

# Biosimilars and the extrapolation of indications for inflammatory conditions

John RP Tesser<sup>1</sup>  
Daniel E Furst<sup>2</sup>  
Ira Jacobs<sup>3</sup>

<sup>1</sup>Arizona Arthritis & Rheumatology Associates, Phoenix, AZ, <sup>2</sup>UCLA Health, Los Angeles, CA, <sup>3</sup>Pfizer Inc, New York, NY, USA

**Abstract:** Extrapolation is the approval of a biosimilar for use in an indication held by the originator biologic not directly studied in a comparative clinical trial with the biosimilar. Extrapolation is a scientific rationale that bridges all the data collected (ie, totality of the evidence) from one indication for the biosimilar product to all the indications originally approved for the originator. Regulatory approval and marketing authorization of biosimilars in inflammatory indications are made on a case-by-case and agency-by-agency basis after evaluating the totality of evidence from the entire development program. This totality of the evidence comprises extensive comparative analytical, functional, nonclinical, and clinical pharmacokinetic/pharmacodynamic, efficacy, safety, and immunogenicity studies used by regulators when evaluating whether a product can be considered a biosimilar. Extrapolation reduces or eliminates the need for duplicative clinical studies of the biosimilar but must be justified scientifically with appropriate data. Understanding the concept, application, and regulatory decisions based on the extrapolation of data is important since biosimilars have the potential to significantly impact patient care in inflammatory diseases.

**Keywords:** biosimilar, extrapolation, inflammatory disease, rheumatology

## Introduction

Biologic therapies provide significant clinical benefit in the treatment of inflammatory diseases, but patient access can often be limited.<sup>1-3</sup> Recent legislation and the expiration of patents on a number of the major biologic therapies have led to the development of products known as “biosimilars”.<sup>4-6</sup> A biosimilar is a biologic product that is highly similar to a licensed biologic (originator) product with the totality of the evidence demonstrating “no clinically meaningful differences compared to the originator biologic in terms of safety, purity, and potency”.<sup>5</sup> Biosimilars for several biologics are in development or are approved for the treatment of inflammatory diseases (Table 1).

Biologic therapies are complex; even minor changes in the manufacturing process could potentially create differences between a possible biosimilar and the originator.<sup>5,6</sup> A biosimilar is not a generic of the originator biologic.<sup>4-6</sup> The European Medicines Agency (EMA), US Food and Drug Administration (FDA), and World Health Organization (WHO) have developed separate guidelines for regulatory approval of biosimilars.<sup>4-6</sup> These processes allow the development of high-quality, safe, and effective biosimilars with the potential to provide savings and efficiencies to health care systems.

One key component of the EMA, FDA, and WHO regulatory guidelines for biosimilars is the provision for regulatory approval of the biosimilar for one or more

Correspondence: John RP Tesser  
Arizona Arthritis & Rheumatology  
Associates, 4550 E. Bell Road, Suite 272,  
Phoenix, AZ 85032, USA  
Tel +1 480 443 8400  
Email jtesser1@cox.net

**Table I** Development status and patent expiration dates for some biosimilars of biologics used in the treatment of inflammatory diseases<sup>8,9,13,14,16,40,41</sup>

Biologic	Indication <sup>a</sup>	USA		EU	
		Patent expiration	Biosimilar status	Patent expiration	Biosimilar status
Adalimumab	RA; juvenile idiopathic arthritis; psoriatic arthritis; AS; Crohn's disease; ulcerative colitis; plaque psoriasis	2016	Phase III trials	2018	Phase III trials
Etanercept	RA; polyarticular juvenile idiopathic arthritis; psoriatic arthritis; AS; plaque psoriasis	2028	–	2015	Approved 2016
Infliximab	Crohn's disease; pediatric Crohn's disease; ulcerative colitis; pediatric ulcerative colitis; RA (with methotrexate); AS; psoriatic arthritis; plaque psoriasis	2018	Approved 2016	2015	Approved 2013
Rituximab	Non-Hodgkin's lymphoma; chronic lymphocytic leukemia; RA (with methotrexate); granulomatosis with polyangiitis	2018	Phase III trials	2013	Phase III trials

**Note:** <sup>a</sup>Indications in USA.

**Abbreviations:** RA, rheumatoid arthritis; AS, ankylosing spondylitis.

additional conditions for which the originator is indicated, but without necessarily conducting biosimilar clinical trials specifically for that disease state.<sup>4-6</sup> For example, the EMA and FDA approved a biosimilar of infliximab (marketed as Remsima; Celltrion, Incheon, Korea [also marketed as Inflectra; Hospira, Maidenhead, UK in the EU]) and granted approval for the full range of indications of the originator product. The initial clinical comparative efficacy and safety study of the biosimilar was assessed in rheumatoid arthritis (RA) and ankylosing spondylitis (AS).<sup>7-13</sup> Recently, the EMA also approved a second biosimilar to infliximab (marketed as Flixabi; Samsung Bioepis, Chertsey, UK) for all indications of the originator. The development program included a clinical comparative efficacy and safety study in RA.<sup>14,15</sup> In addition, a biosimilar to etanercept (marketed as Benepali; Samsung Bioepis) was recently approved for all indications, and the clinical comparative trial was assessed in RA.<sup>16,17</sup> These approvals were extended to multiple indications via extrapolation of all data from the totality of evidence from the respective development programs to demonstrate similarity to the originator, including analytical, nonclinical, and clinical data.<sup>4-6</sup> This review briefly describes extrapolation of indications, including reviewing the regulatory process and the data evaluated for approval of a biosimilar, with specific considerations for the use of biosimilars in the treatment of inflammatory diseases.

## Definition of a biosimilar

Biologics, including biosimilars, could have multiple isoforms owing to posttranslational modifications and minor changes in manufacturing, such as source materials, media,

temperature, and purification techniques. To produce a biosimilar that is highly similar to the originator, a developer must analyze the originator extensively through reverse engineering, with extensive characterization analyses via state-of-the-art methods.<sup>18</sup> Biosimilar developers must have substantial knowledge and expertise regarding the development and manufacture of biologics to develop their own protocols because manufacturing processes for the originator are proprietary.

Even minor changes in the manufacturing process can result in differences (eg, variations in glycosylation or higher-order structural changes, protein folding, and protein-protein interactions) between the biosimilar and the originator biologic.<sup>5</sup> To receive regulatory approval, these modifications must not adversely affect the identity, strength, quality, purity, or potency of the biosimilar or result in clinically meaningful changes in safety or effectiveness.<sup>5</sup>

## Overview of regulatory approval for biosimilars

Many countries outside the USA follow EMA or WHO guidelines, but each country customizes regulations and, therefore, guidelines will vary.<sup>19</sup> Ultimately, however, there are only minor differences.<sup>4-6</sup> Overall, the approval process is a stepwise approach to demonstrate safety, purity, and potency. First, extensive structural and functional analyses are conducted to confirm that the biosimilar has a high degree of similarity to the originator biologic. Next, nonclinical animal studies are performed to assess pharmacokinetics (PK), immunogenicity, and toxicity. Finally, the biosimilar is evaluated in at least one clinical study in patients to

demonstrate that the biosimilar produces comparable efficacy and safety (including immunogenicity) versus the originator, although EMA and FDA reserve the option not to require a clinical study.<sup>4-6</sup>

Beyond bioequivalence, the number of clinical trials required for approval of a biosimilar is reduced, since clinical trials for dose finding and demonstration of the mechanism of action are not required.<sup>4,6</sup> In fact, the majority of data generated for approval of a biosimilar is based on the analytic and nonclinical assessments compared with the robust clinical trial data required for approval of a novel therapy.<sup>20,21</sup> Clinical trials evaluating comparative efficacy and safety of a potential biosimilar versus the originator are conducted in a patient population adequately sensitive to detect differences in PK, efficacy, and safety.<sup>4-6</sup> Interestingly, the population used in the comparative efficacy trial of a biosimilar to comparator may be different than the population used to evaluate clinical efficacy of the originator.

The immunogenicity of a potential biosimilar should be compared with the originator clinically.<sup>4-6</sup> In general, the preapproval evaluation of immunogenicity is designed to assess whether the incidence of antidrug antibodies is different from the originator.<sup>4-6</sup> For example, in comparative clinical efficacy studies of the recently approved biosimilars to infliximab (Remsima/Inflectra) in patients with active AS and active RA, percentages of patients with anti-infliximab antibodies at weeks 14 and 30, respectively, were generally similar for the biosimilar (AS: 9.1% and 27.4%, respectively; RA: 25.4% and 48.4%, respectively) and the originator (AS: 11.0% and 22.5%, respectively; RA: 25.8% and 48.2%, respectively).<sup>11,12</sup> To establish more robust data, additional immunogenicity evaluations may be included in postmarket surveillance plans.<sup>4-6</sup>

## Extrapolation of data

The potential for extrapolation of efficacy and safety data from clinical studies of a biosimilar to other indications is a core concept in the regulatory guidelines but must be justified scientifically with appropriate data.<sup>4-6</sup>

## Study designs

It is a common misconception that decisions regarding extrapolation are based on the clinical data alone. In fact, justification for extrapolation is based on the entire data set, with the physicochemical and functional analyses providing the primary and fundamental basis for the justification.<sup>4-6,22</sup> Thus, regulatory agencies not only consider the clinical data but

also rely heavily on the analytical, functional, and nonclinical data to decide whether the data can be extrapolated.<sup>4-6</sup> Also, multiple additional functional and/or pharmacodynamic studies may be required for regulatory approval if the originator has different mechanisms of action in different diseases.<sup>4-6</sup> These data provide further reassurance that the biosimilar will have similar clinical efficacy and safety in both the tested and extrapolated indications.<sup>22</sup>

## Study population

Clinical evaluations of efficacy of a potential biosimilar assess whether there are clinically meaningful differences compared with the originator biologic.<sup>5</sup> One important consideration in the decision as to whether clinical data can be extrapolated from one indication to another is whether the sensitivity of the population studied is appropriate. For example, demonstrating clinical efficacy in one disease may not predict effectiveness in another disease (eg, patients with RA versus those with psoriasis) since measures of response may differ (eg, American College of Rheumatology 20% [ACR20] improvement criteria for RA versus a 75% reduction on the Psoriasis Area and Severity Index [PASI75] score for psoriasis) or have different discriminatory ability (eg, the placebo-adjusted response in ACR20 is 8%–25% versus 74%–82% for PASI75).<sup>23,24</sup>

As noted, there may be clinically relevant differences in the mechanism(s) of action for different diseases treated by a given biologic. This may impact whether extrapolation of the clinical data is appropriate for all indications when a biosimilar is approved. For example, the mechanism of action of growth hormone (GH) differs in children with GH deficiency versus children with non-GH-deficient short stature (who may be less sensitive to GH treatment).<sup>6</sup> Finally, the use of concomitant methotrexate is required for the treatment of RA, and although this may confound conclusions about potency and/or efficacy of the biosimilar compared with the originator,<sup>23</sup> properly designed comparative efficacy and safety studies account for this by using balanced study designs with concomitant methotrexate administered in all treatment arms. Thus, it is unlikely that the results would change considerably, especially since the goal is to demonstrate comparative efficacy to the originator. Although these considerations raise questions about the appropriateness of extrapolating clinical data from RA studies to other indications, regulatory decisions about whether to allow extrapolation are based on the totality of the evidence and appropriate scientific justification.<sup>4-6</sup>

## Safety

Safety is a separate consideration when extrapolating data because factors such as comorbidities, co-medications, dosing, and the potential for developing antidrug antibodies may impact safety.<sup>23,25</sup> In addition, some product attributes, including differences in glycosylation or cell culture components, may have a greater impact on safety than other attributes (eg, packaging).<sup>23,26</sup> For example, penetration of antitumor necrosis factor agents into different tissues (eg, synovial pannus versus intestinal mucosa) as well as other properties of the biologic (eg, afucosylation and FcγRIIIa receptor binding) may differ and may influence safety in different diseases.<sup>23</sup> Safety evaluations in clinical trials of potential biosimilars are often short term and may not identify rare events, so appropriate postapproval monitoring and pharmacovigilance programs are expected.<sup>4-6</sup> In addition, specific clinical data comparing safety with the originator may be required if there are unique safety issues for the extrapolated indications.<sup>6,27</sup> For example, the Health Canada Summary Basis of Decision for biosimilars of infliximab indicates that risk management plans describing known and potential safety issues, the monitoring scheme, and measures to minimize risks associated with the product were submitted and considered acceptable (currently, these details are not public).<sup>28,29</sup>

## Immunogenicity

Biologics, including biosimilars, can induce immune responses in treated individuals and could impact the safety and efficacy of a product.<sup>5</sup> Although nonclinical data provide good support for confirmation of functional and toxicity data, animal data are not always predictive of immunogenicity in humans.<sup>6</sup> Immunogenicity is affected by multiple factors, such as route of administration, patient immune status, and co-medications. For example, concurrent use of methotrexate is more common with RA than other inflammatory diseases.<sup>30</sup> Methotrexate reduces antidrug antibody formation in some cases, and therefore treatment regimens and other factors need to be considered.<sup>4,22,25</sup> As a result, extrapolation of immunogenicity data requires strong scientific justification (including use of balanced and appropriate study designs) and may, in some cases, require additional immunogenicity data.<sup>4,6,22</sup> For example, WHO guidelines have a provision for requiring additional postmarketing immunogenicity evaluations if any postmarketing immunogenicity issues have arisen with the originator biologic, such as rare antibody-related serious adverse events that are not likely to be detected prior to regulatory approval (eg, cross-reacting neutralizing anti-epoetin antibodies that cause pure red blood cell aplasia).<sup>6</sup>

There are no examples, to date, of regulatory agencies requiring additional data beyond postmarketing plans for any approved biosimilars. It should be noted, however, that the regulatory guidelines are written in anticipation, although not expectation, of needing flexibility to address such issues (should they arise).

## Across indications: case by case and agency by agency

As with regulatory approval, there is also no one-size-fits-all approach as to whether extrapolation for a given biosimilar will be approved for all indications. Biosimilar approval is granted on the basis of totality of the evidence, which allows for a great deal of interpretation. Thus, regulatory agencies may come to different decisions as to whether to allow extrapolation of the data for a given biosimilar. For example, the originator infliximab has wide approval for the indications of RA, AS, psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease.<sup>7,10</sup> Biosimilars of infliximab have only been studied in the clinical disease populations of RA and AS.<sup>11,12,15</sup> The EMA, FDA, and Korean regulators granted approval to the infliximab biosimilar Remsima/Inflectra for the full range of indications of the originator product.<sup>8,9,31</sup> Japan approved these products only for RA, Crohn's disease, and ulcerative colitis; meanwhile, the originator has ongoing patents in other indications.<sup>32</sup> In contrast, Health Canada initially indicated that differences (in antibody-dependent cellular cytotoxicity, afucosylation, and FcγRIIIa receptor binding) between the biosimilar and the originator, which could affect clinical safety and efficacy, did not support extrapolation of the clinical data to Crohn's disease or ulcerative colitis without direct clinical assessment.<sup>28,29</sup> Recently, Health Canada added approvals in Crohn's disease, fistulizing Crohn's disease, and ulcerative colitis based on similarity between the biosimilar and the originator in product quality, mechanism of action, disease pathophysiology, safety profile, dosage regimen, and on clinical experience with the originator.<sup>33</sup> Agency-by-agency differences in granting extrapolation across all indications specifically has, and probably will continue to be, one of the most challenging issues in understanding extrapolation of data for biosimilars.

As mentioned, extrapolation is a logical scientific extension of the biosimilar concept,<sup>6</sup> but concerns about extrapolation of data across indications have been voiced.<sup>22,34-36</sup> The nature of these concerns is twofold. One is concerns about safety (particularly for pediatric patients).<sup>37</sup> Secondly, some specialist groups raise concerns that demonstration of clinical efficacy for a given biologic therapy in one disease may not predict effectiveness in other diseases.<sup>22,34-36</sup> For example,

the European Crohn's and Colitis Organisation indicated that data from patients with inflammatory bowel disease should be required before approval because, they argue, clinical efficacy in this disease cannot be predicted by effectiveness in other indications, such as RA.<sup>38</sup> The regulations, however, already address the latter concern since extrapolation across indications is based on the totality of the scientific evidence (including data regarding different mechanisms of action, and so on) showing that the biosimilar is comparable to the originator, and decisions for approval are made on case-by-case and indication-by-indication bases, rather than explicitly requiring that approval for any one indication requires the biosimilar be granted approval for all indications.<sup>4-6</sup> If biosimilars are not granted approval across all indications, health care providers will need to be aware of the approved indications when prescribing a specific biosimilar for the treatment of inflammatory conditions.

Another concern with extrapolation expressed by learned societies is the requirement for absolute certainty regarding clinical efficacy and safety.<sup>22</sup> Drug approval is based on a probability of response and an expectation of a reasonable range of safety.<sup>39</sup> Absolute certainty for a biosimilar cannot be expected any more than for any new compound.<sup>17</sup> In fact, secondary to the extensive preclinical analysis required of biosimilars, the degree of uncertainty for biosimilars, including around extrapolation, is actually reduced compared with new products.<sup>22</sup> The requirement for biosimilar approval that is adhered to remains that the biosimilar has no clinically meaningful differences versus the originator.<sup>4-6</sup> For example, FDA guidelines indicate differences in the expected safety, purity, or potency of the proposed product and originator would be considered clinically meaningful, whereas slight (numerical) differences in occurrence of certain adverse events would not.<sup>5</sup>

## Summary

Biosimilars for the treatment of inflammatory diseases have been approved or are currently undergoing regulatory review. Each biosimilar is approved on a case-by-case and agency-by-agency basis via rigorous, publicly disclosed processes that ensure approval is based on the totality of the data demonstrating similarity to the originator in terms of structure, function, PK, efficacy, and safety, with no clinically meaningful differences from the originator. Extrapolation is a core concept of regulatory approval of biosimilars, since it reduces or eliminates the need for duplicative clinical studies. Extrapolation is assessed only after biosimilarity is confirmed, and regulatory decisions are based on appropriate scientific justification. Different agencies have and probably

will continue to arrive at different final conclusions regarding extrapolation. Extrapolation can allow approval of therapies within shorter developmental timelines, thus providing health care providers the option to use biosimilars for the treatment of inflammatory diseases. It is important for health care providers to understand the concept and rationale for extrapolation in approval of biosimilars and how this applies to prescribing decisions for the treatment of inflammatory diseases.

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## Author contributions

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