

COMMENTARY

Biosimilar and interchangeable: Inseparable scientific concepts?

As defined by the European Commission, the term interchangeability refers to “the possibility of exchanging one medicine for another that is expected to have the same clinical effect.”¹ In the context of biosimilars the term interchangeability has caused confusion. Likely due to specific regulatory requirements in the United States, physicians sometimes interpret interchangeability as the potential for a biologic to be substituted by a biosimilar at the pharmacy level, without the involvement of a physician. However, interchangeability between a biological reference medicine and a corresponding biosimilar medicine should not be defined by its practical application; whether physician-driven switch or pharmacist-driven substitution. Interchangeability, ie, the possibility of safely and effectively changing a reference medicine by its biosimilar, or vice-versa, in a given patient, should be rather recognized as a scientific concept. In this paper, we review the evidence supporting the assertion that interchangeability is inherent to biosimilarity.

In science, a conclusion is reached when a hypothesis is tested by the use of an appropriate experimental approach. The aim of biosimilar development is to replicate an existing biomedicine. Biosimilarity must be substantiated by robust scientific evidence. To generate such evidence, a hypothesis of high similarity between a biosimilar candidate and the original reference medicine should be verified through well-established and validated methodologies that aim to identify all the potential relevant physicochemical differences, but are also capable of detecting even clinically meaningless differences. The acceptable difference level between the biosimilar candidate and the reference medicine is determined to a great extent by a thorough assessment of multiple batches of the reference biologic. Indeed, no approved biological medicine, whether original or not, is structurally identical to itself, due to an intrinsic batch-to-batch variability that can be enhanced by manufacturing changes. Although different batches of reference biological compounds are not identical to each other, they may be considered essentially equal and therapeutically indistinguishable. Therefore, there is a clinically acceptable range of inherent structural heterogeneity for any biological product.^{2,3} As a consequence, many patients have likely been treated with structurally slightly different versions of any given reference biomedicine, which constitutes a *de facto* switch of insignificant therapeutic concern. The approach used to substantiate biosimilarity represents a refinement of the procedures that have been securely applied for decades to batches of biologics that are subject to manufacturing changes,⁴ but also to the very precise discrimination between native and non-native proteins during the monitoring of

doping in sports. Indeed, the differentiation between an endogenously produced protein, such as erythropoietin, and an externally administered version, such as epoetin alfa or beta, requires extremely sophisticated laboratory techniques.^{5,6} The experience in analysing differences among batches of original biological agents has shown that no clinical comparison of efficacy and safety can match the accuracy and sensitivity of a stringent physicochemical and functional comparability. The rigorous regulation applied to the intrinsic variability of original biologics has thus been extended to the pioneering guidance regarding biosimilar-to-originator comparability put forth by the European Medicines Agency (EMA).⁷ The magnitude of acceptable physicochemical differences between biosimilars and their corresponding reference biologics can confidently be assessed in the laboratory, where the differences in critical quality attributes must be shown not to exceed the batch-to-batch variability of the reference biologic.

In addition to analytical comparability, biosimilarity is further supported by the demonstration of comparable pharmacokinetic, and possibly pharmacodynamic, clinical data.⁸ Furthermore, although clinicians are primarily familiar with the traditional benefit-to-risk balance assessment in patients for new medicines, the paradigm changes when assessing comparability, rather than therapeutic benefit *per se*. Indeed, when a biosimilar designation is to be granted, patient trials are considered to be confirmatory because of the superior value of analytical studies for comparative purposes.⁹ Accordingly, the necessity of patient trials has been a matter of debate for a number of years.¹⁰ In light of current practical evidence, the issue is being raised again.¹¹ In fact, the EMA already allows efficacy trials in patients to be waived for insulin biosimilar candidates,¹² and it introduced the possibility of bypassing patient trials for filgrastim biosimilar candidates.¹³ The totality of the evidence generated under a stringent regulatory framework, such as EMA's, indicates that biosimilars and their reference medicines essentially overlap structurally, thus clinically. Under these circumstances, if two versions of any given biologic were unable to be safely interchanged, whether that refers to two batches of any given biologic or to a biosimilar and its reference product, which treatments could? Hence, because batches of an original biologic can be deemed to be interchangeable, biosimilars and their corresponding reference medicines may also be safely reciprocally interchanged, as endorsed by EMA regulators.¹⁴ Indeed, the best scientific claim for interchangeability is the demonstration of essential sameness, ie, biosimilarity, based on a robust comparability programme.

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Beyond the exhaustive pre-registration requisites that support biosimilarity, more than thirteen years of clinical experience have been amassed while biosimilars have been available on the market, including extensive switching practice, which has provided overwhelming evidence to sustain the safety of interchanging. Indeed, post-marketing clinical studies and real-world evidence may help physicians more accurately calibrate the extent of the safety net when facing a switching decision. The NorSwitch study, fostered by Norwegian health care authorities, was the first independent, phase IV, randomized clinical trial to investigate switching as a primary endpoint.¹⁵ The study confirmed the safety of switching a given patient from being treated with a reference product containing infliximab to being treated with a biosimilar version of the medicine. Moreover, a recent meta-analysis of more than 90 studies, involving over 14 000 patients, confirmed that no specific risks can be attributed to the replacement of a reference medicine with a biosimilar.¹⁶ As highlighted in the meta-analysis, immunogenicity is a common matter of concern for prescribers when making a switching decision. However, the stringent scientific proof of physicochemical and functional comparability is also key to substantiating the conclusion of equivalent immunogenicity. Conclusive molecular overlap between biosimilars and reference medicines is well-illustrated by the finding that anti-drug antibodies (ADA) cross-react equally with both products.¹⁷ Although analytical comparability is reassuring on its own, reference regulatory bodies require case-by-case, pre- and post-authorization immunogenicity-targeted assessment plans.¹⁸ Accordingly, over many years of pharmaceutical surveillance of biosimilar safety and efficacy in European countries, including switching scenarios in Nordic countries^{15,19} and more recently in the United Kingdom,²⁰ no unexpected alerts or warnings have been raised regarding the development of ADA, or any other adverse effect, as a result of the presence of biosimilars on the market. Interestingly, the British Society of Gastroenterology²¹ recommends to switch to the biosimilar version patients stabilized, or in remission, with the reference product containing infliximab. Other learned societies also back the safety of switching stable patients to biosimilars.²² Although the scope of this article does not cover this issue, it is worth mentioning that as new biosimilars for a given reference medicine reach the market, interchangeability among biosimilars is also being debated. Given the stringency of the EMA regulatory framework, patients subject to any biosimilar-to-biosimilar switch are unlikely to face a non-acceptable risk. As experience continues to accumulate, registries of patients who undergo switching may be created to generate supporting evidence, which, in turn, may allow for new clinical guidance to be issued.

Based on the facts reviewed, the demonstration of biosimilarity under strict regulatory standards, such as the EMA's, parallels the claim of interchangeability, and interchangeability therefore represents a scientific concept that is inseparable from the biosimilar nature. Therefore, in contrast to some public positions,^{23,24} there does not appear to be any scientific basis for requiring clinical switching studies before a biosimilar can be granted the designation of "interchangeable." The interpretation of such studies would be far less conclusive and reliable than the data provided by the current totality of the evidence built primarily on the analytical comparability. Indeed, given the degree of

intra- and inter-patient variability in response to treatment, and the minute molecular differences found among biosimilars and the corresponding reference medicines, trials performed in patients would very unlikely provide the level of sensitivity required to confidently reflect the safety of a switching decision. Moreover, requesting such switching studies would question the foundation of the comparability model that has been applied successfully for decades to pre- and post-manufacturing versions of original biopharmaceuticals.

Despite the strength of the science supporting interchangeability, when two medicines are deemed to be interchangeable, physicians should be relevant players in any switching decision. The use of biosimilars should not constitute an exception to this general rule of the medical practice, particularly because there are several factors beyond active ingredients that could impact the therapeutic outcome, such as delivery device-related issues, or the placebo effect caused by a patient's misperception, or expectation, of the treatment. This position is advocated by several medical associations, sometimes in a more cautious manner, like the European Society of Medical Oncology (ESMO), or the Spanish Society of Rheumatology (SER), that support interchangeability in stable patients as long as the switch is decided by the physician in an individualized assessment, and in agreement with the patient.^{25,26}

An in-depth understanding of the scientific background supporting biosimilarity/interchangeability, combined with an appropriate level of communication with patients, can contribute to the maximization of the value of biosimilars.²⁷ Their contribution to sustainability and patient access is the main driver for biosimilars development, and clinicians are being increasingly involved in the management of resources freed up by their use. This has recently been advocated by a decree issued in France that experimentally encourages biosimilars prescription partly based on a redistribution towards the hospital, or the medical department, of the extra budget resulting from an increased biosimilars utilization.²⁸ Similar initiatives are being progressively generalized in the United Kingdom.²⁹ Despite the economic grounds that primarily promote the development of biosimilars, their therapeutic use should rely on scientific principles. A science-based understanding of interchangeability may raise confidence among physicians that currently prescribe biosimilars only in naïve patients, and may make them more comfortable switching from the reference medicine to a biosimilar, to further foster the positive impact of biosimilars.

COMPETING INTERESTS

M.C.-S. has worked as a speaker for Roche, Sanofi, and Astra Zeneca in the previous 5 years and no other relationships or activities that could appear to have influenced the submitted work. M.-A.A. works, or has worked, as a speaker and/or consultant for Biogen, Novartis, Kern Pharma, Lilly, Amgen, Sanofi, Celgene, MSD, Pfizer, Amgen, and Roche in the previous 5 years and no other relationships or activities that could appear to have influenced the submitted work. J.G. has served as a speaker, a consultant, and advisory member for or has received research funding from MSD, Abbvie, Hospira, Pfizer, Kern Pharma,

Biogen, Takeda, Janssen, Roche, Sandoz, Celgene, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, and Vifor Pharma. F.M. works, or has worked, as a speaker and/or consultant for Amgen, Adium, Asofarma, Biogen, Finox, Gebro, Hikma, Hospira, KernPharma, Lilly, Merck Serono, Mylan, Oli Med, Sandoz, Stada, Theramex, and Roche, in the last 5 years, and there are no other relationships or activities that could appear to have influenced the submitted work. A.B. has received honoraria as an advisor and speaker and grants from Pfizer, Abbvie, Roche, UCB, Gilead, Sandoz, Novartis, Lilly, Nordic, Sanofi and Amgen. R.M. is currently working at Sandoz Iberia. M.W. is currently working at Sandoz Biopharmaceuticals c/o Hexal AG. R.D. has received honoraria as a consultant and/or speaker for Amgen, Astellas, Bristol Myers-Squibb, Celgene, Genzyme, Gilead Sciences, Incyte, Jazz Pharmaceuticals, Kiadis Pharma, Merck Sharp and Dohme, Novartis, Omeros, Pfizer, Sanofi Oncology and Therakos-Mallinckrodt in the previous five years, and no other relationships or activities that could appear to have influenced the submitted work. J-M.C. has received consulting/speaker fees and/or has acted as a board member and/or has acted as PI/SI for Novartis, Janssen, Eli Lilly, Celgene, Almirall, Leo Pharma, Abbvie, Sandoz, Mylan and Pfizer, and no other relationships or activities that could appear to have influenced the submitted work. The other authors have no competing interests to declare.

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