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Review

Biosimilars in rheumatology: understanding the rigor of their development

Niti Goel[1,2] and Kamali Chance[3]

Abstract

This article examines the current landscape of biosimilar development in rheumatology. As misperceptions about biosimilars exist regarding their comparability to the reference products for clinical use, we review the development paradigm with the goal of improving rheumatologists' understanding of the rigor with which biosimilars are developed. With an emphasis on European Union and US markets, it gives an overview of some of the challenges and issues related to biosimilar development that need to be considered by rheumatologists in this increasingly growing therapeutic space.

Key words: biosimilar, biologics, rheumatology, development, etanercept, infliximab, adalimumab, rheumatoid arthritis, psoriasis

REVIEW

Rheumatology key messages

- There is extensive scientific rigor applied to support the abbreviated pathways to biosimilar approval.
- Understanding biosimilar development should increase clinician comfort regarding biosimilars for the treatment of rheumatologic conditions.
- Biosimilar development should increase patient access to potentially life-changing therapies.

Introduction

The introduction of biologics to health care has had a tangible effect on patients, especially where these medications have provided the only available treatment for a disease [1–4]. The success of innovator biological products and their costs timed with patent expiries (Table 1) have led biopharmaceutical companies to develop biosimilar products (Table 2) [5]. In the last 5 years, the number of biosimilar mAb products and soluble protein receptor constructs (-cepts) in development for the treatment of immunologic diseases has greatly increased. As a relatively new phenomenon in rheumatology, >80% of confirmatory studies (phase III) for biosimilars have been or were planned to be started from 2013 onward [6].

As more innovator biologics have come into the marketplace for RA, treatment paradigms advocate for patients to be treated sooner and more aggressively [9, 10]. Ready access to innovator biologics has not always been possible due to cost and restrictive policies [11, 12]. Eventually, availability of biosimilars for the treatment of rheumatologic conditions should improve access via decreased medication costs, allowing more patients to be treated for the same health care dollar [13–16]. This is already apparent in Norway via an approved version of biosimilar infliximab [17].

Table 1 Reported innovator biologic patent expiration dates [7, 8]

Biologic	Expected patent expiry year	
	EU	USA
Actemra/RoActemra (tocilizumab)	2017	2022
Cimzia (certolizumab pegol)	2021	2024
Enbrel (etanercept)	2015	2028
Humira (adalimumab)	2018	2016
Orencia (abatacept)	2017	2018
Remicade (infliximab)	2015	2018
Rituxan/Mabthera (rituximab)	2013	2016
Simponi (golimumab)	2024	2024
Stelara (ustekinumab)	2024	2023

[1]Advisory Services, Quintiles, [2]Department of Internal Medicine, Duke University School of Medicine and [3]Biosimilars Center of Excellence, Quintiles, Durham, NC, USA

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Correspondence to: Niti Goel, Advisory Services, Quintiles, Department of Internal Medicine, Duke University School of Medicine, 5927 S Miami Blvd, Morrisville, NC 27560, USA.
E-mail: niti.goel@quintiles.com

Table 2 Definitions of various biologic therapeutics

Term (alternative terms)	Agency	Definition
Biosimilar (follow-on biologic, subsequent entry biologic, similar biotherapeutic product)	FDA [18]	A biosimilar product is a biological product that is approved based on a showing that it is highly similar to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products
	EMA [19]	A similar biological or biosimilar medicine is a biological medicine that is similar to another biological medicine that has already been authorized for use
	WHO [20]	A similar biotherapeutic product is a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product
Biobetter [21] (next-generation biologic)	Not defined by any agency	A biologic with the same target or mechanism of action as a previously approved biological but with structural changes, bifunctional targeting (with or without a biosimilar core) or an improved formulation that may result in an expected improvement in clinical profile
Bioquestionable [22] (biocopy, biomimic, intended copy, non-regulated biologic)	Not defined by any agency	A copy version of a therapeutic protein that has not been developed and assessed in line with the scientific principles of a comparative development programme against a licensed reference product showing similarity in quality, safety and efficacy

EMA: European Medicines Agency; FDA: US Food and Drug Administration; WHO: World Health Organization.

According to a survey of European Union (EU) specialists, more than half claimed to have only a basic understanding of biosimilars and nearly one-quarter could not define or previously had not heard of biosimilars [23]. Comparable results exist from other similar efforts [24–27]. In Canada, the majority of rheumatologist respondents to a 2014 survey indicated a lack of comfort with currently prescribing biosimilars if available [28]. Based on these results, continued education is needed to explain biosimilars, the unmet need for biologics to treat disease and regulatory requirements in place to ensure the scientific rigor supporting the abbreviated pathways to approval of biosimilars.

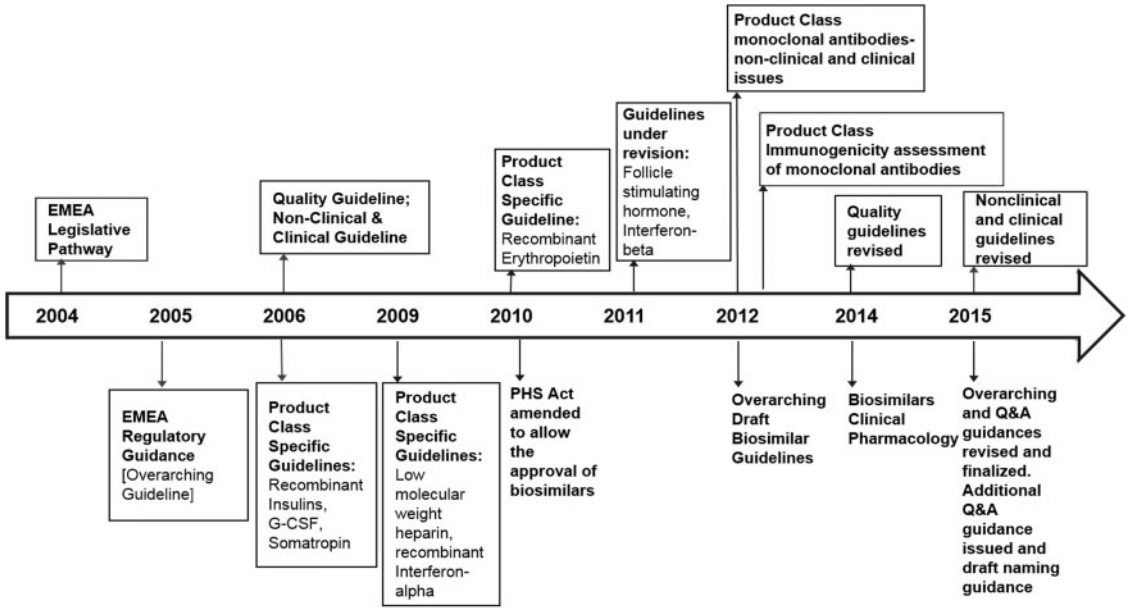
This article provides a current overview of biosimilar development for the treatment of rheumatologic conditions.

Understanding the regulatory framework

The European Medicines Agency (EMA) was the first regulatory agency to develop a biosimilars regulatory framework, establishing guidelines in 2005 (Fig. 1). Countries such as Japan, Canada and Australia have followed the principles of the EMA framework [22]. In 2009, the World Health Organization (WHO) published guidelines to evaluate similar biotherapeutic products [20]. This publication was the basis for, for example, legislation in Korea and countries in Latin America [22, 29, 30].

The US Food and Drug Administration (FDA) approves new drugs, including simple protein products as distinguished from complex biological products, under approval mechanisms in section 505 of the Federal Food, Drug and Cosmetic Act (FDC Act) [31, 32]. It licenses complex biological products under section 351 of the Public Health Service (PHS) Act [32–34]. Until 2010, when the 2009 Biologics Price Competition and Innovation Act (BPCIA) was signed into law, there was no clear regulatory path for the approval of follow-on biologics in the USA. While some follow-on proteins such as hyaluronidase, glucagon and somatropin were approved as drugs, not biologics, under the FDC Act, the FDA only established biosimilar guidelines in 2012 under the BPCIA [31, 32]. The BPCIA created an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product [34]. The BPCIA revised the definition of biological product in the PHS Act to include protein (excluding any chemically synthesized polypeptide) and defined biosimilarity as 'the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and. . .there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product' [33, 34]. A reference product is defined as a single biological product, licensed under

Fig. 1 Biosimilar regulations/guidelines in the EU and USA



Boxed items represent those timeline items related to the EU, whereas unboxed items reflect the USA. EMEA: European Medicines Agency; G-CSF: granulocyte colony-stimulating factor; Q&A: questions and answers.

section 351(a) of the PHS Act, against which a biological product is evaluated under section 351(k) of the PHS Act [33]. A biological product, in a 351(k) application, cannot be evaluated against more than one reference product [34].

The definition of biosimilarity is similar in the EU, except that the reference product has to be licensed in the EU. Whereas the EU has led the charge for biosimilar approvals, with 21 approved since the first in 2006 [35], the USA didn't approve its first biosimilar via the 351(k) pathway, filgrastim, until 2015 [31, 36]. In the EU, among the myriad approved biosimilars, only one biosimilar mAb and one biosimilar -cept have been approved for the treatment of indications that include rheumatologic conditions, that is, infliximab (Celltrion) and etanercept (Samsung) [37, 38]. Subsequently, Celltrion's infliximab biosimilar has been approved in >70 countries worldwide, including in the USA in April 2016 [39, 40]. It is anticipated that with recent biosimilar application submissions to the FDA for etanercept (Sandoz) and adalimumab (Amgen), and to the EMA for adalimumab (Amgen), rituximab (Celltrion) and a second infliximab biosimilar (Samsung Bioepis), other biosimilar options for the treatment of rheumatologic diseases may be on the way.

Differences in biosimilar *vs* innovator biologic manufacturing and development

Generic compounds, small inorganic molecules, can be chemically synthesized to have the same active ingredient as their brand name counterpart. Biosimilars have often been misconstrued as generic versions of biologics. Due to size, complexity and the biotechnology production processes involved, biosimilars are more difficult to duplicate and manufacture than traditional small-molecule medicines. Biosimilar products range from small therapeutic proteins to complex mAbs and -cepts, which are made in living cells. Although the expression system may differ, both the FDA and EMA expect that the biosimilar's expression construct will encode the same primary amino acid sequence as that of the reference product [41, 42].

Biosimilars have the potential for differences to occur compared with their reference products during their manufacture, whether at the translational (primary amino acid sequence, amino acid modification) or post-translational stage (further amino acid modification, higher-order structural changes due to protein folding and interactions). The former can be impacted by the host cell type (e.g. mammalian, yeast, bacterial) and vectors used to create the protein. The latter can be affected by the host cell as well as production and purification processes, formulation and environment (e.g. drug packaging and delivery). Both the FDA and EMA require that the physicochemical assessment of the reference product and the proposed biosimilar should include evaluation of the primary, secondary, tertiary and quaternary structures, post-translational modifications and functional activities (Table 3) [41–44].

Even for innovators, manufacturing changes have been documented to occur over time for a multitude of reasons (e.g. scale-up to produce more drug per batch, different purification processes, new manufacturing site) and have

Table 3 Regulatory requirements for the development of generic drugs *vs* biosimilars

Parameter	Generics (chemical drugs)	Biosimilars
Production source	Chemical synthesis	Living organisms, i.e. cultured yeast, bacteria or animal/plant cells
Active pharmaceutical ingredient	Must be identical to the originator medicine	Although required to contain the same primary amino acid sequence as the reference product, the biosimilar active pharmaceutical ingredient may not be identical to the originator, but rather highly similar due to post-translational modifications
Characterization	Non-comparative	Thorough head-to-head comparative characterization against the reference product using orthogonal methods
In vitro non-clinical testing	Not required	Head-to-head comparison with the reference product: Receptor binding assays Cell proliferation assays Cell potency assays
Non-clinical animal testing	Not required	Comparative PK/PD (if PD marker is available) in relevant species One comparative repeat dose toxicity study in a relevant species that includes toxicokinetic, systemic exposure, local tolerance and immunogenicity assessments. If the relevant species are non-human primates, EMA generally does not require an *in vivo* non-clinical study unless it is absolutely needed to assess an unknown impurity. The FDA is likely to require a small *in vivo* animal study in non-human primates
Clinical—phase I study	Comparative PK study in HV: may be under fed and fasting conditions	Comparative PK/PD (if PD marker available) in HV or patients with scientific justification required for, for example, selection of HV or patient population, sample size
Clinical—phase III studies: safety (including immunogenicity) and efficacy	No	Comparative clinical study(ies) generally required against the reference product; comparison conducted in a single indication if the MoA for all indications is the same. Multiple comparative studies may be required if the MoAs vary by indication. The number of studies required is assessed by regulators on a case-by-case basis
Pharmacovigilance plan	Generally not required, but depends on the product	Generally required, often mimics reference product's pharmacovigilance plan, but may have additional requirements based on observations during clinical development of the biosimilar
Post-marketing studies	Generally not required	Often may be required for, for example, late developing adverse events, additional immunogenicity testing
Paediatric studies	No	In the USA, the need for paediatric studies for biosimilars must be addressed and discussed with the FDA; however, they are not required if the biosimilar is found to be interchangeable with its originator. EMA does not require paediatric studies

EMA: European Medicines Agency; FDA: US Food and Drug Administration; HV: healthy volunteers; MoA: mechanism of action; PD: pharmacodynamics; PK: pharmacokinetics.

resulted in a product not identical to the one originally approved [45]. In such settings, comparability assessments are required, whether analytical, functional, non-clinical and/or clinical, to ensure that the manufacturing changes have not affected the product's safety, identity, purity or efficacy (including immunogenicity) [46]. Biosimilars, unlike innovators undergoing manufacturing changes over time, are reverse engineered from commercial product for their comparability to the innovator without access to the proprietary manufacturing processes of the innovator, usually a trade secret.

Due to anticipated different manufacturing processes for biosimilars *vs* innovators, biosimilar development in the EU and the USA hinges on a stepwise approach

Table 4 Sample of biosimilar analytical, functional and other non-clinical assessments reported for biosimilar infliximab [37]

Assessments		Test methods
Physicochemical	Primary structure	Amino acid analysis, peptide mapping (LC-MS) in combination with MS/MS, peptide mapping (HPLC), N-terminal sequencing, C-terminal sequencing, reduced mass
	Higher-order structure	Disulphide bonds, free thiol analysis, FTIR, circular dichroism, DSC
	Purity/impurity	SEC-HPLC, CE-SDS (reduced/non-reduced)
	Charged isoforms	IEF, IEC-HPLC
	Glycosylation	Sialic acid analysis, monosaccharide analysis, oligosaccharide profiling, N-linked glycan analysis
	Content	Protein concentration (UV_{280}), product specific ELISA
Biological activity	Fc receptor related	Comparative binding to Fcγ receptors using SPR and *ex vivo* assay using NK cells and neutrophils
	F(ab′)2 related	Comparative binding to hTNF-α using ELISA and SPR; comparative tmhTNF-α binding affinity using cell-based ELISA; hTNF-β binding specificities; human tissue cross-reactivity using immunohistochemistry; comparative TNF-α binding affinity using SPR; comparative hTNF-α neutralization assay; comparative apoptosis; comparative reverse signalling; effect of blocking sTNF-α in *in vitro* IBD model by suppression of cytokine secretion and apoptosis in epithelial cell line
	Fc-F(ab′)2 related	Comparative C1q binding affinity using ELISA; comparative CDC; comparative ADCC using tmhTNF-α-Jurkat cells as target cells and hPBMCs as well as NK cells from healthy donors as effector cells; evaluation of regulatory macrophage function by suppression of T cell proliferation by induced regulatory macrophages in MLR assay, quantitation of the induced regulatory macrophages by FACS analysis, and induced regulatory macrophage-mediated wound healing of colorectal epithelium cells; comparative ADCC activity using transfected Jurkat cells as target cells and either PBMCs or NK cells from CD patients or whole blood from healthy donor or CD patients as effector cells, or using LPS-stimulated monocytes from healthy donor or CD patients as target cells and PBMCs as effector cells

ADCC: antibody-dependent cell-mediated cytotoxicity; CD: Crohn's disease; CDC: complement dependent cytotoxicity; CE-SDS: capillary electrophoresis sodium dodecyl sulphate; DSC: differential scanning calorimetry; Fab: antibody fragment; Fc: fragment crystallisable; FTIR: Fourier transform infrared spectroscopy; h: human; IEC-HPLC: ion exchange chromatography; LC-MS: liquid chromatography–mass spectrometry; LPS: lipopolysaccharide; MLR: mixed lymphocyte reaction; MS/MS: tandem mass spectrometry; PBMCs: peripheral blood mononuclear cells; SEC-HPLC: size exclusion chromatography; SPR: surface plasmon resonance; tm: transmembrane; UV_{280}: Small volume protein determination at 280 nm.

(Table 4). This approach includes a comparison of the proposed biosimilar with its reference product with respect to analytical similarity (structure/function), animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD) and, if applicable, clinical efficacy and clinical safety, including clinical immunogenicity [43, 44]. At each step (analytical/functional testing followed by non-clinical and then clinical testing), the sponsor of the proposed biosimilar is expected to evaluate the extent to which there is residual uncertainty about biosimilarity to the reference product and identify the next steps to try to address that uncertainty [43, 44]. For example, the determination of whether a biosimilar product is considered highly similar to its reference product in quality attributes will depend upon the comparative degree of heterogeneity, differences in functional properties, impurity profiles and degradation profiles among others [41, 47]. Resulting differences could influence the PK, PD, immunogenicity, efficacy and safety of the final biosimilar product [43, 44].

For innovators to garner approval, relatively less emphasis is placed on non-clinical assessments, but instead on clinical development demonstrating efficacy and safety, proceeding from phase I to II to III. For a proposed biosimilar, regulatory authorities currently request clinical trials to provide additional evidence of its similarity to the reference product, although both the FDA and EMA have the authority to waive any aspect of the development programme if deemed unnecessary [44, 48]. The intent of clinical trials for biosimilar products is not to demonstrate efficacy *per se* since that was already established with the reference product [43]. Although there are multiple

possible routes to biosimilar approval depending on a biologic's mechanism of action and the jurisdiction's views, the current clinical development paradigm utilized for the EU and the USA includes an initial bioequivalence PK study and then a confirmatory study in a reference indication to obtain regulatory approval [42–44].

Traditional dose-ranging trials are not required for biosimilars because it is assumed that similar efficacy will be demonstrated with the same dose regimens for the biosimilar as for the innovator. The clinical PK biosimilar study focuses on demonstrating PK (and PD if applicable) bioequivalence between the biosimilar and innovator as well as the biosimilar's initial safety [42–44]. If a confirmatory clinical study is required, as it is currently in many countries, our experience indicates that with appropriate regulatory authority review and approval prior to proceeding, the confirmatory trial may be initiated once interim data from the PK bioequivalence study demonstrate sufficient safety.

PK bioequivalence biosimilar trials, like many innovator trials, are typically conducted in healthy volunteers, but not for proposed rituximab biosimilars, as safety risks associated with rituximab exposure are not considered acceptable for healthy volunteers. Rituximab biosimilar PK studies are often conducted in RA patients [6] since RA patients are considered easier to recruit and offer a more homogeneous population for PK determinations than cancer patients. Rituximab biosimilars pose potential hurdles for ethics and regulatory committees regarding the acceptability of interim safety data from the PK study in RA patients to initiate confirmatory studies in cancer populations, as rituximab differs in the doses used as well as the immunogenicity profile for RA *vs* cancer [49]. The agencies have indicated that for a rituximab biosimilar, approvals for autoimmune disease *vs* cancer require separate studies in each setting.

The confirmatory clinical study typically targets a similar patient population utilized to file for an indication for the innovator biologic. Currently, if either EU- or US-sourced product is being used as a sole comparator in a confirmatory clinical study, its use will need to be scientifically justified if approval is sought in, for example, the USA with a confirmatory clinical study utilizing EU-sourced product; EU-sourced product is considered investigational in the USA and vice versa. Currently the justification should include analytical and functional similarity data between the chosen reference comparator and the reference product approved in the country/region of interest as well as a clinical bridge typically built via a three-way (e.g. US-sourced reference product, EU-sourced reference product and the proposed biosimilar) PK bioequivalence study [42, 44, 50]. Both the EMA and FDA also permit use of non-EU or non-USA reference product, respectively, as a comparator in a confirmatory clinical study if an appropriate scientific bridge has been built between the EU/US and non-EU/non-US reference product from an International Council for Harmonization member region or country (currently Europe, Japan, USA, Canada and Switzerland) [43, 44, 50, 51].

The one exception at this time to use of an alternative reference product is to achieve an interchangeability designation in the USA for which data will need to be provided against US-sourced reference as a comparator, regardless of an established bridge to a non-US reference product [50]. Interchangeability means that the biological product is biosimilar to the reference product, i.e. it can be expected to produce the same clinical result as the reference product in any given patient, and with repeated administration, alternating or switching between the biological and the reference products does not result in greater risk in terms of safety or diminished efficacy than with repeated use of the reference product without such alternation or switch [50]. In practice, if a proposed biosimilar is designated interchangeable in the USA at the federal level, products may be substituted for the reference product without the intervention of the prescribing health care provider [50]. Whereas the FDA does have the authority to approve interchangeable biologic products, the EMA does not have that authority; the decision is left to the regulatory authorities in each EU country. In the USA, currently an interchangeability designation may still be restricted at the state level in terms of allowing automatic substitution at the pharmacy [52, 53]. To date, no interchangeable biologics have been approved in the USA via the 351(k) pathway.

Even if an interchangeability designation is not sought, the FDA requests an evaluation of transition from the reference product to the proposed biosimilar within a confirmatory trial, although the guidance suggests this might be optional [44]. Since the need for transition data are often case by case, the sponsor should clarify this requirement with the FDA. In contrast, the EU has no such requirements for a transition or interchangeability evaluation, but may receive such data as part of a global submission package. Further, in the USA, biosimilars are subject to paediatric assessment unless waived, deferred or inapplicable. A paediatric study plan would not be required for a proposed interchangeable product in the USA, as the product is not considered to have a new active ingredient for purposes of the Pediatric Research Equity Act (PREA) [50]. In Europe, a paediatric investigational plan is not required and paediatric approval is instead evaluated via scientific extrapolation.

For biosimilar products with both i.v. and s.c. formulations, unique challenges exist regarding the provision of bridging data between formulations if both are intended to be made available as biosimilars [43, 44]. Even if approval for only the i.v. formulation is sought, the regulatory agency may request studies be performed against the s.c. dosage form, as it is considered a more sensitive route of administration with more inherent variability in PK, efficacy, safety and immunogenicity [50]. As an additional consideration for the administration of s.c. products, if an autoinjector is planned, the FDA currently requests PK evaluation with autoinjectors *vs* the presentation used in the confirmatory clinical or bioequivalence studies if the autoinjector was not utilized. For both innovators and biosimilars, the FDA also requests an

autoinjector study in a representative inflammatory arthritis population to ensure adequate delivery of the drug as well as the usual requisite human factor studies [54].

At the time of the biosimilar's licensure application, if a clinical programme has been conducted, usually fewer patient-years of exposure are required for a biosimilar in contrast to typical large innovator safety databases, for example, current innovator safety databases in an initial indication of RA often exceed 2500 patients. Consider at the time of innovator infliximab approval for its initial indications of Crohn's disease and RA, in 1998 and 1999, respectively, the sizes of the safety databases for the patients exposed to the biologic in each indication were relatively small (n = 177 and n = 342, respectively) [55, 56]. While the safety database of 439 patients exposed to biosimilar infliximab in AS and RA was therefore quite numerically comparable, in contrast the biosimilar achieved approval in all eight indications in the EU based on the scientific justifications provided rather than the innovator's two indications [37]. Regardless, the limited safety profile obtained for the proposed biosimilar has to be comparable to that of its reference product [42–44].

Since the biosimilar's file for licensure may be relatively limited in terms of safety database size and scope of indications evaluated, it necessitates consideration of additional efficacy and pharmacovigilance requirements post-approval. In particular, the risk of less common adverse events that may emerge as related to the biosimilar will need to be assessed, similar to the post-marketing identification of risks including tuberculosis, opportunistic infections, congestive heart failure and demyelinating events associated with innovator TNF inhibitors [57]. Currently for both innovators and biosimilars, the EMA does require a risk management plan and the FDA may require a risk evaluation mitigation strategy if instituted for the reference product [34, 43]. The EMA and FDA both also tend to require post-marketing safety evaluations if late-occurring safety events are of concern [43, 44]. Post-marketing evaluation of Celltrion's infliximab as per EMA's public assessment report is to include participation in various established EU registries [37].

Post-marketing evaluation of biosimilars may or may not be impacted by naming conventions for their proper identification. For many years in the EU, biosimilars have been licensed with the same international non-proprietary (generic) name (INN) as the innovator along with a proprietary brand name. A study evaluating the identification across 7 biosimilars available in 3 marketed classes within the EU pharmacovigilance system was 96.2%, indicating that this approach to naming allows for the appropriate product to be identified [58]. In the USA, the recent non-proprietary Naming of Biological Products draft guidance proposes that the biosimilar and its reference innovator biologic should have the same INN with a unique four-letter suffix appended to the INN to distinguish them along with different proprietary names [59]. This is in contrast to the FDA's previous approaches to biological products approved as drugs or follow-on biologics where, for example, hyaluronidase and somatropin share the same INN but different brand names [60]. It is still unclear as to what naming convention will be applied to products found to be interchangeable. Notably, the first biosimilar filgrastim approved in the USA has the same INN as the reference product with a 4-letter suffix, sndz, appended to it; the reference product has no 4-letter suffix. Similarly, the recently approved biosimilar infliximab has the 4-letter suffix of dyyb while there has been no modification of the reference product's INN.

In a recent review, most biosimilars indicated for rheumatologic conditions appear to be evaluating efficacy, safety and immunogenicity against the innovator in only one indication, with RA being the most common indication evaluated followed by psoriasis (PsO) [6]. The choice of indication(s) studied may be influenced by a number of factors, including effect sizes, relative ease to recruit the indicated population, actual clinical use of the compound in an indication, potential to support data extrapolation and marketing considerations. A biosimilar may obtain extrapolation to other indications for which the reference product is approved without specific studies of those indications, provided that proper scientific rationale is provided for each indication for which extrapolation is requested [42–44]. The rationale for the EU and the USA should address each indication and patient population for which licensure of the biosimilar is sought: the mechanism of action, the PK and biodistribution of the product, differences in expected toxicities and any other factors that may affect the safety or effectiveness of the product. The rationale may not always be sufficient depending on the regulatory authority and their interpretation of the results; for example, the infliximab biosimilar, while approved for all innovator indications in the EU and the USA, did not garner approval in IBD indications in Canada [40, 61–63].

Further considerations in the design of confirmatory clinical studies

The primary indication chosen for evaluation is usually one that is considered sufficiently sensitive and often the most sensitive for evaluation, that is, for the innovator biologic has demonstrated the greatest effect size (difference in response between the treatment arm and comparator arm). Use of the most sensitive indication is not always practical if investigators are not willing to use the innovator to treat that indication and data obtained from such a study will not resonate with clinicians using the innovator to treat other indications. Alternatively, the most sensitive indication may not be clearly delineated [42–44]. For example, for a TNF inhibitor drug, per our analyses and specifically for infliximab as reported by Lee [63], the most sensitive indication has often been PsO. Infliximab is used less commonly than other biologics for PsO treatment, and, to date, infliximab biosimilar development has not utilized the PsO indication [6, 64]. In contrast, the WHO suggests in their guidelines that if extrapolation to other indications is being considered for a biosimilar [20], the population evaluated should be the one that carries the highest risk for immune response,

which may not always be the most sensitive population in terms of effect size.

The selection of endpoints in biosimilar confirmatory studies is another consideration; some regulators may request the use of sufficiently sensitive endpoints [42–44]. Biosimilar trial primary endpoints do not have to be identical to those used for innovator clinical trials, and other primary endpoints may be implemented to facilitate the detection of differences between the innovator and proposed biosimilar based on regulatory authority input. If the primary endpoint selected is other than that considered most sensitive or used for the innovator's pivotal studies, secondary endpoints may include some endpoints in common with those used for the innovator's pivotal trials to ensure more complete evaluation of clinical efficacy [43].

Endpoints based on continuous *vs* dichotomous measures have been considered more sensitive; for example, in RA, use of the 28-joint DAS (DAS28) rather than a 20% improvement in ACR criteria (ACR20) response rates, or in PsO, use of the mean Psoriasis Area and Severity Index (PASI) results rather than achievement of a 75% PASI response rate [65, 66]. Endpoint data analyses should focus on the steep part of the dose–response curves rather than the plateaus, as differences between reference and biosimilar products may be more apparent [42, 44]. Practically, as data from interim points on the dose–response curve may not be readily available in the public domain to ensure proper statistical calculations, these may become secondary endpoints, with primary endpoints mimicking those of the innovator more closely. For example, ABP 501, a proposed adalimumab biosimilar, utilized ACR20 response at week 24 as the primary endpoint rather than, for example, DAS28 at week 12 [67, 68].

Currently, chronically administered biosimilars are required to collect immunogenicity and safety data for at least 1 year if planning to market in both the EU and USA [43, 44]. This requirement may be reduced as more data become available. As assay techniques to detect antidrug antibodies have improved in sensitivity over time, one preliminary finding regarding innovators is that mAbs and-cepts are more immunogenic than previously reported [67, 69].

Another consideration is the magnitude of margins used to determine equivalence in efficacy between the proposed biosimilar and the reference product. In certain situations, it may be acceptable to the agencies to consider a non-inferiority design, but this is the exception rather than the norm [43, 44]. Equivalence margins are based on statistical as well as clinical justifications [70, 71], but the clinically justified margin cannot exceed the statistically justified margin [70]. The FDA has issued guidance for the statistical calculation of equivalence margins, which appears to be acceptable to the EMA [70]. The statistically calculated margins should be based on available data for the innovator in comparison with a placebo or standard of care therapy rather than an active control. Multiple studies are preferred to be the basis of the calculations with data from similar populations, for example, RA patients who are MTX inadequate responders, to capture the potential variability in results that naturally occur from trial to trial. In certain cases, the FDA has allowed the use of asymmetric margins, where the margin allowed for confirming a lack of superiority may be larger than the margin evaluated to confirm non-inferiority [44].

Ultimately, seeking engagement with regulatory agencies early and often is essential to streamline a biosimilar's development pathway and is recommended in both the EMA's and FDA's guidance documents [42, 44]. As the overall goal of biosimilar product development is to demonstrate that the proposed biosimilar is similar in analytical, non-clinical and clinical aspects to its reference product, the FDA and EMA consider the totality of the data and information that is submitted in the file. The FDA intends to use a risk-based approach to evaluate all available data and information submitted in support of the biosimilarity of the proposed product [43, 44]. It is possible that over time the development paradigm will be updated based on an improved understanding of the scientific assessment of biosimilarity.

Summary

Understanding what it takes to bring a biosimilar product to market with regards to head-to-head analytical, non-clinical and clinical similarity assessments against the innovator offers many opportunities for providers and payers to provide cost-effective therapies, and for patients in turn to receive them with assurance of the biosimilar's efficacy and safety. Biosimilar development is an evolving landscape from a clinical trial, regulatory and access point of view, which increases the challenges associated with implementing a successful development programme. As biosimilar development is still a relatively new endeavour, and as more experience is gained, it is expected countries will continue to adapt to allow unique provisions for biosimilar development. Based on the experience gained in the past 10 years, the EMA has modified its thinking regarding biosimilar product development, as shown by revisions not only to the overarching guidelines for non-clinical and clinical development, but also to product specific guidelines [42, 43]. To bring a biosimilar to market still requires a significant investment of money, resources and time, although currently less than that required for an innovator product [13]. To be successful in biosimilar development requires comprehensive, in-depth planning of the entire programme, with a global outlook and the ability to adapt to an ever-changing regulatory landscape. Ultimately, the goal of biosimilar development is to provide more opportunities for patients to have access to these potentially life-changing drugs.

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