



BIOSIMILARS: COMPARABILITY REQUIREMENTS AND MARKET UPTAKE

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Article info

Received date:06-02-2025

Accepted date:27-04-2025

Published date:26-08-2025

ISSN;0975-8216

Keywords:

Biosimilars, Comparability, Interchangeability, Market uptake, Regulatory science

1. INTRODUCTION

Biological medicines such as monoclonal antibodies, insulin, erythropoietin and growth hormone are large, complex proteins made in living cells, and they are expensive. When patents and data protection expire, other manufacturers can develop their own versions, but they cannot copy a biological in the way a generic company copies a small-molecule tablet. The reference product's cell line, process and exact structure are proprietary, and even slight differences in

Abstract

Biosimilars are follow-on versions of biological medicines whose approval rests on demonstrating high similarity to a reference product, not on repeating the full development programme. This narrative review describes the comparability requirements applied in Europe, the United States and under World Health Organization guidance, the analytical, nonclinical and clinical evidence that supports approval, and current thinking on immunogenicity, switching and interchangeability. It then summarises what published work shows about uptake and the policies that influence it. Uptake varies widely between countries and products, driven more by procurement and incentives than by scientific doubt. The article reports no new data; evidence gaps are discussed.

manufacture produce a distinct mixture of molecular variants [1, 2]. Regulators therefore

created a separate pathway in which a new product is judged against its reference by extensive comparison, and the term biosimilar was reserved for products that pass it [3, 4, 5].

The first European approval of this kind, a somatropin product in 2006, was followed by erythropoietins, filgrastims and, from 2013, monoclonal antibodies, and the United States approved its first biosimilar in 2015 after enacting its own pathway [5, 6, 7]. The numbers have grown quickly since then, and biosimilars now exist for most of the big-selling antibodies and fusion proteins used in rheumatology, gastroenterology, dermatology and oncology. Savings are a central motive, because some of these products accounted for a large share of national drug budgets. The scientific case has been tested in many thousands of patients, yet debate about trust, switching and incentives continues in clinics and in health ministries.

This review covers two linked themes: what a manufacturer must demonstrate to show comparability with a reference product, and how those products have fared in practice once approved. It is based on published guidelines, reviews, clinical trials and policy analyses, and it reports no original data. The aim is to explain the logic of the regulatory framework in terms a prescriber or pharmacist can use, to identify the points on which evidence is strong and those on which it is thin, and to describe the reasons that uptake differs so widely from one country, and one product, to the next.

2. REGULATORY FRAMEWORK AND COMPARABILITY

The European Medicines Agency framework is built on an overarching guideline for similar biological medicinal products, supported by separate documents on quality, and on nonclinical and clinical issues, and by product-specific annexes for classes such as monoclonal antibodies and insulins [3, 8, 9]. The core concept is stepwise comparison. Analytical and functional comparison forms the foundation, nonclinical work is tailored to what remains uncertain, and clinical studies are confirmatory in nature rather than aimed at establishing benefit afresh. The WHO guidelines on similar biotherapeutic products

follow the same logic and were written to help regulators in countries without a long experience of biologics [4].

In the United States, the Food and Drug Administration works under a statutory definition: the product must be highly similar to the reference, notwithstanding minor differences in clinically inactive components, with no clinically meaningful differences in safety, purity and potency. Its guidance describes a totality-of-the-evidence approach, within which analytical data are the foundation and the amount of residual uncertainty determines what further studies are needed [5, 6]. The agency has added a distinct higher tier, interchangeability, which allows pharmacist-level substitution without prescriber intervention where state law permits, and for which additional data on switching were at first expected [10].

A different strand of regulatory science, the guideline on comparability after manufacturing changes (ICH Q5E), is relevant here because the same logic applies. Originators change their own processes repeatedly over a product's life, sometimes dozens of times, and each change is accepted after comparability exercises showing that quality attributes remain highly similar, with clinical studies required only occasionally [1]. Observers have pointed out that a biosimilar is assessed with the same principles, though with a larger gap between the two manufacturing processes [11, 12]. This analogy supports the argument that biosimilar approval is not a lower standard but a different route to the same assurance.

Europe has also taken the lead in articulating how the framework should evolve. Regulators and academic groups have discussed whether comparative efficacy trials are always needed, given that analytical methods are often more sensitive to differences than clinical end points, and whether waivers for certain in vivo studies are justified for monoclonal antibodies [7, 13]. Policy documents have emphasised that the requirement for large trials adds cost and delays access without adding much scientific assurance when analytical similarity is strong. These proposals are not yet uniform around the world, which complicates global development

programmes, but they point to a trend toward more streamlined clinical packages for well-characterised antibodies.

Naming and traceability form a smaller but practical part of the framework. International nonproprietary names are shared between a biosimilar and its reference in Europe, so the active substance name alone cannot tell the two apart, whereas the FDA appends a four-letter suffix to the proper name of each biologic to help identify a specific product in prescriptions and pharmacovigilance reports [14, 15]. Neither approach is free of argument. Critics of suffixes say they may suggest a safety difference that does not exist, while supporters point out that reports of adverse events cannot be traced without them. Whatever the system, recording the brand name and batch number is the safeguard on which attribution of rare problems depends.

3. ANALYTICAL AND FUNCTIONAL SIMILARITY

Analytical comparison is the heart of the exercise. A manufacturer characterises the primary structure, higher-order structure, post-translational modifications, charge and size variants, aggregates, impurities and biological activity of its product and compares them with many lots of the reference product, usually sourced from several markets and across the shelf life [8, 16]. Orthogonal techniques are used for each attribute, for instance mass spectrometry, peptide mapping, circular dichroism, hydrogen–deuterium exchange and capillary electrophoresis, and the results are set against ranges derived from the reference lots. Modern instrumentation can detect structural differences that early developers of biologics could not even have measured [16].

Glycosylation attracts special attention because it influences half-life, effector function and immunogenicity. For antibodies, the pattern of glycans on the Fc region affects binding to Fcγ receptors and complement, and so antibody-dependent cellular cytotoxicity. Afucosylated forms, for example, bind FcγRIIIa more strongly and enhance cytotoxicity, so even small changes in their proportion may be functionally relevant for oncology antibodies [16, 17]. Terminal sialic

acid and galactose content, high-mannose structures and C-terminal lysine are among other attributes tracked. Acceptable ranges are set according to the reference product's own variability and a risk assessment of the effect of each attribute on clinical performance [17].

Functional assays complete the picture. For a TNF inhibitor, they would include binding to soluble and membrane-bound TNF, neutralisation of its activity in cell assays, binding to neonatal Fc receptor, and effector functions where relevant. The tests are chosen to represent each mechanism of action thought to contribute to efficacy, and acceptance criteria are set before the comparison [8, 9]. A difference in one assay does not automatically disqualify a product, but it requires explanation and may trigger additional studies. The value of the structure is that every observed difference is examined, quantified and tied to a possible clinical consequence, and not simply dismissed or ignored [12, 16].

Reference lots turn out to vary, and this fact is often missed in public discussion. Studies comparing originator batches over years documented drifts in glycan profiles and other attributes, in some cases larger than the differences later claimed to separate a biosimilar from its reference [11, 17]. Because regulators allow originators to change processes under comparability rules, patients on a single brand have always been exposed to a range of variants. This is not an argument that anything goes. It does show that the aim is to remain within the natural variability of the reference, and it explains why the quality of analytical comparison is so decisive in the assessment [1, 12, 17].

Formulation, excipients and delivery device are not required to be identical to those of the reference, and these differences matter in daily use. A biosimilar may be supplied in a different buffer, may omit a stabiliser or contain a different concentration, and the autoinjector or pre-filled pen may differ in how it is held, primed and triggered [14, 18]. Injection-site pain has been linked to some excipients, notably citrate. Such differences are assessed as part of the approval, but they can affect patient experience and adherence,

and a switch involving a new device calls for training. Pharmacists and nurses are the natural people to supply that training and to check understanding.

Quality-by-design thinking has influenced biosimilar development in a way that is rarely appreciated. Because the target is defined by the reference product's attribute ranges, developers begin by reverse engineering them, selecting a cell line, culture conditions and purification steps that reproduce the desired profile, and then controlling the process within a design space [2, 12]. The process defines the product, as one review put it, and biosimilar manufacturers must therefore maintain control over their own process as strictly as any innovator does. An approved biosimilar is expected to remain consistent over its life cycle, and changes after approval are handled through the same comparability principles [1].

4. NONCLINICAL AND CLINICAL EVIDENCE

Nonclinical studies play a smaller role than in the development of a new drug. In vitro pharmacology on relevant cells is considered most informative, and in vivo animal studies are requested only when the analytical and in vitro package leaves unanswered questions, for example about a new excipient or an unusual impurity profile [9, 13]. Animal models often respond poorly to human proteins because of species differences and the production of neutralising antibodies, so the data are of limited predictive value. This is the reason that regulators and industry bodies have proposed waiving routine in vivo studies in a number of cases, a step that also reflects ethical concerns about animal use [13].

Clinical development usually starts with a pharmacokinetic and, where there is a suitable biomarker, pharmacodynamic study in healthy volunteers or patients, designed to show equivalence of exposure within predefined margins. A comparative efficacy and safety trial in the most sensitive indication follows, typically with an equivalence design and a clinical end point that is both responsive and well accepted [6, 9]. The infliximab biosimilar CT-P13 is an

instructive example, with parallel studies in ankylosing spondylitis and rheumatoid arthritis showing similar pharmacokinetics, efficacy and safety to the reference [19, 20]. Equivalence margins are an important design issue, because overly wide margins may hide differences, while overly narrow ones demand enormous trials.

Immunogenicity is the safety question that most concerned regulators at the outset, and with good reason. Therapeutic proteins can provoke anti-drug antibodies that neutralise activity, alter clearance or, rarely, cross-react with endogenous proteins [21]. The classic warning was pure red-cell aplasia associated with a subcutaneous erythropoietin product in the early 2000s, linked to a change in formulation and handling, and it showed that apparently small manufacturing changes can matter for immunogenicity [22]. Biosimilar guidance consequently requires comparative immunogenicity data from clinical studies, using validated, sensitive assays, with assessment of neutralising antibodies and follow-up long enough to capture late effects [8, 9, 21].

Experience after approval has so far been reassuring. Systematic reviews of the published evidence in chronic inflammatory diseases found no consistent differences in efficacy, safety or immunogenicity between biosimilars and their reference products [23, 24]. Observational registries in Europe, enrolling large numbers of patients over several years, have reported retention rates and adverse event profiles similar to those with originators [24, 25]. Pharmacovigilance is nonetheless a regulatory requirement, with risk-management plans, traceability by brand name and batch number, and periodic safety updates. Good practice therefore includes recording the product by brand, because the generic name alone does not allow identification of a specific biological [14].

Oncology has brought its own questions. Biosimilars of trastuzumab, rituximab, bevacizumab and filgrastim are used in curative as well as supportive care, and the stakes of any loss of efficacy are high [26, 27]. Position papers from oncology societies accept the scientific framework but stress several practical points: that extrapolation of

indications requires a clear rationale, that prescribers need information about the data supporting each product, and that substitution at the pharmacy should not happen without the knowledge of the treating team [27]. Early scepticism reflected in part the novelty of the products, and published comparative trials in breast cancer and lymphoma have mostly met their equivalence margins in the intended populations [26, 27].

Taking the evidence streams together, a pattern is clear. Regulatory and analytical sources set the standard, clinical trials and switching studies test it, and policy analyses describe what follows in the market. The main findings from each stream are summarised in table 1, and fig. 1 shows how the entries divide among the types of evidence. Analytical and regulatory entries are numerous because the approval logic rests on them, whereas uptake entries cluster around a small number of well-studied cases, such as Denmark and the United States. This distribution is itself informative: the strongest evidence concerns product quality, and the weakest concerns long-term outcomes of repeated switching in specific subpopulations.

5. SWITCHING AND INTERCHANGEABILITY

Interchangeability has been the most debated aspect of biosimilar policy. In Europe the question has been seen as a matter for national authorities, with the European regulator confining itself to scientific evaluation, while in the United States it is a formal designation conferred by the FDA [10, 28]. Switching between a reference product and a biosimilar was long felt to carry a theoretical risk of immunogenicity. The scientific basis for such a concern is weak, since immunogenicity depends on product attributes, and not on the patient's history of exposure, though evidence from deliberate switches in the early years was limited [28, 29].

The NOR-SWITCH trial changed the discussion. In this Norwegian randomised, double-blind non-inferiority trial, patients on stable originator infliximab either continued it or switched to CT-P13, and the disease worsening rate over 52 weeks did not differ in

a clinically important way, with similar safety and immunogenicity [30]. Later systematic reviews, covering many dozens of switching studies across products, did not find any consistent loss of efficacy or increase in adverse events or anti-drug antibodies after a single switch [23, 31]. Results for multiple switches and for non-medical switching in particular populations are rarer, and most authors accept that there is less certainty about repeated back-and-forth changes.

Table 1: Comparability evidence and market-uptake findings reported for biosimilars

Topic context	Reported finding	Ref.
Regulatory frameworks EU, WHO, US	Stepwise comparison with analytical similarity as the foundation and confirmatory clinical data.	[3, 4, 6]
Manufacturing change ICH Q5E	Originators change processes repeatedly under the same comparability principles.	[1, 11]
Glycan and charge variants analytical	Acceptable ranges follow reference variability; Fc glycans linked to effector function.	[16, 17]
Reference lot variability originator drift	Natural batch-to-batch and over-time drift in quality attributes documented.	[12, 17]
CT-P13 trials ankylosing spondylitis, RA	Equivalent pharmacokinetics, efficacy and safety versus reference infliximab.	[19, 20]
NOR-SWITCH randomised switching	Switching to CT-P13 was not inferior to continued originator.	[30]
Switching reviews multiple products	No consistent loss of efficacy or rise in antibodies after a single switch.	[23, 31]
Erythropoietin immunogenicity red-cell aplasia	Formulation change associated with antibody-mediated aplasia; shaped guidance.	[21, 22]
European uptake analyses policy comparison	Uptake driven by procurement, incentives and prescriber engagement.	[32, 33, 34]
Danish adalimumab shift national tender	Most patients moved to biosimilar within months of the tender.	[35]

Topic context	Reported finding	Ref.
US experience rebates and litigation	Slower early uptake attributed to contracting and fragmented purchasing.	[36]

A pragmatic consensus has emerged in many professional bodies. The use of biosimilars in new patients is accepted without reservation, and switching from reference to biosimilar for stable patients is accepted when the decision is made in a shared way with the clinician and the patient [18, 25]. Cases in which non-medical switching might be inappropriate are limited, and include those with a history of severe adverse reactions on the reference product. Communication appears to matter. Several reports of higher discontinuation after switching have been attributed to the nocebo effect, in which negative expectations lead to symptoms or reduced perceived benefit, and these are reduced when patients are given clear, positive and consistent information [18, 31].

The legal setting for substitution varies. In the United States, state pharmacy laws govern whether a pharmacist may dispense an interchangeable biologic in place of the prescribed product, and most states require notification of the prescriber and records of the dispensed product. In European countries, substitution at the pharmacy is often not allowed for biologics, or is limited to defined circumstances, and the decision remains with the prescriber [10, 28]. Pharmacists need to know the local rules, since a product may be fully acceptable scientifically and yet cannot be dispensed in its place without authorisation. Educational activities that clarify these distinctions help to prevent errors and reassure patients.

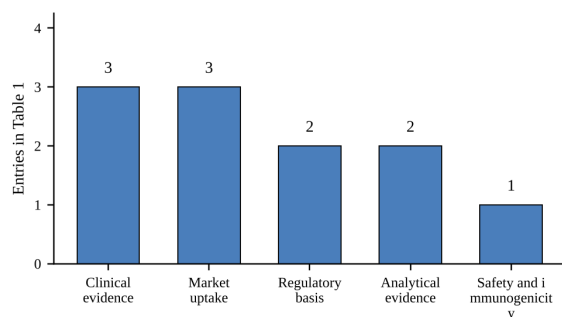


Fig. 1: Number of entries in table 1 by type of evidence

Pharmacists have also drawn attention to how patients respond emotionally to switching. Those who feel the decision was imposed for financial reasons tend to report more symptoms and to stop treatment sooner, even when the clinical course is unchanged [18, 31]. Several centres have therefore moved to a shared decision model, with a short consultation, a written explanation and a point of contact in the first weeks. Programmes of this kind consistently report discontinuation rates close to those of non-switched patients. They are inexpensive to run and fit naturally into pharmacy-led clinics, which is why they are often recommended alongside any formulary change [25, 31].

6. MARKET UPTAKE AND POLICY

Uptake data show a striking spread. Within Europe, the share of volume taken by biosimilars after entry varies from a few per cent to nearly all of the market, depending on molecule and country, and Nordic and some Central European countries tend to move faster than larger Western European markets [32, 33]. Analyses of key drivers point to the importance of pricing and procurement policy, the structure of hospital purchasing, physician and payer incentives and the pharmaceutical competition within a product class [32, 34]. Product features such as route of administration, device and the number of competitors influence results. Differences in scientific evidence do not feature prominently in these analyses.

Policies are of several kinds. Demand-side measures include prescribing quotas or targets, incentives to prescribers and gain-sharing arrangements in which savings are shared between payers and providers, while supply-side measures include tendering that awards volumes to the winning supplier, reference pricing and mandatory price reductions [33, 34]. Studies of the European experience suggest that policy mixes combining a clear political commitment, physician engagement and economic incentives are more effective than any single lever [33]. Experience with tenders is double-edged, since aggressive price competition can drive suppliers from a market and leave a single source, a fragility that policy makers are now more aware of [34,

37].

The Danish response to the adalimumab patent expiry has become a widely cited case. After a national tender, the great majority of patients who had been treated with the originator moved to a biosimilar over a matter of months, with no visible signal of problems in routine outcomes [35]. Elsewhere in Europe, the entry of adalimumab biosimilars in 2018 was followed by price reductions that differed greatly between countries, reflecting the interaction of national pricing rules and the originator's discounting response [38]. These stories show how quickly a market can shift once the incentives are aligned, and how far uptake depends on administrative design, not on any scientific difference in the products.

The United States has seen a different pattern. Despite an approval pathway modelled on the same scientific principles, early uptake for several products was slow, which analysts attributed to patent litigation, contracting arrangements that tie rebates to a reference product's market position, and fragmented purchasing across insurers [32, 36]. Estimates of the savings available from biosimilars were substantial, and the largest effect was seen in products administered in clinics and hospitals, where reimbursement for the biosimilar encourages use [36]. As more competitors have entered, and as large payers have changed formularies, the position has evolved, but a straightforward lesson remains: approval is necessary for uptake, yet far from sufficient for it.

Value arguments are broader than price. Beyond lower acquisition cost, biosimilar competition has been credited with widening access, so that more patients are treated at earlier stages, with encouraging the use of therapy in places that could not afford the originator, and with stimulating innovation in formulations and devices [37]. Savings can be reinvested in other care. Against this, there are concerns about the sustainability of low prices for manufacturers, which may reduce investment, and about the resilience of supply. An honest accounting of market effects therefore needs to consider access, competition and supply security together with the direct cost of a vial or a pen [34, 37].

The setting of care influences uptake as much as national policy. Hospital-administered products such as intravenous antibodies are bought by institutions that can negotiate prices, run tenders and control formularies, so biosimilar share can change rapidly. Pharmacy-dispensed or self-administered products depend on prescribers, patients and reimbursement rules at the point of dispensing, and uptake tends to be slower unless incentives reach the prescriber [32, 34]. Insulins, filgrastims and adalimumab have followed different paths for this reason. A lesson for policy design is that each distribution channel needs its own tools, and that measures effective for hospital tenders may not transfer to community prescribing.

7. LIMITATIONS AND FUTURE DIRECTIONS

The evidence summarised in this review has limits. Most clinical comparisons are in rheumatology and a few other areas, and data on oncology supportive care or on newer product classes are less developed. Randomised switching trials are few and generally short, and real-world analyses carry the usual risks of confounding and reporting bias. Analytical data, the main basis for approval, are held by manufacturers and regulators, and only summaries are public, so independent scrutiny is limited. Studies of uptake are mostly descriptive and vary in the definition of market share, so comparisons across countries and time need care [32, 33, 39].

Several developments will shape the next phase. More complex molecules, including antibody–drug conjugates, bispecific antibodies and products delivered through novel devices, will test the framework, because comparability becomes harder as complexity rises [7, 16]. Regulators are moving toward reduced clinical packages and clearer statements on interchangeability, and prescribers are being asked to accept this without the reassurance of large comparative trials [7, 13]. Pharmacovigilance systems will need to keep pace, with reliable product-level tracking. Improved methods for characterising high-order structure and for linking attribute differences to clinical effects would provide a stronger basis for these

decisions.

Access in low- and middle-income countries raises further issues. The WHO guidelines were intended to provide a route for regulators without large biologics divisions, but capacity to assess analytical data and to run pharmacovigilance remains limited in many settings [4, 37]. Products marketed without a proper comparability exercise have appeared in some markets, and these should not be confused with approved biosimilars. If cost reductions are to widen access to cancer and autoimmune therapies, then regulatory reliance, shared assessments and capacity building are likely to matter as much as the products themselves. This area is less well documented than European and North American experience, and its evidence base deserves expansion.

From a practice standpoint, the evidence supports confident use of approved biosimilars in new and stable patients, careful communication around switching, and monitoring that records the specific product given. Hospital formulary committees should consider the full range of benefits and risks, including supply security. Policy makers might focus on aligning incentives, since the data show these to be the main determinant of uptake, and on funding independent post-marketing studies [33, 34]. For researchers, the open questions include the effect of multiple switches, long-term immunogenicity, and the real-world impact of regulatory changes that reduce required clinical data.

8. CONCLUSION

The case for biosimilars rests on a consistent scientific logic. Extensive analytical and functional comparison against the reference product, tailored nonclinical work and confirmatory clinical studies together establish that no clinically meaningful differences are expected, and the experience that has accumulated since the first approvals supports that expectation [3, 6, 23, 24]. Immunogenicity remains the property needing continued attention, and switching data, led by NOR-SWITCH, are reassuring for single switches [21, 30, 31]. The natural variability of originator products reminds us

that sameness has never meant identity. The label alone does not guarantee quality, but the process behind it is demanding.

Whether patients benefit in practice depends largely on factors outside the laboratory. Uptake follows pricing rules, procurement design, incentives and the confidence of prescribers and patients, with large differences between countries that cannot be explained by differences in the products [32, 33, 34, 35]. Clear communication, product-level pharmacovigilance and policies that sustain competition without risking supply will determine how much of the potential saving is realised. Evidence will need to keep pace with more complex molecules and shifting regulatory expectations. The next decade will test whether the framework adapts without losing public trust.

9. ABBREVIATIONS

EMA-European Medicines Agency, FDA-Food and Drug Administration, WHO-World Health Organization, ICH-International Council for Harmonisation, TNF-Tumour necrosis factor, Fc-Fragment crystallisable, FcγR-Fc gamma receptor, RA-Rheumatoid arthritis, NOR-SWITCH-Norwegian switching trial of infliximab, CT-P13-Infliximab biosimilar product code, PK-Pharmacokinetic, SBP-Similar biotherapeutic product

10. FUNDING

Nil

11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

13. REFERENCES

1. ICH Harmonised Tripartite Guideline. Comparability of biotechnological/biological products subject to changes in their manufacturing process Q5E. Geneva: ICH; 2004.
2. Rathore AS, Winkle H. Quality by design for biopharmaceuticals. *Nat Biotechnol* 2009;27:26–34.
3. European Medicines Agency. Guideline on similar biological medicinal products (CHMP/437/04 Rev 1). London: EMA;

- 2014.
4. World Health Organization. Guidelines on evaluation of similar biotherapeutic products (SBPs). Geneva: WHO; 2009.
5. Kozlowski S, Woodcock J, Midthun K, Sherman RB. Developing the nation's biosimilars program. *N Engl J Med* 2011;365:385–8.
6. Food and Drug Administration. Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. Silver Spring: FDA; 2015.
7. Wolff-Holz E, Tiitso K, Vleminckx C, Weise M. Evolution of the EU biosimilar framework: past and future. *BioDrugs* 2019;33:621–34.
8. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (EMA/CHMP/BWP/247713/2012). London: EMA; 2014.
9. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMA/CHMP/BMWP/42832/2005 Rev 1). London: EMA; 2014.
10. Food and Drug Administration. Considerations in demonstrating interchangeability with a reference product: draft guidance for industry. Silver Spring: FDA; 2019.
11. Declerck P, Farouk-Rezk M, Rudd PM. Biosimilarity versus manufacturing change: two distinct concepts. *Pharm Res* 2016;33:261–8.
12. Vulto AG, Jaquez OA. The process defines the product: what really matters in biosimilar design and production? *Rheumatology (Oxford)* 2017;56(Suppl 4):iv14–29.
13. Chapman K, Adjei A, Baldrick P, da Silva A, De Smet K, DiCicco R, *et al.* Waiving in vivo studies for monoclonal antibody biosimilar development: national and global challenges. *MAbs* 2016;8:427–35.
14. Weise M, Bielsky MC, De Smet K, Ehmann F, Ekman N, Giezen TJ, *et al.* Biosimilars: what clinicians should know. *Blood* 2012;120:5111–7.
15. Declerck P, Danesi R, Petersel D, Jacobs I. The language of biosimilars: clarification, definitions, and regulatory aspects. *Drugs* 2017;77:671–7.
16. Berkowitz SA, Engen JR, Mazzeo JR, Jones GB. Analytical tools for characterizing biopharmaceuticals and the implications for biosimilars. *Nat Rev Drug Discov* 2012;11:527–40.
17. Schiestl M, Stangler T, Torella C, Čepeljnik T, Toll H, Grau R. Acceptable changes in quality attributes of glycosylated biopharmaceuticals. *Nat Biotechnol* 2011;29:310–2.
18. Moots R, Azevedo V, Coindreau JL, Dörner T, Mahgoub E, Mysler E, *et al.* Switching between reference biologics and biosimilars for the treatment of rheumatology, gastroenterology, and dermatology inflammatory conditions: considerations for the clinician. *Curr Rheumatol Rep* 2017;19:37.
19. Yoo DH, Hrycaj P, Miranda P, Ramitterre E, Piotrowski M, Shevchuk S, *et al.* A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis* 2013;72:1613–20.
20. Park W, Hrycaj P, Jeka S, Kovalenko V, Lysenko G, Miranda P, *et al.* A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann Rheum Dis* 2013;72:1605–12.
21. Schellekens H. Immunogenicity of therapeutic proteins: clinical implications and future prospects. *Clin Ther* 2002;24:1720–40.
22. Casadevall N, Nataf J, Viron B, Kolta A, Kiladjian JJ, Martin-Dupont P, *et al.* Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med* 2002;346:469–75.
23. Barbier L, Ebbers HC, Declerck P, Simoens S, Vulto AG, Huys I. The efficacy, safety, and immunogenicity of switching between reference biopharmaceuticals and biosimilars: a systematic review. *Clin Pharmacol Ther* 2020;108:734–55.
24. Jacobs I, Petersel D, Isakov L, Lula S, Lea Sewell K. Biosimilars for the treatment of chronic inflammatory diseases: a systematic review of published evidence. *BioDrugs* 2016;30:525–70.

25. Kay J, Schoels MM, Dörner T, Emery P, Kvien TK, Smolen JS, *et al.* Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. *Ann Rheum Dis* 2018;77:165–74.
26. Mellstedt H, Niederwieser D, Ludwig H. The challenge of biosimilars. *Ann Oncol* 2008;19:411–9.
27. Tabernero J, Vyas M, Giuliani R, Arnold D, Cardoso F, Casali PG, *et al.* Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers. *ESMO Open* 2016;1:e000142.
28. Kurki P, van Aerts L, Wolff-Holz E, Giezen T, Skibeli V, Weise M. Interchangeability of biosimilars: a European perspective. *BioDrugs* 2017;31:83–91.
29. Ebberts HC, Muenzberg M, Schellekens H. The safety of switching between therapeutic proteins. *Expert Opin Biol Ther* 2012;12:1473–85.
30. Jørgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haavardsholm EA, *et al.* Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet* 2017;389:2304–16.
31. Cohen HP, Blauvelt A, Rifkin RM, Danese S, Gokhale SB, Woollett G. Switching reference medicines to biosimilars: a systematic literature review of clinical outcomes. *Drugs* 2018;78:463–78.
32. Rémuzat C, Dorey J, Cristeau O, Ionescu D, Radière G, Toumi M. Key drivers for market penetration of biosimilars in Europe. *J Mark Access Health Policy* 2017;5:1272308.
33. Moorkens E, Vulto AG, Huys I, Dylst P, Godman B, Keuerleber S, *et al.* Policies for biosimilar uptake in Europe: an overview. *PLoS One* 2017;12:e0190147.
34. Vogler S, Schneider P, Zuba M, Busse R, Panteli D. Policies to encourage the use of biosimilars in European countries and their potential impact on pharmaceutical expenditure. *Front Pharmacol* 2021;12:625296.
35. Jensen TB, Kim SC, Jimenez-Solem E, Bartels D, Christensen HR, Andersen JT. Shift from adalimumab originator to biosimilars in Denmark. *JAMA Intern Med* 2020;180:902–3.
36. Mulcahy AW, Hlavka JP, Case SR. Biosimilar cost savings in the United States: initial experience and future potential. *Rand Health Q* 2018;7:3.
37. Dutta B, Huys I, Vulto AG, Simoens S. Identifying key benefits in European off-patent biologics and biosimilar markets: it is not only about price! *BioDrugs* 2020;34:159–70.
38. Moorkens E, Godman B, Huys I, Hoxha I, Malaj A, Keuerleber S, *et al.* The expiry of Humira market exclusivity and the entry of adalimumab biosimilars in Europe: an overview of pricing and national policy measures. *Front Pharmacol* 2021;11:591134.
39. Dörner T, Strand V, Cornes P, Gonçalves J, Gulácsi L, Kay J, *et al.* The changing landscape of biosimilars in rheumatology. *Ann Rheum Dis* 2016;75:974–82.