibility of extrapolating a number of indications is always based upon the compatibility demonstrated between the biosimilar and the reference product with respect to standards of quality, safety and effectiveness in the specific indication as recorded for the approved reference product. Only after having demonstrated comparability in terms of quality and pre-clinical and clinical comparability, can a biosimilar product dossier be allowed to refer to clinical data obtained by the reference product and described in the literature and in the related dossiers.

It should also be emphasized that the Committee for Medicinal Products for Human Use (CHMP) of EMA lays down, on a case-by-case basis, if and when multiple indications can be extrapolated on the basis of scientific evidence obtained from a thorough comparability investigations, in conformity to appropriate scientific justifications.

# Utilization of biosimilars in the framework of law no 648/1996

In Italy law no 648/96 requires, inter-alia, that in the case of a pathology for which no valid alternative therapy is available, medicinal products authorized for another therapeutic indication may be supplied through the NHS (off-label use) for its treatment on condition that appropriate safety and effectiveness data are available from (at least) phase II clinical trials, subject to the prior opinion of the Scientific and Technical Consultative Commission (CTS) of AIFA.

The medicinal products on which the CTS expresses a favorable opinion are set out in a special list in accordance with the Directive dated 20 July 2000 "the institution of the list of medicinal specialties dispensed through the NHS pursuant to law no 648/96".

This measure specifies that the requisites for a medicinal product to be included in this list – as well as their provision through the NHS – require not only the absence of available alternative therapies, but also the availability of safety and effectiveness data gathered during, at least, phase II clinical trials.

Biological products can be dispensed for off-label uses but a biosimilar cannot be automatically added to this list, even if its reference biological medicinal product has been authorized for such uses and is included in the foregoing list. Instead, the CTS will determine – case by case – for what off-label uses the biosimilar can be used on the basis of the available evidence and literature, clinical experience and if possible tracing the therapeutic action to the same mechanism of action.

# Role of biosimilars in the Italian NHS

Biological medicinal products constitute an essential therapeutic resource for the treatment of a variety of serious and debilitating diseases for which no effective therapeutic options were hitherto available. On account of their high development and production costs, such products are particularly onerous for the NHS, and for which the correct allocation of therapeutic and economic resources is an ongoing challenge. In this scenario, biosimilar medicinal products play a fundamental role as they guarantee access to biological medicinal products for all patients that need them while, at the same time, contributing to the financial sustainability of healthcare systems. Thus, by giving biosimilars marketing authorization the access to medicines is improved in two ways: firstly, biosimilars – all things being equal – offset high-priced and less accessible biological medicinal products by virtue of their more sustainable and accessible prices, and stimulate competitive market mechanisms and hence price reductions; secondly, the savings obtained from the use of biosimilars can contribute towards the financing of new medicinal products, including biotechnological ones, thus making therapeutic innovation increasingly accessible.

The European market for biosimilars is important and expanding, not only for the manufacturers of these medicinal products but also for the health systems that sustain the costs of such products. Nevertheless, it should be noted that considerable differences exist between member states of the EU in terms not only of the frequency with which biosimilars are used but also of price fixing and regulation policies.

In Italy, identical pricing and reimbursement procedures exist for biological and biosimilar products and entail a negotiated pricing procedure conducted between AIFA and the manufacturer (CIPE resolution, 1 February 2001). In the case of biosimilars, where pricing procedure is analogous to that for generic or equivalent medicinal products, price negotiation centers upon obligatory price reductions of at least 20% with respect to that of the reference medicinal product.

# Biosimilars as an alternative to innovator biological products: the question of substitutability

The question of substitutability, which characterizes the world of equivalent medicinal products, represents an important aspect for the acceptance of biosimilar medicinal products.

Before dealing in detail with the question of substitutability it is necessary to clarify the two concepts of interchangeability and substitutability.

In terms of medical practice **interchangeability** is defined as follows:

* According to a WHO an interchangeable pharmaceutical product is: "*a product whose clinical effect is forecast to be the same as a comparative product, which it can replace in clinical practice*" (Ref: *WHO Technical Report Series*, No. 937, 2006).
* Interchangeability refers to the medical practice of replacing one medicinal product with an equivalent product in a given clinical context at the initiative of, or in agreement with, a prescribing physician (definition *of the European Generic medicines Association*, EGA).
* Interchangeability refers to the medical practice of replacing one medicinal product with another with the same risk/benefit profile and whose clinical effect, in a given clinical context, is expected to be the same at the initiative of or in agreement with the prescribing physician. (Definition of EFPIA-EBE/EuropaBIO).

On the contrary, and in the exclusive context of the United States, the terms "interchangeable" or "interchangeability" with reference to a biological product indicate that *"a biosimilar product can replace the reference biological product without the intervention of the physician who prescribed the latter."* (*Biologics Price Competition and Innovation* Act, BPCI Act SEC. 7002 b). In this context, the definition of interchangeability of a biosimilar with respect to a reference, is in practice established by a FDA commission on the basis of mandatory documentation that meets specific a priori criteria. Therefore, whenever a biosimilar product is defined as interchangeable the decision of a health operator, in single cases, is no longer necessary.

**Substitutability**, instead, refers to the practice of replacing one medicinal product with another, usually more economic for either the NHS or the patient, whose active principles have the same qualitative and quantitative composition, the same pharmaceutical form and the same means of administration and one that is also bioequivalent to the reference medicinal product on the basis of appropriate bioavailability studies.

**Automatic substitutability** (of equivalent medicinal products) by pharmacists refers to the practice whereby the pharmacist has the faculty, or the duty, in compliance with national or local laws, to dispense an equivalent and interchangeable medicinal product instead of the prescribed product without consulting the prescribing physician.

In conclusion, we should also distinguish between two aspects of substitutability:

* **primary substitutability**, which refers to the medical practice of initiating a new treatment with a biosimilar (or an equivalent) product rather than with the reference innovator product;
* **secondary substitutability**, which, instead, refers to the medical and/or pharmaceutical practice of modifying the therapy of a patient undergoing treatment by replacing a biological products with a biosimilar.

As regards the automatic substitutability of biosimilars, European legislation has given legislative and decisional autonomy to the competent national authorities of the various member states. However, EMA has also specified that its recommendations on the marketing of medicinal products do not extend to stating whether or not it is appropriate to use a biosimilar medicinal product in an interchangeable manner, and that the decision concerning the prescriptive choice of the specific medicinal product to be used -i.e. a reference rather than a biosimilar product – is an exclusive matter for qualified health personnel (Ref. EMEA/74562/2006 Rev. 1; EMA/837805/2011).

In Italy, AIFA's position clarifies that biological and biosimilar medicinal products cannot be considered *sic et simpliciter* on a par with equivalent products, thereby excluding mutual and automatic therapeutic substitutability. Precisely because reference biological and biosimilar medicinal products are similar but not identical medicinal products, AIFA has decided not to include biosimilars in the transparency lists that authorize automatic substitutability as between equivalent products.

Consequently, the decision to use a reference biological or a biosimilar medicinal product in therapeutic treatment remains a clinical decision limited to the prescribing medical specialist. However, AIFA considers that biosimilars not only constitute a therapeutic option available to both operators but also to be preferred whenever they represent an economic advantage, especially as regards the treatment of “*naive*” subjects (i.e. those who have not undergone previous therapeutic treatment for whom previous treatment, in the opinion of the physician, is sufficiently remote in time).

Furthermore, in consideration of the fact that the evaluation process for the designation of biosimilarity is carried out by EMA at the highest level of scientific knowledge and on the basis of all available evidence, no additional comparative evaluations are necessary at either a regional or a local level. However, it should, in conclusion, be noted that AIFA reserves the right to evaluate the applicability of the general principles outlined in this Position Paper on a case-by-case basis, as also its right to amend its position as regards single products and or single therapeutic categories in relation to the period of time when the products in question have been on the market, the scientific evidence acquired, the number of patients treated in clinical practice, the PSUR presented to EMA, PAES and PASS studies and the information gleaned from whatever registers may exist.

# Conclusions

The development and use of biosimilar medicinal products represent an essential opportunity for optimizing the efficiency of health and healthcare systems insofar as they have the potentiality to satisfy a growing health demand in terms not only of the effectiveness and personalization of therapies but also of their safe use. Consequently, biosimilars medicinal products represent an essential tool for the development of a competitive market for biological medicinal products, which, in their turn, is necessary for the sustainability of the health system and innovative therapies, while also guaranteeing safety and quality for patients and ensuring a harmonized and timely access to innovative medicinal products even in the face of public spending cutbacks.

In conclusion, it should also be mentioned that immediately after the publication of this Position Paper, a revision of the guideline “*Draft guideline on similar biological medicinal products (CHMP/437/04 Rev.1)*” was published on EMA's website for purposes of public consultation and to elicit comments (“Comment invited on draft revised guideline on biosimilars” – 08.05.2013). We advise you to consult this document in order to supplement the contents of this Position Paper and to update the bibliography.

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1. Directive 2003/63/EC and Directive 2004/27/EC [↑](#footnote-ref-1)
2. EMA/940451/2001 “EMA Procedural advice for users of the Centralised Procedure for Similar Biological Medicinal Products applications” [↑](#footnote-ref-2)
3. The determination of the active principle or INN (International Non Proprietary Name) is evaluated and registered by the World Health Organization (WHO) followed by the submission of an application by part of the medicinal product's manufacturer. As regards biological and new technological medicinal products, WHO has adopted a denomination system produced by an ad hoc committee of WHO experts (INN Expert Group). In particular, the WHO guidelines allow the manufacture of a biosimilar product to propose a different INN with respect to the reference biological medicinal product [↑](#footnote-ref-3)