

Navigating Biosimilars in Dermatology: A Growing Paradigm Shift

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Abstract: The incorporation of biosimilars into dermatology is an innovative milestone, particularly in treating chronic inflammatory skin disorders such as psoriasis and hidradenitis suppurativa. Even though biologic medicines have had a positive impact on patients' health, their exorbitant price has significantly restricted access. The major benefits of biosimilars include providing safe, effective alternatives to biologic medicines at a lower cost, improving patient access to advanced therapies, and reducing healthcare expenditure. Economically viable alternatives to authorized reference biologics are prevalent in the markets, provided that these biosimilars are cost-effective and have the same safety and efficacy standards. Biosimilars typically cost 20 to 40 percent less than the originator products while maintaining equivalent safety, purity, and efficacy as demonstrated in the clinical trials. In dermatology, this change has shifted the access paradigm for patients, regulations, and even doctors' prescribing habits. The reduction in price compared to the originator drugs has significantly improved patient access, with studies showing an adoption rate of over 60 percent within two years of introduction. While biosimilars have promise, their hurdles lie within the scope of interchangeability laws, regulatory uncertainties, acceptance from the public, and even the practitioners prescribing them. This article analyzes the biosimilars overview in dermatological practice, including the conditions, viz., psoriasis, hidradenitis suppurativa, pemphigus vulgaris, granulomatosis with polyangiitis, and arthritis, alongside the field's infrastructure, clinical concerns, and prospective effects.

Keywords: biosimilars; dermatology; adalimumab; etanercept; infliximab; ustekinumab.

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1. Introduction

The switch from biologics to biosimilars has significantly reduced health care costs and expanded patient therapeutic options in recent years. Biosimilars are structurally similar to the

innovator and are required to show similar pharmacokinetics in assays with the same binding affinity and biological role [1]. Biosimilars are required to demonstrate high analytical similarity, pharmacokinetic (PK), and pharmacodynamic (PD) similarity, and equivalent efficacy and safety to the reference biological. The advent of biosimilars has transformed our ability to bring biologic therapy to patients with psoriasis in a whole new way, particularly from a cost perspective, and they are now in the process of gaining approval in the United States (US). One of the most alluring features of the introduction of so-called biosimilars is the potential to lower production costs and expand the coverage of this kind of medicine to a larger number of patients. The lower cost of biosimilars makes them more favorable as a first-line treatment option compared with conventional systemic choices and new anti-interleukins; however, consensus and clinical guidelines are needed to strengthen their positioning [2]. According to reports, the adoption of biosimilars has grown over time and varied significantly throughout the UK and Ireland; when compared to other TNFi medications, adalimumab had the highest rate of biosimilar uptake [3]. In dermatology, while biologics are widely prescribed, dermatologists tend to be more hesitant to prescribe biosimilars compared to other specialists. In dermatology, biosimilars received approval for managing psoriasis and hidradenitis suppurativa [4]. Tumor necrosis factor (TNF) inhibitors make up a significant portion of dermatological medications used for psoriasis and are recommended as first-line treatments in specific situations. Multiple biosimilar medications derived from the anti-TNF agents adalimumab, infliximab, and etanercept are currently accessible for patients with psoriasis [5]. In the European Union, biosimilars have seen rapid uptake, with some countries achieving over 90 percent penetration for agents like adalimumab and infliximab within a span of a few years.

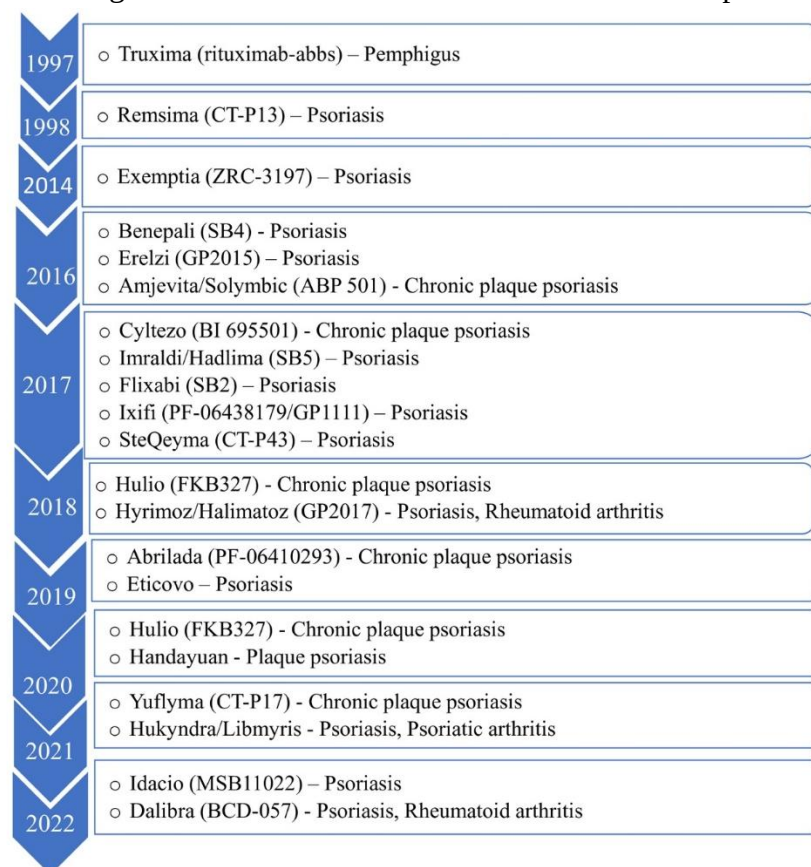


Figure 1. Timeline chart of biosimilar introductions in dermatology.

Rituximab biosimilars reached almost 50 percent market share in top European Union markets, with the United Kingdom (UK) and the Netherlands surpassing 90 percent penetration <https://nanobioletters.com/>

within a year of launch [6]. In the United States (US), biosimilars account for approximately 23 percent of the total biologics market volume. These figures clearly indicate that Europe has integrated biosimilars into clinical practice more rapidly and extensively, while adoption in the US remains slower. The adoption of biosimilars is often hindered by the nocebo effect, whereby negative patient expectations are often amplified by the physician's uncertainty or inadequate framing, leading to higher discontinuation rates. Additionally, the physician's skepticism and low awareness stemming from limited education and promotional outreach by the biosimilar manufacturers further slow the uptake relative to the originator biologics. Also, the market exclusivity strategies involving patent protections and aggressive counter-detailing by originator firms delay biosimilar penetration despite the clinical comparability [7]. The detailed timeline chart of biosimilars introduction in dermatology is represented in Figure 1, and the comparison between the originator biologics and biosimilars has been represented in Table 1.

Table 1. Comparison between the originator biologics and biosimilars.

Characteristics	Biologics (Originator)	Biosimilars	Reference
Unique attributes	A new treatment naturally generated by living organisms	Equivalent to biologics, though not the same	[8]
Production procedure	Produced by a complex biological process in host cell lines	Produced by a complex biological process in host cell lines	[9]
Development period and cost	Takes about 12-15 years to develop and costs approximately~ \$ 1.2-1.3 billion. Cost is higher due to complexity and development costs	Takes about 8-10 years to develop and costs \$100-200 million. Cost is lower, aiming to reduce healthcare costs	[10]
Pre-clinical testing	Necessitates a thorough preclinical evaluation	Comprehensive characterization is necessary, encompassing the mechanism of action (MOA) evaluations	[11]
Clinical development	Extensive clinical studies, including Phase I-III. Phase I studies in healthy subjects are required to evaluate safety, tolerability, and PK/PD. Phase II studies are required to be conducted, and Phase III demonstration of evidence is required for every intended indication	Extensive clinical studies, including Phase I and III. Phase I includes demonstration of PK/PD similarity, Phase II studies are not required, and Phase III is necessary in at least one representative indication, with extrapolation to others supported by scientific rationale.	[11]
Patent	Patentable (20 years of market exclusivity granted)	Non-patentable; introduced in the market after the originator's patent expiration	[8]
Interchangeability	Not interchangeable with other biologics	Some biosimilars may be interchangeable with their reference biological products	[12]
Purpose	Treat severe and life-threatening diseases	Increase access and lower cost to biologic treatments	[8]
Approval pathway	BLA 351(a)	BLA 351(k)	[13]
Approval requirements	Subject to rigorous regulatory standards and a full report of safety and efficacy investigation	Must meet exacting standards, undergo rigorous testing, and be highly similar to RP	[13]

2. Materials and Methods

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The last 5 years (2019 to 2024) of published reports were screened using keywords that included family name in anxiety, viz. “biosimilars in skin disorders” and “biosimilars in dermatology” and “Adalimumab biosimilars in dermatology” and “etanercept biosimilars in dermatology” and “Infliximab biosimilars in dermatology” and

“Rituximab biosimilars in dermatology” and “Ustekinumab biosimilars in dermatology”. A total of 1,144 Scopus-indexed articles retrieved from the Scopus database (ScienceDirect), PubMed, and Google Scholar were screened for information relevant to anxiety, and the gist of 106 selected articles has been presented in this review. The literature search results are illustrated in Figure 2.

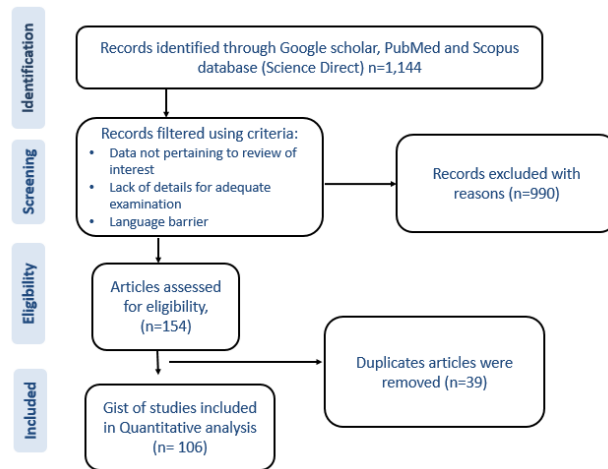


Figure 2. PRISMA flow diagram for screening and selection of literature.

3. Results and Discussion

3.1. Healthcare burden of skin disorders.

3.1.1. Incidence and prevalence of skin disorders.

Skin disorders rank fourth in terms of all human diseases among the leading causes of disease burden worldwide, which include non-communicable diseases, infectious, maternal, neonatal, and nutritional disorders, injuries, and skin and subcutaneous diseases. These impact nearly one-third of the global population, but despite their prominence, their burden is frequently underestimated [14]. People of different ages and socioeconomic backgrounds are impacted by the more than 3000 skin-related diseases that have been identified, both acute and chronic. Skin cancer is one of the potentially fatal ones. But even when this isn't the case, they can nevertheless put a significant financial and quality-of-life burden on patients [15]. According to a study, the leading 10 skin disorders, ranked by their disability-adjusted life years, include Dermatitis, Acne, Psoriasis, Urticaria, Fungal Skin Disease, Viral Skin Disease, Scabies, Melanoma, Pyoderma, and Cellulitis, as reported by the Global Burden of Disease. As per a report, from 2015 to 2020, dermatitis, psoriasis, and melanoma accounted for 29.69% of all articles in PubMed. Of the total articles, the remaining seven skin conditions accounted for just 6.79% [16]. Skin conditions, including connective tissue diseases (scleroderma, morphea, dermatomyositis, primary Sjögren syndrome, and systemic lupus erythematosus), pityriasis rosea, genital herpes, condyloma acuminatum, hidradenitis suppurativa, herpes zoster (excluding children), erythromelalgia, venous stasis syndrome, and venous ulcers, are noted to be more common in females. Psoriasis and psoriatic arthritis, lentigo maligna, squamous cell carcinoma, and basal cell carcinoma (with the exception of females aged ≤ 40 years) were more common in men. Although the exact causes of the sex-based differences in skin and skin-related disease development are still mostly unknown, they are probably complex. Differences in skin layers and physiology, sex hormones, heredity, age, race or ethnicity, lifestyle, and occupation are among the variables that may be considered [17].

3.1.2. Risk factors.

Numerous risk factors that can differ depending on lifestyle, genetic, environmental, and regional factors can have an impact on skin problems. Due to their immature immune systems, children are more vulnerable to infectious skin diseases, and women may be more vulnerable to rosacea and lupus-related skin disorders as a result of hormonal changes [18]. Psoriasis, vitiligo, and eczema are among the conditions that frequently have a hereditary component. Certain conditions, such as acne or melasma, can also be worsened by hormonal changes, such as those that occur during adolescence or pregnancy [19]. Sun exposure remains a major risk factor for photoaging, sunburn, and melanoma. Extreme climatic conditions, including high humidity or cold temperatures, can make bacterial or fungal infections and inflammatory diseases like scabies and eczema more common, especially in susceptible groups [14]. Infectious skin conditions, such as pyoderma, scabies, and fungal infections, can result from poor hygiene. Conversely, excessive use of corticosteroids or cosmetics without appropriate supervision can damage the skin barrier and lead to conditions like dermatitis [20]. Pellagra, dermatitis, and pigmentation disorders have all been linked to specific nutritional deficiencies, including those in vitamins A, B3, B12, and minerals like iron [21].

3.2. Pharmacoeconomics of biosimilars.

Over the past three decades, the burden of non-infectious skin conditions, including dermatitis, urticaria, and psoriasis, as well as infectious skin conditions like scabies, fungal skin disease, and bacterial skin disease, has increased. Due to the significant prevalence of skin and subcutaneous disorders, national programs and health policies must give them the attention they deserve [22]. The burden of skin disorders comprises their high frequency and the long-term morbidity that goes along with them, such as intense itching (as in urticaria and atopic dermatitis) or deformity (as in leprosy). Psoriasis is among the widespread chronic inflammatory skin disorders, and new therapies such as biologics come with a high cost. Certain healthcare systems might encounter financial difficulties due to the elevated prevalence of skin cancer and the associated treatment costs. With the average life expectancy of the world's population increasing, this is likely to deteriorate further [23]. Significant stigma and psychological and socioeconomic costs are frequently caused by skin illnesses, not only for those who have personal experience but also for their families, caregivers, and communities. According to estimates, 42.9 million Disability-Adjusted Life Years (DALYs) were caused by all forms of skin and subcutaneous disorders in 2021; 93% of these years were spent with a handicap. Compared to disorders of any other organ of the body, skin diseases have a greater impact on people's mental health and social interactions because of their high visibility. Despite numerous initiatives that have drawn attention to specific skin conditions, no systematic effort has acknowledged the overall healthcare burden of skin disorders [24]. A study focusing on Canadian healthcare expenditures for skin conditions revealed that the average cost per case rose from 188.88 CAD in 2018 to 246.25 CAD in 2022 (7.59% annually), with skin and subcutaneous infections representing the highest expense among diagnostic categories [25]. There have been reports of daily price increases for medications like apremilast and adalimumab, which have increased the financial load on Medicare programs [26]. A UK-based health economic analysis including psoriasis patients found that biosimilar adalimumab saves significant money without compromising effectiveness. Adalimumab biosimilars MSB11022 (Idacio®) and subcutaneous methotrexate were compared using a cost-per-responder approach.

Idacio's cost-effectiveness at week 52 is similar to that of subcutaneous methotrexate. Biosimilar medications can now be started earlier in the treatment of moderate-to-severe psoriasis and are a more accessible therapeutic option due to their declining costs [27]. Adalimumab biosimilars, risankizumab, and ixekizumab may actually be the best course of treatment, according to the cost-effectiveness analysis results that account for approximate discounts [28]. According to a study on the use of biologic anti-inflammatory drugs in the US population, biosimilars are currently used in relatively small amounts; however, as more biologics enter the market, differences in the use of biologics with similar indications and between biologic originators and biosimilars are likely to increase [29]. The Veterans Health Administration (VA) saved more than 67 million dollars in 2023 by using six currently approved biosimilars for all indications [30].

3.3. Current impact of biosimilars in skin disorders globally.

With biosimilars of infliximab, etanercept, and adalimumab in the arenas of rheumatology, gastroenterology, and dermatology, as well as rituximab, trastuzumab, and bevacizumab in the domains of cancer, the introduction of biosimilar monoclonal antibody medications has been a noteworthy development [31]. The introduction of biosimilar versions of biologic drugs used to treat skin conditions is expected to affect the economy and change dermatologists' prescribing habits. Particularly in Europe, where the experience is longer, biosimilars have generated notable cost reductions and market-share gains. The details vary depending on the country's incentives and drug prescribing policies. The Biologics Price Competition and Innovation Act (BPCIA), which created a simplified approval process for biosimilars, granted the FDA the authority to approve biosimilars in 2010. Numerous biosimilars have received FDA approval and gone on sale since the BPCI Act was passed. For biosimilars currently on the US market, the degree of savings and market share growth has not been achieved. It is unknown to what extent the US biosimilar market share will grow, and to what extent market share will increase in the US remains to be determined [6].

3.4. Current biosimilars used in dermatology.

Biosimilar versions of etanercept, adalimumab, infliximab, and rituximab are currently authorized for treating skin disorders such as psoriasis, psoriatic arthritis (PsA), hidradenitis suppurativa (HS), and pemphigus vulgaris [32]. Most biosimilar molecules in skin disorders were reported for psoriasis or psoriatic arthritis in individuals who had switched from the originator to the biosimilar, according to the screened literature. The details of biosimilar molecules reported in dermatology have been compiled in Table 2.

3.4.1. Adalimumab biosimilars.

Adalimumab, the first fully humanized monoclonal antibody targeting tumor necrosis factor alpha (TNF- α), has received the widest array of approvals among TNF- α blockers and has played a crucial role in the transformation initiated by the advent of biologics. The regulatory approval of Hyrimoz® (GP2017) is supported by the confirmation that it shares analytical, functional, and clinical similarities with Humira® (REF-ADL) [33]. The US Food and Drug Administration and/or the European Medicines Agency have approved eight biosimilars of adalimumab (ABP 501, BI 695501, SB5/GP2017, FKB327, MSB11022, PF-06410293, and CT-P17) for psoriasis treatment, and additional ones are currently under review

[34]. After successful marketing authorization applications and the recent expiration of originator patent protection, a number of adalimumab biosimilars have so far made their way onto the EU market [35]. In 367 Chinese patients with moderate-to-severe plaque psoriasis, a randomized, double-blind phase III study showed that SCT630 and adalimumab were equivalent in terms of effectiveness, safety, and immunogenicity [36]. One authorized biosimilar of adalimumab is SB5. It was mostly used to treat rheumatoid arthritis, but its efficacy data were extrapolated to other conditions like psoriasis, Crohn's disease, or ulcerative colitis. Switching from reference adalimumab to SB5 was not linked to changes in efficacy or clinical consequences in either controlled or "real-world" situations, according to studies [37]. A study examining the effectiveness of adalimumab biosimilars in psoriasis patients found that outcomes for 410 patients receiving the biosimilars were similar to those documented for the original drug [38]. The median persistence of the adalimumab biosimilar SB5 in clinical practice was almost 2.5 years in British patients with severe psoriasis, indicating results that were equivalent to those of reference adalimumab [39]. Similarly, data from a Phase III study showed that BI 695501 and the reference adalimumab were equally effective, safe, and immunogenic in individuals with persistent plaque psoriasis [40]. In a study lasting sixteen weeks that examined adalimumab biosimilar agents for treating moderate-to-severe plaque psoriasis in patients, there was no notable difference in response rates between adalimumab biosimilar agents and their reference counterparts. The biosimilar drugs of adalimumab exhibit a safety and efficacy profile for psoriasis that is similar to that of their reference drugs [41]. However, switching from adalimumab to its biosimilars was linked to a higher discontinuation rate than staying on adalimumab, according to a multinational cohort study that included data from France, Britain, and Spain. As a result, patients on biosimilars were advised to receive closer monitoring and support [42]. In accordance with our hospital's biologics policies, patients in a single-center retrospective cohort study comprising seventeen patients with Hidradenitis Suppurativa were shifted from adalimumab biosimilar for non-medical reasons in order to increase pharmacoeconomic efficiency. In well-controlled patients, switching from the original adalimumab to a biosimilar may indicate issues with adherence and efficacy. Returning to the adalimumab originator seems to address the majority of issues [43]. A Danish cohort study that included 48 psoriasis patients revealed a similar finding [44].

3.4.2. Infliximab biosimilars.

A murine-human monoclonal antibody called infliximab is more effective than topical drugs like methotrexate, calcipotriol, and narrow-band UVB for treating moderate-to-severe psoriasis because it has a quicker onset of action and greater skin clearance. The US Food and Drug Administration (FDA) authorized it in 2006 to treat severe plaque psoriasis. In September 2013, the European Medicines Agency (EMA) authorized Remsima®, a biosimilar of infliximab that is less expensive than the original. Research has shown that infliximab and Remsima do not differ in safety, immunogenicity, or pharmacokinetics, and switching from infliximab to Remsima does not worsen the condition [45]. Empirical data show that switching from infliximab originator to CT-P13 did not affect overall clinical efficacy and safety in individuals with persistent plaque psoriasis [46]. The first biosimilar antibody, CT-P13, was licensed for psoriasis after randomized clinical trials showed it produced clinical outcomes comparable to the original infliximab (IFX) in rheumatoid arthritis. Biosimilar CT-P13 demonstrated outstanding efficacy as a first-line treatment, no clinical challenges after transitioning from IFX, and utility in patients who had not responded to other biologics in a

randomized clinical trial comprising Japanese patients [47]. However, a study evaluating the efficacy of switching psoriasis patients from the original medication to its biosimilar, infliximab (Remicade), found a worse effect in about 25% of patients, while quality of life declined in about 30% [48]. Infliximab and infliximab-abda administration were linked to comparable and noteworthy improvements in disease in a prospective cohort study of patients with hidradenitis suppurativa, indicating that infliximab-abda is probably a viable treatment option for hidradenitis suppurativa [49].

3.4.3. Etanercept biosimilars.

Etanercept, the initial TNF- α inhibitor approved for managing chronic plaque psoriasis in adults and children, is a recombinant tumor necrosis factor α (TNF- α) soluble receptor linked to the Fc region of human immunoglobulin G1 [50]. The safety and effectiveness of etanercept biosimilar SB4 were established in a 24-week study comprising patients with severe psoriasis and/or psoriatic arthritis who were attending Florence University's Psoriasis Center. The efficacy, particularly cutaneous symptoms, was unaffected by the originator-to-SB4 switch over a median observational duration of 24 weeks [51]. Similar safety and efficacy outcomes were noted in patients with inflammatory arthritis, including 26 patients with psoriatic arthritis [52]. A study found no significant differences in the safety or effectiveness of etanercept biosimilars between pediatric and geriatric populations; however, the latter group experienced higher rates of adverse events and dropouts [53]. A case study from Rome of 65 patients with plaque psoriasis, with or without psoriatic arthritis, found no significant differences between etanercept and its biosimilar DB4 across all analyzed parameters, confirming their equivalence [54]. Among eighty-seven psoriatic arthritis patients in an open-label study, SB4 was successful in keeping most of the patients at a state of low disease activity. Nonetheless, a statistically significant percentage of patients (11 participants) did not continue to have low disease activity at the conclusion of the trial. Nonetheless, a statistically significant percentage of patients (11 participants) did not continue to have low disease activity at the conclusion of the trial [55]. In another observational study, switching from the originator drug Etanercept to its biosimilar SB4 was successful in 74 percent of the patients, and most patients who stopped SB4 due to LOE had a clinically stable situation [56]. The combination treatment of rhTNFR-Fc with MTX was found to be efficacious in a randomized double-blind clinical trial in Chinese patients with moderate to severe plaque psoriasis, with a satisfactory safety and tolerability profile [57].

3.4.4. Ustekinumab biosimilars.

In patients with moderate to severe plaque psoriasis, the ustekinumab biosimilar CT-P43 demonstrated comparable efficacy to the original ustekinumab in a 28-week phase III study that was randomized, double-blind, and included similar pharmacokinetic, safety, and immunogenicity profiles [58]. Overall, treatment-emergent adverse effects were similar for both the original medication, ustekinumab, and SB17 in a similar double-blind phase III study enrolling patients with moderate to severe plaque psoriasis [59]. The study confirmed the pharmacokinetic biosimilarity between QX001S and ustekinumab, with considerable inter-subject variability, by examining the tolerance, variability, and pharmacokinetics (PK) of QX001S, a biosimilar for ustekinumab, in a group of healthy Chinese men. In a 52-week, multicenter, double-blind study with 581 patients with moderate-to-severe chronic plaque

psoriasis, the incidence of ustekinumab antibodies had no clinically significant effect, and AVT04 was found to be therapeutically equivalent to ustekinumab over the course of the study [60]. A 52-week randomized, double-blind clinical trial evaluating the ustekinumab biosimilar ABP 654's efficacy and safety in patients with moderate-to-severe plaque psoriasis found no change in efficacy, safety, or immunogenicity when switching from ustekinumab to ABP 654, concluding that there were no clinically significant differences between ABP 654 and ustekinumab [61].

3.4.5. Rituximab biosimilars.

The anti-CD20 monoclonal antibody rituximab is an example of B-cell depletion therapy and has served as a model for developing biosimilars and other anti-CD20 monoclonal antibodies [62]. A study involving a cohort of 52 patients compared the safety and efficacy of the biosimilar (Truxima) and the originator (MabThera) rituximab in individuals with pemphigus. To assess effectiveness, research on the duration until total remission and overall steroid usage for six months' post-rituximab treatment revealed no notable differences between the two groups [63]. Research examining clinical effectiveness and safety information in 12 individuals with pemphigus vulgaris indicated that the Rituximab biosimilar Rixathon is safe for the patients [64]. In a prospective observational study of 110 pemphigus vulgaris patients, biosimilar rituximab produced favorable safety and efficacy results in both newly diagnosed and previously treated patients [65]. In a retrospective investigation of long-term efficacy and safety, 76 Indian patients with pemphigus showed total clinical remission [66].

Table 2. Biosimilars in dermatology that have been approved by various regulatory authorities.

Medicinal category	Originator drug	Biosimilar	Biosimilar proprietary name	Approval country	Date of first approval	Skin disorder	Reference
Anti-TNF agent	Adalimumab	GP2017	Hyrimoz	US	Oct. 30, 2018	Psoriasis	[67]
			Amgetiva/Solymbic	EU	Mar. 22, 2017	Psoriasis	[68]
			Hefiya	US	Jul. 26, 2018	Psoriasis	[68]
			Halimatoz	EU	Oct. 2018	Rheumatoid arthritis, Plaque psoriasis	[69]
Anti-TNF agent	Adalimumab	AVT02	Simlandi	US	Feb. 23, 2024	Chronic plaque psoriasis	[70]
			Simlandi	Canada	Jan. 5, 2022	Plaque Psoriasis, Psoriatic arthritis	[71]
			Hukyndra	EU	Nov. 15, 2021	Severe chronic plaque psoriasis in children	[72]
			Libmyris	EU	Nov. 12, 2021	Active and progressive psoriatic arthritis in adults	[70]
			Ciptunec, Ardalicip	Australia	Nov. 14, 2022	Moderate to severe ulcerative colitis in adult patients	[73]
Anti-TNF agent	Adalimumab	MSB11022	Idacio	US	Dec. 14, 2022	Chronic plaque psoriasis	[27,74]
			Idacio	EU	Apr. 2, 2019	Active and progressive psoriatic arthritis in adults	

Medicinal category	Originator drug	Biosimilar	Biosimilar proprietary name	Approval country	Date of first approval	Skin disorder	Reference
Anti-TNF agent	Adalimumab	ABP501	Amjevita	US	Sep. 23, 2016	Chronic plaque psoriasis	[74]
			Amjevita/Solymbic	EU	Mar. 2017		
Anti-TNF agent	Adalimumab	SB5	Imraldi	EU	Aug. 24, 2017	Chronic plaque psoriasis; Hidradenitis suppurativa	[68,74]
			Hadlima	US	Jul. 23, 2019	Chronic plaque psoriasis	[68]
Anti-TNF agent	Adalimumab	BI 695501	Cyltezo	US	Aug. 25, 2017	Chronic plaque psoriasis	[34]
			Cyltezo	EU	Nov. 17, 2017		
Anti-TNF agent	Adalimumab	FKB327	Hulio	US	Jul. 6, 2020	Chronic plaque psoriasis	[34,75]
		FKB327	Hulio	EU	Sep. 17, 2018		
		PF-06410293	Abrilada	US	Nov. 15, 2019	Chronic plaque psoriasis	[34,75]
		PF-06410293	Abrilada	EU	Nov. 15, 2019		
		CT-P17	Yuflyma	US	May 23, 2023	Chronic plaque psoriasis	[34]
		CT-P17	Yuflyma	EU	Feb. 11, 2021		
		ZRC-3197	Exemptia	US	Dec. 9, 2014	Psoroasis	[30]
		BCD-057	Dalibra	Russia	2019	Rheumatoid arthritis and psoriasis	[76]
		HLX03	Handayuan	China	Dec., 2020	Plaque Psoriasis	[77]
		SCT630	Not assigned (still under development)	Not Applicable	Not Applicable	Plaque psoriasis	[36]
Anti-TNF agent	Infliximab	CT-P13	Remsima	EU	Aug. 24, 1998	Psoroasis	[45]
			Inflectra	US	Apr. 05, 2016	Psoroasis	[68]
		SB2	Flixabi	EU	May 26, 2016	Psoroasis	[68]
			Renflexis	US	Apr. 21, 2017	Psoroasis	[68]
		PF-06438179/G P1111	Ixifi	US	Dec. 13, 2017	Psoroasis	[61]
Anti-TNF agent	Etanercept	SB4	Benepali	EU	Jan. 14, 2016	Psoroasis	[45,46]
			Eticovo	US	Apr. 25, 2019	Psoroasis	[68]
		GP2015	Erelzi	US	Aug 30, 2016	Psoroasis	[46,68]
Interleukin inhibitor	Ustekinumab	CT-P43	SteQeyma	US	Dec. 17, 2017	Psoroasis	[58]
			SteQeyma	EU	Aug. 22, 2024	Psoroasis	[58]
		AVT04	Uzpruvo	EU	Jan. 05, 2024	Plaque psoriasis, Pediatric Plaque psoriasis, Psoriatic arthritis	[78]
		AB654	Uzpruvo	US	Oct. 18, 2024	Plaque psoriasis, active psoriatic arthritis	[79]
CD20-directed cytolytic antibody (monoclonal antibody)	Rituximab	rituximab-abbs	Truxima	US	Nov. 26, 1997	Pemphigus	[62,63]
		CT-P10	Truxima	US	Nov. 28, 2018	Rheumatoid arthritis	[62]
		rituximab-pvvr	Ruxience	US	Jul. 23, 2019	Pemphigus vulgaris	[62]
		rituximab-arrrx	Riabni	US	Dec. 17, 2020	Granulomatosis with Polyangiitis	[62]
		rituximab-arrrx	Riabni	EU	Mar. 07, 2020	Granulomatosis with Polyangiitis	[62]

3.5. Regulatory guidelines associated with biosimilars in dermatology.

Dermatology guidelines are subject to broader biosimilar laws; biosimilars receive special consideration for topical, systemic, and immunologic treatments frequently used in dermatology. An accelerated pathway for biosimilars has been established in the United States by Section 351(k) of the Public Health Service (PHS) Act [80]. The U.S. Food and Drug Administration (FDA) requires analytical studies (comparability in structure and function), animal studies (if necessary), and clinical studies (PK/PD, efficacy, safety, and immunogenicity) for many biosimilars used in dermatology in the United States (e.g., adalimumab, etanercept, and infliximab) for the treatment of psoriasis and atopic dermatitis. An interchangeable biosimilar is a type of biosimilar that meets additional requirements specified by law, allowing the FDA to approve both biosimilar and interchangeable biosimilar medications. A pharmacist can substitute such a product for the original without consulting the prescriber, similar to how generic drugs are substituted for brand-name drugs. This practice, known as pharmacy-level substitution, is governed by state pharmacy laws. Both biosimilars and interchangeable biosimilars are as safe and effective as the original biologic they are compared to. Health care professionals can prescribe either type of product in place of the original biologic. The FDA suggests more research to show that switching between reference and biosimilar products has no effect on efficacy or safety [81, 82]. With an emphasis on stepwise comparability (quality, nonclinical, and clinical characteristics) and sensitive clinical models for endpoints like PASI for psoriasis, the European Medicines Agency (EMA) has approved a number of biosimilars used in dermatology [83]. As long as there is scientific data to support it, EMA allows indications to be extrapolated if the mechanism of action and receptor targets are the same across indications (essential for medications like infliximab) [84]. Through its important publication, the WHO recommendations on Evaluation of Similar Biotherapeutic Products (SBPs), the WHO offers a framework for nations creating their own biosimilar criteria. Through comparative investigations, it focuses on safety, efficacy, and quality, as well as the global harmonization of terminology and fundamental standards [85]. Clinical studies are advised in India by the Central Drugs Standard Control Organization (CDSCO) in its regulatory guidelines on comparable biologics, unless they are waived in the country's population. Guidelines for biosimilars that are relevant to dermatology center on immunogenicity and comparable PK/PD; they also permit the extrapolation of indications if justified [86]. Japan needs safety data, quality equivalency, and comparative research in accordance with ICH recommendations. Moreover, if relevant to the Japanese population, it accepts clinical data from other countries [87]. The worldwide regulatory guidelines pertaining to biosimilars in dermatology are represented in Figure 3, and a comparison between the biosimilar guidelines of the FDA and EMA is presented in Table 3.

Table 3. Comparison of biosimilar guidelines (FDA vs. EMA).

S.No	Aspect	FDA (US)	EMA (EU)	Reference
1	Analytical similarity	Totality of evidence, extensive multi-tier structural and functional comparison to show high similarity, minor differences in inactive components allowed	Stepwise comparability exercise with broad physico-chemical, followed by <i>in vitro</i> functional testing; scope tailored to product class	[88]
2	Role of PK/PD and when efficacy trials can be waived	Clinical pharmacology (PK ± sensitive PD) is typically the most sensitive clinical test; robust analytics, including PK/PD and immunogenicity, may support no separate efficacy trial	Converging toward a tailored approach: with strong analytics, PK/PD, and clear MoA, comparative efficacy trials may be waived more broadly	[89]

3	Clinical endpoints (if an efficacy study is needed)	Use sensitive endpoints and populations to detect potential differences (equivalence/NI margins justified historically); comparative immunogenicity expected	Same sensitivity principle; endpoints/populations chosen for assay sensitivity; equivalence/NI margins justified; immunogenicity, along with RMP required	[89]
4	Extrapolation of indications	Allowed with scientific justification from the totality of evidence: shared MoA, PK/PD, immunogenicity, and pathophysiology across uses	Same principle; justification considers MoA, functional assays, PK/PD, immunogenicity, and disease differences	[90]

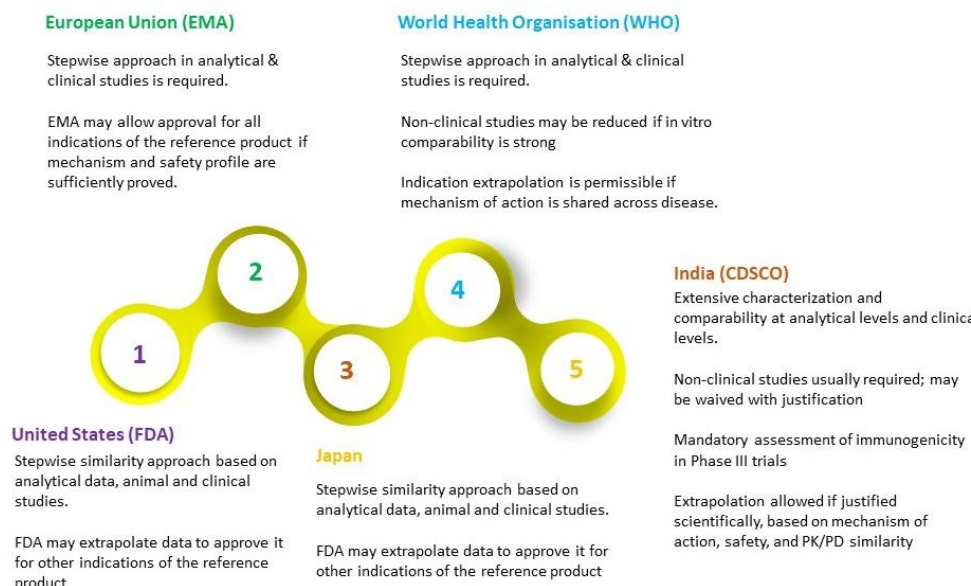


Figure 3. Worldwide regulatory guidelines pertaining to biosimilars in dermatology.

4. Conclusions

Biosimilars can lower the cost of biologic treatment by using reverse engineering to produce a product very similar to an original drug after the patent expires. Biosimilars seem to provide a generally safe, well-tolerated, and effective therapeutic option for individuals with skin conditions. The availability of biosimilar medications lowers the possibility of a princeps drug supply disruption, but their primary economic benefit is lowering the price of expensive princeps biological medications. It is anticipated that as biosimilars are used more frequently, treatment costs will decrease and long-term low pricing will be maintained. This should theoretically allow more patients to have wider access to therapy through reinvestment of savings. The early concerns about switching from princeps to a biosimilar for a particular patient have gradually subsided with the gained clinical experience.

Prescribers must comprehend the development and approval processes of biosimilar medications, and in certain nations, doctors must inform patients of the distinctions. This approach has been supported by literature created by the European Commission and EMA. To help patients and doctors overcome their hesitation and support the continued use of biosimilars for therapy, additional education is required. Using simple, patient-friendly language allows health professionals to reassure patients that replacing a reference product with a biosimilar is both safe and effective. Future research should prioritize strategies to improve patient education and awareness, as misconceptions and the nocebo effect remain barriers to biosimilar acceptance. It is equally important to understand the complex dynamics of insurance coverage, including formulary placement, reimbursement policies, and patient out-of-pocket expenses.

These factors critically influence the real-world uptake of biosimilars. Moreover, global inequities in biosimilar regulation, availability, and affordability persist, particularly in low- and middle-income countries. Addressing these gaps through targeted policy analysis and international collaboration is essential to ensure equitable access to biosimilar therapies worldwide.

Author Contributions

Conceptualization, U.K.; methodology, U.K.; validation, N.C., D.K.C. and S.R.M.; writing—original draft preparation, A.A.; writing—review and editing, M.N.; visualization, U.K.; supervision, U.K. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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