

Biosimilars

The position of Italian pharmaceutical companies

Executive summary

Appropriate use of biosimilars may free resources that could be re-invested thus ensuring access to pharmacological innovation. Only the physician can decide to use either the biosimilar or the originator medicine, and his/her decision cannot be driven by economic criteria

Patients should always be adequately informed by the doctor on their prescribed therapy, and know the reasons of the doctor's choice between an originator and a biosimilar.

There should be a clear indication on drug's labeling to ensure transparent information about the prescribed medicine.

A biosimilar is not the "generic" of a biologic medicine, since its peculiarities are such that it is impossible to reproduce a molecule that can be considered identical in all its aspects. Moving from this principle the Italian Medicines Agency (AIFA) affirmed again that biological and biosimilar medicines cannot be considered equivalent and decided not to include them in the Transparency List (National Pharmaceutical Formulary), thus excluding any automatic substitution for these products.

It is not appropriate to state that a biologic medicine, the manufacturing process of which has been optimized through time, is a biosimilar in itself: manufacturing changes ruled by specific comparability procedures applied to the same medicine, should not be confused with biosimilarity which requires a comparability exercise between 2 drugs originating from different cell lines.

The only comparability, used for regulatory purposes, cannot be automatically translated into clinical overlap, which requires further evidence on efficacy and safety (resulting both from clinical practice and real-world evidence) for all indications and demonstrated in all different subpopulations of patients.

Appropriate use of biosimilars should aim to protect patients' health; continuity of care must be safeguarded in any case when a patient is being treated, even if the treatment is cyclical.

This principle, as well as the prescription freedom of the doctor, was ratified in the 2017 Budget Law, which also established that "automatic substitution between a reference biological



medicine and its biosimilar, or between biosimilars, is not allowed". The 2017 Budget Law also introduced the framework agreement to guarantee patients' access to therapies. It is necessary to identify a single and shared definition of "naïve patient" as the person being treated for the first time with a specific active substance.

It is therefore essential to apply rules homogeneously throughout the country.

Background

All medicinal products authorized by Regulatory Agencies (EMA, AIFA, etc...) must satisfy quality, safety and efficacy requirements to obtain the Marketing Authorization.

Biologic medicinal products (including biotech ones), regardless if they are innovative or biosimilars, must meet the same requirements as well.

The experience of the last ten years indicates that biosimilar competition can offer advantages to EU healthcare systems, as it is expected to improve patients' access to safe and effective biological medicines with proven quality. The availability of biosimilars represents a potential economic benefit to the NHS, restricted resources can be made available, allowing access to new pharmacological and therapeutic opportunities.

However, an economic-based approach, focused only on optimization of purchasing costs, which does not consider cautions and complexities required for the management of biologic medicinal products, might dissolve the benefits that can be achieved through proper use of biosimilars.

A correct assessment of the impact deriving from the use of biological medicines should consider comparison of costs of treatments, including all long-term effects on patients' health and healthcare systems.

Biosimilar ≠ Generic

A biosimilar is a biological medicine similar, but not identical, to another biological medicine already approved in the EU (the so-called "originator").

Biosimilars are not the "generic" version (in other words the equivalent versions) of biologic medicines, since they are made of living organism and have complex molecular structures and production methods as well. These peculiarities don't allow the reproduction of an identical molecule.

Among the peculiar features of biologic active substances there are characterization and quality controls: in addition to chemical/physical/biological analysis, detailed indications about manufacturing process are required.

That's why biosimilars cannot be automatically interchanged or changed with their originators.

A table attached to this document describes the main differences between traditional and biologic medicines.

Biosimilarity and Therapeutic equivalence

Standard bioequivalence is not applicable to biologics.

A medicinal product may be considered bioequivalent to a reference medicinal product only if the qualitative and quantitative composition of its active substances and its pharmaceutical form are the same as the reference product, and if the ratio between bioavailabilities (measured by means of the pharmacokinetic parameters AUC(O-t) and C_{max}) is + 20%.

A comparison of pharmacokinetic parameters allows to determine equivalence only between two low molecular weight medicines deriving from chemical synthesis.

Among biologics, a so-called “comparability exercise” must be carried out between the originator and its biosimilar: considering the uniqueness of the cell line and the complexity of the employed manufacturing processes of biologics, it is impossible to reproduce a molecule that is identical to the reference biologic product. The comparability exercise, however, required for regulatory approval, is not sufficient to support clinical stackability, for which further evidence are needed concerning efficacy and safety (even arising from clinical practice and real-life data) for all the indications authorized for the originator and demonstrated in patient subpopulations.

Biosimilarity and comparability after manufacturing changes

Scientific methods and principles supporting the comparability exercise required after the changes in the manufacturing process of a given biological medicinal product and in the development of a biosimilar medicinal product are the same.

Each manufacturer has its own unique cell lines and develops its own proprietary (unique) manufacturing processes. The biosimilar developer does not have any access to the manufacturing process of the reference product and therefore has to engineer its own manufacturing process and corresponding analytical methods, capable of manufacturing a product as similar as possible to the reference product. The owner of the reference product, on the other hand, not only establishes comparability but has also full understanding of his own manufacturing process and the respective manufacturing change(s).

Summary comparisons of manufacturing change and biosimilar development:

	Manufacturing change	Biosimilar development
Objective	Optimizing an approved process for a product that has previously undergone significant R&D, with a full preclinical program and extensive clinical trial data in each approved indication and regimen.	Attempting to reverse engineer, or create a version of the innovator product starting from published information and the product on the market.
Scientific principles of assessing comparability	Same	Same
Purpose of the assessment	Impact of a manufacturing change on an existing product, i.e. comparability between pre- and post-change product.	Marketing authorization of a new product, i.e. comparability between two individual products in order to show similarity.
Requirements for approval	Risk-based approach, i.e. level of assessment and data required depends on the level of change (e.g. see ICH Q5E)	Comprehensive, comparative analytical and functional testing followed by tailored clinical development, the extent of which is defined in over-arching clinical or product specific guidelines.
Manufacturing process knowledge	Available regarding pre- and post-change product.	Not available for the product with which the biosimilar is compared. Must be developed without knowledge of reference product manufacturing process or control strategies.

Source: European Biopharmaceutical Enterprises, "Biosimilarity and Comparability after Manufacturing changes: Can a biologic become a biosimilar of itself?", February 2016

It is not appropriate to state that a biologic medicine, undergoing manufacturing changes throughout time, is a biosimilar in itself: manufacturing changes ruled by comparability processes within the same medicine, should not be confused with biosimilarity which requires a comparability exercise between 2 drugs originating from different cell lines.

Correct use of biologics

From a regulatory perspective, specific guidelines for Marketing Authorization of different classes of biosimilar products are released by EMA, whereas decisions concerning interchangeability and/or substitution are left to the National Regulatory Authorities.

Farmindustria supports AIFA's position paper which confirmed that biologicals and biosimilars cannot be regarded as equivalent drugs and decided not to include biosimilars in the Transparency list (National Pharmaceutical Formulary), therefore excluding any automatic substitution.

This principle was ratified in the 2017 Budget Law, which established that "automatic substitution between a reference biological medicine and its biosimilar, or between biosimilars, is not allowed", and introduced the framework agreement to guarantee patients access to available therapies.

For this reason, the Ministry of Health should monitor Regional measures, to ensure their compliance with the LEAs throughout the Country, and intervene in case they are not in line with what is defined by Law.

Farmindustria believes that therapeutic continuity must be guaranteed to patients who are already being treated, even when the treatment requires repeated cycles of therapy, and in any case recognizes physician's crucial role in the therapeutic choice for every single patient.

The prescribing physician must always have the option to decide which biological product should be dispensed to the patient.

Treatment decisions should be based first on clinical judgment and cannot be driven only by economic criteria.

Physician's freedom of choice between medicines cannot be limited by setting prescription targets (applying sanctions or incentives) endorsing the use of a particular biological medicine on naive patients.

These principles are expressed in the 2017 Budget Law (article 1, paragraph 407), which states that "physician is however free to prescribe the drug, ... omissis ..., considered suitable to guarantee patients' continuity of treatment".

Some major Italian Scientific Societies, developed a joint paper on biosimilars, pointing out that these principles are "always considered valid regardless the number of medicines based on the same active substance present on the market".

A position shared by Farmindustria.

Patients should always be correctly informed by the physician on the prescribed therapy, and know the reasons of the doctor's choice between an originator and a biosimilar.

Patients should also be informed about risks, benefits and clinical evidences related to the treatment, to be involved in their care path.

To ensure transparency towards the patient it would be desirable to introduce a clear indication on drug's labeling.

Furthermore, Farmindustria considers it important to update the information contained in the Summary of Product Characteristics (SmPC) referring to the studies conducted on biosimilars through comparability exercises.

It is necessary to identify a single and shared definition of "naïve patient" as the person being treated for the first time with a specific active substance.

It must be considered, whatever the complexity of a biological medicine may be, Regulatory Agencies may request - upon its approval - post-authorization Efficacy Studies (PAES) and post-authorization Safety Studies (PASS), as well as any other independent clinical study that might contribute to determine the clinical comparability.

The generation of further safety evidence is monitored by EMA through the trials foreseen in the Risk Management Plan, that is specific for each new biosimilar product as a guarantee that the acknowledged benefit/risk profile is repeatedly confirmed post-marketing.

Extrapolation to all indications of the originator may be granted by EMA only if supported by sufficient data.

Data related to a given indication cannot be directly applicable, in terms of safety or efficacy, to any indication included in another therapeutic area, with a mechanism of action, the dosage or the pharmacokinetics can be different.

This principle should also be applied when evaluating biosimilar's inclusion in the list of reimbursable medicinal products, according to Law no. 648/1996.

As clarified in AIFA's Position Paper, the inclusion of biosimilars in the list of reimbursable medicinal products cannot take place automatically, but it must be decided on a case by case basis by the CTS, which must implement its assessments based on objective, predetermined

and published scientific criteria, since such indications are different from the assessments already carried out by EMA.

Even if multiple products with the same therapeutic indication are available, the choice to prescribe a specific biological medicinal product must be taken by the physician, basing on all the available information and sharing it with the patient.

Safety is a priority aspect for biological medicinal products, especially in terms of immunogenicity, or if any side effects and/or adverse reactions occur even after years of treatment.

To guarantee a correct pharmacovigilance it is necessary to track back to the drug administered (originator or biosimilar) by indicating the brand name, as established by the “Guidance for Heads of Pharmacovigilance in managing notifications in the RNF National Pharmacovigilance Network version 2 Updated as of February 2015” issued by AIFA. In case more than one biologic or biosimilar are available, it's important to be able to track the therapy taken by the patient with absolute certainty in terms of name of product administered, and not only in terms of active substance.

The safety of biosimilars is guaranteed, as for originator, by means of:

- control of quality and stability of the manufacturing process;
- traceability of the product and continuous verification of compliance with GMP-GCP rules;
- active post-marketing pharmacovigilance (Risk Management Plan).

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For a complete consultation of EMA's documents please click on the following link:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002958c

Attached

Attachment

Main differences between traditional and biologic drugs, extracted from the publication "Biosimilar Drugs. Concerns and Opportunities" (Genazzani A. et al. Biodrugs, 2007, 21 (6):351-6)

Main distinguishing elements	Traditional drugs	Biologics
Dimensions	Molecular weight: 50 to 1,000 Dalton.	Molecular weight: 5,000 to 200,000 Dalton.
Synthesis	Replicable in different laboratories. The quality of the product is largely determined by expertise of the operator	Because of the complexity of tools used (expression vectors, cell lines, etc.) repeatability in different laboratories is not guaranteed.
Purification	It is based on standardized procedures with few steps. It is made easier by the fact that the intended final product is often the main component of the reaction; otherwise, the other components are qualitatively limited and known	Methods are adapted to specific situations in consideration of variability of the synthesis process from one laboratory to another. The intended final product is present in a mix of products; contaminants are predominant and may vary between laboratories.

<p>Immunogenicity</p>	<p>Ascribable to the molecule and/or excipients; intrinsic to patients and cannot be easily attributed to a specific pharmaceutical product</p>	<p>May be attributed to product- or patient-related factors. Examples of product-related factors: presence of exogenous or endogenous epitopes; amino acid sequence, degree of glycosylation, type of cells used (prokaryotes or eukaryotes), contaminants, formulation and storage conditions. Examples of patient related factors: genetic predisposition (that impacts production of neutralizing antibodies), concomitant diseases (in particular liver, liver and autoimmune diseases).</p>
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