

**A REVIEW ARTICLE ON BIOSIMILARS IN RHEUMATOLOGY**

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**ABSTRACT**

Biosimilars, based on biopharmaceuticals approved by regulatory agencies that are no longer under patent protection, have efficacy and safety comparable to their reference products, and are a new therapeutic option to treat inflammatory rheumatic diseases (IRD). Before they are approved, biosimilars must undergo a rigorous development process to establish biosimilarity to the reference biological product. After approval, biosimilars must comply with good pharmacological practices for biological drugs. CT-P13, based on infliximab, was the first biosimilar approved for the treatment of inflammatory diseases; however, some countries did not allow extrapolation of indications to all eight diseases for which the reference drug infliximab is approved. Several biosimilar disease-modifying antirheumatic drugs (bsDMARDs) based on the tumour necrosis factor inhibitors adalimumab, etanercept and infliximab have been approved for use in patients with rheumatic diseases. Substantial cost savings can be made if biological-naïve patients begin treatment with bsDMARDs, and patients receiving original biological DMARDs (bDMARDs) are switched to bsDMARDs. The current review article addresses the importance of biosimilar medicines in the treatment of IRD, as well as their innovative development and regulatory pathways, clinical evidence of similarity. It discusses the biosimilars already approved in the past 7 years. With an emphasis on European Union and US markets, it gives an overview of challenges that may undermine their widespread use and success including the definition of strategies for adequate pharmacovigilance to monitor biosimilars after marketing approval.

**KEYWORDS:** biosimilar, biologics, rheumatology, rheumatic disease, development, infliximab, etanercept, adalimumab, interchangeability, switch, extrapolation, budget impact analysis.

**INTRODUCTION**

Rheumatic disorders (RD) including rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PA), and inflammatory bowel disease (IBD) including ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory autoimmune diseases. According to the National Rheumatoid Arthritis Society and the British Gastroenterology Association 690,000 and 240,000 people in the UK are living with RD and IBD respectively.<sup>[143][144]</sup> RA is the leading cause of pain and disability, costing the National Health Service (NHS) £5 billion a year.<sup>[143]</sup> The additional cost to the economy of sick leave and work-related disability has been estimated at between £3.8 and £4.75 billion per year.<sup>[145]</sup> IBD costs the NHS around £900 million annually.<sup>[146]</sup>

Biological disease-modifying antirheumatic drugs (bDMARDs) and biological disease-modifying anti-inflammatory bowel disease drugs (bDMAIDs), as monoclonal antibodies and soluble receptors, are well established as the most effective agents for treating patients with severe RD and moderate to severe IBD and for those unresponsive to conventional agents.<sup>[147][148]</sup>

Given the nature of RD and IBD, both bDMARDs and bDMAIDs are considered chronic therapy and are often continued indefinitely upon commencement unless there is either loss of response or side effects.<sup>[149]</sup> bDMARDs, and bDMAIDs are expensive and contribute highly to RD and IBD bills.<sup>[150]</sup>

Biosimilars are potentially cost-effective alternatives to reference biological medicines and represent a cost containment tool to reduce the biologics bill.<sup>[151]</sup> Biosimilars do not represent a treatment innovation in the sense that they have the same mechanism of action, they perform equivalently in clinical settings and they are used in the exact same indications of the reference drug. They were developed with the purpose of reducing drug related expenditure and improving patient access to biotechnological therapies.<sup>[17]</sup>

They have the potential to provide the NHS with considerable cost savings. The National Institute for Health and Care Excellence (NICE) recently proposed that the use of biosimilar infliximab could provide a 10% saving per cycle for each patient.<sup>[38][142]</sup>

**KEY POINTS**

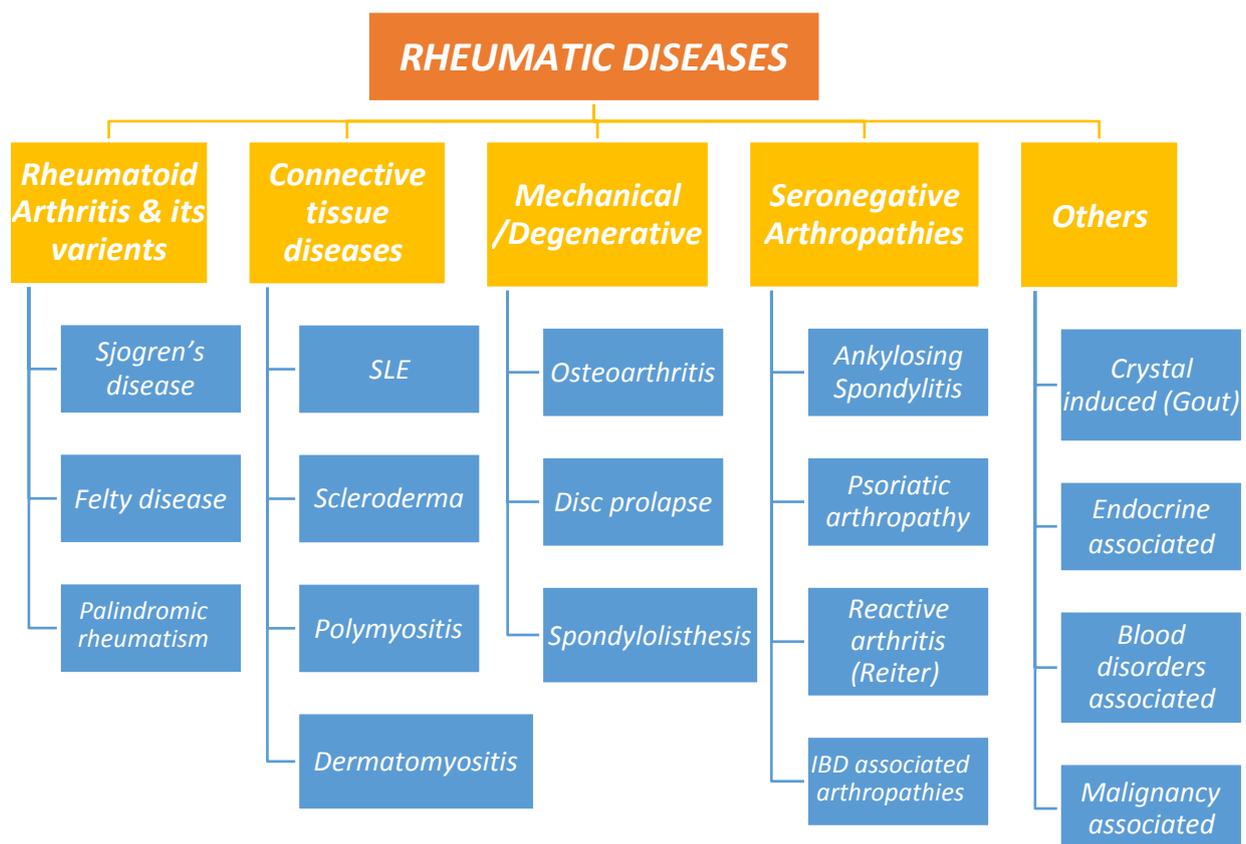
- Biosimilars have efficacy and safety similar to their reference products, but more cost effective.
- CT-P13 (an infliximab biosimilar) was the first monoclonal antibody biosimilar to be approved.
- There is extensive scientific rigor applied to support the abbreviated pathways to biosimilar approval.
- Biosimilar development should increase patient access to potentially life- changing therapies for treatment of rheumatic conditions.
- Biosimilars and their reference agents have been shown to be interchangeable.

**RHEUMATOLOGY**

Rheumatology deals with handling the various conditions that have an effect on musculoskeletal tissues like joints, bones, cartilage, tendons, ligament, and muscles. Rheumatism refers to varied painful conditions that have an effect on these tissues. Rheumatic diseases are those teams of diseases showing pain followed by reduction within the motion and performance of contractor tissues.<sup>[1]</sup>

Most typical forms of rheumatic disease are Rheumatoid arthritis (RA) and systemic autoimmune disorder (SLE). The response diseases (such as RA, SLE, sclerosis, and inflammatory bowel) have complicated pathological process and multiple aetiologies.<sup>[1]</sup> There are several evidences showed that response diseases are multi-genetic and their identification is related to varied forms of genes.<sup>[2]</sup>

There are some genes that induce the expression of proteins concerned in varied key pathophysiological pathways like formation and clearance of immune complexes material, management of innate and reconciling immunity, production of immunologic molecules like cytokines, chemokines, and adhesion molecules. Autoimmune patients have an excellent diversity in their genetic background and also the nature of genes decides what kind of responsiveness is needed to vary the state of system.<sup>[3]</sup>



**Figure 1: Different terms used in rheumatology.<sup>[1]</sup>**

**1.1 Rheumatoid arthritis (RA)**

Rheumatoid arthritis (RA) is a chronic disorder in which inflammatory response develops especially in synovial joints. In this disease, the immune system attacks its own body tissues mistakenly. It mainly affects the lining of the joints and results in painful swelling of the joints that in turn results in bone erosion and causes joint deformity.

The inflammation of the joints can damage the other parts of the body as well.

Rheumatoid Arthritis is seen worldwide and nearly 1% of the world population is affected.<sup>[4]</sup> Women are more likely to have this disease, and it generally occurs at older age. RA generally occurs at an age in between 30 and 50

years of age and its occurrence varies among different populations. The actual cause of this disease is unknown but it is assumed that it probably occurs if a genetically susceptible host gets exposed to an environmental antigen.<sup>[5]</sup>

This might generate immune response leading to the formation of various types of immune complexes, which generate inflammation in the joints.

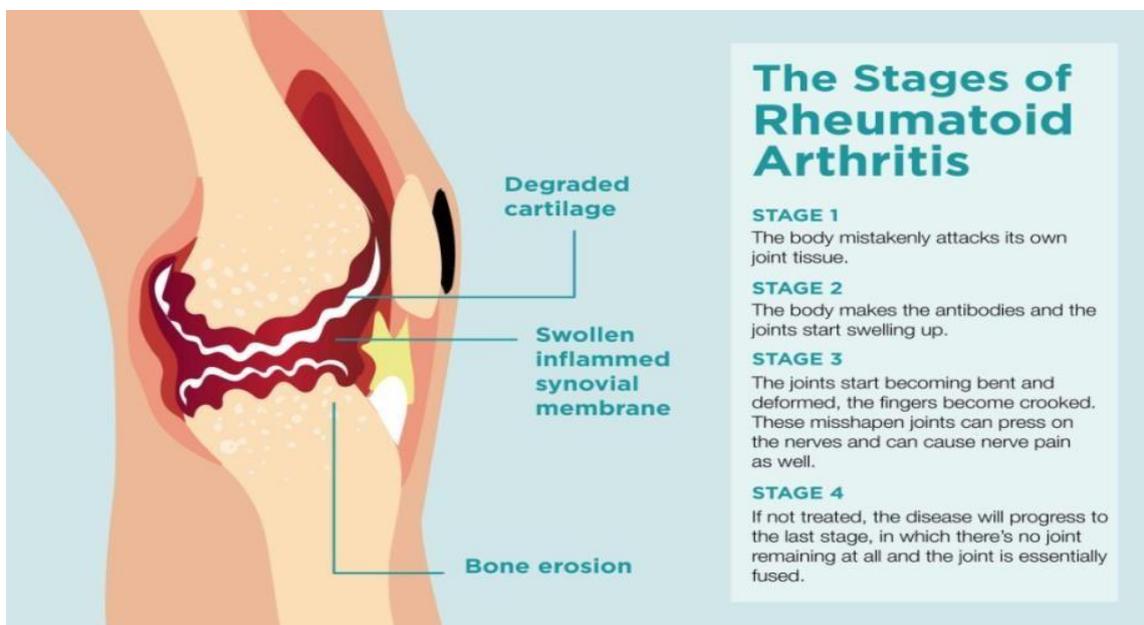


Figure 2: Different stages of Rheumatoid Arthritis (RA).

Recently, a study showed how inflammation occurs in joints of these rheumatoid arthritis patients. Synovial cells produced high concentration of  $16\alpha$ -hydroxyestrone in rheumatoid arthritis patients.<sup>[6]</sup> In spite of normal concentration of  $16\alpha$ -hydroxyestrone in serum and urine, there is a higher level of  $16\alpha$ -hydroxyestrone in the synovial tissues, where activated immune cells are present. Therefore,  $16\alpha$ -hydroxyestrone combined with histone resulted in the formation of  $16\alpha$ -hydroxyestrone-histone adduct that might produce autoantibodies against this antigen. As a result, these antibodies activate

inflammation in the joints of RA patients.<sup>[7]</sup> Regular exercises are recommended to maintain normal function of the joints and anti-inflammatory drugs are given to relieve from pain and swelling in the joints. Disease-modifying anti-rheumatoid drugs (DMARDs) are the choice of drugs if the disease goes beyond 2 months. If the conditions are mild, hydroxychloroquine/minocycline is given, while for moderate conditions, methotrexate followed by tumor necrosis factor (TNF) inhibitors is given.

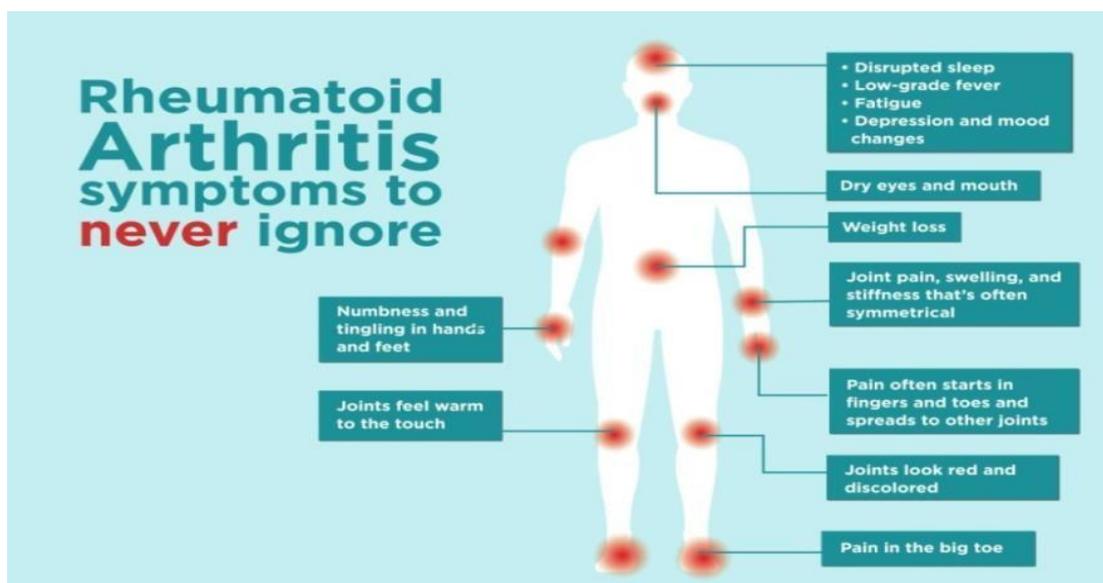


Figure 3: Symptoms to never ignore.

## 1.2 Drugs Used in Treatment of Rheumatic Diseases

Most rheumatic diseases are treated with analgesics, NSAIDs (nonsteroidal anti-inflammatory drug), steroids (in serious cases), DMARDs (disease-modifying antirheumatic drugs), monoclonal antibodies, such as infliximab and adalimumab, the TNF inhibitor etanercept, and methotrexate for moderate to severe rheumatoid arthritis.<sup>[8]</sup> Rituximab is now licensed for use in refractory rheumatoid arthritis.<sup>[9]</sup>

In addition to TNF inhibitors, bDMARDs with other mechanisms of action include abatacept (a Fc fusion protein targeting T-cell co-stimulation), rituximab (a chimeric monoclonal antibody targeting CD20+ B cells) and tocilizumab and sarilumab (monoclonal antibodies, humanised and human, respectively, targeting the interleukin-6 receptor).<sup>[10][11]</sup>

The main goal of anti-rheumatic drugs is to block inflammation. This helps prevent joint damage.<sup>[12]</sup>

**DMARDs:** Disease-modifying antirheumatic drugs (DMARDs) are used to decrease inflammation. Unlike other medications that temporarily ease pain and inflammation, DMARDs can slow the progression of RA.

The most common DMARDs used to treat RA include<sup>[12]</sup> hydroxychloroquine (Plaquenil)

- leflunomide (Arava)
- methotrexate (Trexall)
- sulfasalazine (Azulfidine)
- minocycline (Minocin)

**BIOLOGICS:**<sup>[12]</sup> Biologics are injectable drugs. They work by blocking specific inflammatory pathways made by immune cells. This reduces inflammation caused by RA. Doctors prescribe biologics when DMARDs alone aren't enough to treat RA symptoms. Biologics aren't recommended for people with compromised immune systems or an infection. This is because they can raise your risk of serious infections.

The most common biologics include:

- abatacept (Orencia)
- rituximab (Rituxan)
- tocilizumab (Actemra)
- anakinra (Kineret)
- adalimumab (Humira)
- etanercept (Enbrel)
- infliximab (Remicade)
- certolizumabpegol (Cimzia)
- golimumab (Simponi)

## 2 WHAT IS A BIOLOGIC PRODUCT (DRUG)?

A biologic medicine, regulated by the Food and Drug Administration (FDA), is a large molecule derived from living cells and typically produced by recombinant DNA, hybridoma, or other technologies.<sup>[13]</sup> Biologics are used in the treatment, diagnosis, or prevention of several non-

communicable and some communicable diseases and conditions and include hormones, small proteins, vaccines, monoclonal antibodies, and fusion proteins. The introduction of biologics (e.g., etanercept, adalimumab, infliximab, rituximab, abatacept, and tocilizumab) revolutionized treatment algorithms in rheumatological patients.<sup>[14]</sup>

The first step in the production of antibodies against specific molecules was the cloning of murine genes of variable heavy (VH) and variable light (VL) chains. It was then possible to synthesize chimeric antibodies, containing the murine VH and VL chains fused with the constant region of human origin.<sup>[13]</sup> More specifically, antibodies obtained by this technology show approximately one-third murine and two thirds human sequences. However, the efficacy of murine derived immunoglobulin preparations could be limited by the induction of anti- mouse immune responses, with consequent impairment of the therapeutic efficacy. Hence, recent antibodies of are as human as possible.

## 2.1 How are Biological Drugs Manufactured?

A biologic is manufactured in a living system such as a microorganism, or plant or animal cells. Most biologics are very large, complex molecules or mixtures of molecules. Many biologics are produced using recombinant DNA technology, whereas a drug is typically manufactured through chemical synthesis, which means that it is made by combining specific chemical ingredients in an ordered process.

Chemical drugs have well defined structure and a final drug product can be analysed to determine its components, while it is extremely difficult to assess a biologic by available laboratory methods. It can safely be said that for a biologic the process determines the final product. Even very minor changes in the manufacturing process can alter the living systems used in manufacturing a biologic. Nature and ultimately, the function of a biologic can be affected by only a minute change in the process. Tight control over the source and nature of starting materials is required and manufacturers have to employ hundreds of process controls for assuring predictable manufacturing outcomes which is not the case with chemical drugs. These process controls for biologics are not applicable to a manufacturing process/product created by another manufacturer as these are established separately for each manufacturing product. As process controls may also confidential it would be difficult or impossible for a second manufacturer to replicate the innovator without intimate knowledge of innovator's process.

These biologic proteins or peptides have been developed using recombinant DNA technology in living systems via complex purification techniques.<sup>[15]</sup> These biologics requires proprietary knowledge which precludes duplication, while small molecule products have simpler manufacturing processes.

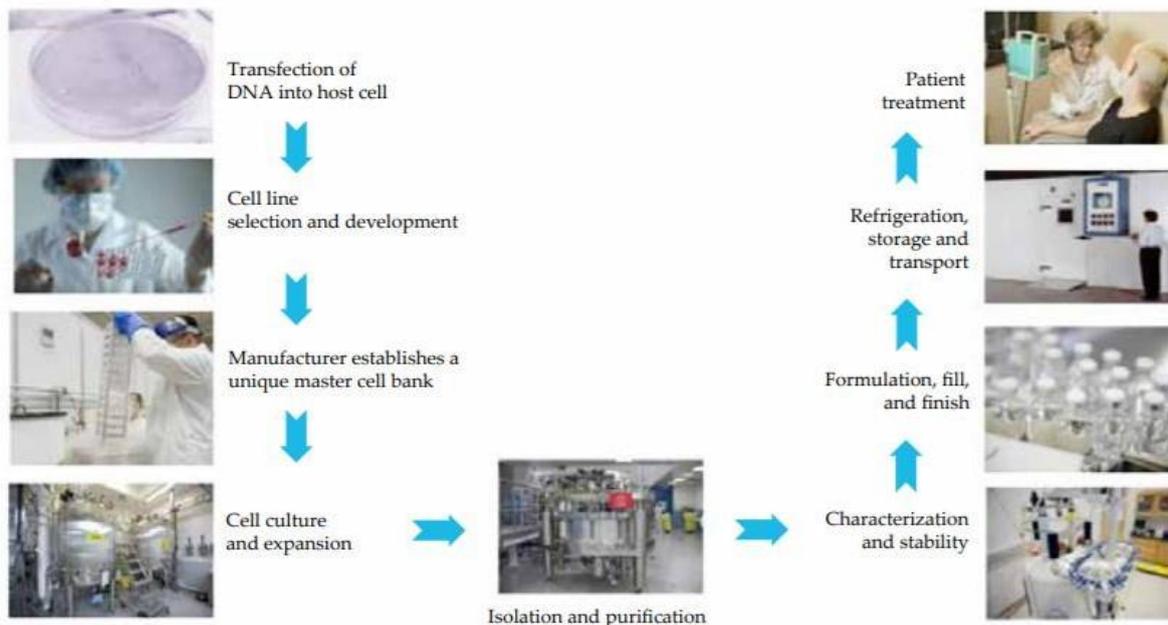


Figure 4: A typical biologic manufacture process includes multiple stages.

### 3 WHAT IS A REFERENCE PRODUCT?

A reference product is the single biological product, already approved by FDA, against which a proposed biosimilar product is compared. A reference product is approved based on, among other things, a full complement of safety and effectiveness data. A proposed biosimilar product is compared to and evaluated against a reference product to ensure that the product is highly similar and has no clinically meaningful difference).<sup>[16]</sup>

### 4 WHAT IS A BIOSIMILAR PRODUCT?

Biosimilar a biologic product considered 'highly similar' but not identical to its reference biologic product. Biosimilars can be defined as similar versions of a previously approved biotechnological medicine (known as originator or reference drug) that enter the market after

loss of patent exclusivity.<sup>[17]</sup>

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.

Table 1. DEFINITIONS OF BIOSIMILAR PRODUCTS BY DIFFERENT AGENCIES

Term (alternative terms)	Agency	Definition
Biosimilar (follow-on biologic, subsequent entry biologic, similar biotherapeutic product)	FDA <sup>[18]</sup>	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 <sup>[19]</sup>	biological medicinal products that contain a version of the active substance of an already authorized, original biological medicinal product (reference medicinal product). A biosimilar agent is similar to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise
	WHO <sup>[20]</sup>	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

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

#### 4.1 Why Biosimilars?

The introduction of biologic medicines, such as the tumour necrosis factor  $\alpha$  inhibitors (TNFi), has revolutionised the management of rheumatological diseases, including rheumatoid arthritis (RA) and the sero-negative spondyloarthropathies (ankylosing spondylitis [AS], psoriatic arthritis [PsA] and non-radiographic axial spondyloarthritis [axSpA]). These medicines block the actions of a number of inflammatory cytokines (e.g. TNF $\alpha$ , interleukin-1 [IL-1] and interleukin-6 [IL-6]) and immune mediators (T cells and B cells) within the body, identified as being causative factors in the joint and tissue damage associated with autoimmune and autoinflammatory diseases.<sup>[21]</sup>

A range of biologic drugs (bDMARDs) is available for use in patients with rheumatic diseases, including five TNF inhibitors: the receptor-Fc fusion protein etanercept, the chimeric monoclonal antibody infliximab, the human monoclonal antibodies adalimumab and golimumab, and the PEGylated humanised Fab' monoclonal antibody fragment certolizumab pegol.<sup>[11]</sup> These bDMARDs improve outcomes in several rheumatic diseases and have significant efficacy in patients who do not have an adequate response to conventional synthetic DMARD therapy alone.<sup>[22-25]</sup>

Despite the ability of bDMARDs to improve the lives of many patients with rheumatic diseases, the high cost of these drugs limits widespread use and contributes to inequalities of care.<sup>[10][26][27]</sup>

Biosimilars were developed with the single purpose of reducing drug related expenditure and improving patient access to biotechnological therapies. The NHS, for instance, reported savings of £99,400,000 with infliximab and £60,300,000 with etanercept biosimilars in 2017 after switch from reference drugs.<sup>[28]</sup>

Furthermore, among those patients who receive a biologic treatment, a significant proportion of patients either do not respond to initial treatment or lose responsiveness,<sup>[29]</sup> and more than 1 in 10 patients typically withdraws due to side effects.<sup>[30]</sup> Access to biologic agents per se, and to a wider range of alternative biologic agents, is therefore a key consideration in improving the treatment, and therefore outcomes, for patients with rheumatic diseases. The development of biosimilar agents that are highly comparable to the reference medicinal product provides a new route to achieving this goal.

As patents for branded TNFi near their expiry, pharmaceutical manufacturers have taken steps to develop medicines with equivalent therapeutic effect to their branded counterparts, but with a considerably lower acquisition cost – 'biosimilars'.

EULAR (The European League Against Rheumatism) recommendations have also addressed health economic aspects and expressed a preference for lower cost therapies when there is similar efficacy and safety. This will improve rational medicine use, defined as use of the most appropriate medicine, dose and duration of treatment to meet individual patient needs at the lowest possible cost to patients and their communities<sup>[31]</sup> in rheumatology practice.

#### 4.2 Biologic vs Biosimilar

It is important to note that biosimilars are not a generic copy of the original biological medicine (originator medicine or reference medicine).

##### Table Abbreviations:

**BLA** = biologics license application; **MOA** = mechanism of action;

**PD** = pharmacodynamic; **PK** = pharmacokinetic

**Table 2. DIFFERENCE BETWEEN BIOLOGIC AND BIOSIMILAR**

Parameter	Biologic	Biosimilar
<b>Definition</b>	<ul style="list-style-type: none"> <li>▪ A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings</li> <li>▪ Referred to as the reference, pioneer, or innovator biologic</li> </ul>	<ul style="list-style-type: none"> <li>▪ The biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that 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</li> <li>▪ Referred to as follow-on biologic.</li> </ul>
<b>Properties</b>	<ul style="list-style-type: none"> <li>▪ Derived from living sources such as cells</li> <li>▪ Complex mixtures whose active ingredients (usually proteins) are hundreds of times larger than the compounds found in most pills</li> <li>▪ Mostly given by injection due to unstable environmental conditions</li> </ul>	<ul style="list-style-type: none"> <li>▪ The active ingredient of biosimilars closely resemble the reference biologic</li> <li>▪ However, they are not identical, generic equivalents due to differences in manufacturing processes, protein source, and extraction/purification processes</li> </ul>
<b>Approval Process</b>	Submitted through the BLA process Requirements: <ul style="list-style-type: none"> <li>▪ Applicant information: Includes name and addresses of manufacturing facilities</li> </ul>	2012 FDA Draft Guidance recommends a stepwise approach to demonstrate biosimilarity. Submitted through an abbreviated BLA.

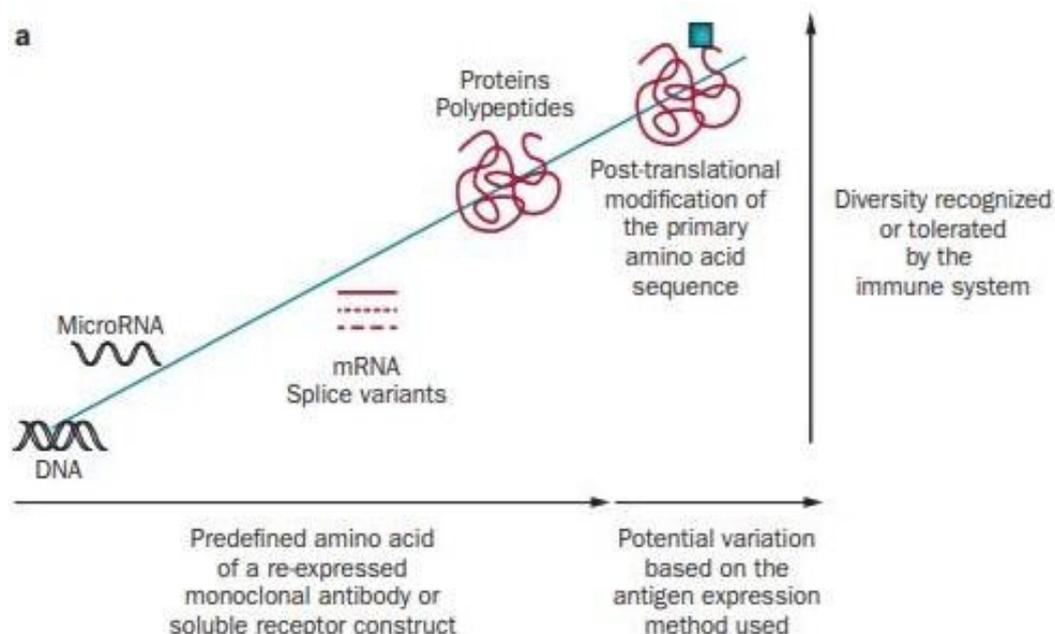
	<ul style="list-style-type: none"> <li>▪ Product/Manufacturing information: Source material/raw material; manufacturing process and controls; formulation; facility information; contamination/cross- contamination information; environment assessment or categorical exclusion</li> <li>▪ Pre-clinical studies: Safety, efficacy, and use</li> <li>▪ Clinical studies: Safety, efficacy, and use</li> <li>▪ Labeling: Safety, efficacy, and use</li> </ul>	<p>Requirements (unless FDA deems unnecessary):</p> <ul style="list-style-type: none"> <li>▪ Structural analyses: Determine structural characteristics of the protein, post- translational modifications, and/or other potential variants</li> <li>▪ Functional assays: Evaluate the pharmacologic activity of the protein (eg, potency and MOA)</li> <li>▪ Animal studies: Include toxicity, PK and PD measures, and immunogenicity</li> <li>▪ Clinical studies: Human pharmacology data, clinical immunogenicity assessment, and clinical safety and efficacy data to demonstrate safety, purity, and potency for the condition(s) the reference product is licensed to be used for.</li> </ul>
<b>Safety data</b>	<ul style="list-style-type: none"> <li>▪ Typically required to have postmarketing safety monitoring</li> <li>▪ Includes the detection, assessment, understanding and prevention of adverse effects after the launch of the biologic onto the market</li> </ul>	<ul style="list-style-type: none"> <li>▪ Include postmarketing surveillance to address immunogenicity and potential rare adverse events when seeking approval</li> <li>▪ May undergo more strict monitoring due to limitations of clinical data compared to the reference product</li> </ul>

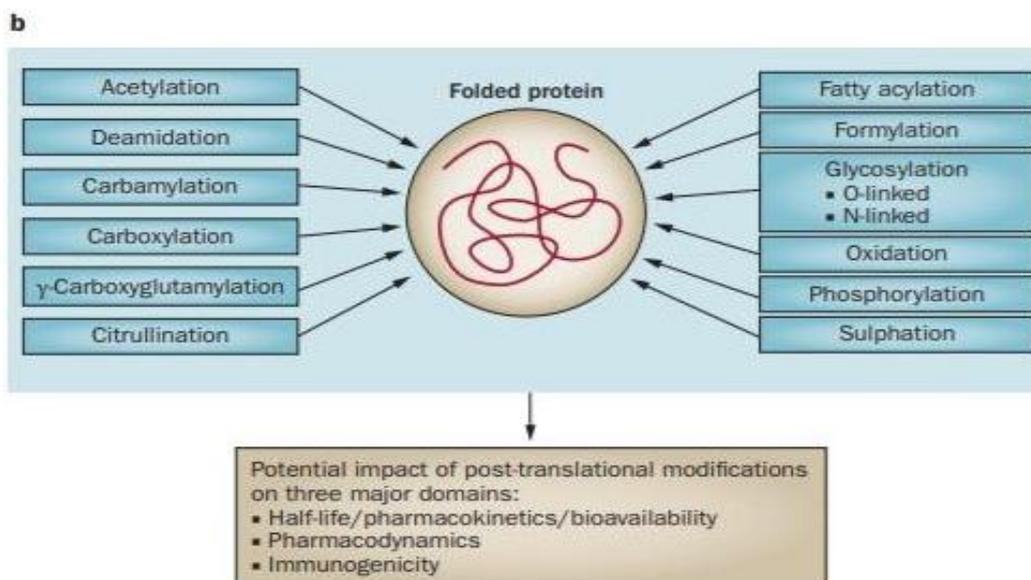
### 4.3 Immunogenicity

Seven years have passed since the ground-breaking approval of CT-P13 (branded names Remsima™ and Inflectra™), based on Infliximab as the first biosimilar of a monoclonal antibody by the European Medicines Agency (EMA).<sup>[32]</sup>

Monoclonal antibodies generated in vitro to be administered to patients are foreign antigens that undergo a set of defined processes from transcription to various post-translational modifications (Figure 5). These

processes can generate heterogeneity of the expressed monoclonal protein, which contributes to its immunogenicity. Although biosimilar agents are produced by cell lines and undergo various purification steps in vitro, studies reported to date have not found substantial differences between biosimilars and their reference products in the three domains rigorously studied during biosimilar development—pharmacokinetics, pharmacodynamics and immunogenicity.





**Figure 5: Mechanisms of protein diversity and consequences for the immune system.**

Protein diversity is dependent on genetic code (DNA), transcription, translation and, most importantly, post-translational modification. These factors can affect the function, diversity and half-life of the final protein.

**a.** Potential post translational modification of proteins can define three important characteristics of biologic agents: pharmacokinetics, pharmacodynamics and immunogenicity.

All these parameters should be assessed at specific stages of the clinical development of biosimilar agents.

Infliximab is a monoclonal antibody that is not fully humanised and individuals exposed to this drug for a period of time will have had a specific anti-drug (B cell) response. Before market authorisation is granted for a biosimilar product, anti-drug B cell response must be evaluated. If the biosimilar contains the same amino acid sequence to the reference product, it should also have the same T-cell epitope. A strong immune response would require a new T-cell epitope.<sup>[33]</sup>

#### 4.4 The Biosimilar Development Process (Regulation, Approval)

Biosimilars are not truly innovative because they are similar versions of well-known biotechnological medicines. The true innovation comes from the regulation and manufacturing processes. EMA was pioneer in both regulation<sup>[34]</sup> and biosimilar approval,<sup>[35]</sup> and was later followed by the World Health Organisation (WHO)<sup>[36]</sup> and the US Food and Drug Administration (FDA).<sup>[37]</sup>

Biosimilar medicines have specific European Union (EU) regulatory pathways that differ from the authorisation process applied to generic medicines.<sup>[38]</sup>

The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) require a biosimilar to have highly similar quality characteristics and biological activity to the reference product, with no clinically meaningful safety or efficacy differences. To get EMA or FDA approval, biosimilars must undergo a comprehensive development process that involves a series of comparability exercises to establish biosimilarity to the reference product, including at least one adequately powered randomised controlled trial (RCT) demonstrating equivalent efficacy of the biosimilar and reference product in an appropriate patient population.<sup>[39][40]</sup> Those presenting **comprehensive totality-of-evidence dossier (figure 6)** of analytical, preclinical, pharmacokinetic, pharmacodynamics and clinical data that demonstrates comparable efficacy and safety of the biosimilar and its off-patent reference biopharmaceutical are endorsed by regulatory agencies as biosimilars.<sup>[41-43]</sup>

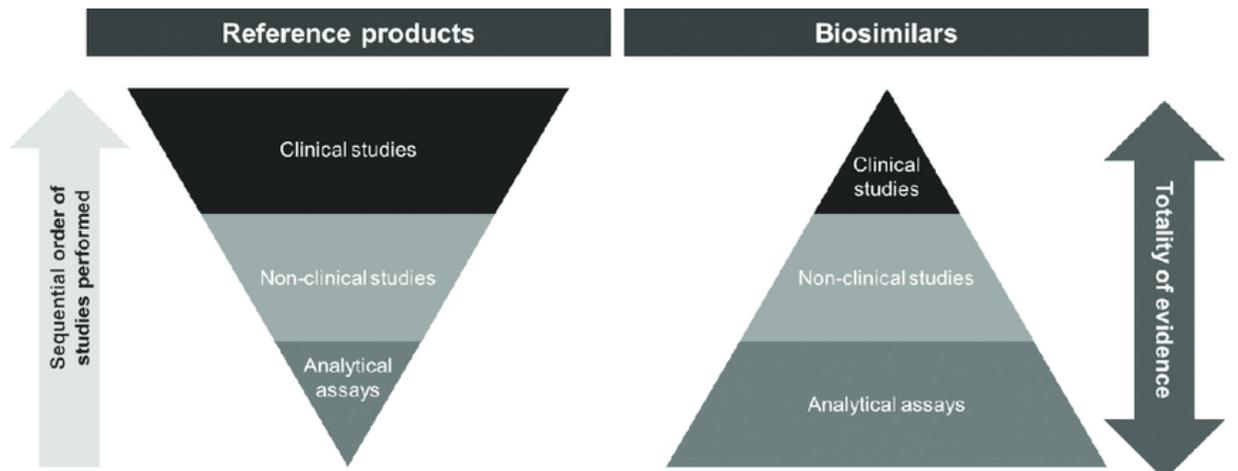


Figure 6: The Totality of evidence approach to the development of reference and biosimilar products.<sup>[39][40][44]</sup>

Due to anticipated different manufacturing processes for biosimilars vs innovators, biosimilar development in the EU and the USA hinges on a **stepwise approach** (figure 7). 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<sup>[45][46]</sup> to confirm that there are 'no clinical meaningful differences' between the reference product and the biosimilar.

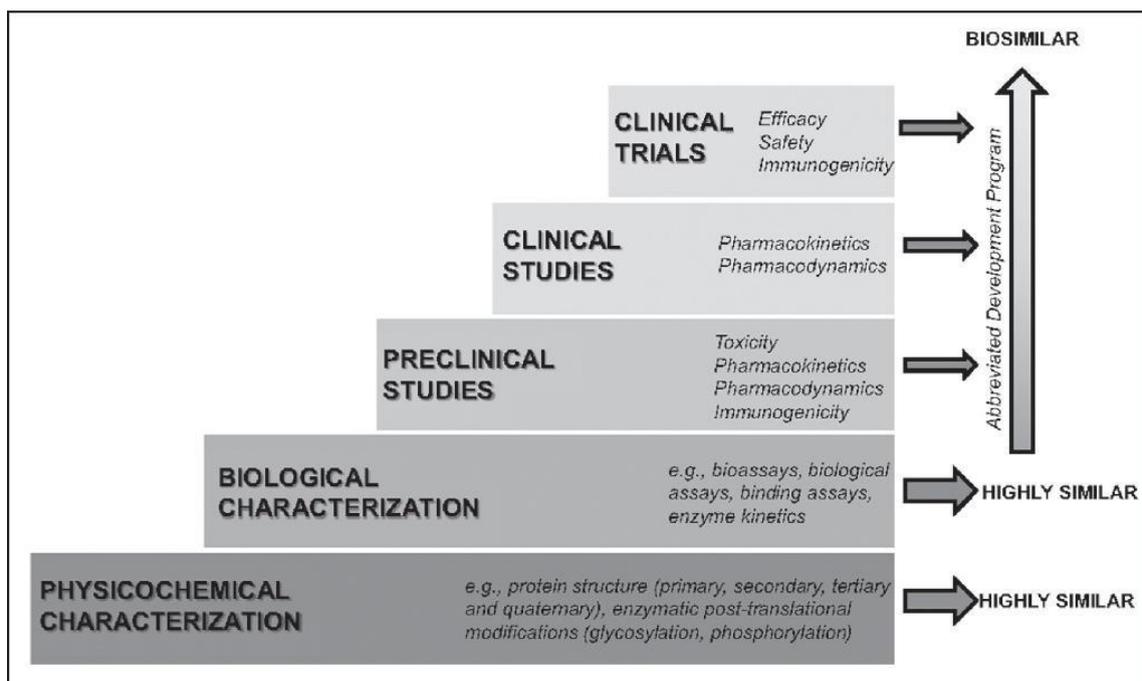


Figure 7: Stepwise approach for biosimilar application reviews.

As well as being assessed during the pivotal clinical efficacy study, clinical safety is initially assessed during clinical pharmacokinetic/pharmacodynamic studies.<sup>[39][40]</sup> Compared with the development process for reference products, there is much more emphasis placed on physicochemical and functional characterisation of biosimilars than on clinical testing.<sup>[39][40][44]</sup> Analyses must demonstrate that the biosimilar and its bio-originator have the same primary amino acid sequence. There must be no significant differences in charge isoforms, glycosylation, other post-translational modifications or

impurities. There may be minor differences, but these must not affect critical quality attributes of the biologic. Subsequent clinical studies must demonstrate PK and PD equivalence and equivalent efficacy in at least one disease for which the bio-originator is approved, as well as comparable safety and no greater immunogenicity of the biosimilar.<sup>[47-53]</sup>

Relevant preclinical and phase I data on a biosimilar should be available when phase III data are published.

<b>Parameter / Study</b>	<b>EMA and FDA Guidance</b>
<b>Production source</b>	tured yeast, bacteria or animal/plant cells

Continued (Table 3)...

<b>Active pharmaceutical ingredient</b>	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
<b>Characterization</b>	Thorough head-to-head comparative characterization against the reference product using orthogonal methods
<b>In vitro non-clinical testing</b>	Head-to-head comparison with the reference product: <ul style="list-style-type: none"> <li>▪ Receptor binding assays</li> <li>▪ Cell proliferation assays</li> <li>▪ Cell potency assays</li> </ul>
<b>Non-clinical animal testing</b>	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 nonhuman 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
<b>Clinical—phase I study</b>	Comparative PK/PD (if PD marker available) in HV or patients with scientific justification required for
<b>Clinical—phase III studies: safety (including immunogenicity) and efficacy</b>	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
<b>Pharmacovigilance plan</b>	Generally required, often mimics reference product's pharmacovigilance plan, but may have additional requirements based on observations during clinical development of the biosimilar
<b>Post-marketing studies</b>	Often may be required for, for example, late developing adverse events, additional immunogenicity testing
<b>EMA:</b> European Medicines Agency; <b>FDA:</b> US Food and Drug Administration; <b>HV:</b> healthy volunteers; <b>MoA:</b> mechanism of action; <b>PD:</b> pharmacodynamics; <b>PK:</b> pharmacokinetics.	

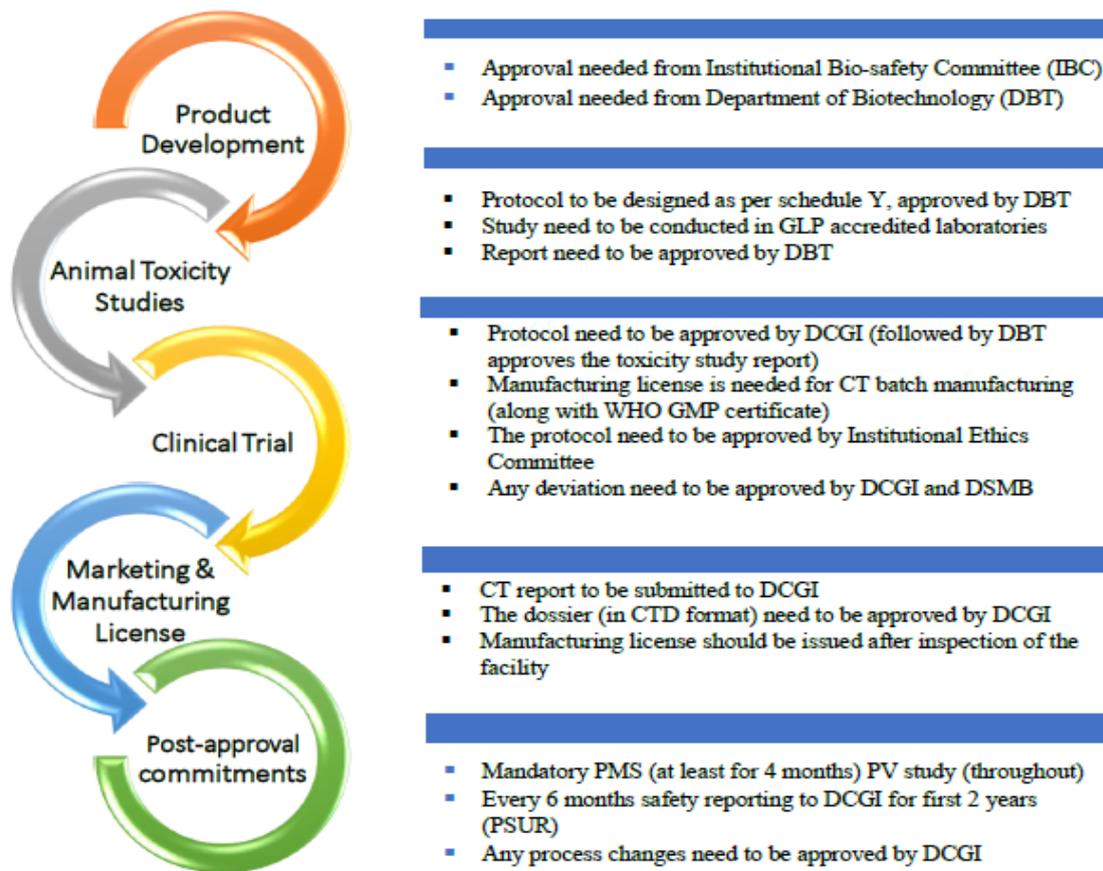


Figure 8: The regulatory pathway for approval of biosimilars in India.<sup>[54]</sup>

## 5 BIOSIMILARS IN RHEUMATOLOGY

The field of biosimilars for the treatment of immune-mediated inflammatory conditions is constantly evolving.<sup>[32]</sup> Biologic agents are an important therapeutic option in the treatment of patients with rheumatic diseases, including RA,<sup>[55]</sup> AS,<sup>[56]</sup> and PsA.<sup>[57]</sup>

CT-P13 was the first to be endorsed in both the European and North American markets (EMA in 2013 and US FDA in 2016, respectively).<sup>[58]</sup> Several biosimilar DMARDs (bsDMARDs) based on adalimumab, etanercept, infliximab and rituximab have been approved for use in patients with rheumatic diseases, and many more bsDMARDs are in the pipeline.<sup>[59][60]</sup>

By June 2019, there were 3 infliximab and 2 etanercept biosimilars approved in Europe and North America; 4 adalimumab biosimilars approved in Europe and 3 in North America; and 2 rituximab biosimilars approved in Europe. All biosimilars had the primary PK (phase 1) and primary efficacy (phase 3) endpoints falling within the prespecified equivalence ranges.

### CT-P13

CT-P13 was the first infliximab biosimilar for which marketing approval was granted by regulatory agencies (Brand names: Inflectra and Remsima). CT-P13 is an IgG1 chimeric human-murine monoclonal antibody produced in the same type of recombinant cell line (murine

hybridoma cells produced by recombinant DNA technology) and with an identical amino acid sequence (30% murine variable amino acid sequence/70% human IgG1 heavy chain constant region and human kappa light chain). Both brands of biosimilar infliximab have the same therapeutic indications,<sup>[61][62][63]</sup> pharmaceutical form and dosage regimes as the original branded Remicade.

This approval was based on two landmark clinical trials in which CTP13 was compared to reference infliximab (Remicade®, Janssen Biotech, Inc.): a phase I study (PLANETAS)<sup>[64]</sup> of 250 patients with ankylosing spondylitis (AS), and a phase III study (PLANETRA)<sup>[65]</sup> of 606 patients with RA who were also receiving methotrexate. Both studies used the standard dose infliximab regimes currently used in clinical practice for the management of these conditions.<sup>[64][65]</sup>

### PLANETRA study

It was a 54-week, phase III randomised, double-blind, multicentre, multinational parallel group study designed to compare the efficacy and safety of biosimilar infliximab (CT-P13) with the original infliximab reference product (INX). For the primary end point, CT-P13 was required to demonstrate equivalent efficacy to the reference product in terms of a 20% improvement in the American College of Rheumatology score (ACR20) at week 30. All patients entering the study had active

disease and a diagnosis of RA for at least one year. All patients needed to be on a stable dose of methotrexate and must not have previously received a biologic medicine. A total of 606 patients were randomised (CT-P13 n= 302, INX n= 304) on a 1:1 basis to receive a two-hour infusion of 3mg/kg CT-P13 or INX at weeks zero, two and six, and then every eight weeks up to week 30. A total of 515 patients completed the 30-week study period and, of these, 16 patients were excluded from the patient population on account of protocol violations. The results were comparable across the two treatment groups for the ACR20 at week 30, in addition, similar results were seen for the ACR50 and ACR70 scores. Incidence of drug-related adverse events (35.2% versus 35.9%) and detection of anti-drug antibodies (48.4% versus 48.2%) were similar between CT-P13 and INX, respectively. Overall, no statistically significant differences in

response or safety data were seen between CT-P13 and INX.<sup>[65]</sup>

Patients who completed the PLANETRA study were eligible for entry into an open label extension phase covering an additional period of 48 weeks. Of the original study population, 302 patients entered the extension study. In this group, 158 patients were maintained on CT- P13 and 144 patients were switched from the originator reference drug (INX) to the biosimilar (CT-P13). Through to week 102, ACR20/50/70 response rates were maintained and were similar for each group: 72.2%, 48.3% and 24.5% (maintenance group) and 71.8%, 51.4% and 26.1% (switch group). Overall, the efficacy and safety profiles of the maintenance group and switch group were comparable.<sup>[61]</sup>

References	Study design	Dosage regimen	Key efficacy outcomes	Immunogenicity	Key safety outcomes	Study conclusions
<b>CT-P13 vs reference infliximab (INX): multinational efficacy and safety studies in patients with RA</b>						
Yoo et al. [20] PLANETRA study to week 30	Phase III, randomized, double-blind multicenter multinational, parallel-group study RA patients <sup>a</sup> CT-P13 (n= 302) INX (n= 304)	3 mg/kg IV CT-P13 or INX, weeks 0, 2, 6 then q8wks + MTX 12.5-25 mg/wk + folic acid ≥5 mg/wk	ACR20 response rate CT-P13: 60.9% INX: 58.6% (95% CI: -6, 10) ACR50 response rate CT-P13: 35.1% INX: 34.2% ACR70 response rate CT-P13: 16.6% INX: 15.5% Mean improvement in CDAI CT-P13: -25.2 INX: -23.6 Mean improvement in SDAI CT-P13: -25.8 INX: -24.4 DAS28/CRP response rate CT-P13: 40.9% INX: 39.0% Good/moderate EULAR response (CRP) CT-P13: 85.8% INX: 87.1% (95% CI: 0.92, 1.06)	ADAs at week 14 CT-P13: 25.4% INX: 25.8%  ADAs at week 30 CT-P13: 48.4% INX: 48.2%	Overall TEAEs CT-P13: 60.1% INX: 60.8%  TEAEs related to treatment CT-P13: 35.2% INX: 35.9% Most frequently reported TEAEs related to treatment CT-P13: latent TB, increased ALT, increased AST; flare of RA activity INX: latent TB, increased ALT, increased AST, UTI Serious TEAEs CT-P13: 10.0% INX: 7% No deaths	CT-P13 demonstrated equivalent efficacy to INX at week 30, with a comparable PK profile and immunogenicity CT-P13 was well tolerated, with a safety profile comparable to that of INX
Yoo et al. [22] PLANETRA study extension to week 54	Phase III, randomized, double-blind multicenter, multinational, parallel-group study RA patients <sup>a</sup> CT-P13 (n= 302) INX (n= 304)	3 mg/kg IV CT-P13 or INX, weeks 0, 2, 6 then q8wks + MTX 12.5-25 mg/wk + folic acid ≥5 mg/wk	ACR20 response rate CT-P13: 74.7% INX: 71.3% (95% CI: -0.05, 0.12) ACR50 response rate CT-P13: 43.6% INX: 43.1% ACR70 response rate CT-P13: 21.3% INX: 19.9% Mean improvement in CDAI CT-P13: -25.7 INX: -24.0 Mean improvement in SDAI CT-P13: -26.3 INX: -24.6  Mean improvement in DAS28/CRP CT-P13: -2.3 INX: -2.2 Good/moderate EULAR response (CRP) CT-P13: 87.4% INX: 82.5%	ADAs at week 54 CT-P13: 41.1% INX: 36.0%	Overall TEAEs CT-P13: 70.5% INX: 70.3%  TEAEs related to treatment CT-P13: 43.7% INX: 45.0% Most frequently reported TEAEs related to treatment CT-P13: infusion-related reaction, upper respiratory tract infection, latent TB, abnormal liver function test, lower respiratory tract infection and UTI INX: infusion-related reaction, latent TB, upper respiratory tract infection, abnormal liver function test, UTI and lower respiratory tract infection Serious TEAEs: CT-P13: 13.9% INX: 10.3% Serious TEAEs related to treatment CT-P13: 7.6% INX: 4.7% One death in INX group; not considered related to treatment	The 54-week findings confirm those previously reported at week 30 [36] CT-P13 and INX were comparable in terms of efficacy (including radiographic progression) and immunogenicity up to week 54 The safety profile of CT-P13 was similar to that of INX
Yoo et al. [23] PLANETRA study switching extension to week 102	Phase III, open-label, extension study RA patients <sup>a</sup> CT-P13 (n= 302) INX (n= 304) for 54 weeks then CT-P13 maintenance (n= 158) or switch to CT-P13 (n= 144) for up to 102 weeks	3 mg/kg IV CT-P13 or INX, weeks 0, 2, 6 then q8wks + MTX 12.5-25 mg/wk + folic acid ≥5 mg/wk to week 54 then CT-P13/MTX/folic acid as above (weeks 64-102)	ACR20 response rate CT-P13 maintenance: 71.7% CT-P13 switch: 71.8% (95% CI: -10, 10) ACR50 response rate CT-P13 maintenance: 48.0% CT-P13 switch: 51.4% ACR70 response rate CT-P13 maintenance: 24.3% CT-P13 switch: 26.1% Mean improvement in DAS28/CRP CT-P13 maintenance: -2.40 CT-P13 switch: -2.48 Good EULAR response (CRP) CT-P13 maintenance: 40.1% CT-P13 switch: 44.4%	ADAs at week 78 CT-P13 maintenance: 44.7% CT-P13 switch: 46.2%  ADAs at week 102 CT-P13 maintenance: 40.3% CT-P13 switch: 44.8%	Overall TEAEs CT-P13 maintenance: 53.5% CT-P13 switch: 53.8%  TEAEs related to treatment CT-P13 maintenance: 22.0% CT-P13 switch: 18.9% Most frequently reported TEAEs related to treatment CT-P13 maintenance: infusion-related reaction, latent TB, upper respiratory tract infection, lower respiratory tract infection, UTI, bursitis CT-P13 switch: infusion-related reaction, latent TB, lower respiratory tract infection, abnormal liver function test, upper respiratory tract infection, UTI, urticaria Serious TEAEs CT-P13 maintenance: 7.5% CT-P13 switch: 9.1% Serious TEAEs related to treatment CT-P13 maintenance: 1.3% CT-P13 switch: 2.8% No deaths	Comparable efficacy and tolerability were observed in patients who switched from INX to CT-P13 for an additional year and in those who had long-term treatment with CT-P13 for 2 years

**Figure 9: PLANETRA study comparing CT-P13 (Biosimilar) and Infliximab (Originator).**

### PLANETAS study

It was a 54-week, phase I randomised, double-blind,

multicentre, multinational, parallel-group study designed to compare the pharmacokinetics, safety and efficacy of

biosimilar infliximab (CT-P13) with the original reference compound (INX) in patients with AS. Eligible patients had a diagnosis of AS for at least three months prior to screening, were biologic naive and had active disease. The primary end points were area under the concentration time curve (AUC) at steady state and observed maximum steady state concentration (C<sub>MAX,SS</sub>) between weeks 22 and 30. Assessment according to the Ankylosing Spondylitis International Working Group criteria (ASAS20 and ASAS40) for improvement of 20% and 40% was performed in addition to required safety outcomes. Patients were randomly assigned on a 1:1 basis to receive either 5mg/kg of the biosimilar (CT-P13) or the original reference compound (INX) at weeks zero, two, six and then every eight weeks up to week 30. Of the 250 randomised patients, 229 completed the 30-week study period (CT-P13: n=125; INX: n=125). The

pharmacokinetic parameters of AUC and C<sub>max</sub> were equivalent for CT-P13 (32765.8 µgh/ml and 147.0 µg/ml) and INX (31359.3 µgh/ml and 144.8 µg/ml). The ratio of geometric means was near a 100% for AUC and C<sub>MAX,SS</sub>. For the clinical response measures of ASAS20 and ASAS40, no statistically significant difference was seen between the two treatment groups at weeks 14 and Overall, at week 30 the efficacy and safety profile was similar between the two groups.<sup>[64]</sup>

Of the 210 patients who completed PLANETAS, 174 entered a one-year open label extension phase.<sup>[66]</sup> Within the open label phase, 88 patients continued with CT-P13, while 86 patients were switched from INX to CT-P13. The comparable efficacy and tolerability profiles seen in the original 54-week study were maintained in the open label extension phase up to week 102.<sup>[21]</sup>

References	Study design	Dosage regimen	Key efficacy outcomes	Immunogenicity	Key safety outcomes	Study conclusions
<p>CT-P13 vs reference infliximab (INX): pharmacokinetic, efficacy and safety studies in patients with AS</p> <p>Park et al. [19] PLANETAS study at week 30</p>	<p>Phase I, randomized, double-blind, multicenter, multinational, parallel-group study</p> <p>AS patients CT-P13 (n=125) INX (n=125)</p>	<p>5 mg/kg IV CT-P13 or INX, weeks 0, 2, 6 then q8wks + continued stable use of glucocorticoids/NSAIDs allowed</p>	<p>CT-P13/INX ratio (95% CI) AUC: 104.5% (94-116) C<sub>max</sub>: 101.5% (95-109)</p> <p>ASAS20 response rate CT-P13: 70.5% INX: 72.4% (95% CI: 0.51, 1.62)</p> <p>ASAS40 response rate CT-P13: 51.6% INX: 47.4% (95% CI: 0.70, 2.00)</p> <p>Mean change in ASDAS-CRP CT-P13: -1.8 INX: -1.7</p> <p>Median change in BASDAI score CT-P13: -3.1 INX: -2.5</p> <p>Median change in BASFI score CT-P13: -2.6 INX: -2.2</p> <p>Median change in BASMI score CT-P13: -1.0 INX: -1.0</p> <p>Median change in chest expansion score (cm) CT-P13: +0.5 INX: +0.5</p>	<p>ADAs at week 14 CT-P13: 9.1% INX: 11%</p> <p>ADAs at week 30 CT-P13: 27.4% INX: 22.5%</p>	<p>Overall TEAEs CT-P13: 64.8% INX: 63.9%</p> <p>Most frequently reported TEAEs related to treatment CT-P13: increased ALT and AST, latent TB, urinary tract infection, serum creatine phosphokinase elevation, γ-glutamyltransferase elevation INX: increased ALT and AST, γ-glutamyltransferase elevation, latent TB</p> <p>Serious TEAEs CT-P13: 4.8% INX: 6.4%</p> <p>No deaths</p>	<p>The PK profiles of CT-P13 and INX were equivalent in patients with AS. CT-P13 was well tolerated, with an efficacy and safety profile comparable to that of INX up to week 30</p>
<p>Park et al. [25] PLANETAS study extension to week 54</p>	<p>Phase I, randomized, double-blind, multicenter multinational, parallel-group study</p> <p>AS patients CT-P13 (n=125) INX (n=125)</p>	<p>5 mg/kg IV CT-P13 or INX, weeks 0, 2, 6 then q8wks + continued stable use of glucocorticoids/NSAIDs allowed</p>	<p>ASAS20 response rate CT-P13: 67.0% INX: 69.4% (95% CI: 0.50, 1.59)</p> <p>ASAS40 response rate CT-P13: 54.7% INX: 49.1% (95% CI: 0.73, 2.15)</p> <p>ASAS partial remission CT-P13: 19.8% INX: 17.6%</p> <p>Mean change in ASDAS-CRP score CT-P13: -1.7 INX: -1.7</p> <p>Median change in BASDAI score CT-P13: -3.1 INX: -2.8</p>	<p>ADAs at week 30 CT-P13: 19.5% INX: 23.0%</p>	<p>Overall TEAEs CT-P13: 74.2% INX: 67.2%</p> <p>TEAEs related to treatment CT-P13: 50.0% INX: 51.6%</p> <p>Most frequently reported TEAEs related to treatment CT-P13: abnormal liver function test, upper respiratory tract infection, infusion-related reaction, latent TB INX: abnormal liver function test, infusion-related reaction, upper respiratory tract infection, latent TB</p> <p>Serious TEAEs CT-P13: 7.8% INX: 6.6%</p>	<p>The 54-week findings confirm those previously reported at week 30</p> <p>CT-P13 and INX have highly comparable efficacy, safety and immunogenicity and PK profiles up to week 54</p>

Continued...

			Median change in BASFI score CT-P13: -2.9 INX: -2.7 Median change in BASMI score CT-P13: -1.1 INX: -0.9 Median change in chest expansion score (cm) CT-P13: +0.7 INX: +0.9			Serious TEAEs related to treatment CT-P13: 3.1% INX: 4.1% Two deaths (one in each treatment arm); both car accidents and not considered related to study treatment
Park et al. [26] PLANETAS study switching extension to week 102	Phase I, open-label, extension study AS patients CT-P13 (n=125) INX (n=125) for 54 weeks then CT-P13 maintenance (n=88) or switch to CT-P13 (n=86) up to week 102	5 mg/kg IV CT-P13 or INX, weeks 0, 2, 6 then q8wks + continued stable use of glucocorticoids/NSAIDs allowed then CT-P13/glycorticoids/NSAIDs as above (weeks 62-102)	ASAS20 response rate CT-P13 maintenance: 80.7% CT-P13 switch: 76.9% (95% CI: 0.58, 2.70)  ASAS40 response rate CT-P13 maintenance: 63.9% CT-P13 switch: 61.5% (95% CI: 0.57, 2.07)  ASAS partial remission CT-P13 maintenance: 19.3% CT-P13 switch: 23.1% (95% CI: 0.37, 1.72) Mean ASDAS-CRP score CT-P13 maintenance: -1.86 CT-P13 switch: -1.97 Mean change in BASDAI score CT-P13 maintenance: -3.19 CT-P13 switch: -3.23  Mean change in BASFI score CT-P13 maintenance: -3.10 CT-P13 switch: -3.25 Mean change in BASMI score CT-P13 maintenance: -2.4 CT-P13 switch: -2.6	ADAs at week 78 CT-P13 maintenance: 23.3% CT-P13 switch: 29.8%  ADAs at week 101 CT-P13 maintenance: 23.3% CT-P13 switch: 27.4%	Overall TEAEs CT-P13 maintenance: 48.9% CT-P13 switch: 71.4%  TEAEs related to treatment CT-P13 maintenance: 22.2% CT-P13 switch: 39.3%  Most frequently reported TEAEs related to treatment CT-P13 maintenance: infusion-related reactions, abnormal liver function test, upper respiratory tract infection, latent TB, elevated serum creatine kinase, lower respiratory tract infection CT-P13 switch: infusion-related reactions, abnormal liver function test, latent TB, back pain, upper respiratory tract infection Serious TEAEs CT-P13 maintenance: 4.5% CT-P13 switch: 4.7% Serious TEAEs related to treatment CT-P13 maintenance: 2.3% CT-P13 switch: 2.3%	This is the first study to show that switching from INX to its biosimilar CT-P13 is possible without negative effects on safety or efficacy in patients with AS

**Figure 10: PLANETAS study comparing CT-P13 (Biosimilar) and Infliximab (Originator).**

### 5.1 Rituximab Biosimilars

Rituximab is a chimeric monoclonal antibody against the protein CD20 and is being used for the treatment of many lymphomas, transplant rejection, rheumatoid arthritis and other autoimmune disorders.<sup>[89-94]</sup>

With patent expiration a large number of companies started the development of biosimilars.<sup>[95]</sup> *Truly Rituximab biosimilars to be released in 2018–2019: Celltrion South Korea CT-P10 Sandoz Switzerland GP-2013 trials in RA Pfizer USA PF-05280586 trials in RA Amgen USA ABP 798 trials in RA and Lymphoma RXTM83 trial in Lymphoma. Boehringer Ingelheim, BI 695500 trial in RA.*

### 5.2 Etanercept Biosimilars

Etanercept (Enbrel) is an anti-TNF agent that acts primarily to bind and neutralize, approved for use in adult patients with moderate-to-severe active and/or progressive RA, active and progressive PsA, severe active AS, severe non-radiographic axial spondyloarthritis and severe plaque psoriasis, and in young people with JIA (polyarthritis, extended oligoarthritis, PsA and enthesitis-related arthritis) and severe plaque psoriasis.<sup>[67]</sup>

The main patent for the use of Enbrel in the USA was to be expired in October 2012 but Amgen announced in the end of 2011 that it was granted a new patent protecting it from competition by other biosimilars until 2028.<sup>[68]</sup> In Europe however, the patent expired in 2015.

**HD203**

- Produced by recombinant DNA technology in Chinese hamster ovary cells, as is the reference product.
- Phase I studies comparing HD203 and reference etanercept demonstrated similar pharmacokinetic profiles.<sup>[69]</sup>
- In November 2014, the South Korean Ministry of Food & Drug Safety (MOFDS) granted Hanwha Chemical Co., Ltd of South Korea approval to market HD203 as Davictrel™ to treat RA.<sup>[70]</sup>

**SB4**

- In 2016 the joint venture between Biogen and Samsung Biologicals were granted approval of the first etanercept biosimilar SB4 (Benepali) for the treatment of RA, Psoriatic Arthritis non radiographic Spondyloarthritis and plaque Psoriasis.
- Although EMA considered Benepali highly similar to Enbrel some structural and side effects of the biosimilar are now being considered and receiving additional attention.<sup>[71][72][73]</sup>
- Switching from etanercept to Benepali did not result in any increase in immunogenicity. Data published confirming switching and maintaining efficacy from etanercept to SB4 was reported by Emery and coworkers.<sup>[74]</sup>
- SB4 was approved In Canada and also in Brazil with a different trade name Brenzys.

**GP2015**

- Developed by Sandoz.<sup>[75]</sup>
- The efficacy and safety of GP2015 were assessed in the randomized, double-blind EGALITY study.<sup>[76]</sup>
- FDA approved the biosimilar with the trade name Erelzi in September of 2016.<sup>[77]</sup>
- Sandoz Enbrel biosimilar has been also accepted for review and approved also by EMA.<sup>[78]</sup>
- approved for all indications of the reference drug but not as an interchangeable medication, which means it may not be substituted for the reference product by a pharmacist without knowledge of the prescriber.<sup>[78]</sup>

**LBEC0101**

- Developed by LG Chem in Korea against the reference etanercept in terms of efficacy and safety in patients with active rheumatoid arthritis inadequately responding to methotrexate.
- It is already licensed in South Korea and in Japan in partnership with Mochida Pharmaceuticals with the trade name Eucept.
- Second Enbrel biosimilar launched in Korea three years after SB4 (Samsung Bioepis) was approved in 2015.<sup>[79]</sup>

**Figure 11: Etanercept biosimilars.**

### 5.3 Adalimumab Biosimilars

Adalimumab is a TNF-inhibiting, anti-inflammatory, biologic medication. It binds to tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), which normally binds to TNF $\alpha$  receptors, leading to the inflammatory response of autoimmune diseases. By binding to TNF $\alpha$ , adalimumab reduces the inflammatory response. It was approved in rheumatoid arthritis and by additional trials approved in psoriasis, psoriatic arthritis, juvenile arthritis, ankylosing spondylitis, inflammatory bowel disease, uveitis and more recently hidradenitis suppurative.<sup>[80][81][82][83][84]</sup>

Patent expiration was expected by the end of 2016 but the manufacturer had applied for extension with seventy additional patents protecting the brand Humira from biosimilar entry until 2022. It was expected a prolonged litigation process which may delay the introducing of future biosimilars in the market.

*Truly Adalimumab biosimilars released in 2018–2019:*

- ABP 501 (Amgen) CT-P17
- (Celltrion) CHS-1420 (Coherus)
- MSB 11022 (Merck)
- M923 (Momenta)
- PF-06410293 (Pfizer)
- SB5 (Samsung-Bioepis)
- GP 2017 (Sandoz)
- FKB327 (Fujifilm Kyowa Kirin Biologicals)
- ONS 3010 (Oncobiologics)

#### ABP 501

- Amgen performed a randomized, double-blind, active-controlled study and evaluated safety, efficacy and immunogenicity of ABP 501 compared to adalimumab in adult patients with moderate-to-severe rheumatoid arthritis who had an inadequate response to methotrexate.
- FDA approved Amgen. Amgen commercial name Amjevita is a biosimilar from Abbvie adalimumab brand however it was not characterized as interchangeable.<sup>[80][81][85]</sup>
- AMJEVITA/AMGEVITA is on the market in Europe and expected to be in the USA by the year 2023.<sup>[86][87]</sup>

#### BI 695501

- Biosimilar candidate to U.S.-licensed Humira® and EU approved Humira® (adalimumab)
- BI 695501 met the clinical study primary efficacy endpoint to establish equivalence with Humira® in patients with active rheumatoid arthritis (RA). The secondary endpoints for efficacy, safety and immunogenicity of BI 695501 vs. Humira®, were also met.<sup>[83]</sup>
- The European agency EMA and the FDA accepted the licensing of Boehringer biosimilar with a commercial name Cytelzo

#### SB5

- third biosimilar candidate to that was submitted to the EMA by Samsung Bioepis, the joint venture between Samsung BioLogics and Biogen.
- On the market in South Korea and in countries such as Turkey with the brand name Imraldi.<sup>[84][86]</sup>
- Although in the USA this biosimilar will not be available until 2023 Biogen and Samsung Bioepis have agreed a licensing deal with the owner of the innovator molecule Abbvie in Europe on a country by country basis.

#### GP2017

- Sandoz a Novartis division evaluated a biosimilar of the reference Adalimumab in adult patients with moderate to severe plaque psoriasis, in a 51 week double blind phase 3 study ran studies.<sup>[88]</sup>

### 5.4 Infliximab Biosimilars

Infliximab (Remicade) is an anti-TNF agent that is approved for use in adult patients with severe active and/or progressive RA, severe active ankylosing spondylitis, active and progressive PsA, moderate to severe plaque psoriasis, moderately to severely active Crohn's disease and fistulizing active Crohn's disease, and in young people aged 617 years with severe active Crohn's disease or ulcerative colitis.<sup>[96]</sup>

*Truly Infliximab biosimilars released in 2018-2019: PF - 064381779 (Pfizer-Sandoz), ABP 710 (Amgen), BOW015 (Epirus), STI-002 (Sorrento Therapeutics), BCD-055 (Biocad).*

CT-P13: The South Korean developer Celltrion launched with the two trade names Inflectra and Remsima (CT-P13 biosimilar).<sup>[97][98][99]</sup>

Amgen ABP 710 and PF -064381779 have finished development but with Hospira acquisition is not expected that Pfizer infliximab would be pursued intensively by the company. The pharmacokinetics and safety attributes of Pfizer infliximab have been confirmed in successive publications. Novartis group Sandoz acquired the rights to Pfizer Infliximab that will be extended to the 28 countries that form the European market. Sandoz intends to complete the phase III program and submit to EMA.

Infliximab BOW015 was investigated in a comparative safety/efficacy equivalence study in patients with RA (n = 189). BOW15 global phase III trial was expected to be finished in 2017 but the parent company Epirus has ceased operations and no information is available of stage of the development. Infimab is being pursued in India by Ranbaxy Laboratories.<sup>[100]</sup>

Samsung Celltrion Remsima/Inflectra and Samsung Flixabi are already available in the market approved in both major markets EMA and FDA. SB2 (Flixabi ®; Samsung Bioepis) SB2 has been studied in a comparative safety/efficacy study to demonstrate

equivalence of efficacy, safety, immunogenicity, and pharmacokinetic outcomes versus infliximab in patients with moderate to severe RA. A positive phase III from

Sorrento Therapeutics Infliximab was reported but no information on licensing is available.<sup>[101-104]</sup>

### 5.5 European Approval of Few Biosimilars (EMA) as of when Review was done (Table 4)

EU has the largest number of approved biosimilar medicines up to date

Active Substance	Reference Product	Biosimilar medicines
Adalimumab (9)	Humira	Amgevita, Imraldi, Halimatoz, Hyrimoz, Hefiya, Hulio, Kromea, Amsparity <sup>[105]</sup>
Etanercept (2)	Enbrel	Benepali, Erelzi
Infliximab (4)	Remicade	Flixabi, Inflectra, Remsima, Zessly
Rituximab (6)	MabThera	Blitzima, Ritemvia, Rixathon, Riximyo, Truxima, MabThera

### 5.6 Some U.S. Approved Biosimilars (FDA) as of when the Review was done<sup>[106]</sup> (Table 5)

Date of Biosimilar FDA Approval	Biosimilar Product	Active ingredient (reference product)
April 5, 2016	Inflectra	Infliximab (Remicade)
August 30, 2016	Erelzi	Etanercept (Enbrel)
September 23, 2016	Amjevita	Adalimumab (Humira)
April 21, 2017	Renflexis	Infliximab (Remicade)
August 25, 2017	Cyltezo	Adalimumab (Humira)
December 13, 2017	Xifi	Infliximab (Remicade)
October 30, 2018	Hyrimoz	Adalimumab (Humira)
November 28, 2018	Truxima	Rituximab (Rituxan)
April 25, 2019	Eticovo	Etanercept (Enbrel)
July 23, 2019	Ruxience	Rituximab (Rituxan)
July 23, 2019	Hadlima	Adalimumab (Humira)
November 15, 2019	Abrilada	Adalimumab (Humira)
December 16, 2019	Avsola	Infliximab (Remicade)

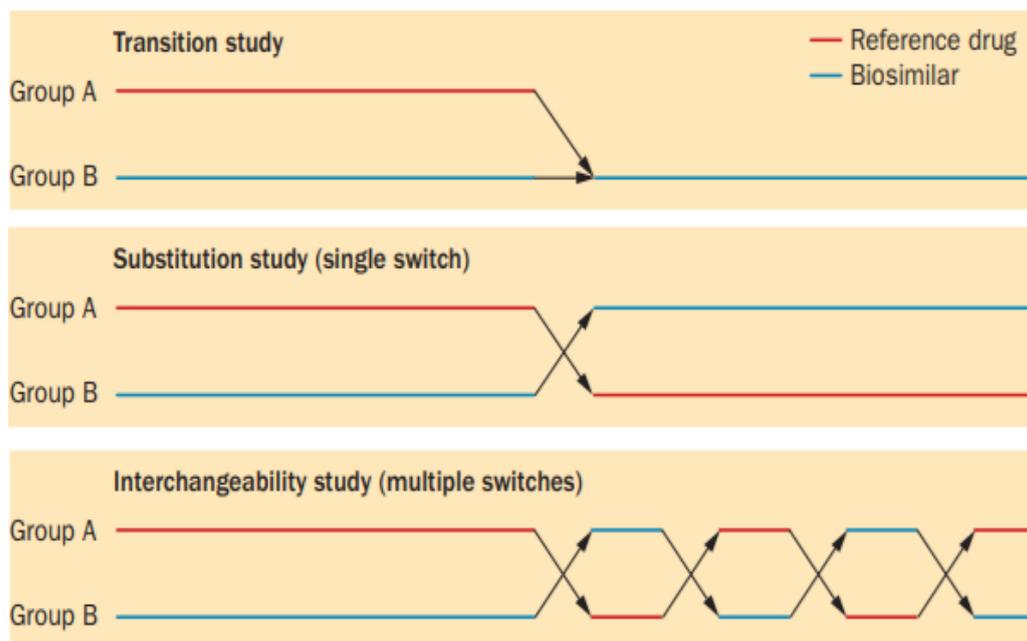
### 5.7 Switching, Substitution and Interchangeability

Drug 'switching' takes place when a patient is transitioned from one biopharmaceutical to another or from a reference biopharmaceutical to its biosimilar (Figure 12). A 'switch' study demonstrating no loss of efficacy nor increase in risk would support the transition under consideration.

Drug 'substitution', on the other hand, refers to the replacement of one biopharmaceutical with another by someone other than the licensed health-care professional who prescribed the medication.

In the USA, according to the Biologics Price Competition and Innovation Act of 2009, if a biosimilar agent is determined to be 'interchangeable' with its reference product, a pharmacist would be allowed to substitute a prescribed biological therapy for a biosimilar agent without involving the prescribing physician.

Substitution, in which a biosimilar is prescribed in place of its bio-originator, must be distinguished from interchangeability, wherein someone other than the prescribing healthcare provider initiates the switch from bio-originator to biosimilar or between two biosimilars. Of note, in the EU, the term 'substitution' implies what is considered in the USA to be 'interchange'. Thus, terminology must be harmonised worldwide.<sup>[107]</sup>



**Figure 12: Study design to compare the efficacy of reference drugs and biosimilars. Switching, as has been carried out in clinical trials of some biosimilars, is compared with substitution involving single or multiple switches, as potential study designs to support the FDA designation of interchangeability. Switch studies are not required for approval by the EMA.**

**In the USA**, a biosimilar agent can be considered interchangeable if a clinical trial demonstrates no loss of efficacy and no increased safety risk following at least a single switch from the reference product. However, demonstration of interchangeability should require testing of repeated switches between the reference product and the biosimilar (Figure 12).

**In the EU**, the EMA does not have the authority to designate a biosimilar as being interchangeable; rather, this judgement must be made by regulatory agencies in each Member State. To support the designation of interchangeability, an RCT that incorporates multiple switches between the two biologics must be conducted.

**The US FDA has issued draft guidance** on demonstrating interchangeability of a biosimilar with its bio-originator, in which it suggests that post-marketing pharmacovigilance data should be combined with data from at least one prospective RCT that compares repeated switching between the bio-originator and the biosimilar to continuous treatment with the bio-originator.<sup>[108]</sup>

**European guidelines** consider biosimilar anti-TNF agents to be interchangeable with their reference anti-TNF products, although they should not be considered as a replacement in the case of failed efficacy or unacceptable toxicity.

Unlike small-molecule drugs, a biopharmaceutical that is repeatedly interchanged with a similar biological agent might elicit immunogenicity that could compromise the efficacy and safety of both medications. Thus, frequent

switching between the original protein product and the biosimilar agent should be avoided, as even subtle differences, such as impurities introduced during manufacturing, can trigger an immune response to biosimilar agents. The ACR position statement on biosimilars clearly states that the “providers must retain the right to write ‘dispense as written’ for all prescriptions,” and expresses concerns that repeated switching carries too many uncertainties.<sup>[109]</sup> Likewise, a number of European medical societies, some of which in agreement with patient groups (such as the EULAR Standing Committee of People with Arthritis and Rheumatism), have issued documents that articulate their strong opposition to automatic substitution.<sup>[110]</sup>

Ideally, the consequences of switching from a bio-originator to a biosimilar should be compared with that of continued treatment with the bio-originator in an RCT, conducted in patients who are receiving stable treatment with the bio-originator. Extensions to phase III RCTs of several biosimilars, in which subjects treated initially with the bio-originator were switched to the biosimilar, have been published.<sup>[74][111][112][113][114]</sup> Observing no loss of efficacy and no increase in the rate of adverse events following this single switch supports making this switch in clinical practice, only if the biosimilar costs less than the bio-originator. However, if a patient has failed to respond to a specific biologic, a biosimilar of that product should not subsequently be prescribed.

An RCT was conducted in Norway to assess the effect of switching from bio-originator infliximab (Remicade) to the biosimilar infliximab CT-P13 on efficacy and safety in the various indications for which both had been

approved (RA, AS, PsA, ulcerative colitis, Crohn's disease and chronic plaque psoriasis). NOR-SWITCH was a 52-week, double blind, non-inferiority, phase IV RCT.<sup>[115]</sup> The primary outcome of the study is occurrence of disease worsening within a 52-week period. Patients entering the study must have been on stable treatment with innovator infliximab (Remicade) for the past six months. This study demonstrated non-inferiority of switching from the bio-originator to the biosimilar, using a non-inferiority margin of 15%, as compared with continuation of treatment with the bio-originator for the aggregate of subjects with the various diseases enrolled. NOR-SWITCH supports the practice of switching patients with stable disease activity from bio-originator infliximab to the biosimilar CT-P13. However, these results cannot be generalised to other biologics and their biosimilars or to frequent switching back-and-forth between bio-originator and biosimilar. For each new biosimilar and application device, an RCT should be conducted to evaluate safety and continued efficacy after switching from the bio-originator or to another biosimilar.

#### *When should biosimilars be used?*

- biologic-naïve patients are clear candidates for use of biosimilars.
- patients who are already on a reference biologic can be considered for transition to a biosimilar after appropriate discussion with a specialist.

*Why patient/physician can be reluctant to the switch?*

- However, the question of switching from a reference product during successful therapy remains undetermined.<sup>[59]</sup>
- Some physicians are being cautious about using biosimilars in clinical practice.<sup>[59]</sup> This reflects potential uncertainties among some prescribers regarding the utility of biosimilars.<sup>[116]</sup>

Confidence in the clinical profile of these agents should arise from an understanding of the extensive and rigorous process undertaken to establish comparability between the biosimilar and the reference medicinal product.

However, even if data from RCTs support the practice of switching from a bio-originator to its biosimilar or between biosimilars, patients must feel comfortable receiving the treatment that they have been prescribed. Patients with rheumatological diseases may be reluctant to switch medications, even when their disease remains active, because of fear of disease worsening or of developing an adverse effect on a new medication.<sup>[117]</sup> To achieve this, rheumatologists should inform patients about the rigorous development process during which biosimilars have been assessed and shown to be highly similar to their bio-origimators. Patient perspectives must be taken into account. Patients should understand that an approved biosimilar may be like another batch of its bio-

originator and should provide similar therapeutic benefit with comparable safety. They also should be informed about the economic implications of switching, which should allow more patients to benefit from treatment with biologics. However, if some patients remain uneasy about switching from the bio-originator to a biosimilar, even with this information, their preferences must be considered when making a therapeutic decision.

In particular, blinded studies have demonstrated that switching from reference infliximab to CT-P13 does not result in any loss of efficacy, increase in AEs or increase in immunogenicity.<sup>[114][118]</sup> Promising results have also been reported in patients switching from reference infliximab to the biosimilar SB2 and in patients switching from reference etanercept to the biosimilar SB4.<sup>[119][120]</sup> It is crucial that high-quality pharmacovigilance and registry data are collected when transitioning patients to a biosimilar. Automatic switching is one area that might cause particular concern, as this would not involve physician consultation and may impact effective pharmacovigilance, which is dependent on the transparent use of nomenclature and treatment history.

#### **5.8 Pharmacovigilance**

Pharmacovigilance, embedded in post marketing surveillance, is of critical importance for biosimilars. As the abbreviated clinical development programme of biosimilar agents is less able to identify small safety risks (compared with the development of reference products), appropriate pharmacovigilance measures need to be implemented after approval is granted. It remains to be seen if manufacturers will establish risk-management plans, or if existing databases created to monitor patients receiving biologic agents will also be used to monitor patients receiving biosimilars. Data collection by organizations outside the pharmaceutical industry would be preferable. This approach has proven to be effective across different national registries such as ARTIS (Sweden), BSRBR (UK), CLEAR (USA), CORONA (USA), NDB (USA), RABBIT (Germany), SCQM (Switzerland) and VARA (USA),<sup>[121]</sup> and has been requested by rheumatology societies such as the ACR.<sup>[109]</sup>

#### **5.9 Extrapolation of Indications**

Biosimilar medicines are not required to have comparative phase III clinical trial data for all the indications of the original product.<sup>[38]</sup> Regulatory agencies have streamlined the development of biosimilar agents by allowing for extrapolation of indications. After having demonstrated efficacy and safety equivalent to its bio-originator in at least one RCT conducted in patients with a disease for which the bio-originator is authorised, a biosimilar may apply for approval in any or all indications for which its bio-originator already has been authorised without an RCT in each indication.

In 2006, the EMA CHMP advised that efficacy data for a

biosimilar agent could be generalized from one indication to another “if the reference product acts by the same mechanism in each disease state.”<sup>[122]</sup> In 2011, the CHMP extended the potential for extrapolation to include safety data in addition to efficacy data. In 2012, *the FDA* issued similar guidance, stating that data from a clinical trial of a biosimilar agent conducted in one disease could be used to support approval for additional indications for which the reference product had already been licensed.<sup>[123]</sup> As mentioned previously, regulatory agencies in other countries have also allowed extrapolation of indications, although not always to all indications applicable to the reference drug. International variation in disease states for which approval is granted also exists for some reference biopharmaceuticals.<sup>[124-131]</sup>

Health Canada initially denied the biosimilar infliximab CT-P13 extrapolation of data from clinical trials conducted in patients with rheumatoid arthritis and ankylosing spondylitis to inflammatory bowel diseases, this decision was ultimately reversed by the same regulatory authority.<sup>[132]</sup>

### 5.10 Economic Impact of New Biosimilars in Rheumatology

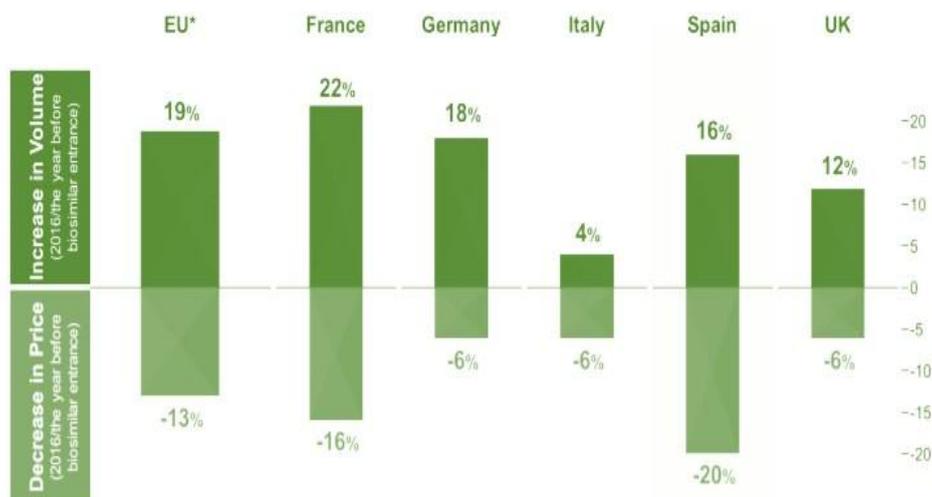
Budget impact analysis (BIA) is an estimation of the potential financial impact of the adoption of a new intervention (medicine) into health systems such as the UK NHS over a short to medium time horizon.<sup>[133][134]</sup> BIA provides health service managers and commissioners (payers) with information to support budget planning and effective resources allocation.<sup>[135]</sup>

The high costs of TNF inhibitors have secured their position as some of the greatest revenue-producing drugs in the world. Adalimumab (Humira), which had no

direct competition from bsDMARDs in 2017, was the world’s best-selling drug (US\$18 billion in 2017 global sales) for immune-mediated inflammatory diseases, while etanercept (Enbrel) and infliximab (Remicade), both of which had competition from bsDMARDs, had sales of about US\$8 billion each.<sup>[136][137]</sup>

Compared with 2016, the year before any etanercept or infliximab biosimilars was available on the European market, the price per treatment day across overall TNF inhibitor use decreased by 13% in the TNF inhibitor biosimilar accessible European Economic Area market, and volume per treatment day increased by 19% (figure 13).<sup>[138]</sup> These changes indicated that etanercept and infliximab biosimilars are not only available at a lower cost per unit but are also facilitating access to these therapies for more patients.<sup>[59][139]</sup>

In 2017, a published budget impact model was adapted to estimate the expected cost savings following the entry of new biosimilars Flixabi®, Erelzi, Solymbic®, Amgevita® and Imraldi® in the UK over three-year time horizon. The model predicted that infliximab and etanercept biosimilars would replace their corresponding reference products by 2020. Adalimumab biosimilars were predicted to achieve 19% of the rheumatology and gastroenterology market by 2020. Without the introduction of further biosimilars, the model predicted a reduction in expenditure of £44 million on biologics over the next three years. With the entry of Flixabi®, Erelzi®, Solymbic®, Amgevita® and Imraldi® the model estimates cumulative savings of £285 million by 2020. The introduction of new infliximab, etanercept and adalimumab biosimilars will be associated with considerable cost savings and have a substantial favourable impact on the UK NHS budget.



\*Included EU countries: Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, UK

Figure 13: Health Economic Impact of anti-TNF in the EU and EU-5 countries in 2016<sup>[138]</sup>

## 6. CHALLENGES OF BIOSIMILARS

- Biosimilars are less stable than chemical based pharmaceuticals and thus require cold chain distribution and have a shorter shelf life. This increases the cost and complexity of distribution.
- Manufacturing process of biosimilars is generally more complex than manufacturing small molecule generics.
- Even if regulatory agencies grant approval to a biosimilar for indications for which the reference product is licensed, but in which the biosimilar agent has not been studied, clinicians might be reluctant to follow this approval. In this context, experts from national and international organizations have argued that convincing data from clinical trials are needed for each individual indication.<sup>[124-131]</sup>

## 7. BENEFITS OF BIOSIMILARS.

- Deliver comparable clinical, safety and efficacy results as the originator drugs:
- Less costly to develop.
- Require less development time.
- fair redistribution of diagnostic and therapeutic resources.
- Potentially increase the number of treated patients
- Modify the clinical practice of rheumatologists, particularly in economically constrained countries
- Improve patient outcomes and compliance with treatment guidelines - the availability of more affordable biotechnologicals allows the earlier introduction of biological therapies whenever a patient fails to respond to conventional anti-rheumatic drugs.<sup>[140][141]</sup>

## 8. CONCLUSION

As with the introduction of targeted biologic therapies at the end of the past millennium, the availability of biosimilars in clinical practice is a paradigm shift in the treatment of patients with rheumatological and other inflammatory diseases.

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. 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.

However, for bsDMARDs to be widely integrated into clinical practice, and for maximal cost savings to be achieved with these drugs, all rheumatology prescribers and patients need to be aware of the consistent efficacy and safety of bsDMARDs in relation to reference

bsDMARDs, as well as their substantial cost benefits. Reassurance by the robust and exhaustive process of evaluation that all biosimilars undergo before and after they are approved is likely to be reassuring and increase successful long-term uptake of biosimilars. Addition of adalimumab biosimilars to the group of anti-TNF bsDMARDs that are already available on the European market will continue to drive savings, allowing rheumatologists to treat a wider range of patients with the most effective available therapies, and for funds to be diverted to other aspects of care, thereby helping to relieve the pressure on tight healthcare budgets

International guidelines on the treatment of RA, in particular, have acknowledged the role of biosimilars in terms of their interchangeability with reference bsDMARDs, except in the case of lack of efficacy or tolerability. August 2016 study concluded that there is sufficient evidence about safety and efficacy of biosimilars to allow for extrapolation of indications. However, there remained concern about switching between two biosimilars or between a bio-originator and its biosimilar on multiple occasions because adequate studies have not yet been conducted to assess these circumstances. NOR-SWITCH supports the practice of switching patients with stable disease activity from bio-originator infliximab to the biosimilar CT-P13. However, these results cannot be generalised to other biologics and their biosimilars or to frequent switching back-and-forth between bio-originator and biosimilar. For each new biosimilar and application device, an RCT should be conducted to evaluate safety and continued efficacy after switching from the bio-originator or to another biosimilar. To facilitate making informed decisions about therapeutic substitution with biosimilars, healthcare providers are encouraged to gather pharmacovigilance data in registries about the outcome of such switches made in the context of clinical practice. drug expenditures.

The development of biosimilars introduced changes in the assessment and quality control of biologic medicines overall. More than just improving quality and post-marketing pharmacovigilance of biosimilars in the market, data from the last five years fosters a new age for the assessment of all biologics. Stringent regulatory frameworks and post-marketing pharmacovigilance programs have provided reassuring evidence on similarity, but the success of biosimilars will depend mostly on the commitment and confidence of smaller stakeholders such as hospital administrations and hospital pharmacies, prescribing physicians and patients with inflammatory rheumatic diseases (IRD).

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