REFERENCE BIOLOGICAL MEDICINES (‘ORIGINATORS’) AND ‘BIOSIMILARS’: COMPETITION AND PATIENT PROTECTION

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Abstract: Biological and, especially, biotechnological medicines are some of the most relevant pharmaceutical innovations both for their influence on the treatment of many conditions and because they led the way to devising new and innovative pharmacological therapies. On the other hand, biosimilars, which can be authorized on the date of expiry of the biological originator’s patent, give an opportunity for the sustainability of the National Healthcare Service. Following a heated debate in legal doctrine and jurisprudence on biosimilars and automatic substitutability between biological and biosimilar, on the purchasing process of such medicines, and also on the imperative physician’s freedom of prescription - intended as framework for patient protection - the 2017 Budget Law has been adopted. This Law encourages the spread of biosimilar products, which is pivotal in making economically viable the use of next-generation medicines in hospitals. It also sets some principles for the definition of the regulatory framework, giving always priority to the physician’s freedom of prescription and to any patient’s safety and protection.

1. THE CONCEPT OF BIOLOGICAL ORIGINATOR AND BIOSIMILAR: REGULATORY FRAMEWORK

While the notion of generic medicine may be considered well framed, both legally and pharmacologically, the same cannot be said for biosimilars. In this case, blindly using the interpretative categories developed for generics, as well as underestimating some distinctions already existing within the category of biological medicine, would be misleading.

According to the European Medicines Agency (EMA), a biological medicine "contains one or more active substances derived from a biological source; some of these active principles may be already present in the human body, for example proteins such as insulin, growth...

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2 Pursuant Art. 10, Paragraph 5b) of Legislative Decree No. 219/2006, it is defined as biosimilar "a medicinal product which has the same qualitative and quantitative composition of active substances and the same presentation of the reference medicine, as well as a bioequivalence with the reference medicine, demonstrated by suitable bioavailability studies". In this regard, see G. F. Ferrari – F. Massimino, Diritto del farmaco, Bari, 2015, 35 ff.

3 Medicinal products that can be considered identical in quality, safety and efficacy to the originator medicine – on the basis of predetermined objective and measurable scientific and methodological criteria – fall within this category. They must be developed and approved following clinical trials which concretely confirmed their quality.
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.\textsuperscript{4} In general, they are products derived from substances present in animals or humans, modified or synthesized in a laboratory, yet maintaining similar structure and characteristics to the related compound synthesized by the human body itself. Therefore, precisely because they consist of living material of a complex structure, biological medicines "have an inherit degree of minor variability (microheterogeneity) which must fall within the acceptable range to ensure consistent safety and efficacy."\textsuperscript{5}

The Position Paper on Biosimilars of May 13, 2013, prepared by the Agenzia Italiana del Farmaco - AIFA ("Italian Medicines Agency")\textsuperscript{6}, on the basis of Doc. Ref. EMEA/74562/2006 Rev. 1, clarifies the distinction between biological medicines in the strict sense of the term – identifiable when the active principle is represented by a substance produced or extracted from a biological system – and biotechnological products, in which the active principle consists of a substance derived from a biological source through biotechnological procedures, including recombinant DNA technologies, controlled expression of genes coding biologically active proteins in prokaryotes and eukaryotes, hybridoma and monoclonal antibody methods. In general, these are medicines that can sometimes prove to be effective in a targeted and selective manner, against a single structure, receptor, protein or DNA sequence (the so-called “Target Therapies”).

Biological medicines, on the other hand, have complex protein structures, high molecular weight, effects depending on their chemical composition and three-dimensional shape, and requiring a particularly difficult production technique, with many hardly controllable variables and a highly complex purification process. They have, therefore, a far greater structural complexity than their traditional, chemically-synthesised counterparts\textsuperscript{7}.

In the scientific field, therefore, a distinction between "simple" and "complex" products has been outlined within the category of biological medicines\textsuperscript{8}. The first ones are those having less structural complexity and limited instability and alterability, such as growth hormones, erythropoietins and G-CSF medicines; the second ones, a category to which the monoclonal


\textsuperscript{6} The same approach was taken by the Second AIFA Concept Paper on Biosimilars, published on June 15, 2016 and available at: http://www.aifa.gov.it/sites/default/files/Secondo_Concept_Paper_AIFA_BIOSIMILARI.pdf

\textsuperscript{7} In this regard, it can be interesting noting that, while the atoms that constitute a classic medicine of chemical origin like Aspirin are 21, those present in monoclonal antibodies of biological origin are about 25,000. See, in that respect, IMS, Biosimilar accessible market: size and biosimilar penetration, April 2012. Besides having a simple structure and low molecular weight, chemically-synthesised medicines are originated by a relatively simple chemical reaction, with easily monitored variables and an easily detectable level of purity. This makes the bioequivalence between generic medicines and reference medicines quite easy to achieve.

antibodies belong, have higher structural complexity, originate from a much more sophisticated productive process – which determines a higher probability of post-translational modifications –, and are intended for more critical healing purposes, such as adjuvant cancer therapy. Because of this, monoclonal antibodies are often developed so as to make them active only against a precise target. This is achieved through a modification that makes them capable of recognizing the diseased structures (cancer cells), or any protein involved in the disease process, as aggressors, thus being able to act directly on these only, without damaging the healthy cells.

According to the EMA, it can be defined as biosimilar "a medicine highly similar to another biological already marketed in the EU (the so-called reference medicine)"9. This is because "the active substance of the biosimilar medicine is equivalent to the one contained in the reference biological medicine. Biosimilar medicine and reference biological medicine are generally used in the same dosage to treat the same diseases"10. As can be inferred from the reference to "equivalenza", and not to the identity of the active substance itself, in this case the concept of equivalence that the pharmacologists have developed to qualify the relationship between the traditional originator medicine and the generic counterpart does not apply. However, in order to achieve the regulatory authorisation, it is required that the biosimilar does not show "clinically meaningful differences compared with the reference medicine"11. As it has already been clarified, each phase of the production is difficult to reproduce, due to the presence of many hardly controllable variables and a highly complex purification process. Therefore, different sources or modifications made to procedures that are already in use can induce a certain unpredictability in the biological properties of the medicine, which may change its quality, pharmacokinetic and/or pharmacodynamic characteristics and clinical activity12. This means that the efficacy of the clinical effect and any adverse reactions of biosimilar are not always fully measurable in advance, and – as it will be clarified in paragraph 3 – it may be necessary to introduce subsequent verification with specific clinical trials, also in order to consider the medicine possible immunogenicity, potentially discernible when an antigen stimulates an immune response, with possible risks for the patient13. It is therefore understandable why the

9 In this regard, see Biosimilars in the EU op. cit. According to the EMA guidelines, entered into force on April 30, 2015, a biological medicine authorised outside the European Economic Area (EEA) can also be used as comparator, so as to facilitate the development and avoid the repetition of clinical trials.


11 See Biosimilars in the EU op. cit.


biotechnology industry can affirm that, for biologicals, "the process is the product"14, thus establishing a conceptual and teleological integration between the production process and its result. Accordingly, there is also a clear reason why the biological medicine development can itself generate an increase in scientific knowledge15.

For this reason, the authorization procedures for biosimilar medicines require the implementation of pre-clinical and clinical trials to demonstrate safety and efficacy comparable to the corresponding originator’s.

In national law, this distinction is established by Paragraph 7 of Art. 10 of Legislative Decree No. 219/2006, which – reflecting Art. 10, Paragraph 4 of Directive 2001/83/EC, as amended by Directive 2004/27/EC – states that "when a biological medicine similar to a reference biological medicine does not meet the defining conditions of the generic medicine on the account, in particular, of differences relating to raw materials or to the production process of the biological medicine and of the reference biological medicine, the applicant shall provide results of appropriate pre-clinical tests or clinical trials related to such experimentations". Compared to the requirements for authorisation procedures for a generic medicine – which only requires conducting bioavailability studies to demonstrate its equivalence to the reference medicine – the legislation requires additional data, as well as the submission of clinical and pre-clinical studies in relation to the originator biological reference medicine, referred to as "comparability exercise". The comparability exercise "is conceived as a step-wise process that is tailor-made for each product; knowledge from the initial quality comparability studies (step 1) is used to determine the extent and type of non-clinical (step 2) and clinical studies (step 3) required in the next step of development, always with the aim of ruling out differences in clinical performance between the biosimilar and the reference medicine16. [...] For larger molecules (e.g. monoclonal antibodies), even when robust quality and in vitro comparability data are provided, a comparative study in patients using a conventional clinical efficacy endpoint is usually required [...] and adequate equivalence margins should be chosen. [...] In the case of monoclonal antibodies, [clinical immunogenicity studies] are always required, as it is more difficult to predict the incidence of unwanted immunogenicity, the characteristics of the immune response or the clinical consequences"17.

On the other hand, once demonstrated the comparability in terms of safety and efficacy, the same safety and efficacy data can also be used, by analogy, to approve other indications of the reference medicine, with consequent reduction of clinical studies.

This is the principle of extrapolation, which is not, as the EMA takes care to point out, specific to biosimilars only, being also adopted in the event of significant changes in the originator's production process. However, the EMA itself states that the application of the extrapolation principle cannot be generalized. If "data from a


15 In this regard, see A. Genazzani, Oltre i biosimilari ("Beyond Biosimilars"), available at: www.biosimilari.eu.

16 See Biosimilars in the EU op. cit.

17 In this regard, see Biosimilars in the EU op. cit. Along the same line, see also the Second AIFA Concept Paper op. cit.
given indication [are not] directly applicable in terms of safety or efficacy to an indication falling within another therapeutic area where the mode of action, posology or pharmacokinetics may be different", or if the mechanism of action of the active substance is complex and involves multiple receptors or binding sites, the specific contribution of which is difficult to assess (as it is often the case with monoclonal antibodies), granting further indications might be conditioned upon conducting additional clinical studies18.

The EMA seems to suggest the adoption of a precautionary approach; as a result the criterion of general eligibility is then mediated and circumscribed by a series of conditions inspired by the precautionary principle, particularly relevant in the light of the complexity of monoclonal antibodies. The AIFA itself is on the same line, reiterating that extrapolation cannot be automatic and must be subject to case-by-case evaluations19.

With regards to the approval process, it should also be stressed that, according to the combined provisions of Art. 3 and of Annex to Regulation (EC) No. 726/2004, medicinal products developed by means of biotechnological processes such as:

i) recombinant DNA technology,

ii) controlled expression of genes coding for biologically active proteins,

iii) in prokaryotes and eukaryotes including transformed mammalian cells,

iv) hybridoma and monoclonal antibodies methods,

as well as those intended for specific indications (e.g. cancer, neurodegeneration and autoimmune diseases), must be authorised in accordance with the EMA centralised procedure. From this procedure derives the European Commission's Authorisation Procedures for Medicinal Products, usually followed by hospital administration regimen (Art. 92 of Legislative Decree No. 219/2006)20. This authorization procedure, therefore, also applies to biosimilars of the same type, without prejudice to the fact

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18 See Biosimilars in the EU op. cit. In any case, it is worth noting that the principle of extrapolation is not applicable to reimbursable therapeutic indications pursuant to Law No. 648/1996, i.e. those with no therapeutic alternative authorised under the applicable regulations. These are, in fact, indications other than those approved for the originator via centralised procedure. Therefore, they require – as it will be better clarified below – a further evaluation by the AIFA's Commissione Tecnico Scientifica ("Scientific Technical Committee"), based on the analysis of Real World Evidence data and an experience of actual use of the biosimilar medicine.

Similarly, extrapolation is not applicable when an originator biological medicine is used in combination with another, if the therapeutic indication has been released for the latter and is therefore present only in this product's SmPC. In other words, since only the different biological medicine has been authorised for the indication in combination with another medicine, a possible use of the biosimilar in that manner would constitute an off-label use. And in fact, pursuant to article 14 (1) of Regulation 726/2004/EC, the data on which the authorisation of the medicine or its indication are based are covered by the Regulatory Data Protection (RDP), an intellectual property right ensuring, for a limited duration of time, the protection of an innovator's proprietary clinical data. During the RDP period of validity, generics or biosimilars cannot rely on the innovator's proprietary data in order to obtain marketing authorizations.

19 See the Second AIFA Concept Paper op. cit.

20 If, however, the biological medicine does not have the characteristics indicated in Art. 3 and Annex to Regulation (EC) No. 726/2006, it may be approved also by national regulatory authorities, by means of national mutual recognition or decentralized procedure. For example, low-molecular-weight heparins fall within this category.
that, if multiple marketing authorizations are requested for the same active substance due to public health or co-marketing reasons (Art. 82 of Regulation (EC) No. 726/2004), subsequent authorisations may also be granted, applying the procedure laid down by Art. 10a of Directive 2001/83/EC for generic medicines.

Price and classification of biological medicines for the reimbursement purposes are regulated by CIPE (the Comitato interministeriale per la programmazione economica, “Interministerial Economic Planning Committee”) Resolution No. 3 of February 1st, 2001, applicable in accordance with the timetable and costs referred to in Art. 12 of Law No. 189/2012, as amended by Art. 44 of Law No. 98/2013, if the biological medicine is "orphan" or has an exceptional therapeutic benefit. It should also be noted that Art. 9b of Law No. 125/2015 added Paragraph 33a to Art. 48 of Law No. 326/2003; this Paragraph provides that, upon expiry of the patent on a biological medicine’s active substance and lacking any commencement of a concurrent price negotiation process for the corresponding biosimilar, the AIFA should initiate a negotiation procedure with the holder of the marketing authorization for the biotechnological originator, in order to achieve a reduction of its reimbursable price at the National Healthcare Service charge. The reason behind this provision is the legislator’s intent to make savings of expenditures, even if the development of the biosimilar, precisely because of its greater complexity in the production process, may be diachronic and delayed with respect to the patent’s expiry date.

At any rate, the regulation on reimbursable price provided for generic medicines is applicable to biosimilars, and thus Art. 1 of the Decree-Law No. 323/1996, converted into Law No. 425/1996, establishing that any offer of a price by at least 20% lower than the originator medicine price, automatically also leads to the same Class A assignment for generic medicines.

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22 In this regard, it should be remembered that the legislator has also transposed the peculiarity of biotechnological products within the patent law framework. By virtue of Art. 43, Paragraph 1 of Legislative Decree No. 131/2010, Art. 81a-g (Sec. IVa) were included in Legislative Decree No. 30/2005 (Codice della proprietà industriale, “Code for Industrial Property”). These Articles clarify those exemptions from general patent legislation specifically applicable to biotechnological inventions, as defined therein.

23 Legislative Decree No. 158 of September 13, 2012, coordinated with the Conversion Law No. 189 of November 8, 2012, had introduced a mechanism of automatic price reduction for generic and biosimilar medicines, along with the guarantee of the same reimburse classification of the originators, whereby such price reductions were cost-effective for the National Healthcare Service. The Ministerial Decree of April 4, 2013, had then defined the "Criteria for the identification of brackets for the automatic negotiation of generic and biosimilar medicines" (published on Gazzetta Ufficiale [Official Journal] No. 131 of June 6, 2013), identifying these reductions as "cost-effective" for the National Healthcare System. Later, the ruling of the Lazio Regional Administrative Court (TAR), Sec. IIIc, No. 3803/2014 annulled the aforementioned Ministerial Decree and, pending the Appeal, the AIFA’s Comitato Prezzi e Rimborso (“Price and Reimbursement Committee”) has believed it suitable – under the Statement of December 2, 2014 - negotiating the price in accordance with the CIPE’s Resolution No. 3/2001.

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2. EFFICACY, SAFETY AND PHARMACOVIGILANCE - ORIGINATORS AND BIOSIMILARS NAME

As is it known, when approving a new medicinal product, regulatory agencies must evaluate three profiles contributing to define quality, efficacy and safety of the product as reflected from clinical studies.

In general, the granting of a marketing authorisation offers a reasonable guarantee that the efficacy of the medicine has been met, on the basis of the adequacy of the clinical data obtained. These data allow the new medicine to compete with other products of the same therapeutic class already on the market, or even to satisfy some unmet clinical needs, thus acquiring additional competitive advantage.

For this reason, in general, the greater or lesser safety, as well as any residual margins of uncertainty, can diversify the various medicines, and thus constitute a factor capable of influencing the choice of any purchasing institutions and prescribing physicians, assuming a significant relevance to the competitiveness of the product.

In this respect, it is therefore useful to note that, alongside the general statements of the EMA, underlining that "no differences are expected in safety and efficacy between originators and biosimilars", European legislation contains multiple interventions inspired by a more cautious approach, which has also been transposed in the recent Italian regulations on public supply of originators and biosimilars.

According to the European legislator, in fact, the safety verification of the medicinal product does not end with its authorisation, rather continuing to be paramount even during its...
subsequent marketing, in order to determine any possible risks not identified in the trial period. More focus is placed on biological than on chemically-synthesised medical products\(^{28}\), and a clear line is drawn between the originator biological products and the corresponding biosimilars.

The legislator's and the regulatory agencies' stand on this issue seems in fact to converge on requiring more pharmacovigilance fulfilments for the most recently authorized biosimilars than for the biological originators already on the market, with a view to increasing the efficiency of the system and the public health protection\(^{29}\).

In particular, Regulation (EU) No. 1235/2010 and Directive 2010/84/EU foresee the possibility to impose on the new marketing authorisation holder the obligation to conduct post-authorisation studies on safety and efficacy (the so-called PASS and PAES), for a better protection of public health (see, in particular, the whereas No. 16 and No. 17 of the Regulation (EU) No. 1235/2010), so that the information on available medicines at the time of their authorisation is complemented after the commencement of marketing.

Such an obligation may be imposed if some therapeutic indications have been granted by the EMA to the new biosimilar through extrapolation\(^{30}\), without them being extended to the corresponding originator. It is evident that, in this case, the post-authorisations studies are aimed at concretely attesting the safety and efficacy of the medicinal product in the "extrapolated" indication, in order to confirm the assessment that the regulatory authority has released in the absence of specific clinical studies\(^{31}\).


\(^{29}\) Under the current legislation, in fact, manufacturers of biological originators and biosimilars are required to establish a system of pharmacovigilance to monitor the safety of their products and to set up a specific "Risk Management Plan" (EU-RMP), which establishes, inter alia, the measures to be taken to prevent or minimise any risk arising out of the use of their medicines. In this respect, see the Second AIFA Concept Paper, op. cit.

\(^{30}\) Moreover, it should be remembered that the biosimilar manufacturing company may also decide not to request all the indications given to the originator. In this case, the marketing authorisation granted by the regulatory agency will be without the indication at issue ("skinny label"). The physician is therefore liable for checking in advance, at the time of the prescription, whether the biosimilar actually has the indication for its intended use. In this regard, see Biosimilars in the EU op. cit. A biosimilar may lack one or more indications if the indications in question are still patent protected, and the manufacturing company wants to prevent the risk of patent infringement.

\(^{31}\) As the Second AIFA Concept Paper, op. cit. also clarifies: "PASS are conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures during marketing of the medicinal product (this specifically includes immunogenicity events, which are a serious problem for safety of any biological medicinal product, and it shall be addressed in the EU-RMP). PAES, on the other hand, are conducted with the aim of evaluating and confirming the efficacy in cases where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed". For a complete summary of the major amendments introduced by the European doctrine on pharmacovigilance, see G. Guerra, Tutela del paziente e obbligo di black symbol per i farmaci innovativi. Gli effetti del regolamento UE n. 198/2013 (Patient protection and obligation for innovative medicines to include the black symbol. The effects of Regulation (EU) No. 198/2013), in Politiche Sanitarie (Health Policies), Vol. DOI: 10.12870/iar-12856
Furthermore, Art. 23 of Regulation (EU) 1235/2010 states that the EMA shall set up and maintain a list of medicinal products subject to additional monitoring, to which both the newly approved originators and biosimilars are subject32, thus equating the requirements for newly marketed biosimilar medicines – essentially complex monoclonal antibodies – with those intended for medicinal products containing a new active substance. It is therefore significant that the legislation aims to achieve a day-by-day confirmation of the safety profile established at the time of the marketing authorisation, not only for new biological originators, but also for biosimilars, which were also previously authorised on the assumption of their substantial comparability to other products on the market for years and, therefore, they should not need to meet any additional requirements.

From this standpoint, therefore, the marketing authorisation for biosimilars seems to be the requirement to establish, above all, a presumption of safety of the product, capable of achieving "full proof" status by effectively carrying out the post-authorisation studies laid down by the existing legislation and by the additional monitoring.

Consequently, in order for the healthcare professionals to clearly distinguish biosimilars and newly authorised originators subject to additional monitoring from all other medicines, marketing authorisation holders are obliged to include, in the Summary of Product Characteristics (SmPC) and in the package leaflet, the statement "This medicinal product is subject to additional monitoring" (Art. 25, Par. 5, of Regulation (EU) 1235/2010), preceded by the upside-down "black triangle" symbol33. European legislation aims to make the identification of medicinal products subject to additional monitoring clear, not to scaremongering, but to alert clinicians that the current knowledge about the product may be completed, thanks to the ongoing actions.

On the other hand, also in order to ensure a proper monitoring of biological originators and biosimilars "because of their specific safety profile" (see Regulation (EU) 198/2013, Whereas No. 1), their brand name plays a key role. It shall be used continuously by physicians at the time of the prescription, and Member States

32 Article 23 states that additional monitoring refers to "(a) medicinal products authorized in the Union that contain a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the Union; (b) any biological medicinal product not covered by point (a) that was authorised after 1 January 2011". Pursuant to that provision, the Commission Implementing Regulation (EU) No. 520/2012 of 19 June 2012 further clarified EMA obligation to make public a list of medicinal product subject to additional monitoring, including (a) all products containing a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in Europe, (b) biological medicinal products and biosimilars, (c) products whose authorisation is granted subject to certain conditions or in exceptional circumstances, (d) products subject to post-authorisation safety studies (Art. 14, Paragraph 8, Regulation (EU) No. 726/2004).

33 The graphical characteristics of the symbol are specified in Regulation (EU) No 198/2013, which also clearly states the time limit within which the marketing authorisation holders shall include the symbol in the SmPC and the packet leaflet.
shall accordingly ensure its correct tracking and identification. As also stated by the doctrine, the Community legislation requires the identification of the product by its trade mark, since an identification by the name of the active substance alone is not enough, for the purpose of pharmacovigilance. Precisely because the safety profile of biosimilar medicines may not be entirely comparable to the reference originators, the provision’s aim is to monitor the specific biological medicine taken by the patient, and not just the name of its active substance.

34 With regard to this last aspect, Art. 102 (e) of Directive 2010/84/EU imposed on Member States to ensure, through the collection of information and through the follow-up of suspected adverse reactions, that all appropriate measures are taken to identify clearly any biological medicine prescribed, dispensed or sold in their territory. All the foregoing "with due regard to the name of the medicinal product, in accordance with Article 1(20), and the batch number".


36 The document Biosimilars in the EU, op. cit., takes the same view, stating that "for identifying and tracing biological medicines in the EU, medicines have to be distinguished by the tradename and batch number and this is particularly important in cases where more than one medicine with the same INN exists on the market. This ensures that, in line with EU requirements for ADR reporting, the medicine can be correctly identified if any product-specific safety (or immunogenicity) concern arises". In this regard, it is significant that the Summary of Product Characteristics (SmPC) of some biological medicines, as approved by the regulatory agencies, provides the obligation to identify the product in the patient’s card with its tradename. The need to ensure a correct identification of biological medicines also inspired Directive 2012/52/EU of 20 December 2012 on cross-border healthcare, which, in order to facilitate the recognition of medical prescriptions issued in another Member State and the correct identification of medicinal products under different brand names across the Union, accepts that "the brand name should only be used to ensure The conceptual assumption of the provisions of the European Union lies in the awareness of the scientific alterations of each originator and its corresponding biosimilar. This is reflected in the interest, on the one hand, to distinguish them for the purposes of monitoring and, on the other hand, to identify them separately at the time of the prescription.

As further support to the importance of the name of originators and biosimilars, the World Health Organization (WHO) also intervened, within its field of competence about the development of international standards for medicinal products, with particular reference to the attribution of International Nonproprietary Names (INN), namely the "generic name" used to identify the pharmaceutical substances or the active ingredients.

The WHO, in fact, stressed the need to change its current policy on attribution of INNs to biological and biosimilar medicines, because of the complexity of their production process, which has been considered as a crucial step in defining the product’s final features. Precisely for this reason, and also to prevent a possible accidental transition from originator to biosimilar and vice versa (the so-called switch, on which clear identification of biological medicinal products", because of the "special characteristics of those products" (see Whereas No. 4 of Directive 2012/52/EU), thus considering the brand name as a necessary element of differentiation between originators and biosimilars.

37 In the definition of INN, the World Health Organization states as follows: "International Nonproprietary Names (INN) facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A nonproprietary name is also known as a generic name" (see http://www.who.int/medicines/services/inn/en).
we will further focus in the next paragraph), which may compromise the safety profile of the product, the WHO (within the framework of the 55th INN Consultation held in Geneva in October 2012) suggested that biosimilars based on the same active substance should be identified in a peculiar way, combining the common name with a suffix or an identifier, so as to be distinguishable from their originators.  

Lastly, in October 2015 the INN Expert Group suggested that the WHO adopt a system of Biological Qualifiers (BQ) to be assigned to all "biological substances having INNs, to provide a uniform global means of identification to avoid the proliferation of Differing national schemes". In fact, an INN is specific to a given defined substance regardless of the manufacturer and manufacturing site, and therefore has been adequate to identify simple, well-characterised chemical substances, while the complex, microheterogeneous nature of biological medicines does lead to differing efficacy and safety profiles of these substances, therefore requiring additional measures of identification.

Ultimately, it can be noted that the regulatory framework is very precautionary, relativizing or even ignoring the notion of equivalence of biological medicines and therefore – as it will be clarified later – limiting the indiscriminate use of substitution, switch and interchangeability, inevitably affecting the defining of tender lots and, by extension, competition among companies.

All the more reason why the same precautions and the motivation inspiring them must also be transposed into the doctor-patient relationship, so that the latter may acquire information about the therapy suitable for implementing of the patient's right to self-determination, recognized by our legal system.

By virtue of the constitutional principle that no health treatment may be carried out or pursued in the absence of the prior express consent of the person concerned (Art. 32 of the Constitution of Italy), in general, patients are entitled to receive an adequate and comprehensive information on the treatment to which they should be undergoing, thus being able to independently perform a risk/benefit assessment of the medicine and to decide

38 In that regard, see The Food and Drug Law Institute, "It's All About the Name: What is the Imperative of Adopting Unique Names for Biologic and Biosimilar Therapeutics?".

39 According to the WHO document Biological Qualifier, An INN Proposal: "The BQ is an additional and independent element used in conjunction with the INN to uniquely identify a biological substance to aid in the prescription and dispensing of medicines, pharmacovigilance and the global transfer of prescription. The BQ is a code formed of four random consonants in two 2-letter blocks separated by a 2 digit checksum". The referred document is available at: http://www.who.int/medicines/services/inn/WHO_INN_BQ_proposal_2015.pdf?ua=1.

40 See Biological Qualifier, An INN Proposal op. cit. However, it should be noted that, at European level, the proposal to adopt a BQ does not receive unanimous support, as the current EU thinking remains that biosimilars should be closely aligned with their reference medicinal products and that identification by INN together with a qualifier or code for each biosimilar would be contrary to such alignment. For these guidelines, see https://ec.europa.eu/health/files/files/committee/75meeting/pharm697_who_biological_qualifier.pdf. The guidelines of the Federal & Drugs Administration (FDA) seems to be more compliant to the WHO's. After the approval of the Affordable Care Act in 2010, the Agency produced a draft guidance reflecting its current thinking on biological nonproprietary naming, according to which originators and biosimilars should have a four lowercase letter suffix to distinguish similar products, with a unique suffix for each biologic product. For more detailed information on FDA's stance, see http://www.raps.org/Regulatory-Focus/News/2015/08/27/23081/FDA-Issues-Long-Awaited-Biological-Product-Naming-Guidance/.
whether or not to receive the treatment\textsuperscript{41}. Doctor’s obligation of transparency is even more relevant for medicinal products administered in hospitals, where the patient has no possibility to inspect the packaging and see the “black triangle”, at the risk of an informed consent violation\textsuperscript{42}.

More specifically, on the basis of their own peculiarity and of the various precautions dictated by the regulations\textsuperscript{43}, such an obligation is also significant in the relationship between originators and biosimilars. It is therefore appropriate for the physician to assess whether to inform patients about their therapeutic choice, so as to let the patients exercise their right of self-determination\textsuperscript{44}. On the other hand, alongside the role of the patient, the freedom of choice currently attributed to the healthcare practitioner is also paramount.

European legislation attributes without question the final decision on the treatment to be administered to physicians\textsuperscript{45}, with a preference for the medication they consider safer for the patient\textsuperscript{46}. Any liability for the chosen therapy also lies with the doctor, as confirmed by case-law and national legislation\textsuperscript{47}.

\textsuperscript{41} In this regard, see L. Pani, S. Montilla, G. Pimpinella and R. Bertini Malgarini – Italian Medicines Agency, Biosimilars: the paradox of sharing the same pharmacological action without full chemical identity, in Expert Opin. Biol. Ther.13/2013, 2.


The on same issue, see G. Guerra, Farmaci di origine biologica e biosimilari: quale livello di sicurezza per prodotti innovativi? (Biological medicines and biosimilars: what level of safety for innovative products?) (parte I), published on the Fondazione Giannino Bassetti’s website (http://www.fondzionebassetti.org/it/focus/2013/03/farmaci_quale_cicurezza_per_produit_innovativi.html).

\textsuperscript{44} On medical information about the available biological alternatives, see G. Guerra, Farmaci di origine biologica e biosimilari: profili di responsabilità medica (parte II) (Biological medicines and biosimilars: medical liability issues - part 2), published on the Fondazione Giannino Bassetti’s website (http://www.fondzionebassetti.org/it/focus/2013/04/farmaci_di_origine_biologica_e_b.html). In this article, the author particularly assumes the possible content of the report given by the doctor to the patient in case of administration of biological medicines, taking account of their particular complexity (for example, the possible therapeutic alternatives, the molecular peculiarities of the medicine, the precautions about the medicine label imposed by European legislation). More in general, see C. Brignone, Auto determinazione e informazione, salute e consenso informato: tra strumenti normativi e prassi giurisprudenziali (Self-determination and information, health and informed consent: regulatory instruments and jurisprudence), available at: www.fondazionebassetti.it. The patient’s active and preventive involvement is even more necessary if the doctor intends to modify the current therapy, switching from the originator to the biosimilar and vice versa, a process on which we will focus in the next paragraph. In this regard, see Biosimilars in the EU, op. cit.

\textsuperscript{45} See Court of Justice, 5 May 2011, Case C-316/09, MSD Sharp & Dohm, ECLI:EU:C:2011:275.

\textsuperscript{46} See Judgment of Court of Cassation, Third Civil Division, No. 8875 of 8 September 1998.

\textsuperscript{47} See Judgment of Court of Cassation No. 4391/2012, Judgment of Court of Cassation, Fourth Criminal Division No. 8257/2011. For a wide examination on the issue of liability in the prescription of medicines, see F. Massimino, La responsabilità nella prescrizione dei farmaci tra scienza, coscienza e condizionamenti normativi (Liability in the prescription of medicines: science, conscience and regulatory conditioning), in Danno e Responsabilità (Damage and Liability), No. 1, 2013, p. 5.

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In this context, the recent provision contained in Law No. 232 of 11 December 2016 (Budget Law 2017) gives the clinician the opportunity to opt from time to time for the *originator* or biosimilar medicine considered to be more appropriate for the individual patient, if the biological active substance authorised for the same treatment is consistent, even through a public tendering procedure that respect the principles of competition. For this reason, as it will be better observed later, it is legitimate that the pharmaceutical companies manufacturing *originators* or biosimilars release scientific information and advertising to the medical community, illustrating the features of their medicinal products in order to present to the prescribers the trial, clinical and pharmacovigilance data capable of better helping them in the therapeutic choice, placing them in the conditions to provide patients with any appropriate information on the chosen medication.

### 3. BIOSIMILARITY, INTERCHANGEABILITY, AUTOMATIC SUBSTITUTABILITY AND SWITCHING

As specified by the AIFA, the *originator* and its biosimilars are "essentially similar in terms of quality, safety and efficacy"\(^{48}\), or – as stated by the EMA – "no differences are expected in safety and efficacy"\(^{49}\). These statements are based on the concept of biosimilarity – which cannot in any way be mistaken with therapeutic equivalence, only applicable to medicinal products manufactured by chemical synthesis\(^{50}\) – and of a prognostic assessment made by regulatory agencies, pending the confirmation of the clinical data.

On the other hand, the current legal framework confers to the AIFA the exclusive competence to determine whether there is an equivalence among medicinal products containing different active substances, as a prerequisite for their grouping in the same tender lot\(^{51}\). The practical application of this regulation generated significant litigations regarding public tenders for the procurement of medicinal products, including also biological *originators* and their corresponding biosimilars\(^{52}\).

Moreover, trying to clarify the interpretative and enforcement uncertainties, the AIFA issued Resolution No. 204 of 6 March 2014, summarizing the guidelines for the correct

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\(^{48}\) See the *Second AIFA Concept Paper* op. cit.

\(^{49}\) As so in *Biosimilars in the EU*, op. cit.

\(^{50}\) See F. Massimino, *Medicinali biologici originatori e biosimilari* (Originator biological medicines and biosimilars), op. cit., p. 333. In particular, as to the differences between the therapeutic equivalence of biological medicine and chemically-synthesized medicines, see Molise Regional Administrative Court, Judgment No. 118/2013 of 15 February 2013; G. Guerra, *Farmaci di origine biologica e biosimilari: quale livello di sicurezza per prodotti innovativi? (parte I)* (Biological medicines and biosimilars: what level of safety for innovative products? - part I), op. cit.

\(^{51}\) In particular, this principle has been regulated by the Decree-Law No. 95/2012, converted into Law No. 135/2012, which has determined, at Art. 15, Par. 11b, that "in adopting decisions based on therapeutic equivalence among medicinal products containing different active substances, Regions shall adhere to the motivated and documented assessments made by the AIFA".

\(^{52}\) For any additional information on the case law on therapeutic equivalence between originators and biosimilars, see F. Massimino, *Medicinali biologici originatori e biosimilari* (Originator biological medicines and biosimilars), op. cit., p. 348.
enforcement of the aforementioned Article, thus defining the procedure for the provision of the equivalence assessment and the scope of the regulation. However, the "originator biological medicines and their corresponding biosimilars" are excluded from said regulation. The AIFA believes, in fact, that the identity of the active substance and the assessment of biosimilarity through comparability studies carried out by the EMA at the time the marketing authorisation was granted may exclude the presence of clinical differences with their originators so considerable to require an additional assessment by the AIFA on their comparability. The same concept was subsequently confirmed with Resolution No. 458 of 31 March 2016, under which the criteria for the equivalence assessment among different medicinal products have been clarified in more detail. However, following the criticism coming from the medical community and the litigation introduced by pharmaceutical companies, Resolution No. 458/2016 was revoked by the AIFA “in autotutela” (through self-correction procedure) with Resolution No. 1571 of 20 December 2016.

The question remains as to whether AIFA – whereby assimilating the assessment of equivalence to the regulatory assessment of biosimilarity, pursuant to Art. 15, Par. 11b of Decree-Law No. 95/2012 – intended speeding up and facilitate competition between originators and biosimilars, and for purpose, came to the conclusion that, in pharmacological terms, seems to be rather hasty.

On the other hand, a similar aim seems to also inspire the judgment of the Consiglio di Stato (“Council of State”) No. 5478 of 3 December 2015. It acknowledges, with inconstant motivations, that originators and biosimilars can never be fully identical, then stating that "although, to some extent, different from each other [...] they may be used as if they were equivalent". Not without some scientific and logic approximation, the Consiglio di Stato concludes that the residual differences are not such as to exclude the possibility that originators and biosimilars can be used "as if they were equivalent", and therefore enter the same competitive tenders.

However, the same regulatory agencies are not totally persuaded that originators and biosimilars may be prescribed and administered "as if they were equivalent", and for this reason recommend additional caution to that already discussed in the previous paragraph.

In this respect, it is necessary to recall what the same AIFA specifically stated, clarifying on several occasions that originators and biosimilars can be considered interchangeable only on the basis of the clinician’s assessment, and, above all, that they cannot be automatically substituted by pharmacists, who therefore cannot arbitrarily replace their judgement with that of the prescribing physician upon dispensing [the medicinal product]. The pharmacist is therefore subject to a restriction of the discretionary power.

53 See the Second AIFA Concept Paper op. cit.
54 According to WHO’s definition, an interchangeable medical product is "one which is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice" (ref. WHO Technical Report Series, No. 937, 2006). Interchangeability refers to the medical practice of substituting one medicine with another which is expected to produce the same clinical effect in a given clinical context and in any patient. The switching can be carried out at the initiative or with the agreement of the prescribing physician (Biosimilars Consensus Information Paper’s definition).
attributed to them by Law No. 405/2001 regarding the substitution of chemically-synthesised generic medicines, which can actually be "used as if they were equivalent", and therefore administered in a fungible way.

According to the AIFA, therefore, the choice of treatment with a reference biological medicine or with a biosimilar remains a clinical decision, entrusted to the prescribing physician. Such consideration also applies to patients already going under treatment: here too, the opportunity to switch remains entrusted to the doctor’s judgement. Lacking any adequate switching studies, therefore, the physician is the only person empowered to decide on the possible switch among biological medicines, on the basis of the individual characteristics of the patient and after consultation with the latter.

In this perspective, then, the public tender and the structuring of lots shall guarantee the physician’s prescriptive freedom and, above all, the therapeutic continuity for patients already administered with the originator or biosimilar, on sustainable conditions and prices for the National Healthcare Service. The cautions recommended by the regulatory agencies, do not exclude any competition between originators and biosimilars, rather requiring that their grouping in a single lot – specifically in the early stages of marketing of the biosimilar, when there are certain margins of uncertainty about their effects – does not preclude the plurality of choices available to the doctor.

Moreover, with reference to epoetin alfa biosimilars, present on the market since 2008, in 2016 the Società Italiana di Farmacologia (Italian Society of Pharmacology) has detected the existence in Real World Evidence clinical data that fully confirms their safety and efficacy, even in case of switching. See file:///C:/Users/Massim0f/Downloads/sif_position_paper_working_paper_biosimilari_set16.pdf.

56 On the active involvement of the patient, see Biosimilars in the EU, op. cit.

57 With reference to the price difference between originators and biosimilar and, more specifically, to the jurisprudence on the reference price of biologicals in public tenders, in the light of Art. 17 of Law No. 111/2011 on rationalising healthcare expenditure, see F. Massimino, Medicinali biologici originatori e biosimiliari (Originator biological medicines and biosimilars), op. cit., p. 354.

58 See G. Guerra, farmaci: quale livello di sicurezza per prodotti innovativi (parte I) (Biological medicines and biosimilars: what level of safety for innovative products? - part I), op. cit.; S. Cassamagnaghi and V. Miani, Miani, Gare per l’acquisto di farmaci tra tutela della salute e le esigenze di contenimento della spesa pubblica. Il caso dei biosimiliari (Tendering procedures for buying-in of medicinal products: health protection and need for the containment of public spending. The case of biosimilars), op. cit.

55 On this matter, see C. Scavone, C. Rafaniello, L. Berrino, F. Rossi, A. Capuano, Strengths, weaknesses and future challenges of biosimilars’ development. An opinion on how to improve the knowledge and use of biosimilars in clinical practice, in Pharmacological Research, November 2017, whose abstract reads as follows: “The development of biosimilars follows a well-defined step-wise approach, the so-called comparability exercise, which aims to compare non-clinical (mainly quality features and biological activity) and clinical (efficacy and safety profiles) features of new biosimilars with their respective reference products. Despite the undeniable advantages of such procedure, there are still some concerns about it (such as the absence of switching studies or the evaluation of efficacy and safety in all therapeutic indications). In particular, the European regulatory framework on biosimilars approval does not include the conduction of switching studies demonstrating the interchangeability to be carried out before marketing authorization. This is one of the main aspects negatively affecting healthcare professionals' clinical decisions on switching. In order to achieve a better knowledge on safety and efficacy of biosimilar drugs, real world data should be collected and post-marketing efficacy and safety clinical studies (including those evaluating specific endpoints, therapeutic regimens and patients’ population), should be planned. Furthermore, the conduction of well-designed switching studies is highly advisable, especially when biosimilar drugs are used in oncology settings. Lastly, considering the critical role of anti-drug antibodies on efficacy/safety profile of biologic drugs, studies based on therapeutic drug monitoring would be useful in order to achieve treatment optimization. Implementing the above strategies could be helpful to fill the gap in knowledge observed in the present European biosimilar regulatory framework”.

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For this purpose, they provide the presence of separate lots for therapeutic continuity and potential exclusive indications, or in any case ensuring the possibility of purchasing medicines not awarded through tender, without constraints or restrictions being applied. In paragraph 5.3 we will analyse the procedures and criteria whereby competition between originators and biosimilars in public tenders was reconciled with the principle of prescriptive freedom of the doctor and therapeutic continuity, on the basis of the discipline provided by Art. 1, Par. 407 of the 2017 Budget Law.

4. AGCM'S ADVOCACY ON BIOLOGICAL ORIGINATORS AND BIOSIMILARS

Although the first biosimilars have been authorised in Italy for only a few years, the Autorità Garante della Concorrenza e del Mercato (the “Italian Competition Authority”, hereinafter, "AGCM" or "Authority") has already taken care of their competitive relationship with originators on several occasions.

The first fact concerns the Recommendation of 22 March 2011, issued pursuant to Art. 21 of Law No. 287/1990, in which the AGCM dwelt on a draft law under consideration in the Parliament. It contained the prohibition of grouping biological originators and their corresponding biosimilars in the same lot, and the Agency has criticised the possible negative impact on competition.

As it is known, the specification of tender lots constitutes a potentially delicate phase, because the identification of required products and their characteristics allows the institution identifying the purchased good and selecting – since a preliminary phase of the procedure – the participating companies. This activity, therefore, shall be exercised by the institution in accordance to Art. 30, Par. 1 of the Decree-Law No. 50/2016, which quotes the provisions under Art. 2, Par. 2 of Decree-Law 163/2006 (Codice degli Appalti Pubblici, “Public Procurement Code”). This Article states that the entrusting of medical supplies shall be of quality, take place in accordance with the principles of economy, effectiveness, timeliness and fairness, and also ensure free competition, equal treatment, proportionality, non-discrimination and transparency. Similar aims – to be reconciled

59 As it is well known, some therapeutic indications may be secondary-patent protected, and therefore – even in the presence of a biosimilar on the market – it is necessary that, in defining the tender lots, the contracting authority takes into account the exclusive right of the originator's patent holder. Similarly, when defining the lots, it shall also be taken due account of the indications for which the originator has been recognised as reimbursable according to Law No. 648/1996. As also confirmed by the Second AIFA Concept Paper, op. cit., the granting of this extraordinary reimbursement to the biosimilar is not automatic, but decided, case by case, by AIFA's Commissione Tecnico Scientifica ("Scientific Technical Committee"), on the basis of an evaluation of clinical data, after its marketing. Before this decision, the holder of the originator shall benefit from the exclusivity for such indication, which is further reflected in the tender lots.

60 Bull. 11/2011. More specifically, the AGCM pushed for the amendment of the Draft Law No. 1875, as submitted during the 16th Legislature. With reference to AGCM's advocacy of biologics originators and biosimilars, see. R. Chieppa, Tutela della salute e concorrenza – concorrenza, qualità e sostenibilità per il welfare sanitari, in Sanità pubblica e privata, 1/2017, p.10 ff.

61 With regard to the general theme of public tenders for medicinal products, see the Indagine conoscitiva sulle gare per la
with the need to ensure that physicians are free to prescribe the medicine they consider to be the most appropriate for the treated conditions – have traditionally been transposed by institutions through the issue of defined public tenders, so that to each active substance, or even to each formulation, correspond a single lot, subject of independent and separate award (the so-called "Simple Lots").

Notwithstanding such procedure, however, some Regions, Aree Vaste ("Large Administrative Areas") or Hospitals – especially for certain classes of chemically-synthesised medicines considered to be therapeutically comparable, but sometimes also for some specific categories of biological medicines – decided to group different active substances in the same lot (the so-called "Composite Lots"), identifying, through the tender, only one medicine per pathology.

In the light of the fact that the draft law intended to substantially prohibit the grouping of reference biologicals and biosimilars in the same tender lot, in March 2011 the AGCM pinpointed a potential distortion of competition, determined by what appeared as an improper segmentation of a single relevant market. According to the Authority, the protection of health could have been safeguarded by means of tender clauses ensuring the therapeutic continuity of patients already treated with the biological medicine, without prejudice to the possibility that the competition between originators and corresponding biosimilars in the same lot could guarantee greater savings to the purchasing institution.

In May 2013, the AGCM came back to evaluating the competitive parameters related to public tenders of biological medicines. More specifically, with respect to the statements made in March 2011, the Authority confirmed its recommendation to strengthen the tender as a competition instrument, by directly comparing – through the new procedures (Art. 15, Par. 3(d) of Decree-Law No. 95/2012, converted into Law No. 135/2012) – originators and equivalents or biosimilars upon patent’ s expiry, and not only by renegotiating the supply price with the awarding undertakings on an exclusive basis.

However, the AGCM also covered the eventuality that exclusive purchasing of biological originators were carried out, provided that they were subject to objective criteria (i.e. percentage of patients already treated vs. naïve drug patients) and to subsequent revisions, in the event of a biosimilars’ competitive development. Although public tenders were believed to be a key competitive factor, the possibility of separate

62 On the composition of tender lots for biological medicines and the corresponding competitive issues, see F. Massimino, Farmaci biologici e biosimilari e tutela della salute e della concorrenza (Biological medicines and biosimilars, protection of health and competition), in Dir. Industriale (Industrial Law), 4/2012, 328 et seq. It is useful to point out that, with Ruling No. 1744 of 31 October 2012, the Regional Administrative Court of Toscana declared unlawful the Regional Council Resolution No. 528/2011, which confirmed the therapeutic equivalence of two biological medicines intended to treat rheumatic and dermatological diseases, in the absence of adequate scientific investigation.

63 See Bull. 21/2013.
lots for **originator** biological medicines and biosimilar were considered.

This provision, however, appears no longer to apply, in favour of the most recent Authority guidance on the competition relations between biotechnological medicine and their corresponding biosimilar versions, as well as a result of the novelties introduced by the 2017 Budget Law.

On November 17, 2016, in fact, the AGCM expressed an opinion pursuant to art. 22 of Law No. 287/1990, in relation to Art. 59 of the Draft Law Bilancio di previsione dello stato per l’anno finanziario 2017 e bilancio pluriennale per il triennio 2017-2019 (State’s Estimate Budget for the financial year 2017 and Multi-Annual Budget for the three-year period 2017-2019), at the time under consideration at the Camera dei Deputati (“Chamber of Deputies”). In short, Art. 59 of the Draft Law provided: (a) that biotechnological medicines (originators or biosimilars) could only be purchased through framework agreements with a basis of the call for tenders corresponding to the highest price of the originator medicine, that is to say, the most expensive product among those available; (b) the exclusion of any possible automatic substitutability between the originator medicine and its biosimilar version, as well as among biosimilar versions of the same originator; (c) the prohibition of direct tender of medicinal products with the same therapeutic indications but having different active substances.

With reference to the aforementioned regulation, the AGCM, in view of an incentive for the use of biosimilars, stated that the provision that biotechnological drugs and their biosimilars should be purchased on the basis of framework agreements is to be appreciated but, at the same time, it strongly contested the choice of considering the maximum price as a basis for the purchase of biosimilar drugs. The Authority bases its criticism essentially on the consideration that setting the starting invitation to tender at the highest price level "discourages any possible stimulus to the presentation of competitive offers", whereas the starting invitation to tender – according to the Authority – could have been fixed at price levels attributable to the availability of several competing products (e.g.
at an average of the prices of the products, or, along the same lines of the actions taken with the so-called transparency lists for the purchase of a generic medicine, once the originator’s patent has expired. Furthermore, as it regards the modality of continued supply of the framework agreements, the AGCM stated that the application of such instrument should be assessed in relation to the operational reality of biotechnological medicines purchases. The definition that patients should be treated with one of the first three drugs in the ranking of the framework agreement, together with the specificity of these products (which restricts their number), implies that a good part of all the products available on the market may be included in the purchase agreements (i.e. the reference biological and its few biosimilar versions). If this can be evaluated in a positive way, because of the guarantee of a wide therapeutic availability for clinicians, in a competitive perspective the discipline of competition should be developed in order to stimulate the comparison – on the lowest price, that is on the most economically advantageous offer – among operators who are suitable to supply.

It should also be noted that, in the opinion at issue, there is no lack of investigation into the exclusion of any possible automatic substitutability between the originator and its biosimilar version, or among biosimilar versions of the same originator. More specifically, the Authority acknowledges that the aforementioned Article 59 reiterates operational conditions already in force in Italy, but it also notes that this position could block any possible future developments in the perspective of an automatic substitutability between an originator biotechnological medicine and its biosimilars. Furthermore, in the opinion of the Authority, the prohibition of issuing a call for tenders for medicines with the same therapeutic indications but different active substances could constitute an obstacle to direct competition of medicines with different active substances not only in relation to biotechnological products, but also for chemical-based ones.

In other words, the AGCM does not seem to fully transpose the cautions recommended by the national and European regulatory authorities, instead proposing its own point of equilibrium and conciliation between public health needs and the aim of enhancing competition.

As it will be explained in more detail in the following paragraphs, when drawing up the 2017 Budget Law, the legislator transposed some of the assessments set out in the Authority opinion.

5. THE 2017 BUDGET LAW

The effect of the choice to use biological and biosimilar medicines is extremely important, considering the criticalities inherent to these medicinal products and the need to combine the protection of competition with a high degree of patients’ safety and the freedom of the prescribing physician to choose the treatment he/she deems to be right.

The choices of all the involved parties in using these medicinal products affect, directly or indirectly, the safety of the patients being treated with biological or biosimilar medicines.
and the sustainability of the NHS. For this reason, all players involved are expected to act responsibly: (i) pharmaceutical companies shall market their medicine having in mind both patients' and NHS' needs, in addition to their own profit-seeking; (ii) the physicians shall be transparent and choose advisedly the most appropriate medicines, sharing with the patient every information useful for them to be actively involved with the treatment; (iii) the public administration shall provide for tenders taking into appropriate account the peculiarities of the biological/biosimilar medications and the need to ensure that doctors have access to said medications when facing real clinical needs.

In order to pursue all the above-mentioned purposes, the regulatory framework for the purchase of biological and biosimilar medicinal products by the NHS has been definitively clarified by the law No. 242 of December 2, 2016 (2017 Budget Law), which introduced, in Article 1, Paragraph 407, an amendment to Article 15 of Decree-Law No. 95 of 6 July 2012 (converted, as amended, by Law No. 135 of 7 August 2012)

The amendments introduced were aimed at encouraging the spread of biosimilar medicinal products, once the patents of the reference medicine expire, and at stimulating price competition between off-patent medicines, which is essential to make the inclusion of new-generation medicines in hospitals economically viable (for this reason, in general, with a high price), taking always into account as a priority the safety and protection of patients, of which the doctor is the guarantor.

The key principles of the 2017 Budget Law, which will be considered in detail below, are: (i) the prohibition of automatic substitutability between a reference biological medicine and its biosimilar or between different biosimilars; (ii) the priority given to the physician's freedom of prescription; and (iii) the tool of framework provisions shall apply: (a) the public procurement procedures shall be carried out by use of framework agreements with all economic operators when medicinal products based on the same active substance are more than three. To this end, the regional central purchasing agencies shall provide a single lot, for the establishment of which it shall be considered the specific active substance (Fifth level ATC), the same dosage and route of administration; (b) in order to ensure effective rationalisation of expenditure and at the same time a wide availability of therapies, patients should be treated with one of the first three medicines in the framework agreement ranking, classified according to the lowest price criterion or the most economically advantageous bid. However, the physician is free to prescribe the medicine, among those included in the procedure referred to in point (a), which is considered appropriate to ensure the therapeutic continuity to patients; (c) in the event of expiry of the patent or the supplementary protection certificate of a biological medicinal product during the period of validity of the supply contract, the contracting agency shall, within sixty days from the date of marketing of one or more biosimilar medicinal products containing the same active substance, open the competitive comparison between these [products] and the reference originator medicine in accordance with the provisions of points (a) and (b); (d) the contracting entity shall be obliged to supply to the prescribers the products awarded in accordance with the procedures laid down by Legislative Decree No. 50 of 18 April 2016; (e) any additional economic charges arising from failure to comply with the provisions of this paragraph shall not be charged to the National Healthcare Service".
agreement in public procurement procedures for biosimilar medicines.

5.1 Automatic substitutability

Pursuant to the aforementioned provision of the 2017 Budget Law: "The existence of a biosimilarity relationship between a biosimilar medicine and its biological reference only exists where it is established by the European Medicine Agency (EMA) or the Agenzia Italiana del Farmaco (Italian Medicine Agency), with due regard to their respective competences. Automatic substitutability between the reference biological medicine and its biosimilar or between biosimilars is not permitted".

Hence, the exclusive competence of finding a biosimilarity relationship between a biosimilar medicine and its reference biological lies with the European Medicine Agency (EMA), while the assessment about the reimbursability of the medicine, and the resulting application of the rules for the negotiation of prices already provided for generic medicines, falls within the scope of the AIFA.

As to EMA’s exclusive competence, it is worth underlining that it could have already been inferred from the European legislation. The Italian provision, therefore, is more of an element of reinforcement, useful in preventing distortions in the procurement procedures at a regional or central level, for the purpose of grouping biological medicines with different active substances in the same tender lot.

Moreover, the provision prohibits the substitution between the biological originator and the corresponding biosimilar and between different biosimilars, a prohibition already upheld by the case-law.

The concept of substitutability refers to the possibility of substituting a medicinal product with another bioequivalent, more cost-effective for the NHS or for the patient, with the same qualitative and quantitative composition, form and route of administration. The bioequivalence must be confirmed by suitable bioavailability studies.

In this context, it is the pharmacist who plays a crucial role in his/her faculty or obligation to automatically substitute the medicine, even modifying a therapy that has already been initiated, subject to the indication of non-substitutability issued by the treating physician.

An example in this sense is contained within Art. 7 of Law No 405/2001 regarding generic medicines, which provides for the drawing up of a transparency list, configuring a case of "secondary substitutability", implicitly based on price

67 In this regard, see Judgment of the Consiglio di Stato ("Council of State") No. 616/2017, and Judgment of Lazio Regional Administrative Court (TAR) No. 3654/2017, which expressly recall the principle in question, stressing that "the automatic substitutability between reference biological medicine and its biosimilar or between different biosimilars is not permitted".

68 Quite different is the concept of "interchangeability", which the Second AIFA Concept Paper, op. cit. – on the basis of the statements made the World Health Organization – defined as the clinical practice of substituting, on the initiative or with the agreement of the prescribing physician, a medicine with another, having the same risk-benefit balance and expecting to have the same clinical effect. In the latter case, the clinician is the key figure, called upon to determine if two medicines can really be comparable in relation to the individual patient. See WHO Technical Report No 937, 2006. According to the document Biosimilars in the EU, the decision on whether to allow interchangeable use of the reference biological medicine and the biosimilar can be taken at a national level.
competition between undertakings. In the presence of more chemically-synthesised medicines, in fact, the pharmacist is \textit{a fortiori} entitled to dispense the more affordable one, without consulting the prescribing physician, on the basis of relevant legal provisions on prescription per active substance\textsuperscript{69}.

As far as biosimilars are concerned, the European \textit{soft law} entrusted each State's Regulatory Agencies with decision-making autonomy on automatic substitutability. In particular, the EMA has published its own guidelines on development and authorisation of the different categories of biosimilars\textsuperscript{70}, thus seeking to steer the Regulatory Agencies – more than the health professionals – in this direction. The European Agency stated that its recommendations on the marketing of medicinal products do not specify whether biosimilar medicines should be used in an interchangeable way: the decision on prescribing a specific medicine, originator or biosimilar, is to be entrusted to qualified health personnel\textsuperscript{71}.

In Italy, the AIFA has drawn up a clear line of demarcation between what is permitted for chemically-derived medicinal products and their generics – which are equivalent, and

\textsuperscript{69} The issue of whether to allow prescription by mention of the active substance alone (or together with the trademark of the reference medicine), if more than one equivalent medicine is available on the market, has been the subject of multiple and troubled interventions by the legislator. Starting from Article 11, Paragraph 12 of Law No. 27/2012 ("Decreto Liberalizzazioni"), the discretion of the doctor or the pharmacist has been extended or reduced from time to time, also attributing to them variable information obligations to the patient. With specific reference to this aspect, see S. Marino, \textit{Informazione sui farmaci e tutela del paziente nel c.d. "decreto liberalizzazioni" (Information on medicines and patient protection in the so-called "Decreto Liberalizzazioni")}, in Dir. Ind. (Industrial Law), 2012, 3, 263.

Art. 13a of Law No. 221/2012 replaced Art. 15, Paragraph 11a of Decreto-Law No. 95/2012, converted into Law No. 135/2012, which had in turn amended Article 11, Paragraph 12 of Law No. 27/2012, and established that – in the event that generic medicines are present on the market – the physician treating a patient for the first time for a chronic disease or for a new episode of a non-chronic condition is required to indicate in the prescription the name of the active substance, or the trade name of the medicinal product accompanied by the indication of the active substance. The indication of a specific medicinal product is binding for the pharmacist if the clause of non-substitutability referred to in Art. 11, Par. 12, of Decreto-Law No. 1 of 24 January 2012, converted as amended, into Law No. 27 of 24 March 2012, is specified in the prescription, and accompanied by a concise justification.

\textsuperscript{70} Starting from 2005, the EMA, through the "Committee for Medicinal Products for Human Use" (CHMP), issued general guidelines on the production process of medicines containing active substances derived from proteins, with particular emphasis on pre-clinical, clinical, quality and immunogenicity related issues. More guidelines followed, relating to more specific categories of medicines, such as those containing recombinant erythropoietin, low molecular weight heparin, somatropin or interferon alpha, and monoclonal antibodies. For all these products, the rudimentary definition of "highly complex biosimilars" was created, in an effort to highlight their being more technically complex than other biosimilars already on the market.

At the national level, in addition to the AIFA Position Papers, it is appropriate to recall the aforementioned document of the \textit{Società Italiana di Farmacologia ("Italian Society of Pharmacology")}, addressed both to health institutions and to prescribers. It contains precautionary recommendations for the prescription of medicines still subject to additional monitoring, which seem to be inspired by the scaling principle, aimed at achieving a definitive assessment of their safety profiles prior to their generalised adoption (on a similar view, see L. Pani, S. Montilla, G. Pimpanella and R. Bertini Malgarini – Italian Medicines Agency, \textit{Biosimilars: The paradox of sharing} op. cit., 3). For this reason, the prescription of the complex biosimilar must be preceded by an evaluation specific for each patient, based on the available safety data, avoiding any automatism implying its use for the naïve patient.

\textsuperscript{71} Doc. Ref. EMEA/74562/2006 Rev. 1; EMA/837805/2011. On the same line, more recently, \textit{Biosimilars in the EU}, op. cit.
therefore reciprocally substitutable —, and what applies to biosimilars and reference originators.

Although there is definitely a relationship of similarity between biological and biosimilar, this affinity cannot be understood in terms of identity, and this contributes to exclude the possibility that the pharmacist can autonomously decide to actively intervene on a choice made by the doctor at the time of prescription, substituting the biological originator with its biosimilar or vice versa.

With this in mind, the AIFA decided, with its own Position Paper on biosimilars of May 2013 (updated in June 2016), not to include biosimilar medicines in the transparency lists allowing automatic substitutability between equivalent products. This decision was made with the aim of excluding biological medicines from a mechanism which, for chemically-synthesis products, limits the reimbursability to the lowest-price product on the market containing the same active substance, based on the assumption of complete interchangeability derived from equivalence assessment made on a statistically significant population of patients.

According to the AIFA, therefore, the biological originator and the biosimilar are different and alternative therapeutic options, between which the doctor can choose according to each patient's need, his/her clinical presentation and the benefit-risk balance determined on a case-by-case basis.

Additional caution should be exercised in assessing indications granted via extrapolation and, therefore, authorised by the regulations but not necessarily corroborated by strong clinical data.

The need to protect the patient, naïve or already treated, from the potential risk of modifying an ongoing therapy, by substituting a medicine with another whose effects have not been assessed on the single patient, outweighs the price and competition logic, entrusted to the pharmacist's management. The guarantor of this protection can only be the physician, the person who better knows the patient's clinical picture.

On the other hand, the decision of the AIFA not to consider the biological originator and biosimilars comparable and substitutable also emerges from the provisions contained in 2013 and 2016 Position Papers, concerning the maintaining of the list referred to in Art. 1, Par. 4 of Law No. 648/1996.

By this provision, the legislator aims to protect the patient's health by allowing him/her to access unauthorised medicines without any direct payment, if there are no authorised therapeutic alternatives.

The financial burden...
at the NHS charge, if the medicine used off-label is included in a special list, as drawn up and periodically updated to this end by the Commissione Unica del Farmaco ("CUF") ("Single Medicine Committee") 75.

Law No. 648/1996 therefore provides exceptional NHS funding of an unauthorised pharmacological treatment, albeit founded on to constant uncertainty related to the characteristics of medicines which have not yet concluded the clinical trial process. In this case, the AIFA has considered it inappropriate exposing the patient to a situation of uncertainty about a biosimilar of which no clinical data for such use are available. In the 2013 and 2016 Position Papers, it excluded the automatic insertion of a biosimilar in list 648, even if its reference biological originator is already present.

The inclusion may occur only as a result of a case-by-case assessment carried out by the CTS, "on the basis of the available evidence and scientific literature, of the clinical experience and of the imputability of the therapeutic action to the same mode of action."

On the basis of the considerations summarized here, the 2017 Budget Law – by a hierarchically higher act than the opinion expressed by the Regulatory Agency – confirmed the exclusive role of the physician in the prescription choice, which must be exercised by specifically indicating the biological medicine’s brand name and by including a detailed record keeping of possible adverse effects (Directives 2010/84/EU and 2012/52/EU). The hospital’s pharmacist shall not be able to interfere in any way with this choice by substituting the prescribed biological medicine with another. As said before, the principle of non-substitutability relates to scientific assessments, which require to be interpreted and correctly applied under competition rules, by carefully evaluating if prohibiting the substitution implies that originators and biosimilars are not interchangeable and, therefore, should be placed within distinct relevant markets. In the following paragraphs, we will examine the balance among these issues identified by the 2017 Budget Law.

5.2 The physician's freedom of prescription

Since substitution has been prohibited, the role of the treating physician becomes of fundamental importance, as set forth in the 2017 Budget Law, specifically in the part pertaining to tender procedures. Article 1, paragraph 407(b) provides that "in order to ensure effective rationalisation of expenditure and, at the same time, a wide availability of therapies, patients should be treated with one of the first three medicines in the framework agreement ranking, classified according to the lowest price criterion or the most economically advantageous bid. However, the physician is free to prescribe the medicine, among those included in the procedure referred to in point (a), which they consider appropriate to ensure therapeutic continuity to patients".

As it will be better clarified in the next paragraph, the structure of public tenders, by means of framework agreements, must ensure

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75 As a result of Law No. 326/2003, the AIFA’s Commissione Tecnico Scientifica (CTS) ("Scientific Technical Committee") has replaced the CUF ("Single Medicine Committee") in the functions it has been conferred by the legislation, including the list 648 updating.
that the doctor have "a wide availability of therapies", so as to allow him to choose the most appropriate medicine for each case, among the first three in the ranking list. This without prejudice to the freedom of the physician to prescribe the medicine ensuring therapeutic continuity for the patients already under treatment, provided that it falls among those which participated in the tender procedure.

Besides, the same AIFA - in its 2013 and 2016 Position Papers - already stressed that the choice to treat a patient with a reference biological medicine or with its biosimilar constitutes a clinical decision and, therefore, must be entrusted to the prescribing physician only, with no external interference. The well-established principle, in relation to a specific type of pharmacological therapy, whereby the practising health professional is accountable for the medical treatment administered to each patient, to the best of their knowledge and belief, and in accordance with the scientific information, is thus reaffirmed also at the regulatory level.

In the light of these assumptions, one of the guiding principles that steer the medical practice is now recognized also by a budget law. This is not a trifling detail, being indeed a sign of the legislator's full awareness of the need to subordinate health priorities to financial needs. The freedom to choose the treatment and the resulting accountability are the basis for the doctor's professional activity. This is instrumental to the application of Art. 32 of the Italian Constitution, which raises health to the level of citizen's inviolable and absolute right, both in relation with private individuals and with the public administration.

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76 See Alessia Squillace, Claudio Amoroso, Sabrina Nardi, Tomino Accetti (eds.), Indagine civica sull’esperienza dei medici in tema di aderenza alle terapie, con focus su farmaci biologici e biosimilari (Civic survey on medical experience with adherence to therapies, with focus on biological and biosimilar medicines), http://www.cittadinanzattiva.it/files/rapporti/salute/indagine-aderenza-terapie-focus-farmaci-biologici-biosimilari.pdf.

77 Along the same line, see also the Second AIFA Concept Paper, op. cit.

78 Art. 13 of the Italian Code of Medical Ethics of the Federazione Nazionale dei Medici Chirurghi e degli Odontoiatri ("National Federation of Surgeons and Dentists"), in the edition of December 2006 currently in force, gives to the professional the freedom of choice and, on the other hand, the accountability for the information given to the patient, aimed at achieving their consent to the treatment (Articles 33-35). The general practitioner's right to prescribe, to the best of their knowledge and belief, is legislated by Art. 15a of the Presidential Decree No. 70/2000. In respect to the doctor's freedom of prescription, see F. Massimino, La responsabilità nella prescrizione dei farmaci tra scienza, coscienza e condizionamenti normativi (Accountability in the prescription of medicines: science, conscience and regulatory conditioning), in Danno e Responsabilità (Damage and Accountability), 2013, 1/2013, 5 ff.


80 In this respect, see the Constitutional Court's Ruling No. 88 of 26 July 1979, in Giur. It. (Italian Case Law), 1980, I, 9 ff., annotated by G. Alpa, Danno biologico e diritto alla salute davanti alla Corte Costituzionale (Biological damage and right to health before the Constitutional Court). The decision of the Constitutional Court on biological damage No. 184 of 14 July 1986 takes the same view, in Giust. Civ. (Civil Justice), 1986, I, 2324 ff. and in Foro it., 1986, I, 2953, annotated by G. Ponzanelli, La Corte Costituzionale, il danno non patrimoniale e il danno alla salute (The Constitutional Court, non-material damage and damage to health), and P. G. Monateri, La Costituzione ed il diritto privato: il caso dell'art.32 e del danno biologico (Staatsrecht vergeht, Privatrecht besteht) (Constitution and Private Law: the case of Art. 32 and biological damage).

81 In this regard, it is most informative the parliamentary motion No 1-01694 of 18 September 2017, which commits the Government to guarantee the freedom of prescription and the prohibition of automatic substitutability of biological medicines at a national level, without differences between regions.
We might point out that the 2016 provision is, in some respects, complementary to Art. 5 of Law No 24/2017 ("Disposizioni in materia di sicurezza delle cure e della persona assistita, nonche' in materia di responsabilita' professionale degli esercenti le professioni sanitarie", Provisions on the safety of care and of the patient, as well as on professional accountability of health professionals), which states that, in the performance of their professional service, health professionals shall adhere to the recommendations laid down in the guidelines, "without prejudice to the particularities of the case at issue", meaning to emphasise the importance of the personalisation of the cure on the basis of individual needs.

The case-law already established this principle: a recent opinion of the Piemonte Regional Administrative Court underlines that public tenders in which medicines based on the same active substance are put in the same lot inherently tend to award the supply of that active substance to a single pharmaceutical company. For this reason, in the abstract these tenders may compromise the right to healthcare for those patients who cannot benefit from the specific product supplied by the winner of the tender. That is why it is necessary that the tender competition’s lex specialis allow the contracting authority to procure different medicines for those patients for whom the treating physician makes an express request. Under these conditions, on the one hand, the tender guarantees an effective competition among pharmaceutical companies and, on the other hand, it allows the supply of additional medicines without compromising the patients’ right to health, ensuring them the so-called "continuity of treatment" or otherwise the possibility of accessing the medicines most suitable to them. The Consiglio di Stato also made a statement on similar matters, establishing the legitimacy of competitive tenders offering only medicines containing a certain active substance, but also providing the possibility for the contracting authority to source extra-tender medicines, in order to preserve the doctor's freedom of prescription and to protect patients with special needs.

82 The Constitutional Court also took the same view. In Judgment No. 196 of 12 July 2017, it reiterated "the personal nature of health care, so that law provisions cannot be an obstacle to the doctor assessing on a case by case basis, according to the most up-to-date and accredited technical-scientific knowledge, the most suitable therapy to ensure the protection of the patient's health". In this regard, see, amongst other Judgments of the Constitutional Court, Judgment No. 151/2009.

83 See Ruling of the Piemonte Regional Administrative Court No. 10/2016 of 9 June 2016. Also, the Rulings of the Piemonte Regional Administrative Court No. 382/2017, No. 385/2017 and No. 485/2017 take the same view, in assessing that the regional restriction on the possibility to prescribe medicines in the absence of an AIFA evaluation is detrimental to the latter's competence (of which we already said in this document) and, indirectly, of the freedom of prescription of the doctor (implied in Par. 11b of the same Article), who is entitled to choose the active substance to prescribe and administer to the patient.

84 In this regard, see the Rulings of the Consiglio di Stato ("Council of State") No. 3572/2011 and No. 3539/2012. This is also the view of the Ruling of Puglia Regional Administrative Court No. 243 of 17 February 2014, which replaced a regional resolution requiring doctors to prescribe molecules chosen from those with expired patents, with possible derogation from this obligation only in case of a reasoned therapeutic choice. In that case, the Puglia Regional Administrative Court considered that the setting of restrictions to the prescription of medicines is the national legislator competence, so as to standardise at a national level rights and essential healthcare levels ("Livelli Essenziali di Assistenza, LEA"). The same principle can be found in the Ruling of Lazio Regional Administrative Court No. 4514 of 29 April 2014, which – in addition to confirming the exclusive competence of the AIFA in assessing the equivalence among medicines – highlights that an
On the other hand, the same concept was already present in the Community legislation, as confirmed by the aforementioned Judgment of the Court of Justice of 5 May 2011 on Case C-316/09, which – although referring to a case of advertising to the general public – stresses in an incidental question the primacy of the doctor in determining the medication.

It is undoubtedly necessary for the doctor to carefully evaluate the biosimilar option and the economic benefit it might cause, but this cannot be an obstacle or a restriction to the imperative physician’s freedom of prescription. When a

administrative decision affecting the full reimbursability of class A medicines and the doctor’s right to prescribe them, is to be considered unlawful. More so, when the "recommendation" to use certain medicines in place of others comes from subjects who do not have the competence, which is reserved by law for the AIFA as guarantor of the national standard of the pharmaceutical system (Art. 48, Par. 2 of Law No. 326/2003). Similarly, also the Sicilia Regional Administrative Court, with the Ruling No. 603 of 28 February 2014, stated that any broad guidelines leading, for reasons of financial viability, to prefer the less expensive medicinal product cannot be considered as binding for the physician, who must have the possibility to prescribe, when they deem it more appropriate, a different medicine than the one recommended by the Region, not only for patient already being treated, but also for naïve patients. In the same view, the recent Ruling of the Consiglio di Stato ("Council of State") No. 4546 of 29 September 2017, which states the unlawfulness of the recommendations by the Veneto Region restricting – or even advising against – the use of a certain medicine, thus violating the LEA and setting prescriptive limits "which cannot affect the choice of prescribing physicians, who are strongly and inevitably influenced by these recommendations, aimed at steering their choice in the direction of the medicine considered more appropriate, in terms of therapeutic efficacy, but also less expensive". The Consiglio di Stato continues: "it is clear that the recommendations in question inevitably guide the prescription of the medicine in a certain direction, affecting the therapeutic choice [...]".

In this regard, see the recent Ruling of the Consiglio di Stato No. 3627/2017, whereby the judges of Palazzo Spada stated that the physician has exclusive competence and accountability to prescribing the most expensive medicine to the naïve patient, regardless the less expensive medicine having won the tender, in case of insufficiently documented clinical response by the patient to the latter, both in terms of less tolerance to the medicine as well as of lower efficacy.

5.3 Public tenders and framework agreements

Biological medicinal products and biosimilars, being used mainly in hospitals, are purchased via a public tender, whereby there is a competition among the companies concerned. In this context, it is important that the health authorities
launching the public procurement procedures for biological medicines are aware of the peculiarities of these medicinal products, in order to consistently lay down the terms of the invitation to tender that comply to the "lowest bid" scheme and ensure fairness, free competition, proportionality, non-discrimination and transparency (Decree-Law No. 50/2016).

As clarified before, the tender specification is a delicate phase, because this is the time when the health institution has to define the award criteria and the goods to be purchased according to their own clinical needs, all factors undoubtedly influencing the companies participating in the tendering procedure. For this reason, the general purpose of stimulating competition in the pharmaceutical market must be reconciled with the need to ensure that doctors have the freedom to prescribe the medicines deemed most appropriate for the conditions under treatment, and to protect public health. In view of this, the structuring of tender lots by the public authorities is essential, in case biological and biosimilar medicines are present in the same grouping.

Tendering procedures for the procurement of medicinal products have traditionally been structured so that every medicine based on the same active substance (or even having the same formulation) are grouped in the same lot, which will be separately and independently awarded (the so-called "Simple Lots"). By way of derogation from this procedure, in the recent past, the contracting authorities decided to group medicines with more than one active substance in the same lot (the so-called "Composite Lots"), using the tender to select only one medicine for each condition. This had the effect of reducing the number of purchased medicines and also of limiting the prescriptive choice of physicians, who – at the end of the procurement procedure – find themselves with only one medicinal product for each therapeutic indication, subject to exceptions to be motivated. If, on the one hand, this orientation is aimed at minimising costs, using competition in the tendering procedure as a leverage for better pricing, on the other hand, it affects the prescriptive choice of the physician, who may be induced to prescribe a medicine that is not deemed appropriate for the individual patient's treatment.

However, it should be pointed out that this grouping of different active substances was put in place by the contracting authorities on the basis of an equivalence assessment implemented at a local level, a view usually shared by the clinicians involved, before Art. 15, Par. 11b of Decree-Law 95/2012, converted into Law 135/2012, attributed to the AIFA the exclusive competence on this matter. Moreover, it should be noted that the tendering procedures in question were mostly aimed at procuring chemically-synthesised medicines, which are

87 With regard to public tenders with composite lots for the procurement of biological medicines with different active substances, there is a precedent. This has resulted in a dispute, at the end of which the Emilia Romagna Regional Administrative Court and the Consiglio di Stato, in the Ruling 1/2009 and 7691/2009, respectively, legitimised the decision of the Bologna AUSL (“Azienda Unità Sanitaria Locale,” “Local Health Authority”), that in 2008 grouped inside two lots diverse biological medicines with the same indications, considering them comparable in the therapeutic efficacy. In this case, the administrative courts considered that, despite being unable to determine a concrete comparability of different active substances for the same indication, the institution could not be prevented from conducting its own investigation to assess that different medicines may be interchangeable and, so, compete
mainly used outside hospitals, and only anticipated the actual prescription by physicians on the territory, without constituting a real priority for companies in terms of expected profit.

The situation is different for biological medicines used in hospitals and, for this reason, the relationship between biological originators and the corresponding biosimilars gave rise to a major legal dispute on the structuring of tender lots, initially directed by an advisory opinion expressed by the Consiglio di Stato.

against each other. The aforementioned judgments – which have undoubtedly aroused perplexity, having considered as conclusive the assessment of an internal committee of the contracting authority on the very important scientific issue of comparability among medicines having different active substances – shall be regarded as outdated, in the light of further regulatory developments in the field of therapeutic equivalence. On this subject, see M De Rosa, Gare: Biosimili ammessi in comparazione terapeutica ma determinate condizioni, in TEME, September 2010, and F. Massimino, Farmaci biologici e biosimilari e tutela della salute e della concorrenza (Biological medicines and biosimilars, protection of health and competition), in Diritto Industriale (Industrial Law), 4/2012.

88 At the request of the Molise Regional Administrative Court, the Consiglio di Stato (Division I, Opinion No. 3992/06 of 20 June 2007) pointed out that adopting the therapeutic equivalence criterion in public tendering procedures poses a major problem in the case of biotechnological medicines, because a therapeutic equivalence of efficacy can be asserted, without concerns about safety, only for medicines of chemical origin. The manufacturer of biotechnological medicines can produce, as scientific data, only the safety and efficacy profile of its own medicine. This implies that there is not high replicability of the effects and of the possible adverse reactions. In essence, there is no evidence of an “acceptable replicability rate of the products”. The Consiglio di Stato, with the Ruling No. 7690/2009, established what already stressed in the aforementioned Opinion, stating that biological originators and biosimilars, “even if marketed in the same therapeutic indications, are not equivalent, unless this equivalence is specifically ascertained on the occasion of the structuring of the invitation to tender”: an assessment to be carried out, therefore, on a case by case basis. This guideline was confirmed by the Toscana Regional Administrative Court: by Decision dated 31 October 2012, the Court upheld the appeal submitted by four pharmaceutical companies, declaring null and void the resolution of the Toscana Region grouping in the same therapeutic category biological medicines with different active substances, so as to structure a single invitation to tender and, thus, implying the comparability of the expected therapeutic effects. In this regard, by way of example, we may recall the three twin sentences of the Umbria Regional Administrative Court Nos. 254, 255 and 256 of 26 April 2013, following the appeals submitted by some pharmaceutical companies against the tender competition’s lex specialis, that allowed the Commissione Terapeutica Regionale (“Regional Therapeutic Committee”) to choose, after the award, the molecules to use within homogeneous classes and on the basis of overall economic and pharmacological assessments. The applicants reprimanded both the absence of a prior AIFA judgment on the existence of therapeutic equivalence among the medications – with the consequent inability to compare active substances of the same therapeutic category – and the possibility, provided for by the lex specialis, to choose the molecules to be purchased after each provision has been assigned.

The Umbria Regional Administrative Court upheld the appeals, mainly on the basis of the aforementioned Art 15, Par 11b of the Decreelaw No 95/2012 (the so-called "Spending Review" Decree, converted into Law No 135/2012), according to which "in adopting any decision based on the therapeutic equivalence among medicinal products containing different active substances, Regions shall adhere to the motivated and documented assessments of the Agenzia Italiana del Farmaco". Although this rule had entered into force after the invitation to tender, it was considered

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acknowledgeable to principles that could have already been deduced from the law and from the distribution of competences between the State and the Regions referred to in Art. 117 of the Italian Constitution, whereby the AIFA is responsible for ensuring the unity of the pharmaceutical sector. In this perspective, therefore, the Umbria Regional Administrative Court stated that the contracting authorities may provide a single lot for the reference biological medicine and the corresponding biosimilar only if the relative therapeutic equivalence has already been asserted by the AIFA.

As already mentioned in Paragraph 3, in Resolution No. 204 of 6 March 2014, the AIFA subsequently ruled out that – in the light of the comparability exercise already carried out by the EMA – an equivalence assessment by the national regulatory agency is necessary for biological originators and their biosimilars and, therefore, endorsed the possibility that they are grouped in the same tender lot, thus increasing the degree of potential competition.

However, the above considerations in relation to the peculiarities of biological medicines remain valid. They may have an impact on the tender's structure and on the competition among companies.

In the light of the above, it is essential that the contracting authorities duly consider the need to safeguard the therapeutic continuity for patients already under treatment with an originator medicinal product, if the treating physician deems the switch to biosimilars inappropriate.

Similarly, until the biosimilar have been asserted by the AIFA's CTS as eligible for reimbursement for any unauthorised indications, according to Law No. 648/1996, the structuring of the tender's lots shall provide for the exclusive use of the originator medicine also for such therapeutic needs. The exclusivity must be preserved if certain uses of the originator are still covered by secondary patents.

In other words, the structuring of public procurement procedures for originators and biosimilars is the crucial point of several considerations, based on the specific features of these products and on their exclusive rights. They reflect the primacy of the prescriptive choice of the physician, based on the assumption of the absence of automatic substitutability for biological medicines and of the healthcare practitioner exclusive competence in deciding the right therapy for each clinical case.

The contracting authority is, therefore, required to achieve maximum competition in public tenders and, at the same time, to ensure compliance with the above-mentioned priorities. In this perspective, the civil servants are required to provide for at least two lots for each patent-expired biological medicine, formulation and route of administration being equal: one intended for naïve patients, the other for any other administration reserved for the originator.

It follows that the competitive confrontation can fully express itself in the first tender lot: the contract can be awarded both to the originator and the biosimilar manufacturing company, and it is therefore necessary that the definition of the quantities to be assigned to one lot or the other be implemented in an objective, rational and scientifically based way, so that no choice might discriminate against any of the participants.
It is common knowledge, for the public and private stakeholder, that reconciling interests and objectives that are not always complementary is very difficult. To this end, the 2017 Budget Law provided the industry players with guidelines, to be followed under certain shared principles.

In particular, Art. 1, Par. 407 of 2017 Budget Law removes any doubt as to the criteria for the structuring of tenders for the procurement of biological and biosimilar medicines. It provides that in public procurement procedures different active principles cannot be grouped in the same lot, even if they have the same therapeutic indications. With this provision, therefore, the legislator forbids equivalent tenders for different active principles, an issue that has already been very problematic for the AIFA.

The provision also stipulates that the procurement procedures must be carried out by means of framework agreements (referred to in Art. 54 of the Decree-Law No. 50 of 18 April 2016) with all economic actors if more than three medicines based on the same active substance are present on the market. For this reason, the regional purchasing institutions shall structure a single lot, for which they must consider:

i) the specific active substance (Fifth Level ATC). ATC stands for “Anatomical Therapeutic Chemical Classification System”, used by the WHO. It is an alpha-numerical classification system dividing the medicines according to a five hierarchical levels scheme, in which the Fifth Level stand for the chemical sub-group specific for each chemical substance;

ii) same route of administration;

iii) same dosage.

The criteria for the inclusion in the lot are very strict because the legislator needs to ensure uniformity in the biological medicines to be purchased via the procurement procedure. That in order to avoid further therapeutic inaccuracy and to ensure that the competition may be carried out among basically equivalent products, to be separated if there are significant differences amongst them, as in the case of different routes of administration.

The framework agreement, on the other hand, constitutes a general and procedural effective tool, that the public administration can use to consolidate purchases of repetitive and homogeneous goods and services, avoiding the continuous use of competitive tenders, thanks also to the possibility of subscription with one or more economic operators.

Regarding patent-expired biological medicine, the legislator’s choice is justified by the advantages it offers.

Firstly, the framework agreement is a flexible contractual tool, which allows to safeguard the doctor's freedom of prescription, giving him the chance to have access to several medicinal products based on the same active substance. Originators and biosimilars may, therefore, be chosen on the basis of the patient's clinical

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89 In this regard, see Le nuove procedure di acquisto dei farmaci biosimilari, in attesa del voto al Senato (The new procurement procedures for biosimilar medicines, waiting for the result of the vote in the Senate), by Reforming.it, December 2016.

90 In this regard, see the Ruling of Trento Regional Administrative Court No. 178/2017, pointing out that the wording of the aforementioned provision “does not leave a margin of uncertainty as to whether [in this circumstance] the use of framework agreements with all economic actors is prescribed”.
needs, and even the percentages initially bestowed to the awarding undertakings shall be applied in a loose way. The aforementioned freedom of prescription shall hence be carried out to the best of their knowledge and belief, without being subject to forcing or improper obligations to give reasons for their choice. This considering the fact that the same legislator already recognized and endorsed, even if only implicitly, the scientific reasons underlying a responsible choice.

Secondly, in principle, the framework agreement allows the contracting authority to obtain price reductions by acquiring larger quantities of goods, as well as to ensure the plurality of competing operators, mitigating the risk of depending on a single exclusive supplier.

Irrespective of the obligation to adopt the framework agreement when the originator and biosimilar medicines on the market are more than three, the Italian Public Procurement Code (“Codice dei contratti pubblici”) also gives the contracting authority the discretion to resort to it even if fewer competitors are present. In this case, even if alternative tendering procedures are taken, the obligation to structure the lots according to the criteria of safeguard of the therapeutic continuity described above shall remain in force.

On the other hand, the 2017 Budget Law requires that also the procuring entities launch the tendering procedure within sixty days after the marketing of the first biosimilar, and reiterate the tender within the same period every time a new biosimilar is marketed. It is therefore clear that the legislator wants to encourage the development of the market through the reiteration of the tendering procedures, avoiding the crystallisation that may result from the passivity of the contracting authorities. Thus, the tender becomes the preferred tool to determine the purchase conditions. All the specifications that, when an authorisation for a biosimilar is issued, imposed an automatic adjustment of the originator's price must therefore be considered outdated. Moreover, this adjustment, pending a new procedure, would make rebate on the originator's price inevitable, thus threatening to limit its competitive effectiveness.

In relation to this aspect, it should also be noted that not all the reservations expressed by AGCM on the draft law, already examined in Paragraph 4, were accepted in the final text. In fact, the final text has transposed the recommendations of the Anti-Trust Authority mainly regarding the elimination of the maximum sale price to the NHS as opening bid for patent-expired biological active substances, thus leaving a substantial freedom of determination to the procuring entities.

As it regards the award criteria and the price, Art. 1, Par. 407 of Law No. 242/2016 provides that patients should be treated with one of the first three drugs in the ranking list of the framework agreement, classified according to

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91 Art. 54 of the Decree-Law No 50/2016.

92 It is necessary to underline that Art. 1, Par. 407 of Law No. 242/2016 still allows the doctor to prescribe a medicine which has not been ranked among the first three, providing that it is "among those included in the procedure". This means...
the lowest price or the lowest bid criterion, in order to ensure an effective rationalisation of expenditure and an appropriate availability of therapies.

In this regard, it should be remembered that Art. 95, Par. 2 of the Public Procurement Code provides that, in accordance with the principles of transparency, non-discrimination and equal treatment, the contracting authorities shall award contracts according to the lowest bid criterion, identified on the basis of the price-quality ratio or comparing costs and efficacy.

Without entering into the details of the subject, it is worth mentioning that the contracting entities wishing to award [the contract] using the lowest price criterion, pursuant to Art. 95, Par. 5\(^{91}\), must give adequate reasons for the choice made and clarify the criterion they used in the call [for tender].

In the new Public Procurement Code, there is a strong preference for the awarding of contracts in accordance with the lowest bid criterion, thereby reducing the importance of the lowest price criterion. However, a goal to be carefully evaluated is how to combine all this with the health sector and, specifically, with the procurement procedures for medicinal products.

The guidelines of the National Anti-Corruption Authority (“Autorità Nazionale Anticorruzione, ANAC”) tend to consider medicines as standardise goods, to be purchased only according to the price. In the event of biological medicines, however, it is better to explore all possible scenarios of the awarding of supply contract according to the lowest bid criterion, giving value not only to the quality of the product itself, but also to the additional, innovative services of the medicine or of the treatment of the related condition. It is significant, in this context, that the Public Procurement Code seems to pay attention also to the potential and added value of the tendering company, and not only to the proposed product, thus disclosing the possibility for a more articulate consideration.

The supplier's organization, expertise, qualifications and certifications, together with a number of after-sale services (such as pharmacovigilance, bibliographic support or logistics), which can benefit the agency, the health workers and, indirectly, the patients may all become benchmarks for quality assessment, which shall not be only linked to the quality of the product, but may also take into consideration the quality of its manufacturer.

It is clear that, during the structuring of a public procurement procedure, the interaction between contracting agencies and economic operators plays a key role, because it allows the acquisition of information, consultancies and technical reports that the agency can use to better
design the tender specifications, including upon their request those innovative services and qualitative aspects that the competing companies may offer for the better treatment of the conditions, thus going beyond the mere lowest price criterion. In this regard, it is not by chance that article 66 of the Public Procurement Code sets forth a specific provision, so that the contracting entity may discuss with the economic operators in order to know their products and their specific characteristics.  

Most relevant to the present article, Art. 66 also provides that "This advice may be used in the planning and conduct of the procurement procedure, provided that such advice does not lead to the distortion of competition and does not result in a violation of the principles of non-discrimination and transparency." It is therefore necessary that the tender technicians and the tender manager ("Responsabile Unico del Procedimento, RUP") work to ensure that the procedure, even in the presence of a natural and inevitable "conditioning", pursues the public interest in clarifying the technical specifications and requirements, and that it does not violate the equal treatment of all competitors and the impartiality and objectivity standard of the procedure, in order not to distort the correct dynamics of the market.

The same degree of attention used in defining correctly the lowest bid criterion must be demonstrated by the central contracting entity also in assessing the quality/price ratio. That is to prevent any arbitrary and unfair actions by the agency, that may result in competitive distortions for the benefit of a single company.

The Public Procurement Code links the price to the cost, which has to be assessed with regard to the entire life cycle of the product. In this respect, considerations on the Health Technology Assessment and conditional reimbursement agreements into which the company may be entered with the AIFA for the purpose of an A or H (medicines used in hospitals) classification can become of relevance: the NHS, in fact, may pay a lower price than the one initially paid, if a therapeutic failure implies that the company has an obligation to give back to the institution the previously collected amounts.

Furthermore, in granting discounts, the originator manufacturer must take into account that, upon expiry of the patent, it may be the proprietor of a significant market share of specific therapeutic indications. It is therefore appropriate that it proceed to the assessments of its possible dominant position, also for the purpose of determining the discounts to be granted in the procurement procedure.

In this regard, we would like to recall the definition of "dominant position", as set out in Art. 102 TFEU and Art. 3 of Law No. 287/90, which is – according to the traditionally accepted case-law – "a position of economic power whereby the undertaking holding it is capable of
hindering the persistence of an effective competition on the market in question, and has also the possibility of behaving rather independently of its competitors, clients and, ultimately, consumers.96 In this respect, the presence of patents or other intellectual property rights generally constitutes a wall for the access of potential competitors to a single relevant market 97, more so in the pharmaceutical industry, since, as it is known: “intellectual property rights, in the form of patents and trademarks are relatively more important in the pharmaceutical industry than in other sectors”98. On the other hand, the fact that an undertaking has a technological advantage over its competitors can be considered as a clue to on? its potential dominant position99.

96 In case law see, amongst others, Court of Justice, 14 February 1978, Case 27/76, United Brands v Commission, in ECR, p. 207, point 65; Court of Justice, 13 February 1979, case 85/76, Hoffmann-La Roche v Commission, in ECR, p. 461, point 38; Court of Justice, 9 November 1983, case 322/82, Michelin v Commission, in ECR, p. 3461, point 30; General Court, 1 July 2010, case T-321/05, AstraZeneca v Commission, in ECR, p. II-2610, point 241. See also the Communication from the European Commission, Guidance on the Commission’s enforcement priorities in applying Article 82 of the EC Treaty to abusive exclusionary conduct by dominant undertakings, in OJEU, C 45 of 24 February 2009, p. 7 ff., particularly Par. 10.

97 See, among the many judgments, Court of Justice, 5 October 1988, case 53/87, Mèxicar v Renault, in ECR, p. 6039, points 14-16; General Court, 1 July 2010, case T-321/05, AstraZeneca v Commission, in ECR, p. II-2610, point 270. See also the European Commission Decision of 28 August 2005, case M.3687, J&B / Guidant, and of 15 June 2005, case A.37.507, Generica / AstraZeneca, particularly point 517 ff. At a national level, see, for example, the AGCM Decision of 11 January 2012, Ratiopharma / Pfizer, Bull. 2/12.

98 Of the same opinion is the OECD report cited by the European Commission in the Decision of 15 June 2005, case A.37.507 Generica / AstraZeneca, op. cit., point 518, to which we refer for further consideration.


However, the Court of Justice has stated on several occasions that intellectual property rights do not automatically attribute a dominant position to those who hold them, given that it is necessary, in principle, taking into account the possible existence of producers of similar goods and their position on the market.100 In this sense, any assessment of substitutability of different medicinal products is of particular complexity, in the light of the difficulty of uniquely correlating the therapy with the type of patient, also based on the cost to the NHS.101 As a general rule, the greater the market share and the period of time for which it is held, the more likely becomes the existence of a dominant position.102 In this regard, it is known that, on the basis of an established case-law, from extremely high market shares it is possible to deduct the existence of that condition for the undertaking, unless there are exceptional circumstances.103 However, it should be stressed that, in the case of biological medicines, the identification of the relevant market does not constitute a trivial

100 See, to name just one, Court of Justice, 29 February 1968, case 24/67, Parke, Davis & Co. v Probel et al., in ECR, p. 81.

101 With regard to the doctor’s judgement on the substitutability of medicines, see AGCM Provision No. 33858 of 29 September 2016 on the Aspen case, confirmed by the Lazio Regional Administrative Court under Judgment No. 8945 of 26 July 2017.

102 See the Communication from the European Commission, Guidance on the Commission’s enforcement priorities in applying Article 82, op. cit., particularly Par. 15.

103 See, amongst others, Court of Justice, 13 February 1979, case 85/76, Hoffmann-La Roche v Commission, op. cit., point 41; Court of First Instance, 23 October 2003, Case T-65/98, Van der Bergh Foods v Commission, in ECR, p. II-4653, points 154 and 155.
exercise: in fact, the administration of the same drug may occur in particularly delimited segments of patients, not only due to their specific conditions, but also to the subjective response to the cures, which can be modified by not always foreseeable variables, such as individual genetic mutations. In this regard, researchers and clinical practitioners move more and more towards the so-called "precision medicine", whereby the pharmacological treatment should be personalized for the individual patient. This suggests a reflection upon the compatibility of this evolution to the traditional concept of market, which does not address even the combination of two or more different medicines.

To confirm such complexity, we can recall that some biological medicine may also be prescribed – and reimbursed by the NHS – for unauthorised therapeutic indications, for example those included in the 648 list. In this case, we should ask ourselves whether the notions of relevant market and dominant position are really appropriate, provided that the undertaking holder of the marketing authorisation is obliged to maintain a position of neutrality about the doctor’s autonomous and spontaneous choice to prescribe the medicine for unauthorised use and, therefore, refrain from any action that may have a promotional or commercial impact on the sales of that medicine.

In addition to the market share, it is then necessary to consider all the factors eligible to ensure significant competitive advantages to the company which is believed to hold a dominant position\textsuperscript{104}, even once the patent of the active substance has expired. Among these, the availability of know-how and the intellectual property rights, as well as any secondary patents of formulation, indication or combination, together with other elements like the economic and financial capabilities of the company, the time advantage acquired on competitors, the ownership of privileged information assets, a consolidated reputation with consumers, the size of its product list, the cost advantage on importers.

On the other hand, it is useful to recall that the European Union case-law clarified that even if an undertaking no longer occupies a dominant position at the time when the abusive behaviour produces its effects, this does not change the legal classification of its acts, when these were committed at a time when the company was in a dominant position and it had a "special responsibility" not to compromise, with its conduct, effective and undistorted competition within the market\textsuperscript{105}. This clarifies all the assumptions in which, for example, the conduct of the originator manufacturing company, although having real effects on the market only after the expiry of the patent, have been put in place before the expiration itself.

As far as public procurements are concerned, it

\textsuperscript{104} In this regard, see, for example, M. Todino, \textit{Art. 102 TFUE (Art. 102 TFEU)}, in L.C. Ubertazzi (ed.), \textit{Commentario breve alle leggi su proprietà intellettuale e concorrenza (Brief commentary on intellectual property and competition laws)}, p. 2897 ff., particularly p. 2903.

\textsuperscript{105} Thus, for example, the General Court, 1 July 2010, case T-321/05, \textit{AstraZeneca v Commission}, op. cit., point 379.
should be noted that, according to the case-law, the holder a dominant position is not - in any way - forbidden to propose some discounts in order to be awarded with the supply contract. This, in fact, favours the reduction of prices for the benefit of the NHS and the patients. It would be paradoxical, in fact, if the originator manufacturing undertaking was unreasonably prohibited to apply rebates: this would benefit biosimilars manufacturing companies, and crystalize the market before it was even able to express its potential for price reduction.

There is no doubt, however, that discount policies applied in the context of public procurement procedures by an originator manufacturing company close to the expiry of the patent or in the phase immediately following that deadline must be assessed with particular care, on the basis of the antitrust regulations, since they may discourage or delay the entry of newcomers into the market and, thus, unlawfully restrict competition. It is therefore necessary to assess whether the price reductions of the originator in the procurement procedure are likely to determine an "anticompetitive foreclosure", which occurs if this foreclosure is likely to have anticompetitive effects. In particular, this is the case if such a large part of the market is foreclosed that the dominant firm’s competitors are likely to suffer from scale disadvantages, which could make them a weaker competitive force or drive them out of the market completely. As it is well known, according to the European Commission, in order to determine whether even a hypothetical competitor as efficient as the dominant undertaking would be likely to be foreclosed by the conduct in question, it is necessary to examine the economic data relating to cost and sales prices and, in particular, whether the dominant undertaking is engaging in below-cost pricing. This will require that sufficiently reliable data be available. Where available, the Commission will use information on the costs of the dominant undertaking itself. If reliable information on those costs is not available, the Commission may decide to use the competitors’ cost data or any other comparable reliable data. If the data clearly suggest that an equally efficient competitor can compete effectively with the pricing conduct of the dominant undertaking, the Commission will, in principle, infer that the dominant undertaking's pricing conduct is not likely to have an adverse impact on effective competition and, thus, on consumers, and it will therefore be unlikely to intervene. If, on the contrary, the data suggest that the price charged by the dominant undertaking has the potential to foreclose equally efficient competitors, then the Commission will integrate this in the general assessment of anti-competitive foreclosure.

106 See Court of First Instance, 14 December 2005, Case T-210/01, General Electric v Commission, in ECR, p. II-5575, point 215, where the Court also notes that in the context of procurements procedures with high-value sales and continuous negotiations, "tenderers will inevitably make some form of economic concession, this phenomenon being an integral part of the negotiation process".


taking into account other relevant quantitative and/or qualitative evidence.

Taking these principles into account, we can conclude that the regulatory and normative framework on biological medicines with expired patents makes it very unlikely an abuse of a dominant position by the originator manufacturing undertaking, through discounts in the tender.

Firstly, it should be remembered that, as stated in Paragraph 1, the access of a biosimilar to reimbursement is subject to the granting of a price at least 20% lower than the originator’s. Furthermore, the biosimilar manufacturing company usually applies further discounts in each tender. In this way, the biosimilar undertaking defines pricing thresholds, which the originator company may not be able to reach or actually break, applying the pricing policies often used by multinational groups. Even if this happens, it constitutes "predatory pricing" only if the dominant undertaking sells its products below cost. This must be assessed according to the criteria indicated by the Commission, and on the basis of the medicine business in its entirety, and not on the intra-group cost and on the single transaction\textsuperscript{109}. It is clear, in fact, that the sale price charged by the parent company to the local subsidiary also includes a profit margin and, therefore, it cannot be equal to the actual production cost.

Moreover, in a market characterized by a number of purchasing bodies and procurement procedures, the originator manufacturing undertaking could create a barrier to access for biosimilars only by systematically adopting policies of predatory pricing, which they should maintain throughout the entire term of the supply contract until the award of a new tender, thus making almost impossible (in the short term) the recovery of losses generated by selling below cost.

In any case, it should be remembered that the same principle of freedom of prescription and the consequent contractual structure of the framework agreement favours access to the market to a plurality of competitors, minimising the possibility of exclusive agreements capable of restricting competition and privilege a single company\textsuperscript{110}.

\textsuperscript{109} In this sense, see the judgements of the French Court of Appeal and the French Supreme Court in the Flavelab case of 8 April 2008 and 17 March 2009, respectively, overruling the Decision of the French Competition Authority on 14 March 2007.

\textsuperscript{110} Not surprisingly, the British Biosimilar Association came out in favour of the framework agreement: "We are supportive of Framework Tenders but not of Single Award Tenders. Framework Tenders allow multiple products to compete ensuring that best value decisions are made in terms of formulation including devices, quality and service, and not price alone. This respects clinicians’ choice and mitigates the risks in respect of sole supplies. Public procurement should foster this diversity of suppliers by ensuring that final allocation of contract is not limiting doctors and patients to one treatment choice. New biosimilar products should be allowed to compete within each regional framework, with NHS authorities ensuring that their policies contain scope for access, once a new biosimilar has joined a framework tendered for after their entry on the market. This is crucial to ensure that UK remains an attractive healthy economy for manufacturers to bring biosimilar medicines to the market.” See http://britishbiosimilars.co.uk/hot-topics.
6. SCIENTIFIC INFORMATION AND ADVERTISING OF ORIGINATORS AND BIOSIMILARS

As stated above, the procurement procedure is the playing field for competition between originator and biological medicines. They both compete in terms of price or general benefits, after a series of assessments made by the contracting agencies, which can legitimately interact with companies, especially regarding the appropriate structuring of the procurement process.

It is clear that the procurement process is already a competitive context in itself, and so is the relationship between companies and health professionals, a relationship that can still condition the choice of public officials, albeit in a regulatory framework that had widened the distance between buyers and prescribers.

The manufacturing companies have the responsibility for ensuring that healthcare professionals have a very precise knowledge of their clinical studies, so as to allow them not only to choose – with full knowledge of the risk-benefit balance – whether to prescribe the biological originator or the corresponding biosimilar, but also to push the central purchasing agencies for full availability of the medicines necessary to their therapeutic needs. It is paramount, therefore, that the companies also compete in terms of scientific information pursuant to Decree-Law No. 219/2009, differentiating and diversifying their medicinal products using comprehensive and persuasive scientific data.

Not only the competitive component of price, but also the quality and number of clinical data, is of the utmost importance, and it shall be made available to healthcare professionals with proper and exhaustive advertising. These aspects may determine a primary competitive value of the product, since they can influence the doctors’ prescriptive choice in the most appropriate way for the clinical needs of their patients. Not without reason, the AGCM itself acknowledged that one of the primary variable determining the medicines' demand is indeed information, provided by pharmaceutical sales representatives to health practitioners.

It being an important competition leverage for companies, information should be provided throughout the whole medicine's life cycle, especially in the patent's post-expiration phase, when the originators start to compete with their biosimilars.

This activity is also under the supervision of the AIFA, guarantor of fairness, scientific accuracy and objectivity of the information provided. The legislator entrusts companies with the task to inform health professionals in

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111 The Public Procurement Code and the Regulations on the soggetti aggregatori ("aggregated entities") (Law No. 89/2014) narrowed the number of possible purchasers in public procurement procedures, since they no longer coincide with the health facilities using the products.

112 "Precisely because the physician is the prescriber selecting the medicines suitable for the treatment of any specific condition, the advertising and information activities of the pharmaceutical companies are targeted to them. Accordingly, these activities are one of the main areas of competition for the pharmaceutical companies" (see Servor Italia-Biological Drug Institute Case, AGCM Provision No. 7337 of 1 July 1999, and Istituto Gentili-Merck Sharp & Dohme Case, AGCM Provision No. 1333 of 25 February 1999).
a balanced, accurate and comprehensive way, pursuant to the legislation applicable.

Despite some doubts popped up in the doctrine\textsuperscript{113}, the legislation concurs that the doctor’s freedom of choice cannot be fully implemented without the scientific data disseminated by pharmaceutical companies. That’s the only way for a physician to prescribe the medication that is most appropriate for the patient’s clinical picture and capable of minimizing any risk of adverse reactions. The therapeutic option cannot be affected or conditioned by a procurement procedure that could limit the availability of products, and therefore require the doctors to justify themselves each time their decision is directed towards a medicine outside the award of the tender.

We should ask ourselves, then, how advertising and scientific information can be legitimately provided by originators manufacturing companies without damaging the interests of biosimilar companies, since they might have obligations and responsibilities resulting from a dominant position within specific market segments achieved before the patent expiry\textsuperscript{114}.

In this regard, it should be remembered that – as previously stated – originator biological medicines and biosimilars cannot be considered as equivalent, and it is therefore licit that companies compare their clinical data and the competitors' using comparative advertising\textsuperscript{115}, which nevertheless cannot be misleading\textsuperscript{116}.

This shall be done in accordance with certain procedural and organizational requirements, which not only allow the company to attune the content of their scientific information to its recipients (doctors, pharmacists or RUPs), but also to subdivide the activities between the sales department, the medical department or the market access department, depending on the issues dealt with, minimising the compliance risk.

\textsuperscript{113} In this regard, see I. Arnadolo, Equivalenti, biosimilari, gare. Appunti di governo concorrenziale dello spesa farmaceutica (Equivalent, biosimilars, procurement procedures. Notes on competition in the pharmaceutical spending), in Mercato, Concorrenza, Regole (Market, Competition, Rules), 2/2013, 339 ff.

\textsuperscript{114} For a thorough clarification on this subject, see S. Gorza, L’informazione scientifica e la pubblicità in materia di biologici originatori e biosimiliari: profili concorrenziali, presentazione nel Convegno (Competition in scientific information and advertising of biological originators and biosimilars) “Farmaci originatori, biosimilari e antitrust (Originator Medicines, Biosimilars and Anti-trust)”, Milan, 30 May 2017. The presentation is available at: http://www.rucellaieraffaeelli.it/docs/news/relazioni/Sara%20Gorza.pdf.

\textsuperscript{115} As stated by the AGCM in Misleading and comparative advertising: a small guide for consumer protection: "comparative advertising is fair if the comparison is made between competitors, if it doesn’t deceive consumers – also by confusing different products – , if the relevant information is about essential, pertinent and nonetheless verifiable characteristics, and if it does not have the sole purpose of discredit the competitor”. If correctly implemented, therefore, in the opinion of the AGCM, comparative advertising is a fundamental information tool available to consumers. It increases the transparency of the market potentially enabling each manufacturer to promote the specific qualities of its medicine to consumers, who could determine the product’s success.

\textsuperscript{116} According to the Code of Ethics of Farmindustria (Italian Association of Pharmaceutical Companies), in the version of 12 October 2016: "[...] companies must not damage the image and products of any competing companies. The companies required to promulgate specific internal policy directives for their employees are also ethnically and professionally liable for their behaviour [...]". With regard to misleading advertising, see also Decree-Law No. 145 of 2 August 2007.
All the organizational measures aside, the content of the advertising must be correct, objective and balanced, so that the competition may be implemented on the merits, without any ambiguity.

The originator manufacturing company may focus its communication on the specificities of its own originator product, on the consolidated clinical experience (e.g., on real world evidence data), and also comment on head-to-head studies between biosimilars and originators using truthful scientific references, types of therapeutic treatment, patient settings, and the number of treated patients. The originators manufacturing company is also allowed to report to prescribers or purchasers the existence of still patented exclusive indications not included in the biosimilar's skinny label, and to highlight the absence of an indication for the use of a biosimilar in combination with another biological medicine, whose clinical studies have been conducted only with the originator product, the data of which are still covered by the RDP (see Paragraph 1). Each of these issues constitutes the expression of a true competition on the merits, insofar as the clinical data, the therapeutic indication or the patent are the result of a thorough process of research and development that may have an impact also in the structuring of the procurement procedures, and it is not a mere attempt to exploit a "parasitic" income.

Furthermore, the originator manufacturing company may clarify legal aspects, concerning also the doctor's liability, mentioning the prohibition of automatic substitutability and the principle of therapeutic continuity, promoting the doctor's freedom of prescription and ensuring that the contracting agencies respect these principles in structuring the procurement procedures and in setting the percentages allocated to the successful tenderers of the framework agreement. It is also licit to objectively report the specificities of the approval process of biological medicines and the simplifications applicable to biosimilar medications (e.g., similarity exercise, extrapolation of indications), as well as to cite the importance of the brand name in the prescription and the necessity of the correct reporting of adverse reactions. Finally, in the context of a fiduciary relationship with the health professionals, the originator manufacturing companies may deal with matters such as the doctor's obligation to give the patient transparent information in the case of administration of biosimilar medicines, recalling, if necessary, the Position Papers of the AIFA, the EMA or any other scientific society.

Moreover, in case of unlawful conduct by central purchasing agencies or by health facilities, companies have the right to dispute in court any regional resolution or procurement specifications that contain unfair provisions, such as the obligation to use an arbitrary percentage of biosimilar medicines – at the expense of therapeutic continuity or exclusive rights – or rewards for Director-Generals supporting the interests of biosimilar manufacturing undertakings. This does not constitute a case of sham litigation that may result in an abuse of dominant position, as referred to in Art. 102 of the TFEU. Far from preventing or delaying access to market for biosimilar, in fact, the legal proceedings in question aim at balancing procurement procedures that are biased in favour of some
competitors and, therefore, do not follow the legal framework, as lastly defined by the 2017 Budget Law\textsuperscript{117}.

On the contrary, emphasizing the inevitable elements of uncertainty of the medicinal products when they are marketed for the first time, stating possible reservations about their approval procedure, or above all using expressions that may make the biosimilar's extrapolated indications appear, in themselves, as a risk for the patient's health, are all conducts that are damaging to the image of the competitors and of the regulatory authorities' choice. Making false correlation between a small number of patients treated with the biosimilar and its higher hazard ratio, or stating that the absence of an indication for the biosimilar is indicative of an inferior quality, is also a defamatory conduct toward the competitors. The same logic applies if an originator manufacturing company is ambiguous about the existence of exclusive or still patented indications for their own medicinal products, if it raises doubts about the biosimilar's efficacy profile, or exploits the black triangle to suggest that biosimilar medicines are less safe.

In summary, therefore, it is necessary to identify a correct balance between the right to stress the real, substantial differences between originators and biosimilars and the need to avoid spurious or misleading information that may constitute a denigration of competitors or - even - an abuse of dominant position.

At a strictly interpretative level, the French cases of Plavix and Subutex, tried by the Autorité de la concurrence in May and December 2013, are particularly interesting. The cases concern the advertising activities carried out by originator manufacturing companies about their own medicines, which included also comparative advertising with their biosimilar counterparts. These provisions, both confirmed on appeal, clarify that if the information provided is accurate, complete, precise and valid – for the benefit of their own product, and also in comparison with the competitor's –, it is legitimate and may not be considered as detrimental. On the other hand, if the data used in the advertising are ambiguous, partial and/or unverified, this constitute a defamatory conduct and a case of abuse of dominant position, pursuant to Art. 102 of the TFEU\textsuperscript{118}.

The fairness of an advertising is to be assessed also bearing in mind its target audience. In this regard, the Judgment of the Court of Cassation, First Division, No. 12960 of 22 June 2016, is particularly significant. It states that the potential conditioning of the information activity shall be ascertained on the basis of the competence of the target audience, and that the significance of the

\textsuperscript{117} Regarding sham litigations, see G. Muscolo, Abuse of litigation, abuse of patent and abuse of dominance: where do we stand?, in Competition and patent law in the pharmaceutical sector – An international perspective, G. Pitruzzella & Gabriella Muscolo (eds.), The Netherlands, 2016, 107 ff.

\textsuperscript{118} For more information on this issue and the cases at issue, see B. Lasserre, Raising artificial barriers against generic entry: the French experience, in Competition and patent law in the pharmaceutical sector – An international perspective, G. Pitruzzella & Gabriella Muscolo (eds.), The Netherlands, 2016, 187 ff. Consistently, on December 20, 2017 the French Competition Authority has published a press release informing about a fine of 25 million euros imposed on an originator pharmaceutical company for having first prevented and then restricted the development of generic versions of Durogesic. The press release is available at: http://www.autoritedelaconcurrence.fr/user/standard.php?id_rub=663&id_article=3096&lang=en.
inaccuracies, if any, must be assessed in relation to the degree of competence of the recipients. Therefore, if the information on the medicinal product is provided to specialist medical personnel and to civil servants, their level of competence is higher enough to reduce the charges against the originator manufacturing company, thus excluding market distortion and unfair competition, according to Art. 2598 of the Italian Civil Code119.

7. CONCLUSIONS

In the light of the above, it is clear that the regulatory authorisation granted to new biological originators and biosimilars guarantees a legal presumption as to their safety and efficacy that must be integrated by further, predictive data, related also to any extrapolated indications and possible, rare adverse reactions. A similar caution is required, a fortiori, when dealing with "complex" biosimilars, intended for treating serious conditions, such as cancer, in subgroups of patients who already demonstrated a high probability of complete remission.

In this context, and in the light of the precautionary principle, it is arbitrary to establish a priori a total comparability between biological originators and the corresponding biosimilars before the monitoring and pharmacovigilance tools introduced by the Community legislation are put in place. These were created with the aim of definitively ascertaining, by using the Real World Evidence, the safety profile of new biosimilars on a larger patient sample than that already tested in the clinical trials, especially for the therapeutic indications that may be authorised by extrapolation.

As already stated by authoritative scientific societies120, the point of equilibrium identified by the Italian legislator with the 2017 Budget Law 2017 seems acceptable. It safeguards the freedom of prescription of the physician, to whom the decision on the possible switch between originator and biosimilar is exclusively entrusted, excluding the possibility of automatic substitutability by the pharmacist. In the same perspective, the identification of the framework agreement as a form of compulsory contract in the presence of more biosimilars appears appropriate to reconcile different objectives, such as the protection of the physician and the patient, the sustainability of the NHS and the competition.

In relation to the latter aspect, on the other hand, it is essential that, in a sector so scientifically complex, the one-dimensional view of competition among undertakings, solely tied with the economic aspect, be overcome, in order

119 With regard to the judgment of the Court of Cassation invoked here, see F. Massimino, Brevetto nullo di medicinale e concorrenza sleale: quali limiti ed obblighi per il titolare (Invalid medicine patent and unfair competition: holder’s limitations and obligations), in Diritto industriale (Industrial Law), 1/2017, 39 ff.

120 In this respect, see Documento Congiunto FADONI, SIF, SIN, SIR a norma biologici biosimiliari contenuta nell’art. 1 comma 407 della Legge n. 232/2016 (Joint Document by FADONI (Italian Federation of Associations of Internist Hospital Manager), SIF (Italian Society of Pharmacology), SIN (Italian Society of Neurology) and SIR (Italian Society of Rheumatology) about the provision on biological biosimilars set out in Art. 1, Par. 407, of Law No 232/2016), available at: http://sinitaly.org/wp-content/uploads/2017/05/Documento-congiunto-1.pdf.
to make the scientific fact another discriminating factor for the conscious choice of the medicine by the doctor, and also a competitive lever, even within a system of purchases focused on public procurement procedures\(^{121}\).

The regulatory system, in fact, aims to guarantee the doctor's right/duty to choose between the *originator* biological medicine and the biosimilar for each patient, regardless of whether or not they are already being treated with a medicine, and without the tender being a conditioning factor in determining the right therapeutic option. In other words, it is the physician's freedom of prescription that must condition and direct the procurement procedures, and not vice versa.

This conclusion is also respectful of the recommendations expressed by the EMA and the AIFA, to which antitrust authorities must also abide by, at least with respect to any scientific considerations. In this respect, the recent view of the aforementioned Lazio Regional Administrative Court No. 8945/2017 on the Aspen Case, is of particular interest: invoking the Judgment of the *Consiglio di Stato*, Fourth Division, 15 May 2015, No. 2479, A428 - *Wind-Fastweb/Condotte TI*, it reiterated that the relationship between regulatory authorities and competition authorities must not be a factor "for exclusion and overlap", i.e. "not for antithesis, but for complementarity". The AGCM's measures cannot replace scientific or regulatory assessment of the exclusive competence of the AIFA, but – starting from them – must be implemented "where the regulatory provisions allow companies to keep anti-competitive conducts" (Par. 3.7).

The AGCM's advocacy measures themselves, and in particular the view expressed in the Opinion dated 17 November 2016, do not deviate from the AIFA's position, confirming the relevance of the doctor's freedom of prescription and of the principle of therapeutic continuity, which, however, can and must be both reconciled with the NHS's saving targets. For this purpose, it is essential that the contracting agencies carefully structure the tender lots and adopt a prudent negotiation policy. The AIFA, for its part, must renegotiate the reimbursable price agreements of the originator biological medicines, usually lasting two years. On the other hand, it should be remembered that the legislation on hospital pharmaceutical expenditure (Art. 15 of Law No. 135/2012, as subsequently amended) provides for some corrective mechanisms, such as the reduction of budgets for companies with patent expired medicines. As a result, even in the presence of single lot tenders, the company owner of the originator products would still be encouraged to grant discounts, or, alternatively, it would be required to settle-off with a pay-back any exceeding of the allocated budget, paying to the Regions an amount equal to 50% of the surplus.

\(^{121}\) The new Directive on public procurements and award of concession contracts were published in the Official Journal of the European Union, L 94 of 28 March 2014. They entered into force twenty days after the publication, repealing the Directives 2004/17/EC and 2004/18/EC as from 18 April 2016. For the purpose of this paper, the Directive 2014/24/EU is particularly relevant. In this paper the price-quality ratio is identified as main system for enhancing the technological differential between products and supplies.
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