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# The Advent of the Biosimilars

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**The Advent of the Biosimilars**

The official member magazine of the American Society of Clinical Oncology (ASCO) of march, present year provides an extensive dissertation in favor of the introduction of biosimilars in clinical pratice[1]. Facing*' a dramatic and unsustainable rise in healthcare costs'*, the US should, in the experts' opinion, accelerate the use of these agents for the treatment of cancer.
In fact 'biosimilar' is a regulatory definition in reference to a higly similar molecule to an approved drug, that however is not identical. The article examines the possible scenarios and emphasizes the importance of a careful pharmacovigilance, underlying that it cannot be ascribed to the common regulation strategies used for generic drugs.
Even though the Experts furnish convincing arguments to sustain their thesis, a lot of scientific and economic factors have to be taken into account.
Biosimilars have been used in Europe since 2006, when the European Medicines Agency (EMA) approved a somatotropin equivalent, so starting from growth factors and hormones to recently close the land of biologic antineoplastic agents.
The reported savings are 20 to 30 %, reaching more than the 70% for the infliximab substitute, introduced one year ago as reminded by Prof. Schellekens.
The diffusion of biosimilars is expected to produce a largely positive impact on the healthcare costs, but this could negatively affect research and development of the whole pharmaceutical sector. Analyzing the economic features of the generic drugs and small-molecule agents, that do not require in their development recombinant DNA technology in living systems,it is possible to assert that the inferior cost is due to a streamlined policy of approval, essentially focused on the demonstration of the bioequivalence.
The Guidance for Industries delivered by the FDA Center for Drug Evaluation and Research highlights the definition of bioequivalence, for which '*the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions*' [2] . The techniques to estabilish bioequivalence include '*pharmacokinetic, pharmacodynamic, clinical, and in vitro studies*', specifically setting pharmacokinetic endpoints ($C_{max}$, the peak plasma concentration, $T_{max,}$ the time-to-peak drug plasma concentration and the area under the plasma concentration time curve) inaccessible biological matrix. The comparative clinical studies are however recommended '*when it is not possible to use the previously described methods*'. This permits to have fewer costs of development and approval and so to sell the product at a significanty inferior price in comparison with the labeled product.
This approach cannot be transferred to the biologic agents, for which the in vivo variability may be prohibitive in retaining a 'generic' drug equivalent. The potential issues related to the complications in the synthesis of these drugs regard the creation of folding isoforms, the uncontrolled enzymatic (translational or post-translational) modifications and the complex purification process discrepancies. Therefore the bioequivalence of the biosimilars cannot be easily assessed and controversy exists regarding the evaluation of their efficacy,potentially affected by the above-mentioned biologic variability. Nontheless a number of studies have demonstrated the

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comparability of synthetized biosimilars and the original drugs[3,4], but other evidences have emerged about safety imbalances between them. For instance PF-05280014, a biosimilar to trastuzumab, has shown some discordances in pharmacokinetics that may require additional clinical trials[5]. Moreover their immunogenicity is often comparable to the labeled drug; it is the case of the biosimilar CT-P13, equivalent to infliximab. ELISA assays have showed that antibodies to infliximab have identical reactivity towards it in patients suffering from rheumatoid arthritis and spondyloarthritis, that should be considered a contraindication for its administration in theseclinical setting[6].

Dr. Rifkin states that a '*properly powered clinical trial to determine absolute equivalence between a biosimilar and its reference drug would require thousands […] of patients*', and this is not a requirement for the FDA approval since it is retained that '*extensive preclinical analytic structural and functional essays, coupled with pharmacokinetic, pharmacodynamic, and immunogenicity studies*' characterize a sufficient evidence to predict the clinical conformity and interchangeability.But also confirmatory studies are included in the recommendations even though'*it is unlikely that clinically meaningful differences would be detected in subsequent trials*'[1].

The inferior prices of products in this case are imputable, as it happens for generic drugs, to the cost reduction of development and approval processes. Some experts have raised questions about the clinical equivalence of biosimilars.

From an economic standpoint it is mandatory to consider the consequence of this policy, admitting that the most influential innovations in medicine undoubtedly come from the private initiative. Pharmaceutical corporations, that are of course profitable businesses, reinvest the main part of their earnings in research and development, to mantain their role in a strongly competitive environment. The introduction of measures leading to a forced reduction of their profit, due to apparently convenient healthcare restrictive fiscal policies, could have as a secondary effect an important deceleration on the innovation in medicine and labor market. This could decrease the quality of research, that cannot be left only to a less efficient public sector. In addition the most probable source of the biosimilars in the future is expected to be Asia, and this could add further issues regarding western pharmacovigilance process and the competitiveness of the current progress-maker corporations.

In this context the role of the entrants in the biosimilar production business could negatively affect the market, since the incentive to research and development of new drugs may decrease.

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The regulation of biosimilars represents a multifacedscenario, which includes potentially positive and negative outcomes that have to be carefully evaluated.