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Clinical considerations for biosimilar antibodies

*Håkan Mellstedt**

Professor of Oncological Biotherapy, Department of Oncology–Pathology, Karolinska Institute, SE-171 76 Stockholm, Sweden

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Biosimilar agents are *approximate copies* of branded biologic therapies. Since the first biosimilar was authorized in the European Union in 2006, fifteen additional agents have been approved by the European Medicines Agency, including two biosimilar monoclonal antibodies (mAbs). Biosimilar mAbs represent a distinct class given their large molecular size, complex protein structure, and post-translational modifications. While guidelines have been established for the development, approval, and use of biosimilars, further scrutiny and discussion is necessary to fully understand their potential impact on clinical outcomes. This review takes a critical look at the structural complexity of biosimilar mABs, the feasibility of indication extrapolation, the impact of product variability on immunogenicity, the importance of comprehensive pharmacovigilance, and the potential for ongoing pharmacoeconomic impact.

1. Introduction

Biological medicinal products, or biologics, are a class of recombinant, protein-based therapeutics, produced by living organisms (e.g., plants, animals, yeast, and bacteria) [1]. Over the past two decades, biologics have revolutionized patient management in multiple disease states, including solid tumors, hematologic malignancies, autoimmune diseases, and hormone deficiencies. As many of these "blockbuster" drugs reach the end of their exclusivity rights, the door to the development of copy versions opens. However, unlike the generics of small-molecule drugs, exact replicas cannot be made of biologics because of their structural complexity and complicated manufacturing process [2,3]. The term biosimilars was coined to describe any copy of an authorized branded biologic originator that has demonstrated similarity in a rigorous comparability exercise [3].

Until recently, the only approved biosimilars were copies of lower molecular weight biologics, such as growth hormones and hematopoietic growth factors. However, in 2013 the European Medicines Agency (EMA) approved the first biosimilars of a monoclonal antibody (mAb), infliximab [4,5]. Biosimilars of other mAbs, including rituximab and trastuzumab, are in development, with approval of some expected as early as 2014. The intrinsic complexity of antibody structure, the heterogeneity introduced by subtle changes in product manufacturing, and the potential complications associated with the introduction of biosimilar mAbs to the marketplace must be brought to the forefront of critical discussion. While there appears to be great potential in how biosimilar mAbs may impact the treatment landscape and benefit patients, there remain a number of concerns and obstacles that must be addressed.

2. The complexity of monoclonal antibodies

The first regulatory guidelines for biosimilars were published by the EMA in 2005 [6]. Compared with small-molecule generics and new biologic agents, biosimilars are evaluated via an abbreviated approval pathway

*Tel.: +46 8 5177 4641; fax: +46 8 31 27.
E-mail address: Hakan.Mellstedt@ki.se (H. Mellstedt).

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Table 1 – Summary of approval process for small-molecule generics, new biologic agents, and biosimilars [2]

	Small-molecule generic	New biologic agent (full dossier)	Biosimilar (reduced dossier)
Quality	• Individual quality assessment • Comparison with reference product	• Individual quality assessment	• Individual quality assessment • Comprehensive comparison with reference product
Pre-clinical	• No data required	• Full pre-clinical program	• Abbreviated pre-clinical program (tolerance, PK/PD)
Clinical	• Bioequivalence study	• Phase I • Phase II • Phase III in all indications • Risk-management plan	• Phase I PK/PD study • Phase III study in a sensitive, representative indication • Risk-management plan

Table 2 – Biosimilars authorized for use in the EU [7]

Biosimilar brand name	Active substance	Therapeutic area	Year of authorization
Abseamed	Epoetin alfa	Anemia, cancer, chronic kidney failure	2007
Binocrit	Epoetin alfa	Anemia, chronic kidney failure	2007
Epoetin Alfa Hexal	Epoetin alfa	Anemia, cancer, chronic kidney failure	2007
Retacrit	Epoetin zeta	Anemia, autologous blood transfusion, cancer, chronic kidney failure	2007
Silapo	Epoetin zeta	Anemia, autologous blood transfusion, cancer, chronic kidney failure	2007
Biograstim	Filgrastim	Cancer, hematopoietic stem cell transplantation, neutropenia	2008
Filgrastim Hexal	Filgrastim	Cancer, hematopoietic stem cell transplantation, neutropenia	2009
Filgrastim ratiopharm [a]	Filgrastim	Cancer, hematopoietic stem cell transplantation, neutropenia	2008
Nivestime	Filgrastim	Cancer, hematopoietic stem cell transplantation, neutropenia	2010
Ratiograstime	Filgrastim	Cancer, hematopoietic stem cell transplantation, neutropenia	2008
Tevagrastim	Filgrastim	Cancer, hematopoietic stem cell transplantation, neutropenia	2008
Zarzio	Filgrastim	Cancer, hematopoietic stem cell transplantation, neutropenia	2009
Inflectra	Infliximab	Rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis	2013
Remsima	Infliximab	Rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, psoriasis	2013
Omnitrope	Somatropin	Pituitary dwarfism, Prader–Willi syndrome, Turner syndrome	2006
Valtropin [a]	Somatropin	Pituitary dwarfism, Turner syndrome	2006

[a] Withdrawn.

(Table 1) [2]. Approval of biosimilars is contingent on the results of the comparability exercise, which may include quality data, pre-clinical and clinical data, and demonstration of clinical therapeutic equivalence. If the comparison fails at any stage, the product is not eligible as a biosimilar. Only copy versions that successfully complete the comparability exercise can be called "biosimilar" [2,3].

The first biosimilars approved by the EMA Committee for Medicinal Products for Human Use (CHMP) were of lower molecular weight biologics, including two biosimilars of somatropin, five erythropoietin biosimilars, and seven biosimilars of filgrastim [7]. Because the development of biosimilar mAbs is considered more complex than that of these smaller biologics, the EMA issued separate guidelines for biosimilar mAbs in 2012. While similar to the overarching guidelines, the updated guidelines require more stringent clinical testing and immunogenic assessment [2]. To date, 16 biosimilars have received marketing authorizations from the EMA (Table 2) [7]. This includes two agents that have since been withdrawn (Filgrastim ratiopharm® [filgrastim]

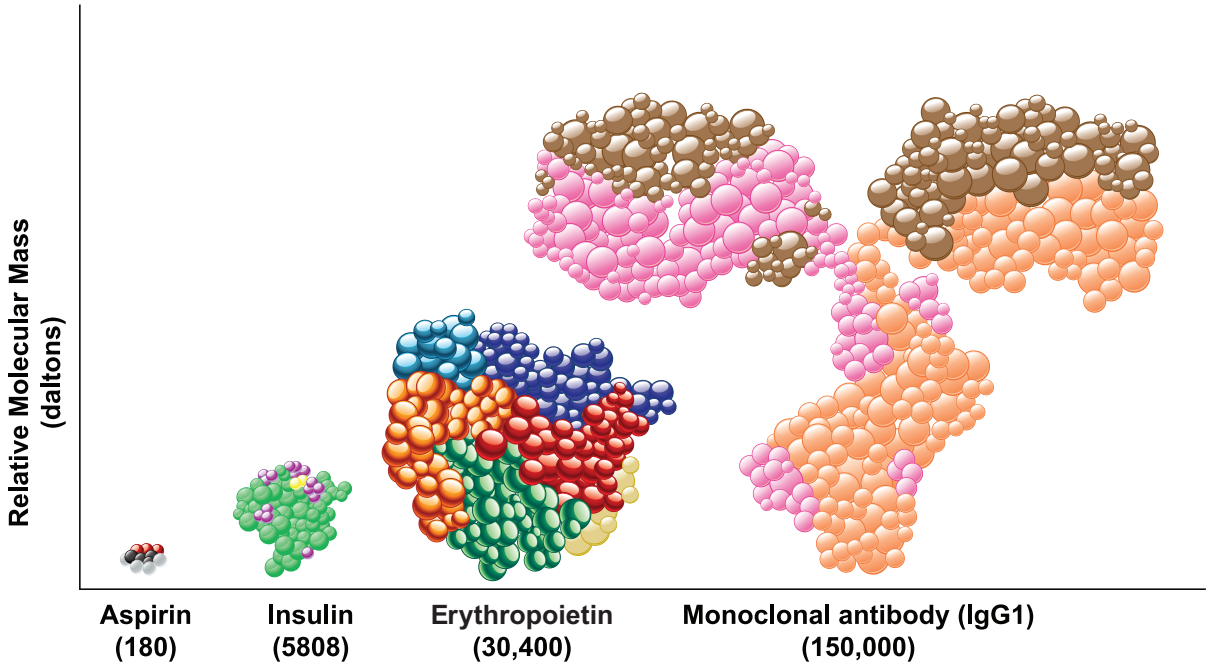

Fig. 1 – Monoclonal antibodies are structurally more complex than small-molecule agents and lower molecular weight biologics. [8–10]

and Valtropin® [somatropin]) and the approval of the first two biosimilar mAbs, Inflectra™ (infliximab) and Remsima™ (infliximab) [7].

It is clear that biosimilar mAbs are a therapeutic class separate from the epoetins, filgrastims, and somatropins. Monoclonal antibodies are typically higher molecular weight proteins (~150 kDa) with complex secondary and tertiary structures subject to post-translational modifications (Fig. 1) [8–10]. They often comprise mixtures of similar molecules that are closely related, yet not identical [1]. The development of biosimilar mAbs is complicated by manufacturing and technological limitations. While the developer of a biosimilar has access to the originator as a final product, there is no direct access to the proprietary development data. The developer of the biosimilar must purify the originator and pursue a reverse engineering process. Thus, the production of the biosimilar takes on a unique manufacturing process, likely different from that of the originator. This may allow for quality-related risks to be introduced, including process- and product-related impurities, micro-heterogeneities, and excipients [3,8].

The ability to compare a biosimilar mAb to an originator mAb on an analytical level remains limited as well. Laser-induced fluorescence detection, mass spectrometry techniques (e.g., hydrogen deuterium exchange mass spectrometry and electrospray ionization mass spectrometry), and nuclear magnetic resonance may be utilized to compare biosimilars and their originators [11–13]. However, additional techniques are needed to refine this process and enable further characterization, including that of the antigen–antibody interaction, determination of secondary structure, and differences in protein structure [8].

In September 2013, the EMA issued final approval for two biosimilar infliximab products, Inflectra and Remsima. These agents are indicated for the treatment of rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriatic arthritis, and psoriasis [4,5]. The EMA decision supporting Inflectra and Remsima not only validates the established EMA process for biosimilars, but opens the door to approval of biosimilars of other products nearing or passed their patent expiry dates, including Avastin® (bevacizumab), Enbrel® (etanercept), Erbitux® (cetuximab), Herceptin® (trastuzumab), Humira® (adalimumab), MabThera®/Rituxan® (rituximab), and Synagis® (palivizumab) [14]. Development of several novel biosimilar mAbs is ongoing, including multiple rituximab biosimilars (CT-P10 [Celltrion], GP2013 [Novartis/Sandoz], BI 695500 [Boehringer Ingelheim], TL011 [Teva/Lonza], SAIT101 [Samsung BioLogics], PF-05280586 [Pfizer], MK-8808 [Merck]), and CT-P6 (Celltrion), a biosimilar of trastuzumab in phase III development [12,15–17]. However, there are several issues with the continued development and approval of biosimilar mAbs, and we cannot expect the experience with biosimilar mAbs to be fully aligned with the collective experience with lower molecular weight biosimilar agents.

Scan for more information on how biosimilar antibodies differ from other biosimilars.

3. Extrapolation of indications

Because biosimilars are approved through an abbreviated clinical trial program and may not be tested in all indications of the originator, extrapolation of indications is an issue of great concern. The 2012 EMA guidelines on similar biological medicinal products containing mAbs indicate that efficacy and safety data in support of a biosimilar mAb in one disease state may be extrapolated to other indications of the reference mAb – even if that indication was not specifically studied during the clinical development of the biosimilar – if the evidence of the comparability exercise is compelling and there is adequate justification. The guidelines suggest that if different mechanisms of action are considered or suspected to be relevant, "applicants should provide relevant data to support extrapolation to all claimed clinical indications", including discussion of available literature related to the involved antigen receptors and mechanisms of action, potency assays, *in vitro* assays that describe the functionality of the molecule, and any relevant clinical data [2].

Supporters of extrapolation suggest that extrapolation of scientific evidence should be seen as a logical consequence of the comparability exercise principle, which is founded in physiochemical and biological characterization. Any uncertainties, such as slight differences of unknown relevance to clinical performance, should be addressed via comparative clinical data. Furthermore, Schneider et al. state that the totality of evidence for each biosimilar applicant should be reviewed as a whole on a case-by-case basis, with extrapolation viewed not as a "bonus" for the developer of the biosimilar, but rather as the applicant's burden to collect and demonstrate stringent scientific evidence [18].

The EMA approval of Inflectra is an example of extrapolation of indications. The Inflectra phase I program focused on patients with active ankylosing spondylitis, and the phase III program enrolled patients with active rheumatoid arthritis with inadequate response to methotrexate [19,20]. However, the EMA approved Inflectra for six indications, namely rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriatic arthritis, and psoriasis [4]. While this experience may not prove typical, and is certainly not expected to be repeated without justification with other biosimilar products, the issue of extrapolation requires further consideration.

Those more cautious of extrapolation voice concern about oversimplification. Given that mAbs have complex mechanisms of action that in many cases are poorly or only partially understood, and that dosing, administration, clinical study endpoints, and clinical study populations often vary between indications, extrapolation will likely not be straightforward [21–24].

While simple cytokines typically have a single active site that binds the same receptor or family of receptors in each indication, mAbs typically perform diverse functional activities, with multiple aspects of the same molecule interacting with diverse receptors [21,25,26]. The net contribution of each mode of action *in vivo*, including antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis, is unknown. Furthermore, dosing can vary widely between indications. For example, MabThera is indicated for follicular non-Hodgkin lymphoma (NHL), diffuse large B cell lymphoma, chronic lymphocytic leukemia, and rheumatoid arthritis, with dosing ranging from 375 mg/m^2 administered weekly to 1000 mg administered as two doses 14 days apart. Duration of treatment may range from 2 weeks to 2 years, depending on the indication [22].

Efficacy endpoints utilized in the clinical development of an agent may also vary across clinical studies. For MabThera, phase III trials have included response rate [27], progression-free survival [28], event-free survival [29], and overall survival [30] as primary endpoints. The EMA guidelines suggest that in some cases, overall response rate may be a sufficiently sensitive endpoint for mAbs; however, this may not correlate with survival [2,31]. In addition, the EMA suggests that survival data should be interpreted with caution given confounding patient and disease factors. Unfortunately, reliable surrogate markers of efficacy have not been established for mAbs, necessitating reliance on clinical markers.

A final challenge for extrapolation may be the variation in patient characteristics across the populations served by each indication. For example, patients receiving Herceptin may have a diagnosis of HER2-positive metastatic breast cancer, HER2-positive early breast cancer, or metastatic gastric cancer [32]. Focusing on breast cancer, patient populations with early disease and metastatic disease are known to differ by disease burden, chemotherapy regimens, concomitant medications, and immune response. While immunogenicity, efficacy, and safety data may be extrapolated from the early breast cancer population to the metastatic population, the reverse, extrapolation from the metastatic population to the early disease population, may represent a risk for patients. Despite these issues, a phase III study designed to demonstrate equivalence in efficacy and safety of CT-P6, a trastuzumab biosimilar, is ongoing in 475 patients with HER2-positive metastatic breast cancer [17].

In 2013, the European Crohn's and Colitis Organisation released a position statement on the use of biosimilars in the treatment of inflammatory bowel disease (IBD). The organization stated that "a biosimilar proven effective and safe for one indication may not necessarily be effective and safe for a second indication for which the reference biologic has been shown to be safe and

effective". Furthermore, the group urged that studies in patients with IBD be required to establish efficacy and safety for this indication given that experience with current biologics has shown that efficacy in IBD does not necessarily correlate to efficacy in other indications, such as rheumatoid arthritis. The European Crohn's and Colitis Organisation's statement represents the first time a group of physicians has taken an open stance against extrapolation of indications for biosimilars [33]. The Association of the British Pharmaceutical Industry (ABPI) has also provided a position statement against automatic indication extrapolation for biosimilar products, noting that each biosimilar should demonstrate safety and efficacy through robust phase III trials, mirroring the requirements placed on originator agents [34].

4. Product variability and the potential for immunogenicity

The current framework for development of biosimilar mAbs aims to use advanced technology to demonstrate that there are no relevant differences between the biosimilar and the originator. Slight differences in structure of the active substance, post-translational modifications, and impurity profile may be considered acceptable by the EMA, given adequate justification and non-clinical and clinical data [2]. This may be based on the principle that it is common for originator biologics to undergo manufacturing process improvements over time that trigger subsequent comparability exercises [35]. These manufacturing changes may lead to micro-variants within the drug profile, which may have no clinical effect or may completely shift the immunogenicity profile, with changes in immune reaction potentially leading to altered efficacy and safety [2,36,37]. The presence and acceptance of these variations speak to the level of tolerance of non-clinically significant micro-variants within the regulatory authorities. However, the issue of immunogenicity may pose an even greater challenge as biosimilar mAbs, and thus additional variability, are introduced into the treatment landscape. The EMA acknowledges that "the immunogenicity of mAbs is complex and there are a number of often poorly understood factors which make it difficult to predict with any certainty whether a therapeutic or diagnostic monoclonal antibody is likely to provide a clinically relevant immune response." [38]

Glycosylation is one way in which antibodies introduce variation. This may include differential addition of sugars and alternative branching of sugar chains. The presence or absence of even one sugar residue can affect the biologic activity of the agent [37,39,40]. For proteins produced in bacteria, such as insulin, this is not a concern, as bacteria do not typically induce glycosylation. However, for proteins produced via more complex eukaryotic organisms, the presence of glycosyltransferases and glycosidases induces modifications. For example, altered glycosylation patterns may change the shielding of the protein backbone, affecting the immunogenic properties of the molecule [1,38]. At this time, characterization of these variations is limited by available technology and procedures. This is further complicated by the fact that glycosylation is neither standardized nor template-driven, but rather relies on the interrelated activity of the endoplasmic reticulum, Golgi apparatus-based enzymes, and downstream processing. Therefore, while an originator biologic and a biosimilar possess the same polypeptide sequence, they may differ in the composition of their attached sugar chains. Such similar, but not exact, replicas are known as *glycoforms* [1,40].

In a study comparing biosimilar erythropoietins from around the world using high-resolution gel electrophoresis, the composition of the agents was found to vary and the balance of glycoforms was not uniform [41]. While some advances have been made, including the manipulation of host cells to produce favored glycoforms, complete control of glycosylation has yet to be established [42]. Not only does the presence of non-standardized glycoforms pose a risk, but the technology to routinely determine composition equivalence between a biologic originator and subsequent biosimilars is not yet available. These subtle differences in glycosylation may impact the patient experience as changes in glycosylation may ultimately influence binding, immunogenicity, and effector activity [8].

Small production fluctuations, such as those related to cell culture pH, temperature, and media ingredients, also may impact the final product, introducing micro-heterogeneities such as alternative disulfide pairings/disulfide shuffling, deamidation, (methionine) oxidation, crystallization of N-terminal glutamine residues, and partial enzymatic cleavage [8,43–45]. Subtle changes in the molecular shape of the protein may trigger insolubility of the protein, loss of biological function, or increased immunogenicity due to the uncovering of antigenic portions of the molecule that would normally be hidden from the immune system [1,46–48]. Indeed, the immunogenicity of biologics, including biosimilars, should be viewed as unpredictable and unforeseeable.

The development of anti-drug immune reactions has been well established with the use of biologics [47,48]. A well-known example of these reactions is the increase in antibody-mediated pure red cell aplasia (PRCA) associated with a single formulation of Eprex® (epoetin alpha) used in patients requiring chronic dialysis. It is hypothesized that a minor manufacturing change, likely a switch from human serum albumin to polysorbate 80 in an effort to avoid potential contamination from viruses and prions, induced an immune reaction in which the patient's antibodies neutralized not only the drug, but also the body's natural epoetin [49]. While mAbs do not

typically induce antibodies that cross-react and neutralize an endogenous counterpart, such as what occurred with Eprex, this example does speak to the potential significant impact of small manufacturing variations between products and within individual products.

Additionally, consideration should be taken when different host cells are used for production of the biosimilar and the originator. For example, a biosimilar may be perceived to have a low risk of immunogenicity given the mechanism of action established for its originator counterpart. However, if it is produced using a novel expression system, this risk may be changed due to the introduction of impurities [38].

While the potential for development of immunogenicity is clear, the assessment of immune response may not always be straightforward. Adult patients with psoriatic arthritis who are managed with infliximab monotherapy (5 mg/kg) are 5 times more likely to develop anti-drug antibodies (ADAs) than patients receiving combination therapy with infliximab (5 mg/kg) and methotrexate. This is likely due to the immunosuppressive qualities of methotrexate. Furthermore, compared to patients with psoriatic arthritis treated with higher-dose infliximab (5 mg/kg), adult patients with rheumatoid arthritis who are treated with lower-dose infliximab (3 mg/kg) have a two-fold higher risk of developing ADAs. When immune response is compared between adult patients with rheumatoid arthritis and adolescent patients with juvenile idiopathic arthritis, there is a five-fold increase in unwanted immune response in younger patients, even though both groups are treated with the same dose (3 mg/kg). When the adolescent dose was raised to 6 mg/kg, the immune reaction in this population was reduced by approximately a factor of four. While cross-trial comparison of data is inherently flawed, these data do highlight potential differences in immune response based on dosing, regimen, indication, and patient population [50,51].

Assessment of immunogenicity in non-clinical animal models is not reliably predictive of unwanted immune response in humans. The CHMP guidelines therefore do not require non-clinical studies aimed at predicting immunogenicity in humans [2]. However, the currently required duration of comparative studies between biosimilars and their originators may not be long enough to detect potential immunogenicity effects. For example, EMA guidelines on somatropin biosimilars require only one randomized controlled trial of at least 6 months duration prior to marketing authorization [52]. Unfortunately, there has been a push for limiting non-clinical and clinical development programs for biosimilars based on the clinical profile and post-marketing safety data available for the originator product [8]. However, given the propensity for variation between products and the increased risk for immunogenicity, it is likely that these limited development programs will be insufficient to demonstrate appropriate efficacy and safety of biosimilars. It is recommended that a robust and systematic clinical program be developed to assess, characterize, and mitigate potential risks and that post-marketing surveillance be employed to further ensure patient safety.

5. Challenges in pharmacovigilance

A risk management plan, including immunogenicity assessment, should be in place for all biologics, including biosimilars. The goals of the plan should be to collect additional information as early as possible to further characterize the risk profile and to inform the safe and effective use of the product [53]. The EMA recommends that a comprehensive pharmacovigilance plan be submitted as part of the original approval application, taking into account immunogenicity risks identified during product development as well as any anticipated future risks. The risk management plan should take a multidisciplinary approach and include pre-authorization and post-authorization testing. Additional post-marketing safety commitments may include targeted questionnaires, phase IV studies, registries, and specialized follow-up for long-term use [54,55]. Evaluation of immunogenicity should include immune-response case definitions, infrastructure for further processing patient samples, and support for physicians reporting adverse drug reactions [2,53,55].

Starting in the fourth quarter of 2013, an inverted black triangle (▼) and a statement summarizing the additional monitoring requirements and responsibility of healthcare professionals to report any suspected adverse reactions must be placed on the summary of product characteristics (SPC) for all medical products subject to additional monitoring, including new biologics and biosimilars. All materials distributed to patients and healthcare professionals that include information on an agent subject to additional monitoring are required to include information about the monitoring requirements. A list of medicines with additional monitoring requirements will be published by the EMA and reviewed monthly by the Pharmacovigilance Risk Assessment Committee (PRAC). Of note, this legislation affects only those agents authorized in the European Union (EU) after 1 January 2011. Agents will typically be assigned the inverted black triangle for an initial duration of five years, with the option for regulators to extend this time period [53,56].

In order to support the pharmacovigilance plan, it is important that each agent administered to a patient be clearly identified and traceable. As mandated by the World Health Organization (WHO), biosimilars are allocated the same international non-proprietary name (INN), also referred to as a generic name, as their

originator biologic. In some instances in which significant differences in glycosylation have been identified, such as with the epoetins, an additional Greek letter may be assigned (e.g., epoetin alfa and epoetin zeta). Based on the use of identical INNs and the potential differences between biosimilars and their originators, the Medicines and Healthcare Products Regulatory Agency (MHRA) and the ABPI recommend that a product's brand name be used when prescribing a biologic or biosimilar and when reporting adverse drug reactions associated with a biologic or biosimilar [34,57,58]. In anticipation of biosimilars of the mAb rituximab, Section 4.4 of the MabThera (rituximab) SPC was revised to read "in order to improve the traceability of biological medicinal products, the trade name of the administered product should be clearly recorded (or stated) in the patient file." [22]

Given that biosimilars are similar to but not identical to their originators, there is no scientific basis to substitute a biosimilar for a branded product, and automatic substitution could potentially put patients at risk by preventing adequate traceability or encouraging switching between products. While there is currently no EU-wide guidance on automatic substitution with biosimilars, this action is not allowed in most countries (Table 3) [59–63].

6. Pharmacoeconomic impact of biosimilar antibodies

Biopharmaceuticals are a fast-growing segment of the worldwide pharmaceutical market, with growth estimated at over 20% per year, bolstered by a robust development pipeline, approval of newer agents for more common disease states, increased utilization, and expanding indications [64,65]. The European Generic Medicines Agency has estimated that, as of 2010, the top ten bestselling biosimilars had generated a savings of €1.4 billion for the European healthcare system [66]. Global Industry Analysts, Inc. forecasts that the global market for biosimilars will reach US$ 18 billion by 2017 [34].

While it requires an estimated US$ 1–2 million and up to three years to bring a standard generic to market, it is estimated that it requires US$ 10–40 million and takes six to nine years to bring a biosimilar to market. The set-up investment for a novel manufacturing process is estimated at US$ 250–450 million [65,67]. Furthermore, while generics are typically marketed at as low as 20% of the brand cost in the United Kingdom (UK), biosimilars are marketed at as high as 70–85% of the brand cost, a significant decline in savings for the consumer [65,68].

Uptake of biosimilars has varied across Europe from close to 0% (Belgium) to approximately 70% (Romania and Greece). While there has been significant uptake of filgrastim biosimilars in several countries, reaching 80% in the UK, uptake of biosimilar somatropin remains consistently low (<20%) across the EU. Future growth is anticipated with around US$ 25 billion in sales forecasted by 2020, expected to be driven largely by the United States market expansion [69].

7. Summary

The first biosimilars, somatropins and erythropoietins, were introduced in the EU in the mid-2000s. The most recent agents approved in this space are biosimilars of mAbs. The development of biosimilar mAbs is complicated by their complex molecular structure, potential for post-translational modifications, and multidimensional manufacturing process. In an effort to ensure patient safety and to address issues of microheterogeneities between biosimilars, including the potential for immunogenicity, robust clinical development programs must be required for each new agent. Each marketing application should include studies supporting the use of the agent in target disease states and patient populations, as well as a robust post-marketing pharmacovigilance plan. Biosimilars have the potential to benefit patients and change the overall treatment landscape; however, they also require great responsibility from the wider healthcare community to ensure their appropriate development and use.

Scan for more information and expert commentary on the incorporation of biosimilar antibodies into oncology and hematology.

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9. Conflict of interest statement

Håkan Mellstedt, MD, PhD, has no relevant financial relationships to disclose.

Table 3 – EU countries with specific measures limiting or prohibiting substitution of biosimilars [59]

Country	Year	Summary
France	2006	Automatic substitution of biosimilars is prohibited
Germany	2008	Automatic substitution of biosimilars is prohibited
	2011	A pharmacist may substitute a product for an identical product, even if the brand name is different. The German Pharmacists Association states that in the case of biological products, only those biologics that contain the same raw material and undergo the same manufacturing process are "bio-identical" and qualify for substitution. [60]
Greece	1976	Pharmacists are obliged to provide the exact pharmaceutical product mentioned in a medical prescription, and prohibited from switching to another pharmaceutical product
	1993	Pharmacists may not substitute the pharmaceutical product stated in a prescription with any other product
	2013	The Greek National Organization for Medicines recommends against automatic substitutions/interchangeability of reference biologicals and their biosimilars [61]
Italy	2007	Based on guidance from the Ministry of Health, the Italian Council of State issues an opinion stating that biosimilars cannot be substituted
Slovenia	2008	Slovenian Medical Society guidelines prohibit the substitution of biologics
Spain	2007	The Spanish Health Agency states that biologics are not substitutable
Sweden	2007	The Swedish Medicines Agency issues a statement indicating that biologics are not interchangeable and are not recommended for substitution
	2011	Biosimilars are included on a list of drugs not suitable for extended substitution on the basis that they are not medically comparable and might elicit different immunologic responses
UK	2010	Automatic substitution of biologics is prohibited. The Department of Health (DoH) and the Association of the British Pharmaceutical Industry (ABPI) propose to the Medicines and Healthcare Products Regulatory Agency (MHRA) that biologics/biosimilars be exempt from automatic substitution and that biologics only be substituted with the prescribing physician's knowledge and prior consent. The MHRA states that it is best practice to prescribe by brand name to ensure traceability.
Czech Republic	2008	Automatic substitution of any originator product with a generic must be prohibited by the physician
	2009	The Czech Society for Oncology issues a statement noting that biosimilars are not interchangeable with their originators [62]
Denmark	2010	Biosimilars can be substituted for each other, but not for originator products on the substitution lists issued by the Danish Medicines Agency
Finland	2009	The Finnish Regulatory Agency states that products given parenterally are not substitutable
Hungary	2009	Biosimilar products are not on the positive substitution list provided by the Hungarian National Institute of Pharmacy
Norway	2010	Biosimilar products are not on the positive substitution list provided by the Norwegian Medicines Agency
Slovakia	2008	Biosimilar products are not on the positive substitution list provided by the Slovak Ministry of Health
Austria	2005	Physicians are obliged to prescribe by brand name and to look for the cheapest but best medicines for their patients. Therefore, there is no obligation to substitute biologics, and the responsibility lies with the physician.
	2012	The Austrian Regulatory Authority recommends against pharmacists automatically substituting an originator product with a biosimilar [63]

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