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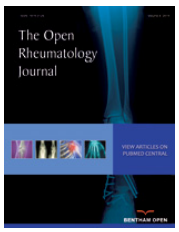

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REVIEW ARTICLE

Regulatory Perspectives on Biopharmaceuticals for Chronic Inflammatory Diseases in North Africa: A Narrative Review

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Abstract: Introduction of innovative biopharmaceuticals has dramatically changed the treatment of chronic inflammatory diseases, but access to these very effective agents may be limited by economic constraints in some regions. The development of biosimilar products at a lower cost may allow wider access to treatment, but rigorous scientific evaluation is required to ensure similar quality, efficacy, and safety. The World Health Organization, European Medicines Agency, and United States Food and Drug Administration have created stringent guidelines for biosimilar regulatory approval, stipulating that high similarity be demonstrated in comprehensive comparability studies. Although these regulatory standards have been adapted in many countries, the legal/regulatory frameworks required for biosimilar authorization remain in development elsewhere, including North Africa. In some countries, "intended copies" are available despite inadequate evidence of comparability to the reference product and failure to satisfy biosimilar regulatory requirements. In North Africa, as the regulatory pathway for biosimilars is established, regulators will address several important challenges, including criteria for comparability, switching/substitution, post-marketing monitoring/risk management, and product naming conventions. Caution is advised to ensure that lower cost and broader access are not achieved at the expense of patient safety, and educational initiatives should be undertaken for clinicians/patients. In this review, we define the various types of biopharmaceuticals currently available for the treatment of chronic inflammatory disease, provide an overview of regulatory requirements for biosimilar approval and an update on the availability of these agents globally and in North Africa, and discuss crucial concerns related to their use from the viewpoint of North African rheumatologists.

Keywords:: Rheumatic diseases, Biopharmaceutical, Biosimilar, Intended copy, Switching, Chronic inflammatory.

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1. INTRODUCTION

By the end of the 20th century, advances in science and technology facilitated the development of complex biological molecules capable of modifying intercellular signaling pathways using a targeted approach not previously achieved with chemically synthesized drugs [1]. These innovations brought a class of biopharmaceuticals that revolutionized the treatment paradigm for a wide range of chronic inflammatory diseases. Produced biologically with living cell-line cultures and recombinant DNA methods, monoclonal antibodies and fusion proteins that target Tumor Necrosis Factor alpha (TNFα) and other pro-inflammatory mediators have been shown to effectively control symptoms in patients with rheumatologic, gastroenterologic, and dermatologic inflammatory conditions who fail to respond to conventional first-line therapies [2 - 6]. However, the research and development costs for biologic agents are very high [7], as reflected in the market price, and, with increasing evidence and recognition of their effectiveness, they have become more extensively prescribed, leading to escalating healthcare costs [8].

Over the past decade, patent expiration for the anti-TNFα biologic agents adalimumab, etanercept, and infliximab, and the B cell-directed monoclonal antibody rituximab, created the opportunity for the development of "biosimilar" products, which are similar (but not identical) to the original biologics in protein structure, biologic activity, efficacy, and safety. Because research and development costs are lower for bio-

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similars than for original biologics, their introduction allows greater access to biologic treatment for more patients [9]. The World Health Organization (WHO) [10], the European Medicines Agency (EMA) in the European Union (EU) [11], and the Food and Drug Administration (FDA) in the United States (US) [12] have provided important guidance on biosimilarity and well-respected regulatory frameworks for biosimilar authorization. However, regulatory pathways and standards for biosimilars are still being formulated in many countries and, when available, may differ regionally and nationally. Moreover, in some countries, copies of reference products have been introduced without market authorization, without the guidance of experts, and without satisfying the rigorous regulations for biosimilars established to protect patient safety [13].

Many challenges posed by biosimilars are shared worldwide, while others may be specific to individual countries or regions. In the North African countries of Algeria, Morocco, and Tunisia, a regulatory framework for biosimilar approval remains in development. Few biosimilars for rheumatic diseases are currently available in North Africa and clinicians in this region have limited experience in prescribing them. Biosimilar use in clinical practice varies among Western countries and will likely also differ among countries in North Africa when these agents become more broadly available in the region. With limited biosimilar experience in North Africa, it is imperative that Healthcare Professionals (HCPs) gain a thorough understanding of these agents and the implications of their use. The objectives of this narrative review are to define and describe the various classes of currently available biopharmaceuticals; summarize current regulatory requirements and provide an update on approval, globally and in the North African region; and present key issues related to biosimilar use from the perspective of practicing rheumatologists in North Africa. Although many differences and similarities in clinical practice are evident between Western countries and North African countries, and may be of interest, such a comparison is beyond the scope of the current review.

2. BIOPHARMACEUTICALS IN CHRONIC INFLAMMATORY DISEASES: OVERVIEW

2.1. Background/Definitions

Biologic agents are large molecules derived from living cells, usually manufactured using recombinant DNA or other biotechnologies. These agents (*i.e*., reference, originator, or innovator products) have greater complexity than chemically synthesized drugs because of their structural heterogeneity and specific activity within biologic systems, and their cost is usually higher [5, 14, 15]. Biologic Disease-Modifying Anti-Rheumatic Drugs (bDMARDs) such as anti-TNFα agents are very effective in the treatment of chronic immunoinflammatory diseases [4, 16, 17], but access is limited in many regions, including North Africa, partly because of cost constraints [18, 19].

Pharmaceutical companies are developing biosimilar versions for regulatory approval and introduction into global markets. Because of the natural inconsistencies in biologic sources and the unique, intricate (and usually proprietary) processes involved in engineering biologics, biosimilar manufacturers are unable to precisely replicate reference products [20]. Rigorous evaluation of biosimilars is thus required to establish their similarity to reference products in chemical structure, biologic activity, and clinical profile.

Although currently available in some countries, intended copies (*i.e*., non-comparable biologics or biomimics) are not supported by adequate evidence of comparability with reference products and fail to satisfy the requirements for biosimilarity established by regulatory authorities [13]. Certain intended copies have received regulatory approval based on generic drug standards [13].

2.2. Regulatory Pathways

Generic drugs are typically small, easily characterized molecules manufactured by chemical synthesis to produce exactly the same molecules as their respective reference products. Therefore, the demonstration of bioequivalence between generic and reference products in bioavailability studies is sufficient to assume therapeutic equivalence [10]. However, this approach is inappropriate for biosimilars as reference biologics are larger, more complex molecules that are more difficult to characterize and have clinical profiles that may be influenced by the manufacturing process. Consequently, biosimilar agents are not considered generics of biologics and are required to undergo more extensive investigation than generic drugs to obtain regulatory approval. To demonstrate biosimilarity, differences between biosimilar and reference products can be no greater than those expected between different batches of the same reference product and cannot affect the biosimilar's safety or efficacy.

In 2009, the WHO Expert Committee on Biological Standardization established global guidelines for evaluation and regulation of biosimilars [10, 21], which are reflected in a broad range of regional/national regulatory standards (Table **1**). The WHO authorization process for biosimilars requires data from stepwise comparability exercises, including quality, non-clinical, and clinical studies. Similarly, for the EMA, comprehensive comparability studies must be conducted to demonstrate high similarity between the biosimilar and reference product in structure, biologic activity, safety, immunogenicity, and efficacy (Fig. **1**) [11, 20]. In the US, licensure by the FDA requires a robust characterization of the biosimilar based on a "totality of evidence" [22, 23], with sufficient clinical data to support the biosimilar's "safety, purity, and potency" when administered for one or more of the indications of the reference product.

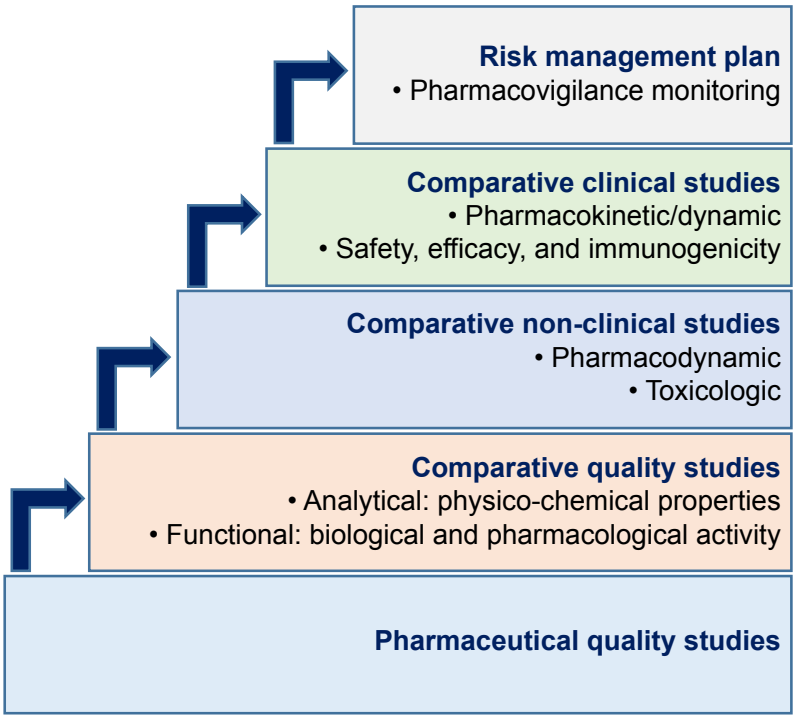

Fig. (1). Stepwise biosimilar development program required by European Medicines Agency guidelines [11,20].

Table 1. Summary of key regulatory pathways and requirements for biosimilar approval.

Requirement	Regulatory authority		
	WHO[a-c]	EMA (EU)[d,e]	FDA (US)[f-i]
Approval pathway/ development	• Reference product (RP) must be licensed in region/ country where biosimilar approval is sought • Biosimilar authorization is based on a stepwise comparability exercise o Quality studies: head-to-head comparisons of quality and heterogeneity (*e.g.*, physicochemical, biological, immunochemical properties); documented manufacturing process; stability studies o Non-clinical studies: Pharmacokinetic (PK), Pharmacodynamic (PD), and toxicological o Clinical studies: clinical comparability exercise (*i.e.*, PK/PD studies followed by pivotal clinical studies to show comparable safety/effectiveness/ immunogenicity) • Varying amounts of data may be requested by individual national regulatory authorities • Post-marketing surveillance is required	• Abbreviated approval pathway o EU-wide marketing authorization granted via centralized EMA procedures o Requires manufacturer submission of a Marketing Authorization Application (MAA) o MAA evaluated by EMA's Committee for Medicinal Products for Human Use, Pharmacovigilance and Risk Assessment Committee, and Biologics/Biosimilar Working Parties • Data required from stepwise comprehensive comparability studies o Pharmaceutical and comparative quality studies o Comparative non-clinical studies o Comparative clinical studies of safety/efficacy, PK/PD, and immunogenicity • If biosimilarity is shown, safety/efficacy findings from clinical trials of the RP may be used to support MAA o Allows for shorter and less costly drug development program • Post-marketing surveillance is required	• Abbreviated approval pathway o Created by the Biologics Price Competition and Innovation Act under the Affordable Care Act *in* 2010 (§351[k], Public Health Service Act)[j] o Requires manufacturer submission of a Biologics License Application (BLA) o BLA evaluated by the FDA's Centers for Drug/Biologics Evaluation and Research • Data required from 3 study types o Analytical studies (*e.g.*, physicochemical, functional properties) o Non-clinical studies (*e.g.*, toxicology) o Clinical studies (*e.g.*, PK, PD, immunogenicity) • If biosimilarity is shown, safety/efficacy findings from clinical trials of the RP may be used to support BLA o Allows for shorter and less costly drug development program • Post-marketing surveillance is required
Extrapolation	• If biosimilarity is shown, the biosimilar may obtain approval for other clinical indications of the RP, even if not directly assessed in clinical trials • Scientific justification required	• If biosimilarity is shown, the biosimilar may obtain approval for other clinical indications of the RP, even if not directly assessed in clinical trials • Scientific justification required	• If biosimilarity is shown, the biosimilar may obtain approval for other clinical indications of the RP, even if not directly assessed in clinical trials • Scientific justification required

(Table 1) contd.....

	Regulatory authority		
Requirement Interchangeability/ switching/ substitution	• No guidance • Practices to be defined by national authorities	• No guidance • Practices to be regulated by legislation in individual EU countries	• Interchangeability requires data from 3 transitions from reference to biosimilar product • Switching requires data from 1 transition from RP to biosimilar
Nomenclature	• Reference and related biosimilar products share same nonproprietary name (*i.e.*, the International Nonproprietary Name [INN]) • Reference and related biosimilar products will have unique "biological qualifier" (BQ) added to the INN (2015 proposal) o BQ = 4 random lower-case consonants • Example (fictitious) o SBP = replicamab-jnzt o RBP = replicamab-kngx	• Reference and related biosimilar products have distinct proprietary names • Reference and related biosimilar products share same nonproprietary name (*i.e.*, INN) • Example (actual) o Biosimilar = Remsima® (infliximab) o RP = Remicade® (infliximab) • Proprietary names and batch numbers should appear on product packaging	• Reference and related biosimilar products have distinct proprietary names • Reference and related biosimilar products have a non-proprietary proper name that combines a shared core name plus a unique suffix o Core name = the name selected by the US Pharmacopeial Convention for the active substance (same for biosimilar and RP) o Suffix = 4 random lower-case letters attached to the core name by a hyphen (distinct for biosimilar and RP) • Example (fictitious) o Biosimilar = replicamab-jnzt o RP = replicamab-kngx

[a]Reference [10]. [b]Reference [21]. [c]Reference [44]. [d]Reference [11]. [e]Reference [20]. [f]Reference [12]. [g]Reference [22]. [h]Reference [23]. [i]Reference [45]. [j]Reference [48]. EMA: European Medicines Agency; EU: European Union; US FDA: United States Food and Drug Administration; RP: reference product; WHO: World Health Organization.

2.3. Currently Approved Biosimilars for Chronic Inflammatory Diseases (EU/US)

Several biosimilars of the reference products adalimumab, etanercept, infliximab, and rituximab have been approved by the EMA or FDA, and many others are currently under review or in development (Table **2**). In addition, biosimilars or intended copies of these reference agents are marketed globally or are in a pre-market development phase outside the EU and US (Table **3**).

3. BIOSIMILARS FOR CHRONIC INFLAMMATORY DISEASES IN NORTH AFRICA

Countries in North Africa, including Algeria, Morocco, and Tunisia, have their own laws/regulations concerning registration of new pharmaceutical products but have not yet established legal/regulatory frameworks to help guide use of biosimilar products. In addition, no regional agency currently exists to provide overarching guidance on their regulation. In May 2018, the African Union adopted a treaty to establish the African Medicines Agency, but several important steps remain to be taken before this agency becomes a reality [24]. Indeed, a consensus on regulations may be difficult to achieve in this region because of between-country differences in healthcare systems and policies. Despite ongoing interest in these innovative agents, relatively few biosimilars are currently available for chronic inflammatory diseases in the region. North African regulatory authorities have not rushed biosimilar approvals as they assemble the necessary regulatory framework and await applications for suitable biosimilars.

3.1. Algeria

Biosimilar legislation is expected to be introduced soon in Algeria, based largely on the work of the country's expert committee in rheumatology. Launched in 2017 to oversee new product registration and approval, the National Agency of Pharmaceutical Products (ANPP) includes several expert committees of different specialties assembled to examine biosimilar registration applications. Relying in part on the recommendations of the WHO, EMA, and FDA, the ANPP will confirm that registered products satisfy biosimilarity, quality, efficacy, and safety standards; scrutinize manufacturing/marketing sites; and review post-marketing pharmacovigilance plans.

The Algerian Ministry of Health, Population, and Hospital Reform (MSPRH) routinely schedules meetings to allow review and discussion of product dossiers (including information on manufacturing, clinical/non-clinical study findings, and pharmacovigilance monitoring) by expert committee members. Meetings on biopharmaceuticals for rheumatic diseases include rheumatologists and other specialists involved in managing approved biologic/biosimilar products in their fields. The committee sends decisions regarding product approval/rejection to the Directorate of Pharmacy of the MSPRH, which makes the final decision and subsequently notifies applicants.

Biosimilars used in hematology, oncology, diabetology, and endocrinology have already been introduced in Algeria. In rheumatology, although several dossiers have been submitted, only a biosimilar of infliximab (Remsima®) has received marketing authorization (in 2017).

Table 2. Biosimilar approval status in the European Union (EU) and/or United States (US) for chronic inflammatory diseases.

Biologic reference product	Biosimilar product (proprietary name)	Regulatory authority					
		EMA			FDA		
		Status (date [month/year])	Company	Indication	Status (date [month/year])	Company	Indication
Adalimumab (Humira®)[a]	ABP 501 (Amgevita® [EU/US]; Solymbic [EU])	Approved (01/2017)	Amgen	CD, HS, JIA, Ps, PsA, RA, UC, uveitis	Approved (09/2016)	Amgen	AS, CD, JIA, Ps, PsA, RA, UC
	BI 695501 (Cyltezo® [US])	Approved (11/2017)	Boehringer Ingelheim	—	Approved (08/2017)	Boehringer Ingelheim	AS, CD, JIA, Ps, PsA, RA, UC
	SB5 (Imraldi®)	Approved (06/2016)	Samsung Bioepis	CD, HS, JIA, Ps, PsA, RA, UC, uveitis	—	—	—
	FKB327	MAA submitted (05/2017)	Fujifilm Kyowa Kirin Biologics	—	—	—	—
	GP2017	MAA submitted (06/2017)	Sandoz	—	—	—	—
	ONS-3010	In phase III development	Oncobiologics	—	In phase III development	Oncobiologics	—
	PF-06410293	—	—	—	In phase III (RA) development	Pfizer	—
	M923	—	—	—	In phase III (Ps) development (positive results reported in 2016)	Momenta Pharma-ceuticals	—
	CHS-1420	—	—	—	In phase III (Ps) development (positive results reported in 2017)	Coherus Biosciences	—
	N/A	In preclinical development	Adello Biologics	—	In preclinical development	Adello Biologics	—
	N/A	In pipeline	AET BioTech/ BioXpress Therapeutics	—	—	—	—
Etanercept (Enbrel®)[b]	SB4 (Benepali®)	Approved (01/2016)	Samsung Bioepis	axSpA, JIA, Ps, ped Ps, PsA, RA	—	—	—
	GP2015 (Erelzi®)	Approved (07/2017)	Sandoz	axSpA, JIA, Ps, ped Ps, PsA, RA	Approved (08/2016)	Sandoz	axSpA, JIA, Ps, ped Ps, PsA, RA
	CHS-0214/BAX 2200 [B]	—	—	—	Global phase III trials: Ps (RaPsODY) and RA	Coherus/ Baxalta (US)	—
	BX2922 [B/IC]	In development	BioXpress Therapeutics (Switzerland)	—	—	—	—
Infliximab (Remicade®)[c]	CT-P13 (Remsima® [EU]; Inflectra® [US])	Approved (09/2013)	Celltrion	AS, CD, Ps, PsA, RA, UC	Approved (04/2016)	Hospira	AS, CD, Ps, PsA, RA, UC
	SB2 (Flixabi® [EU]; Renflexis® [US])	Approved (05/2016)	Samsung Bioepis	AS, CD, Ps, PsA, RA, UC	Approved (04/2017)	Merck	AS, CD, Ps, PsA, RA, UC
	PF-06438179 (IXIFI™)	Approved (12/2017)	Pfizer	AS, CD, Ps, PsA, RA, UC	Approval recommended (03/2018)	Sandoz	AS, CD, Ps, PsA, RA, UC

(Table 2) contd.....

	STI-002	—	—	—	Phase III study in RA (05/2016)	Sorrento Therapeutics (US)	—
	NI-071	—	—	—	Phase III study in RA (RADIANCE; completion: 12/2018)	Sagent (US)	—
	N/A	In development	BioXpress Therapeutics (Switzerland)	—	—	—	—
	ABP 710	—	—	—	In development (positive results of functional similarity tests reported in 2017)	Amgen (US)	—
Rituximab (MabThera®/ Rituxan®)[d]	CT-P10 (Blitzima/ Ritemvia/Truxima [EU])	Approved (07/2017)	Celltrion	RA	BLA submitted (06/2017)	Teva/Celltrion	RA
	APB 798	—	—	—	In phase III (RA) development	Amgen/ Allergan	—
	APO-RITUX	—	—	—	In phase III (RA) development	Apotex (Apobiologix; Canada)	—
	PF-05280586	—	—	—	In phase III development	Pfizer (US)	—
	GP2013 (Rixathon/ Riximyo)	Approved (06/2017)	Sandoz (Switzerland)	RA	BLA rejected (05/2018)	—	—
	N/A [B]	In development	BioXpress Therapeutics (Switzerland)	—	—	—	—
	JHL1101	In development	JHL Biotech (China)		—	—	—
	N/A [B]	In development	Mabion (Poland)/ Mylan (Ireland)	—	—	—	—
	N/A	In development	Richter (Hungary)/ Stada (Germany)	—	—	—	—

[a]Reference [49]. [b]Reference [50]. [c]Reference [51]. [d]Reference [52].

AS: Ankylosing Spondylitis; axSpA: axial spondyloarthritis (non-radiographic axSpA and AS); [B]: Biosimilar; BLA: Biologics License Application; CD: Crohn's disease; EMA: European Medicines Agency; FDA: US Food and Drug Administration; HS: hidradenitis suppurative; [IC]: Intended Copy; JIA: Juvenile Idiopathic Arthritis; MAA: Marketing Authorization Application; N/A: Not Available; ped Ps: pediatric psoriasis (plaque); Ps: psoriasis (plaque); PsA: psoriatic arthritis; RA: Rheumatoid Arthritis; UC: Ulcerative Colitis..

3.2. Morocco

In the absence of laws or regulations on the use of biosimilars or intended copies, the Moroccan Drug and Pharmacy Directorate approves registered agents for chronic rheumatic diseases based on the opinion of an expert committee, including rheumatology/internal medicine pro-fessors and pharmacists. These experts examine evidence related to the product's manufacturing, structure and biological activity, safety/efficacy demonstrated in clinical studies, and plans for post-marketing pharmacovigilance. The Directorate's assessment is sent to the Moroccan Ministry of Health, the body responsible for final decisions regarding approval and pricing. In 2015, the Ministry of Health indicated that biosimilars are a better alternative for patients from a financial standpoint without providing more specific guidance. Remsima® is currently the only biosimilar authorized in Morocco.

The national safety institution and public/private insurance companies in Morocco currently provide reimbursement for biologic therapies according to treatment guidelines published for rheumatoid arthritis and ankylosing spondylitis, and as established by vthe Moroccan Society of Rheumatology [25, 26]. In these guidelines, biosimilars are mentioned as TNF-inhibitor options, with the same indications as the reference products, but no switching recommendations are offered.

3.3. Tunisia

The Tunisian Directorate of Pharmacy and Medicine is ultimately responsible for regulatory submissions and authorization of new products in Tunisia. The assessment process is multi-layered, involving the National Medicine Control Laboratory, specialized scientific commissions, and the Technical Committee for Proprietary Medicinal Products. With national regulations on biosimilars lacking, the Tunisian authorities apply procedures recommended by the WHO, EMA, and FDA. Several biosimilars for other diseases have been approved in Tunisia (*e.g.*, erythropoietin, filgrastim, and somatropin biosimilars). Remsima® was the first biosimilar for rheumatic disease to be introduced in Tunisia, generating discussion about its possible exclusive use given the country's current socioeconomic situation. Tunisian authorities recently revealed plans to approve the least expensive product, *i.e.*, Remsima® or Remicade®.

Table 3. Biosimilars and intended copies approved, or in development, outside of the European Union/United States (US) for chronic inflammatory diseases.

Biologic reference product	Biosimilar [B] / intended copy [IC] (proprietary name)	Status (date [month/year])	Company	Indication
Adalimumab (Humira®)[a]	ZRC3197 [IC] (Exemptia)	Approved in India (12/2014)	Zydus Cadila (India)	RA
	Adfrar [IC]	Approved in India (01/2016)	Torrent Pharmaceuticals (India)	AS, Ps, PsA, RA, UC
	ONS-3010 [B/IC]	In phase III development	GMS Tenshi (China, India, Mexico)	—
	LBAL [B/IC]	In phase III (RA) development	LG Life Sciences (Korea)/Mochida Pharmaceutical (Japan)	—
	BCD 057 [B/IC]	In phase III (Ps, RA) development	Biocad (Russia)	—
	PBP1502 [B/IC]	In phase I development	Prestige BioPharma (Singapore)	—
	N/A [B/IC]	In development	PlantForm (Canada)/ Axis Biotec Brasil (Brazil)	—
	N/A [B/IC]	In preclinical development	mAbxience (Spain)	—
	CT-P17	In pipeline	Celltrion (Korea)	—
Etanercept (Enbrel®)[b]	SB4 [B] (Brenzys®)	Approved in South Korea (09/2015), Australia (07/2016), Canada (08/2016)	Samsung Bioepis (Korea)/MSD (US)	axSpA, JIA, ped Ps, Ps, PsA, RA
	GP2015 [B] (Erelzi®)	Approved in Canada (08/2017)	Sandoz (Switzerland)	axSpA, JIA, ped Ps, Ps, PsA, RA
	HD203 [B] (Davictrel)	Approved in Korea (11/2014)	Hanwha Chemical (Korea)	AS, RA, Ps, PsA
	LBEC0101 [B]	Phase III trials ongoing in RA; filed for approval in Japan	LG Life Sciences (Korea)/Mochida Pharmaceutical (Japan)	—
	ENIA11 [B] (TuNEX®)	Registered (RA; Taiwan); Phase III trials in RA/AS (Japan, Korea)	Mycenax Biotech/ TSH Biopharm (Taiwan)	—
	CT-P05 [B/IC]	In development	Celltrion (Korea)	—
	AVGO1 [B/IC] (Avent™)	Patented in India (2010); similarity demonstrated in preclinical trials[e]	Avesthagen (India)	—
	Intacept® [B/IC]	Approved in India (03/2015)	Intas Pharmaceuticals (India)	AS, JIA, RA, Ps, PsA
	N/A [B/IC]	In preclinical development	mAbxience (Spain)	—
	PRX-106 [B/IC]	In preclinical development	Protalix Biotherapeutics (Israel)	—
	Etanar®/Etart®/Etacept®/ Yisaipu® [IC]	Approved in Colombia, Mexico, India, China	Shanghai CP Guojian (China) Cipla (India)	AS, RA, Ps AS, JIA, RA, Ps, PsA
	Infinitam®	Approved in Mexico	Probiomed (Mexico)	RA
Infliximab (Remicade)[c]	CT-P13 [B/IC] (Remsima/Inflectra/others)	Approved in 79 countries (as of 01/2017)	Celltrion	AS, CD, Ps, PsA, RA, UC
	SB2 [B] (Renflexis)	Approved in Korea (12/2015), Australia (11/2016)	Samsung Bioepis/MSD (Korea/US)	AS, CD, Ps, PsA, RA, UC
	Infliximab BS [B/IC]	Approved in Japan (07/2014)	Nippon Kayaku (Japan)	CD, RA, UC
	BOW015 [IC] (Infimab)	Approved in India (09/2014); global phase III study initiated in RA (02/2016)	Ranbaxy Laboratories/Epirus Biopharmaceuticals (India/US)	AS, CD, Ps, PsA, RA, CD
	NI-071 [B/IC] (Nichi-Iko)	Approved in Japan (09/2017)	Nichi-Iko/Zeria (Japan)	—
	STI-002 [B/IC]	Positive phase III study findings in RA reported (05/2016)	MabTech/Sorrento Therapeutics (China/US)	—

(Table 3) contd.....

Rituximab (MabThera/Rituxan)[d]	CT-P10 (Truxima)	Approved in Korea (11/2016)	Celltrion	RA
	BCD-020 (Acellbia [Russia/India]; USMAL [Bolivia/Honduras])	Approved in Russia, Bolivia, Honduras Pre-registration for RA in India (2017)	Biocad (Russia)	
	Reditux	Approved in Bolivia, Chile, Ecuador, Paraguay, Peru, India (2007)	Dr. Reddy's Laboratories	RA
	Novex	Approved in Argentina (2013)	mAbxience/Laboratorio Elea (Spain/Argentina)	RA
	Kikuzubam	Approved in Bolivia, Chile, Mexico, Peru	Probiomed (Mexico)	RA
	MabTas	Approved in India (2013)	Intas Biopharmaceuticals (India)	RA
	N/A	Approved in India (2013)	Zenotech Laboratories (India)	RA
	Maball	Approved in India (2015)	Hetero Group (India)	RA
	N/A [IC]	In development	Torrent Pharmaceuticals (India)	—
	HLX01 [IC]	In phase III development	Shanghai Henlius Biotech (China)	—
	JHL1101	In phase III development	JHL Biotech (China)	

[a]Reference [49]. [b]Reference [50]. [c]Reference [51]. [d]Reference [52]. [e]Reference [53]. AS: Ankylosing Spondylitis; axSpA: axial spondyloarthritis (non-radiographic axSpA and AS); CD: Crohn's disease; JIA: Juvenile Idiopathic Arthritis; ped Ps: pediatric psoriasis (plaque); Ps: psoriasis (plaque); PsA: psoriatic arthritis; RA: Rheumatoid Arthritis; UC: Ulcerative Colitis.

The Tunisian League Against Rheumatism (LITAR) and the Tunisian Gastroenterology Society have recommended that safe and effective treatments be made available to Tunisian patients at the lowest cost possible. However, all new medications must be introduced with caution to ensure patient safety. These societies are developing a biosimilar position paper based on clinical study findings, relevant policies of other rheumatology/gastroenterology societies, and the country's current economic circumstances. Biosimilar approval and use should be based on multiple factors, including safety, efficacy, and traceability/interchangeability. While the value of introducing biosimilars in Tunisia is recognized, a strict legal and regulatory framework must be in place and prescription of biologic/biosimilar products must remain a clinical decision, made in consultation with patients and in consideration of possible health consequences, safety concerns, and economic impact. LITAR does not approve switching a patient who is stable on a biotherapy to a biosimilar to reduce costs without prior consent of the prescriber and patient. Biologic-to-biosimilar switching requires careful consideration on a case-by-case basis, not automatic implementation. Interchangeability studies have demonstrated safety and efficacy when switching from reference product to biosimilar, but not the inverse. Moreover, the societies have reservations about the importation of products that have not undergone rigorous quality control, *e.g.*, intended copies.

4. ESSENTIAL CONCERNS: PERSPECTIVES OF NORTH AFRICAN RHEUMATOLOGISTS

4.1. Adherence to Established Regulatory Biosimilarity Standards

Regulatory pathways for biosimilar approval by the EMA and FDA require the submission of data from head-to-head clinical studies carefully designed to rule out the possibility of clinically relevant differences between biosimilar and reference products [11, 23]. Ideally, the pathways established by these large regulatory authorities will be universally adopted at regional and national levels around the world, including North Africa. Biosimilar approval based on international criteria has been shown to instill confidence among clinicians [27]. However, achievement of such harmonization will be challenging given the profound cultural/political/social/economic disparities among continents, countries, and regions.

In North Africa, as elsewhere, adoption of legislation defining the pathway for biosimilars should ideally precede establishment of the regulatory framework for the biosimilar approval process. Acceptance of a statutory basis for this process will help ensure that stakeholders have the opportunity to offer their input and expertise in developing and evaluating fundamental principles. Moreover, subsequent changes to regulation or guidance would need to be consistent with the statute, providing stakeholders with a stable, predictable regulatory environment.

Many North African rheumatologists are aware of the potential cost/access benefits of biosimilars but may not favor biosimilar authorization unless manufacturers have received authorization from other globally respected regulatory agencies. Intended copies with limited or non-comparable data are not expected to receive market authorization in this region because they do not satisfy stringent regulatory approval criteria and may pose a threat to patient safety.

4.2. Biosimilar Data Availability and Comparability

A substantial number of biosimilar products, including biosimilars of adalimumab, infliximab, etanercept, and rituximab, do not have published the evidence of structural and functional comparability from non-clinical studies [28]. Additionally, much of the evidence from registration studies has only been published in conference abstracts. Release of findings from biosimilar trials in the public domain as full-text publications is essential to ensure that HCPs and patients are well informed.

Clinicians may have safety concerns related to biosimilar immunogenicity, as small or indiscernible differences arising during production may result in antidrug antibody formation [28]. Differences in immunogenicity between biosimilars of

monoclonal antibodies or fusion proteins and their reference products may be especially likely because of the large size and complexity of the reference biomolecules and post-translational modifications. Considerable differences in immunogenicity rates among biotherapies used to treat chronic inflammatory diseases have been reported in some clinical trials, with the highest rates seen with adalimumab, infliximab, and the infliximab biosimilar CT-P13 [29].

In a recent randomized controlled trial, Emery *et al*. observed a significant difference in the incidence of antidrug antibodies in patients treated with reference product versus biosimilar (SB4) etanercept, although this difference was not considered clinically relevant [30]. By contrast, in another study, the incidence of antidrug antibody development was consistent among patients receiving reference product and biosimilar (SB2) infliximab [31]. Immunogenicity can result in reduced therapeutic levels and loss of efficacy after months or years of treatment, requiring dose increases and/or shortening of dosing intervals in some patients. However, despite the frequency and clinical consequences of biologic immunogenicity, relatively limited data have been published on immunogenicity in biosimilar clinical trials.

The comparability of efficacy between biosimilars and anti-TNFα agents has also raised questions. In phase III comparative studies, biosimilars of reference TNF inhibitors satisfied pre-specified criteria for equivalence in efficacy in patients with rheumatoid arthritis [30] and plaque psoriasis [32]. However, higher treatment response rates were observed with both biosimilars and their reference biologics in recent comparative clinical trials than with the reference biologics in pivotal registration trials [33]. Although these differences in efficacy may have resulted from differences in study design and/or patient characteristics, the findings warrant additional research. Because definitive conclusions cannot be drawn from a comparison of findings from clinical trials with different designs and methodology, a strong argument can be made in favor of standardization of future biosimilar studies [34]. Greater uniformity across biosimilar clinical studies may also increase HCP confidence in these biopharmaceuticals.

4.3. Interchangeability, Switching, and Substitution

Future regulations for biosimilar approval in North Africa may include guidelines on interchangeability, switching, and substitution among biologic and biosimilar products. According to the EMA, interchangeability is defined as the possibility of replacing a reference product with a biosimilar (or the inverse) or replacing one biosimilar product with another [20]. The clinician may decide to exchange one product for another, with the same therapeutic intent, a practice known as "switching." Alternatively, one interchangeable product may be dispensed instead of another at the pharmacy level without consultation with, or the consent of, the prescriber, which is known as "substitution."

Because established regulatory authorities such as the WHO and EMA do not require switching studies for biosimilar approval and do not provide guidance on this practice (Table **1**), the effects of switching are often not evaluated in biosimilar registration studies [35]. However, the FDA does require the submission of data on alternating (one transition) and switching (three transitions) to support these practices [36].

In a 2012 review, Ebbers *et al*. found no evidence of safety concerns related to switching from biologic to biosimilar agents in clinical studies or post-marketing surveillance [37]. Similarly, in a 2017 review, Moots *et al*. found no differences in safety/efficacy outcomes with or without switching between the reference biologics adalimumab, infliximab, etanercept, and rituximab and their biosimilars [35]. The authors nonetheless concluded that the available evidence is qualitatively and quantitatively insufficient to confirm the safety /efficacy of switching. In systematic literature reviews of randomized controlled trials and real-world studies, Numan *et al*. [38] and McKinnon *et al*. [39] reached similar conclusions with regard to non-medical switching, which occurs as a result of non-medical concerns such as treatment costs. The studies conducted in patients with chronic inflammatory diseases were not adequately designed to assess efficacy and safety after non-medical switching, and evidence from these studies was often inconsistent and inconclusive. Even when assessing only the 17 randomized controlled trials found in their literature searches (January 2012 to February 2018; (Table **4**), Numan *et al*. found that none satisfied all of the study design elements considered important for robust switching studies [38].

Given that the goals of switching from a stable biologic to a biosimilar are cost savings and broader access, because biosimilars have not demonstrated better safety or efficacy, regulatory agencies will need to determine whether they may be substituted for reference biologics for non-clinical reasons. To date, in the EU, no country has explicitly authorized the automatic substitution of products from different manufacturers without clinician/patient involvement. In many regions, including North Africa, pharmacy-level substitution is generally not considered appropriate unless stringent legal and regulatory criteria are satisfied in addition to biosimilarity requirements. Prescribing clinicians are also supported as primary decision-makers, with the right to prescribe the most appropriate product based on their clinical judgment, scientific evidence, and individual patient profiles, and to override automatic substitution not deemed in a patient's best interest.

4.4. Pharmacovigilance

Plans for post-marketing monitoring and risk-management activities, at least as rigorous as those for reference biologics, are essential for biosimilar approval [10, 11, 20, 23], and are expected to be mandatory in the legal/regulatory framework for biosimilar authorization in North Africa. As with all medications, adverse events related to biosimilar use in daily practice can only be detected through continuous post-approval surveillance at the clinical level [40]. The importance of post-marketing surveillance in identifying safety concerns related to intended copies was demonstrated with the rituximab intended copy Kikuzubam®, as reports of anaphylactic reactions in rheumatology patients switched to this biosimilar in the Mexican pharmacovigilance program resulted in its removal from the market [41, 42].

Table 4. Summary of randomized controlled non-medical switching studies in chronic inflammatory diseases [38].

Rheumatic Disease	Study (Study Name)	Biosimilar (n) Product [Switch Group] / Biologic Reference Product (n) [Control Group]	Post-Switch Follow-up Duration, wk	Patients Discontinuing Treatment, n (%) (Switch vs. Control Group)
RA	Cohen *et al*. 2018 [54] (VOLTAIRE-RA)	BI695501 (n=147) / adalimumab (n=147)	24-34	9 (6%) vs. 8 (5%)
	Genovese 2017 [55] (ARABESC-OLE)	FKB327 (n=108) / adalimumab (n=213)	76	NR
	Weinblatt *et al*. 2017 [56]	SB5 (n=125) / adalimumab (n=129)	28	8 (6%) vs. 5 (4%)
	Cohen *et al*. 2017 [57, 58]	ABP 501 (n=237) / adalimumab (n=229)	46	30 (13%) vs. 25 (11%)
	Emery *et al*. 2017 [59]	SB4 (n=119) / etanercept (n=126)	48	6 (5%) vs. 7 (6%)
	Smolen *et al*. 2018 [31]	SB2 (n=94) / infliximab (n=101)	16	6 (6%) vs. 5 (5%)
	Tanaka *et al*. 2017 [60]	CT-P13 (n=33) / infliximab (n=38)	105	11 (33%) vs. 6 (16%)
	Yoo *et al*. 2017 [61] (PLANETRA)	CT-P13 (n=144) / infliximab (n=158)	48	16 (11%) vs. 25 (16%)
	Taylor *et al*. 2016 [62]	BOW015 (n=53) / infliximab (n=104)	38	NR
AS	Park *et al*. 2017 [63] (PLANETAS)	CT-P13 (n=86) / infliximab (n=88)	48	9 (10%) vs. 7 (8%)
Ps ± PsA	Blauvelt *et al*. 2017 [64] (ADACCESS)	GP2017 (n=63) / adalimumab (n=127)	34	16 (25%) vs. 23 (18%)
	Hodge *et al*. 2017 [65]	CHS-1420 (n=124) / adalimumab (n=129)	8	NR
	Papp *et al*. 2017 [66]	ABP 501 (n=77) / adalimumab (n=79)	36	9 (12%) vs. 8 (10%)
	Griffiths *et al*. 2017 [32, 67] (EGALITY)	GP2015 (n=96) / etanercept (n=151)	40	6 (6%) vs. 14 (9%)
CD, UC, RA, Ps, PsA, SpA	Jørgensen *et al*. 2017 [68, 69] (NOR-SWITCH)	CT-P13 (n=240) / infliximab (n=241)	78	18 (8%) vs. 25 (10%)
IBD/CD	Volkers *et al*. 2017 [70] (SIMILAR)	CT-P13 (n=15) / infliximab (n=6)	30	NR
	Ye *et al*. 2018 [71, 72]	CT-P13 (n=55) / infliximab (n=54)	24	NR

AS: Ankylosing Spondylitis; CD: Crohn's Disease; IBD: Inflammatory Bowel Disease; NR: Not Reported; Ps: Psoriasis (plaque); PsA: Psoriatic Arthritis; RA: Rheumatoid Arthritis; SpA: Spondyloarthritis; UC: Ulcerative Colitis.

Over the past few decades, awareness of the importance of pharmacovigilance to the healthcare system in Africa has increased [43]. Morocco and Tunisia were among the first African member countries of the WHO International Drug Monitoring Programme (1992–1993), and Algeria subsequently became an associate member. In North Africa, post-marketing monitoring of drug safety is hindered by several common obstacles, including HCPs' lack of awareness of surveillance requirements and reporting forms, unfamiliarity with product labeling, inability to identify adverse events, and hesitation to report events because of guilt or fear of legal action. Improved HCP education/training and greater financial/logistical support for pharmacovigilance systems are needed to overcome these challenges.

4.5. Biopharmaceutical Nomenclature

Biosimilars require names that can be easily distinguished from those of reference biologics to ensure accurate identification and effective pharmacosurveillance, and to reduce the risk of unintended substitution of non-interchangeable products. Guidance on biologic and biosimilar names has been provided by the WHO, EMA, and FDA [20, 44, 45], as summarized in Table **1**. To date, recommended approaches are inconsistent, which may lead to confusion, but further refinement is expected.

4.6. Accessibility and Cost Issues

Since the first biosimilar (Omnitrope®) was approved in the EU in 2006, the biosimilar pipeline has seen remarkable growth. Introduction of biosimilar products is anticipated to reduce costs and expand patient access in public and private healthcare systems [46, 47]. Although the difference in price between reference and biosimilar products may be <30%, such a cost saving is sufficient to generate considerable interest, particularly in countries with negative economic forecasts. In addition to wider access for patients of all socioeconomic levels, competition in biosimilars may lead to lower prices of the reference biologics. In countries facing a difficult economic situation, such as Tunisia, competitive pricing of reference biologics is particularly important.

Accessibility to healthcare and treatment is problematic across North Africa, but each country has specific challenges. In Algeria, the state provides free treatment for the entire population, regardless of socioeconomic status, but costs must remain below a specified threshold. In Morocco and Tunisia, patients covered by the social security system are entitled to receive free treatment. However, the number of patients requiring specialist care and biopharmaceuticals affects access, so that a cost reduction of only 20-30% for biosimilars is expected to improve access. Nonetheless, rheumatologists are cautious that lower cost for, and increased patient access to, biosimilars is not achieved at the expense of patient safety.

CONCLUSION

Biosimilar versions of original biologic agents used in a wide range of chronic inflammatory diseases may allow greater patient access to treatment through cost savings. However, they pose several challenges, particularly in developing countries. In North Africa, work is underway to establish the legal/ regulatory framework for biosimilar authorization to ensure that patients and HCPs are protected. HCPs will require information about the regulatory pathways in place in their countries and the clinical profiles of the biosimilars authorized by their regulatory agencies. Their perspectives on switching and substitution require consideration, allowing for clinical decision-making on a case-by-case basis in alignment with scientific evidence and patient-, disease-, and product-specific factors.

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