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BIOSIMILARS
THE POSITION OF THE ITALIAN PHARMACEUTICAL COMPANIES

EXECUTIVE SUMMARY

With over 7.000 medicines at an advanced stage of development for various diseases, pharmacological innovation will offer many new therapies soon which will provide increasingly effective and personalized answers in terms of survival and quality of life.
A fundamental part of this innovation is represented by biological medicines, which also include biotechnological medicines.
Biological medicines are vital to health and the sustainability of the healthcare system, resulting from the most advanced research carried out by companies in this sector, in synergy with centers of excellence all over the world.

WHAT IS A BIOSIMILAR

- A biological medicine is a medicinal product which contains active substances, that are not small molecules but originate from a biological source.
  A "biosimilar" is a biological medicine similar but not identical to another biological originator already approved in the EU and for which patent protection has expired.
  Entry in the market of biosimilar medicines can make resources available for innovation and research.

- As with all medicinal products, the Regulatory Agencies test and approve biosimilars, according to high international standards. Biosimilars have the same profile of the originator in terms of effectiveness and safety.

- The complexity and use of cell systems to produce biological medicines do not allow the reproduction of an identical molecule.
  Biosimilars are neither equal to the originator nor between them and thus they are not automatically substitutable, a principle reiterated by the 2017 budget law.
  AIFA as well decided not to include biosimilars in the transparency list, therefore excluding any automatic substitution.

THE CHOICE OF THE BEST THERAPY FOR THE INDIVIDUAL PATIENT IS UP TO THE PHYSICIAN

- The choice of prescribing an originator or any other biosimilar depends on the patient's individual characteristics, which only the physician can assess to the best of his scientific knowledge. The doctor's responsibility is also reiterated by AIFA in its "*second position paper on biosimilars*".

- Interchangeability, i.e. the possibility to switch from one to another medicine during therapy, the originator and its biosimilar and vice versa, must not be promoted for economic reasons up to becoming mandatory for the physicians. They are the only ones capable to assess the best therapeutic approach in the best interest of each individual patient – particularly those patients already under treatment – on the basis of solid clinical evidence.

- Information on the choice of the therapy, on the related risks and benefits must be clear and thorough. In fact, it represents a fundamental element of the communication between physician and patient, as well as for the patient's engagement in his own treatment.

- For these reasons it is important that the prescriptive freedom of the physician is uniformly guaranteed throughout the national territory. The Council of State[1] has repeatedly reaffirmed the importance and centrality of prescriptive freedom and the right to health of the patient[2].

OPPORTUNITIES AND CAUTIONS

- Biosimilars represent an opportunity for national healthcare. Their arrival allows to reduce financial charges borne by the healthcare service, ensuring a broader access to innovation for all patients, also through the framework agreement in the tenders as provided for by the 2017 budget law.

- The current global tendency to personalize therapies makes it even more necessary to consider the clinical condition of the individual patient.

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[1] Council of State, no. 3621/2017
[2] Istituto Bruno Leoni "I biosimilari e il prezzo dei diritti", June 2018

The identification of the optimal therapy by the physician is the result of an accurate evaluation over time aiming at achieving the best balance between treatment effectiveness, compliance and safety.
In particular, in the interest of the patients' health, it is essential to guarantee the therapeutic continuity in patients already stabilized thanks to the chosen therapy, as provided for by the 2017 budget law.

- Pharmacovigilance must represent a fundamental instrument for the assessment of biological medicines in terms of both effectiveness and safety. The continuous monitoring can in fact provide all needed elements for decisions in both clinical and regulatory fields.

ITALY IS ALREADY A LEADER IN EUROPE IN THE USE OF BIOSIMILARS

A recent study, carried out by IQVIA, shows how Italy ranks first among major European countries (Belgium, France, Germany, Italy, United Kingdom, Spain and Sweden) for the use of biosimilars in 2017.

Background

All medicinal products authorized by Regulatory Agencies (EMA, AIFA, etc.) must comply with quality, safety and effectiveness requirements to obtain a marketing authorization.
Biological 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 benefit EU healthcare systems[1], by improving the access of patients to safe and effective biological medicines of proven pharmacological quality. The availability of biosimilars represents a potential economic benefit to the NHS, by freeing up resources to be reinvested in pharmaceutical innovation and research.

However, a merely economic approach - focused solely on the optimization of purchasing costs - might dissolve the benefits that can derive from the proper use of biosimilars. In fact, it does not take into account the complexity and caution required by the management of biologic medicinal products.
A correct assessment of the impact of the use of biological medicines should consider comparing the cost of treatments, including all long-term effects on healthcare systems of specifically monitored therapies.

Biosimilars

A biosimilar is a biological medicine similar but not identical to another biological medicine (the so-called *originator*) already approved in the EU[1] and for which the patent protection has expired. Its complexity and the use of cell systems for production do not allow the reproduction of a molecule that can be considered effectively identical.

Characterization and quality controls are among the specificities of biological active substances: in addition to chemical/physical/biological analysis, detailed indications about manufacturing process are required.
In fact, biosimilars are not automatically interchangeable between them or with their originators (as provided for by the 2017 budget law, article 1, paragraph 407).
Table 1[2] attached to this document describes the main differences between small molecules and biological medicines.

Biosimilarity and Therapeutic equivalence

The concept of bioequivalence does not apply 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 $AUC_{(0-t)}$ and C_{max}) is ± 20%[3].
A comparison of pharmacokinetic parameters allows the determination 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 process of biologics, it is impossible to reproduce a molecule that is identical to the active substance of the reference biological product. However, the comparability exercise required for regulatory approval, must be corroborated with further evidence on effectiveness and safety - including evidence from clinical practice and real-life data - for all authorized indications for the originator and demonstrated in patient subpopulations.

Comparability after manufacturing changes and Biosimilarity[4]

The regulatory criteria to the evaluation of post-approval manufacturing process modification and to the demonstration of biosimilarity for a biologic medicine during the registrative procedure are different.

The company has full knowledge of its own manufacturing process and of related changes.
The cell line used to produce a biological medicine is unique and owned by the manufacturer that develops the medicine through specific production processes.
It is therefore incorrect to claim that a biological medicine, which can experience changes in the production process over time, is a "biosimilar of itself".
Demonstration of biosimilarity entails an exercise of comparability between two medicines originating from different cell lines.
The biosimilar developer does not have, in fact, any access to the manufacturing process of the reference product. Therefore, it must engineer its own manufacturing process and the corresponding analysis tools, to obtain a product as similar to the reference product as possible, starting from a different cell line.

Instead, in case of a change in the production process of any biological medicine, comparability procedures referring to the same medicine deriving from the same cell line are applied.

Other differences are well exemplified in the table in appendix (Table 2).

Correct use of biologics

From a regulatory perspective, EMA released specific guidelines for Marketing Authorization of different classes of biosimilar products[5], whereas decisions concerning interchangeability and/or substitution are left to the National Regulatory Authorities.

Farmindustria supports AIFA's position, which reaffirmed that biologicals and biosimilars cannot be regarded as equivalent medicines. AIFA thus decided not to include biosimilars in the transparency lists, therefore excluding any automatic substitution.

This principle was enacted by 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 a framework agreement in the tenders to guarantee the access of patients to available therapies.

For this reason, the Ministry of Health should monitor regional provisions, to ensure their compliance with the ELAs throughout the Country and intervene in case they are not in line with what provided for by the law.

Farmindustria believes that therapeutic continuity must be ensured to patients already under treatment, even when the treatment requires repeated cycles of therapy. At any rate, Farmindustria recognizes the physician's crucial role in the therapeutic choice for every single patient.
Centrality of the physician is stressed by the second AIFA position paper on biosimilars.

The choice of treatment with a biological reference medicine or with a biosimilar is a clinical choice. As such, it can only be entrusted to the physician, who contributes to the appropriate use of both the medicine and the other resources, but at the same time cannot be conditioned solely by economic reasons.

Physician's freedom of choice among medicines cannot be limited by setting prescription targets - by applying sanctions or incentives - imposing the use of a certain biological medicine.

These principles are expressed in the 2017 budget law (article 1, paragraph 407), which states that "physician is however free to prescribe the medicine [...] that is deemed to be suitable to guarantee patients' continuity of treatment".
Some major Italian Scientific Societies[6], developed a joint paper on biosimilars, pointing out that these principles are "always to be considered valid regardless the number of medicines which contain the same active substance on the market".
Farmindustria shares such position.

Patients should always be correctly informed by the physician about the reasons for the choice of the therapy and whether the medicine is an originator or a biosimilar.
Patients should also be informed about risks, benefits and clinical evidences related to the treatment, to be engaged in their care path.
The introduction of a clear indication on medicine's labeling would be desirable to ensure transparency towards the patient.
Furthermore, Farmindustria considers it important to update the information contained in the Summary of Product Characteristics (SmPC) with relation to the studies conducted on biosimilars through comparability exercises[7].

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

It must be considered that regardless of their complexity, upon approval of biological medicines, Regulatory Agencies may request Post-Authorization Efficacy Studies (PAES) and Post-Authorization Safety Studies (PASS), as well as any other independent clinical study that might determine their clinical comparability.
The production of further evidence of safety is monitored by EMA through the trials included in the specific Risk Management Plan for each new biosimilar product as a guarantee that its benefit/risk profile is confirmed each time by post-marketing experience.

Extrapolating all the indications approved for the originator may be granted by EMA only if sufficient data support it.
In terms of safety or effectiveness, especially the data related to a given indication cannot be directly applied to any indication pertaining to a different therapeutic area, where the mechanism of action, the dosage or the pharmacokinetics can be different[7].

Such principle should also apply when evaluating the inclusion of a biosimilar in the list of reimbursable medicinal products, according to Law no. 648/1996.

As reaffirmed by AIFA's second position paper, the inclusion of biosimilars in the list of reimbursable medicinal products cannot take place automatically. It must be decided on a case by case basis by the Scientific Technical Committee, which must carry out its assessments based on objective, predetermined and published scientific criteria, since such indications are different from the assessments already carried out by EMA.

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

As in the case of originators, the safety of biosimilars is guaranteed 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).

To guarantee a correct pharmacovigilance it is necessary to be able to track the administered medicine (originator or biosimilar) by always indicating the brand name and the batch number in the adverse medicine reaction reporting form, as established by EMA in the "guideline on good pharmacovigilance practices (GVP)" and cited by AIFA in its communiques. In case more than one biologic is available, it is therefore important to be able to track the therapy followed by the patient with absolute certainty in terms of name of product administered, and not only in terms of active substance.

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For a complete consultation of EMA's documents please click on the following link: https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview

Appendix

Table 1. Differential features of traditional pharmaceuticals and biopharmaceutical products relevant to the regulation of generic and biosimilars

Feature	Traditional pharmaceuticals	Biopharmaceuticals
Dimensions (molecular weight)	0.05-1 kDa	5-200 kDa (e.g. insulin ~5800Da, growth hormone ~22000Da, erythropoietin ~34000Da)
Synthesis	Product quality determined largely by experience of the operator and replicable in different laboratories	Tool-driven (e.g. expression vectors and cell lines), resulting in variable final product between laboratories
Purification	Often based on standardized procedures composed of a few steps. Also, facilitated by final product often being the principal component of the reaction, and when it is not, other product components are qualitatively limited and known	Desired product is very poorly represented in the mixture. Also, contaminants are qualitatively preponderant and probably vary among laboratories
Stability	Usually degrade with first-order kinetics, which can normally be modeled using the Arrhenius equation	Unlikely that the principles applying to degradation of traditional pharmaceuticals can also be applied to biopharmaceuticals, due to their size, complexity of tertiary structure, and post-translational modifications
Immunogenic reactions	Reactions to active ingredient or excipients are intrinsic to the patient and, therefore, not easily attributable to a specific pharmaceutical product	Reactions to biotechnology products may be attributable to both product- and host-related factors[a]

[a]Product-related factors: presence of exogenous and endogenous epitopes (e.g. human vs nonhuman agents), amino acid sequence, glycosylation state, type of eukaryotic/prokaryotic cell used, residual contaminants, formulation and storage modality, dose and length of treatment. Host-related factors: genetic predisposition (affecting neutralizing antibody production); concomitant disease (particularly renal, hepatic, and autoimmune diseases).

Source: Genazzani A. et al., "Biosimilar Drugs. Concerns and Opportunities", Biodrugs, 2007, 21 (6):351-6

Table 2. Main differences between 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. It 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