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Review Article

Biosimilars: Review of regulatory, manufacturing, analytical aspects and beyond

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ABSTRACT

Biologics have more complex production processes compared to small-molecule drugs. They may even prove labile when drifting from batch-to-batch or in different production locations. The development of new similar biological product was regulated early to face the relevant challenges of this industry. As a result, since 2006 biosimilars were introduced to biotechnology arena with a massive competition in pharmaceutical industry. In this review, the aspects related to similarity testing of biosimilars to the original biological products are discussed involving manufacturing challenges to ensure the quality, safety, and efficacy of these products to the patient health. Immunogenicity studies are highlighted as an important part of the safety assessments. Additionally, several analytical methods that are usually used to evaluate biosimilars in comparison to their reference biologic are summarized and categorized in terms of the intended physicochemical and biological characterization. On the other hand, the international efforts of several regulatory agencies including the European Medicines Agency, World Health Organization and United States Food and Drug Administration for biosimilar development are discussed according to updated revised guidelines.

1. Introduction

Biopharmaceuticals patent expiration opened the door to tremendous competition between pharmaceutical companies worldwide. Economically, the global market value for biosimilar is continuously growing and is expected to rise by about 25% by 2026 compared to the value in 2020 [1]. Among others, monoclonal antibodies are considered the highest selling class of biopharmaceuticals [2]. Since their introduction more than a decade ago, biologics have shown high contribution in therapies of several serious diseases such as cancer, crohn's disease, turner syndrome, diabetes, and rheumatoid arthritis. As such, some of the innovator biologics are scheduled to come off patent license. Actually, pharmaceuticals that contain small drug molecules have relatively simple structures in terms of their active substances. Thus, identical copies of patents, which are known as generic, can be easily achieved. The approval of these generic drugs depends on the equivalent proof compared to the reference drug product [3]. This abbreviated approval eliminates the costly clinical trial of drug development and allows manufacturers to provide small molecule generics at a lower price [4]. Biopharmaceuticals have a totally different pathway. They are developed using living cells, such as blood and plasma products, vaccines, recombinant proteins, and monoclonal antibodies [3]. Therefore, the active substance in biological medicine is not only one molecule but an entity population of different molecules reach to several hundreds of small molecules (Fig. 1). Manufacturing of these large molecules is subjected to unintended changes or drift during manufacturing processes such as batch-to-batch variability, a change in characteristics, strength, and purity. Producing a new identical copy of these kinds of medicines cannot be achieved [5].

Herein, biosimilar was born to be an alternative term for "biogeneric" medicinal product whereas it is defined as a similar copy of officially registered reference biological product [6].

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Consequently, the demand to new regulations pushed the global regulatory agencies to put guidance for manufacturing these types of biomolecules with addressing many challenges related to quality, safety and efficacy assessment.

This review article aims to present a comprehensive review in biosimilars development through discussing aspects related to the manufacturing, analyses, safety and quality assessments with updated regulatory guidelines.

2. Regulatory framework and related aspects

Biosimilar regulations have been an international issue since 2004 with regard to the evaluation system and identification problem. It meets an important agreement point that biosimilars should have their regulations rather than those of generic small molecule drugs. As such, the approval needs a similarity proof of biosimilars with originator biologics supported by reliable data of quality, nonclinical, and clinical evaluations. The tremendous efforts via the European Medicines Agency (EMA) and the World Health Organization (WHO), are considered the basement to develop biosimilars national guidelines worldwide. EMA guideline was the first regulation to be established globally and to be adopted by the Committee for Medicinal Products for Human Use (CHMP) as "Guideline on similar biological medicinal products". This guideline described the development of similar biological products according to their similarity to already registered reference biological product. Actually, EMA was the initiator to address this issue scientifically as CHMP/437/04 guidelines which came into effect on 30 October 2005 [7,8]. Moreover, this guideline adopted the former International Council for Harmonization (ICH) guidelines such as ICH/Q5C for the stability testing of biotechnological/biological products, ICH/Q6B for test procedures and acceptance criteria for biotechnological/biological products, and ICH/S6 for preclinical safety evaluation of biotechnology-derived products as relevant guidelines in developing similar biological medicinal products [9–11]. However, the proposed version of (CHMP/437/04 Rev1) was amended by adding of (EMA/CHMP/BWP/247713/2012) guideline for quality issue and (EMEA/CHMP/BMWP/42832/2005 Rev) guideline for non-clinical and clinical issue as a relevant guideline and should be taken into account instead of the former ICH guidelines which are still involved in the relevant specific documents of EMA guidelines. Moreover, ICHQ5E is still the scientific principle for comparability exercise to evaluate the impact of changes in the manufacturing processes. One more update was published in the EMA guidelines about the recognition of "stand-alone" term if relevant differences between intended biosimilar and reference medicinal product are present [12].

In 2009, WHO adopted guidelines for evaluation of biosimilar products named "Guidelines on the evaluation of similar biotherapeutic products (SBPs)". WHO aimed to provide general standards for licensing SBPs globally. This effort came in collaboration with experts representing different member states [13]. Indeed, WHO guidelines are similar to EMA guidelines in most requirements for quality, clinical and non-clinical issues. However, it gives flexible regulatory framework adaptable to the national regulatory authorities (NRAs) according to their needs. For instance, the stability studies in EMA guidelines should be determined according to ICHQ5C guidelines, while in WHO guidelines it should comply with relevant guidances according to NRAs recommendation. Another example in the quality section is the analytical consideration during comparability exercise of biosimilar to reference product, where both guidelines mentioned the main purposes to obtain a high level of assurance for the quality and demonstrate the slight differences between biosimilar and reference product. However, the WHO guidelines were supported with many analytical techniques as guidance examples, where the EMA guideline focused on general purposes of analytical methods. Obviously, WHO guidelines in this context are broader than EMA guidelines and it lefts many spaces for NRAs responsibilities. Therefore, WHO explained clearly in a separated section the different responsibilities of NRAs toward the requirements of biosimilar development. In fact, EMA and WHO paved the way for NRAs overworld to set up the appropriate guidelines for evaluating and developing new biosimilar products. Herein, some examples of NRAs that adopted EMA guidelines [14–16] and other NRAs adopted their guidelines in line with WHO guidelines [17–19].

A decade after the first biosimilar guideline, the United States Food and Drug Administration (USFDA) published in 2015 biosimilar

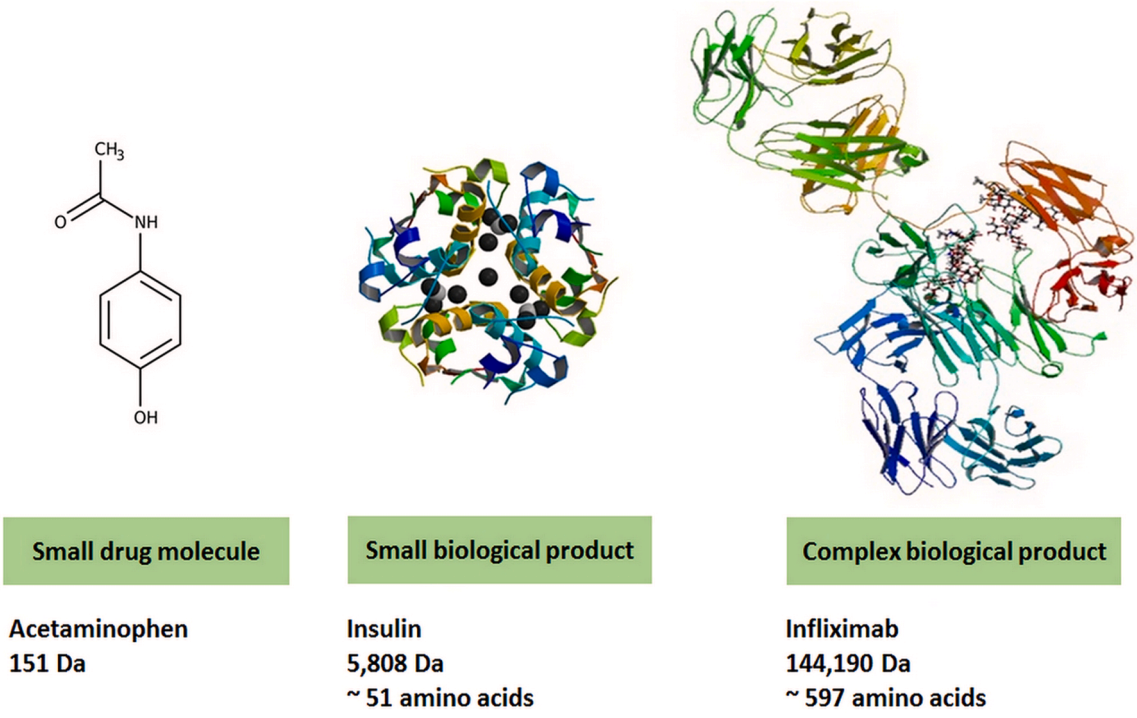

Fig. 1. Complexity of biosimilar components compared to small molecule and single protein.

guidelines after extensive reviews for international regulatory guidelines and comparison with initial three drafts issued in 2012 related to biosimilars [20]. USFDA introduced guidance documents as Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product [21]; Scientific Considerations in Demonstrating Biosimilarity to a Reference Product [21]; and Biosimilars: Questions and Answers Regarding Implementation of the Biologic Price Competition and Innovation (BPCI) Act of 2009 [22]. These guidelines deal with the quality, clinical and non-clinical issues as a general consideration. In 2016, USFDA published extra guidelines for clinical pharmacology data to support a demonstration of biosimilarity [23] with emphasis to support biosimilarity through pharmacokinetics (PK) and pharmacodynamic (PD) studies, immunogenicity testing and clinical safety as well as the need of further studies according to the residual uncertainties in each phase. One more step took place via USFDA by publishing a guideline of labeling for biosimilar products which addressed all information that are relevant to identification, contents and prescribing in 2018 [24]. In May 2019, USFDA published a guideline for the demonstration of biosimilar interchangeability with a reference product [25]. Although USFDA responded later to biosimilarity assessment and registration but all guidance documents address most biosimilar concerns well whereas, the guidelines for labeling and interchangeability demonstration are published and clearly defined. In contrast, EMA and WHO stated that the interchangeability demonstration and labeling issues are out of their remit and are subjected to member states policies. Principally, the regulatory guidelines that adopted via either EMA, WHO and USFDA are approximately similar for approval of new biosimilar products. Table 1 lists the approved biosimilars by either EMA or/and USFDA. Despite the development in this advanced and complex industry, there are massive challenges related to the future of biosimilars. Among these challenges, is the existence of biobetters as a result of the development in the manufacturing process (with better claims to the reference products) instead of biosimilarity even though they are used for the same indications and the same targets. Interchangeability between the reference products and alternative biosimilars is defined in different ways for EMA, USFDA, and WHO therefore, the practice will be different accordingly. The aforementioned challenges will be discussed below in detail.

2.1. Could biosimilar be better than the reference product?

Two different terminologies are still controversial in the biotechnology arena and are not clearly distinguished in any regulatory guidelines. To answer the aforementioned question, the difference between biosimilars and biobetters should be clear in a scientific point of view. Biosimilar is defined as a similar copy to reference biological medicinal product. By means it has the same claim of indication and works with the same target. Thus, the framework guidelines of biosimilar manufacturing and testing were established by EMA as a first regulatory agency to assure that biosimilar can be identified as non-original biologic and can also be used for the same indications. However, due to the nature of biotechnological techniques, some manufacturing processes led to small modifications in biomolecule structure thereby these changes were addressed well in different guidelines with comparable assessments to reference product for assuring the safety and efficacy [26,27]. Whilst claiming the better indication was invented in 2007 by GV Prasad as “biobetters” and since that date, biobetters have been distinguished from biosimilars with superiority to the reference products although they are working against the same target [28]. Obviously, biobetter is a marketing term and to date, there is no regulatory framework to deal with better claims for new biologics and it is a good opportunity for biopharmaceutical companies to improve some versions of original biologics depending on the former bits of knowledge. Herein, several biobetters have been developed from already approval original biologics. Margetuximab® is a biobetter of Trastuzumab® (originator biologic) with improved cell killing properties. Panitumumab® is a second-generation antibody of Cetiximab® with a lower dosing frequency (every 2 weeks). Ocartuzumab® is a biobetter that has a higher affinity than its reference biologic (Rituximab®). Pegfilgrastim® is a non-mAb biobetter of Filgrastim® which has been modified to reduce the dose to be administered every 3 weeks. In order to improve the biotherapeutic performance, various approaches have been applied such as chemical modification, protein fusion, and altered amino acid sequences. As a result, the new products are claimed to have better efficiency or clinical specificity, lower adverse effects, and a longer half-life [29]. At the same time, several reports [26,28,30] emphasized that biosimilar concept is still fair to be used in regulatory guidelines in spite the biobetters have more advantages and both of them are related to each other in one way or another.

2.2. Biosimilar interchangeability to the reference product

The switching between innovative biologics and alternative biosimilar is argued over the past 10 years. The debate still persists due to the raised concerns about immunogenic reactions resulting from switching of one product to another. Although, it is considered one of the most adverse effects within the different batches of the same biologics. There are three aspects that should be outlined for biosimilars interchangeability. The first aspect is the different requirements for interchangeability among the international regulators. EMA abstained to address clear guidelines for biosimilar interchangeability and confirmed that the biosimilars interchangeability is under each state assessment and outside the remit of EMA/CHMP [12,31]. However, numerous European countries declared that the biosimilar products can be safely interchanged under the supervision of treating physicians [32]. USFDA considers the substitution product to be not only similar but also interchangeable with the reference biologic after a support with sufficient data about interchangeability demonstration in switching studies between the two products [25]. This led to the second aspect about the real need for extra clinical trials to demonstrate biosimilar interchangeability as requested by USFDA. The aim is to clear any concern regarding immunogenic reactions during treatment switch. EMA has a different view to interchangeability and considers that each highly two similar products could be interchangeable in principle without the need to support with extra clinical trials. This view was based on the long experience via switching between several biopharmaceuticals such as growth hormones, epoetins, and interferons without triggering immunity responses [32–34]. The third aspect is related to the treatment providers, where in European countries the substitution of original biologics with biosimilar should be under physician supervision. However, USFDA regulations permit the pharmacist to switch between biological medicines directly. Therefore, the practice is different between two levels of health care professionals is strict to physicians as legislated in the EU or flexible to be switched directly via pharmacist as legislated in the US [33,35,36].

2.3. Manufacturing aspects

Biologics suffer from a number of challenges in development due to the large molecular size, poor permeability, and gastrointestinal stability. For these reasons, most biologics are available only as injection dosage forms. Moreover, protein-based biologics consist of amino acid sequences that are folded into specific conformations. The amino acid structure is held by weak peptide bonds and weak intramolecular interactions. Consequently, a small change in the structural integrity may interfere with its specificity to the receptor which could cause immunological reactions and change in therapeutic responses [37]. With the intention of product safety and efficacy, a well-managed quality system needs to be applied to mitigate drift especially during the manufacturing processes [38]. However, biologics open up opportunities for expanding access to health systems. Therefore, the fall-off patents provide enormous changes for the biosimilar market of more affordable therapy

Table 1
List of approved biosimilars by EMA and USFDA A) EMA approved biosimilars.

Original biologics	2006–2015	2016	2017	2018	2019	2020
Adalimumab			Amgevita, *Cyltezo, Imraldi, Solymbic	Hefiya, Hyrimoz, Halimatoz, Hulio	Idacio	Amsparity
Bevacizumab				Mvasi	Zirabev	
Enoxaparin sodium		Inhixa, Thorinane				
Epoetin alfa	(2007) Abseamed Binocrit Epotin Alfa Hexal					
Epoetin zeta	(2007) Silapo, Retacrit					
						Nepexto
Etanercept		Banepali	Erelzi			
Filgrastim	(2008) *Ratiograstim Tevagrastim (2009) Zarzio, Hexal (2013) Grastofil (2014) Accofil					
Follitropin alfa	(2013) Ovaleap (2014) Bemfola					
Infliximab	(2013) Inflectra, Remsima	Flixabi		Zessly		
Insulin glargine	(2014) Abasaglar		Lusduna	Semglee		
Insulin human	(2015) Solumarv					
Insulin lispro			Admelog			Lyumjev
Pemetrexed	(2015) Permetexed- medac					
Pegfilgrastim				Udenyca Fluphila Pelgraz Pelmeg	Grasustek Mundipharma	
Rituximab			Ritemvia Blitzima,, Rixanthon Riximyo Truxima *Tuxella			Ruxience
Somatropin	(2006) Omnitrope (2013) Somatropin-Bioparters					
Teriparatide		Movymia	Terrosa			
Trastuzumab			Ontruzant	Ontruzant Ogivri Herzuma Trazimera Kanjinti		

(B) USFDA approved biosimilars

Original biologics	2015	2016	2017	2018	2019	2020
Adalimumab		Amjevita	Cyltezo	Hyrimoz	Hadlima Abrilada	Hulio
Bevacizumab			Mvasi		Zirbev	
Epoetin alfa				Retacrit		
Etanercept		Erelzi			Eticovo	
Filgrastim	Zarxio			Nivestym		
Infliximab		Inflectra	Renflexis Ixifi		Avsola	
Rituximab				Truxima	Ruxience	Riabni
Pegfilgrastim				Udenyca Fulphia	Ziextenzo	Nyvepria
Trastuzumab			Ogivri	Herzuma	Kanjinti Trazimera, Ontrruzant	

*withdrawn product

options that are safe and effective. Even though, it is still expensive in comparison to small molecules medicines. The manufacturing of biosimilars are high process dependent through biotechnological synthesis and reverse-engineering in the development stage [39,40]. Process control and process validation seem to be a critical part that affects the product quality which also explains the paradigm 'the process is the product' [4,41]. It is reasonable for the innovator company not to provide manufacturing information that could accelerate and support competitors. Therefore, an identical biosimilar to the reference biologic would not be possible to achieve. In order to provide the affordable biological medicines with a high similarity to the originators, a head-to-head comparability approach is applied in biosimilars development. However, implementing abbreviated clinical trials considered a worthy step for cheaper alternative product [41]. Eventually, minor differences are allowed as long as they do not result in clinically meaningful differences with regard to safety, purity, and potency compared to the reference product [38]. The steps of the manufacturing process are represented in (Fig. 2).

2.4. Analytical aspects

The analytical procedures can be considered the "eyes and ears" in this process to tell just how similar the generic protein is to the reference. The first pass in the comparability testing are the results of routine QC tests against existing specifications. Afterward, the primary structure of the targeted protein is evaluated using a peptide map that has been confirmed by mass spectrometry (MS). Nowadays, the use of a multiplexed combination of different characterization methods is available to ensure the complete confirmation of its primary structure.

With regards to its physicochemical properties, biologics are not only big molecules, but also exhibit more complex pharmacokinetic behaviour compared to small molecules. Indeed, biologics require different testing methods rather than a simple evaluation of low molecular weight drugs. A key step in the analysis of biologics is an extensive characterization, due to small structural alterations which possibly initiate substantial changes in drug stability, immunogenicity, and efficacy. Characterization using bioassay, immunoassay, electrophoresis, mass spectra, and chromatographic methods are applied to obtain detailed structural information. During the early development of biologics, further analysis including in-vitro, non-clinical, and clinical studies are required to prove the drug's safety and efficacy. Therefore, copying biologic to a similar product is challenging in each development step.

In general, the analytical assessment of biosimilars is the main challenge [37]. Thereby the analytical procedures to confirm the structural and functional similarity is the predominant phase in biosimilar development. In contrast, the development processes of new biologics need extensive clinical trials before getting the approval (Fig. 3). A subsequent process of analytical, nonclinical and clinical studies should be applied as part of a stepwise approach which involves several stages such as physicochemical characterization, biological characterization, nonclinical studies in animals, clinical studies in humans and pharmacovigilance studies [42].

A comparability study of biosimilars to the originator begins with physicochemical and biological characterization. Analytical methodologies that are currently used in QC testing are summarized in Table 2 [43,44].

2.4.1. Quality attributes and analytical methods

Quality control becomes a crucial part of biosimilarity assessment including physicochemical and biological characterization. A wide range of analytical methods is involved in biosimilarity determination concerning structural characterizations, molecular mass, homogeneity, purity, immunogenicity, and biological activity. Indeed, choosing a suitable analytical technique is not a trivial task. For instance,

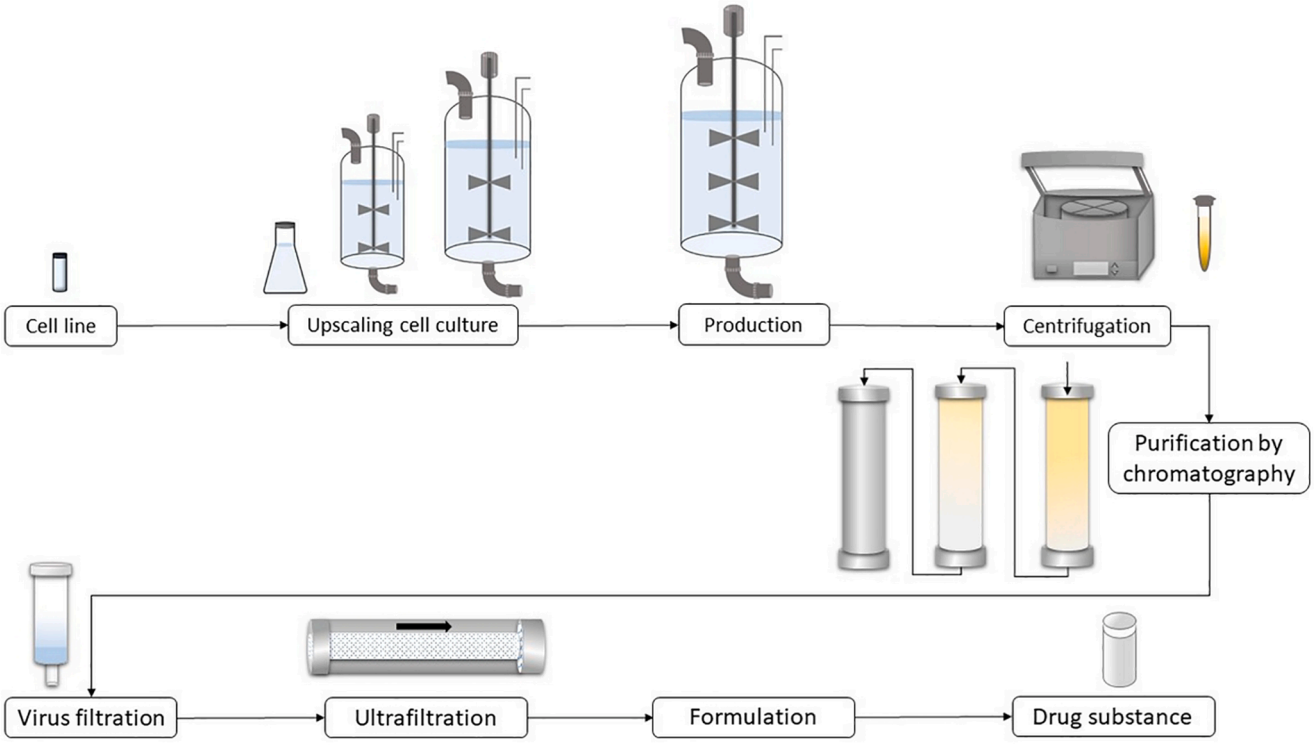

Fig. 2. Representative diagram of the biologics manufacturing process. The cell culture initiated by a specific cell line, subsequently upscaling to the production stage under controlled growth conditions such as media, pH, and temperature. Centrifugation is employed to separate unwanted impurities and supernatant. In the further stages, the free impurities supernatant is purified using chromatography method through a specific binding approach, followed by virus filtration, ultrafiltration, and diafiltration. Finally, concentration and formulation of the target biological properties complete the manufacturing process. Information is taken from [10,46].

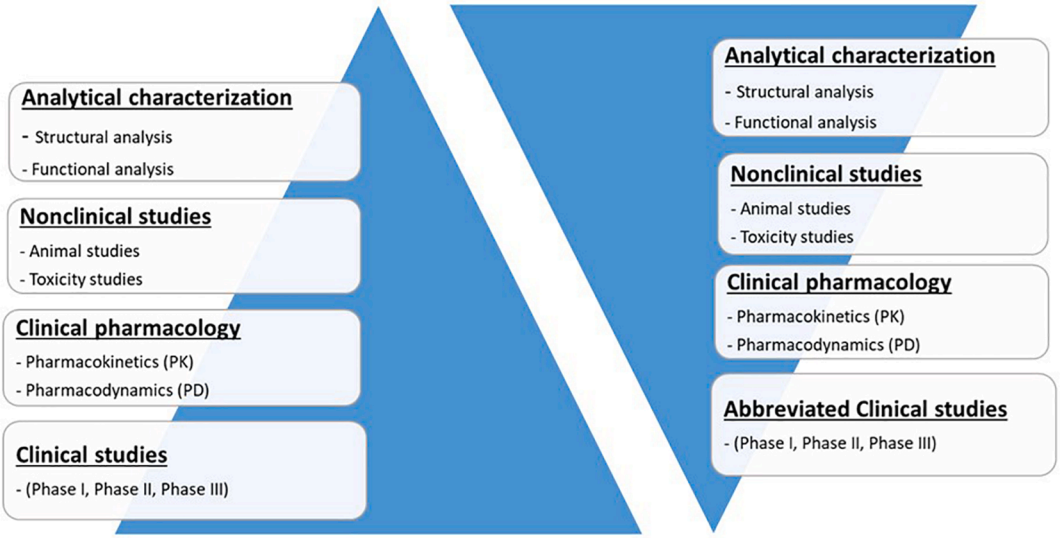

Fig. 3. The 'stepwise' evaluation of biosimilar compared to the originator biologic. Information is taken from [26] and [3].

characterization of the large biomolecules compositions such as proteins is usually carried out via biochemical assays or instrumental assays while each approach has advantages and drawbacks. However, in both approaches, the direct quantification of the protein entity is tedious due to its complexity. For this reason, protein should be subjected to hydrolysis to generate analyzable units of amino acids or peptides. Quantification and characterization of the proteins in this manner, are easier to be deduced.

Furthermore, improving the LOQ and sensitivity of the analytical method may result in a change in the obtained quantitative values. In such cases, the analysis of samples pre and post change manner in the same assay ("side by side" comparisons) is a standard approach for assessing the impact of the methodological changes. In addition, admixture studies have been useful in helping to identify true differences in chromatographic separations. Thus, the assessment of comparability data should include a consideration of method changes and attributes via careful interrogation of analytical practices as a possible explanation for the obtained results.

Biochemical methods such as bioassays and immunoassays are widely used in protein quantification due to their simplicity and lower cost, but they suffer from poor reproducibility. Therefore, the accuracy of the methods might be affected [42]. In contrast, several instrumental methods of analysis based on liquid chromatography (RP-HPLC, HILIC, LC-MS, 2D-LC, SEC-HPLC), and electrophoresis (SDS-PAGE, CZE) are employed to provide reliable scientific data with better reproducibility and higher accuracy than biochemical methods [32,40]. However, the instrumental methods of analysis are considered expensive techniques and time-consuming related to method optimization and samples preparation. Nevertheless, the standard in this regard is the capability of the analytical method to quantify biosimilar product and reference product within the assay variability limits. Therefore, several sensitive and robust analytical methods have been developed to support the need for a comprehensive characterization in high complexity substances of proteins as listed in Table 3.

2.4.2. *Physicochemical studies*

Physicochemical studies on protein characterization including glycosylation, peptide mapping, molecular mass, protein concentration, and higher order structures are addressed as initial monitoring of alteration during the manufacturing process [32,38,45]. As an important quality attribute, glycosylation analysis may affect stability, solubility, half-life and in vivo activity of biological products [46]. Structural characterizations of biosimilars need at least two analytical techniques to obtain a consistent result due to the high-order structure of the products. For instance, size exclusion chromatography, capillary gel electrophoresis, mass spectrometry, and analytical ultracentrifugation are used to calculate the molecular weight of biomolecules. Each technique has different principles; therefore, the results are required to be corroborated. Another example is the determination of primary, secondary, tertiary and even quaternary structures which is complicated and principally depends on different analytical strategies. Primary structures can be determined through peptide sequence analysis which is carried out mostly by mass spectrometry. Secondary and tertiary structures, on the other hand, are determined by spectroscopic techniques such as nuclear magnetic resonance (^{1}HNMR), circular dichroism (CD), differential scanning calorimetry (DSC), dynamic light scattering (DLS), and infrared spectroscopy (IR) [47].

Furthermore, a spectroscopic profile of biomolecules is capable of discriminating different proteins including α-helix and β-sheet substructures. Thus, protein labeling with specific fluorescent dyes might support the determinations of proteins greatly in terms of structural characterization [48].

As required by the EMA and FDA, glycan analysis for glycoprotein-based biological products, involving its carbohydrate, amino sugar, sialic acids contents, oligosaccharide structure, and glycosylation site(s) have to be evaluated. In order to fulfill the requirement, capillary electrophoresis-laser induced fluorescence (CE-LIF), liquid chromatography-electrospray-mass spectrometry (LC-ESI-MS) and matrix-assisted laser desorption/ionization-time of flight mass spectroscopy (MALDI-TOF-MS) are particularly used for oligosaccharide profiling [45,49]. High-pH-anion-exchange chromatography-pulse amperometric detection (HPAEC-PAD) is used for monosaccharide [47]. An evaluation example of a proposed biosimilar to its originator is represented by the electropherogram shown in Fig. 4 [50].

2.4.3. *Biological studies*

Biological characterization of biologics is mainly based on the activity by in vitro (receptor binding, cell proliferation activity) and in vivo (potency, pharmacokinetic) assays [10,40]. The specific binding properties can be studied via the use of several biochemical analytical techniques such as enzyme-linked immunosorbent assay also known as (ELIZA), surface plasmon resonance (SPR), isothermal titration calorimetry (ITC), microscale thermophoresis (MST), affinity capillary electrophoresis (ACE), Affinity chromatography (AC), and many spectroscopic techniques [51–61]. Actually, there is no ideal technique for all types of binding studies therefore, it is critical to select the technique

Table 2
Analytical methodologies currently used in QC testing and characterization studies as part of comparability assessments for a typical IgG1 monoclonal antibody product[a] based on comparability case studies.

Monitoring of product quality attribute	Analytical methodology	QC testing	Characterization studies
Protein aggregation or fragmentation	SE-HPLC[b]	X	X
	SDS-PAGE[c], cSDS[d]	X	X
	SE-HPLC[b] with light scattering		X
	Analytical ultracentrifugation		X
Subvisible particles	Light obscuration	X	
	Microflow digital imaging		X
Confirmation of molecular weight and size distribution profiles	MALDI-TOF-MS[e]		X
	ESI-MS[f]		X
Charge heterogeneity profile	IEF[g], cIEF[h]	X	X
	HPIE-HPLC[i]	X	X
Confirmation of primary amino acid sequence	Peptide map	X	X
	Peptide map with MS detection		X
	N-terminal sequencing		X
	C-terminal sequencing		X
Confirmation of post-translational modifications	Peptide map	X	X
	Oligosaccharide map	X	X
	MALDI-TOF-MS[e]		X
	Monosaccharide compositional analysis		X
	Sialic acid compositional analysis		X
Confirmation of secondary and tertiary structure	Circular dichroism		X
	Differential scanning calorimetry		X
	Sedimentation velocity AUC		X
Confirmation of biological activity for mAbs: activity	In vitro potency assay	X	X
Confirmation of biological activity for mAbs: binding	In vitro antigen binding by ELISA[j]	X	X
	In vitro antigen binding by surface plasmon resonance	X	X
	Binding by flow cytometry	X	X
Confirmation of biological activity for mAbs: Fc effector function	Generation of soluble C5b-9		X
	Binding to human FcgR[k] I and IIIA		X
	Binding to human FcRn[l]		X
	Antibody dependent cellular cytotoxicity		X

[a] IgG1 example product mechanism of action in this case is Fab binding
[b] Sodium dodecyl sulfate polyacrylamide gel electrophoresis
[c] Capillary sodium dodecyl sulfate
[d] Matrix-assisted laser desorption-ionization time-of-flight mass spectrometry.
[e] Electrospray ionization mass spectrometry
[f] Isoelectric focusing
[g] Capillary isoelectric focusing
[h] Ion-Exchange high performance liquid chromatography
[i] Enzyme-linked immunosorbent assay
[j] Fc-gamma receptor
[k] Fc receptor

that provides reproducible binding data with acceptable precision. However, biosimilar kinetic and thermodynamic binding should be demonstrated in comparison to the reference product [21]. On the other hand, animal-based biological assays are essential to obtain the biological response toward biological product thereby, all pharmacokinetic studies are undergoing these measurements and according to many guidelines, it is substantial to accomplish biological characterization of biosimilar product [7,25].

2.5. Safety assessment aspects

2.5.1. Immunogenicity testing

Immunogenicity study is one of the safety assessments involving immune responses in biological systems [46]. In general, immunogenicity may initiate two main unwanted responses of altered efficacy or compromised safety. Altered efficacy means to cause the loss of effect, cross-reaction, and altered pharmacokinetics. The other possibilities are compromised safety response such as anaphylaxis and hypersensitivity [48,62]. Therefore, the comparability study between the biosimilar and its reference product should be conducted under the same assay format and sampling schedule.

Moreover, a case-by-case approach for a duration 6 to 12 months monitoring is applied, depending on the treatment course, the washout period, and the emergence time of humoral immune response [39]. In terms of comparative clinical studies, an immunogenic assessment is required in every phase (I-III). In phase I, immunogenicity is completing the early stage study of PK/PD. Whereas, in phase II/III immunogenicity is intended to figure out the residual uncertainty after efficacy and safety comparative study of the biosimilar to its reference has been conducted [45]. In addition, the patient population, dose, endpoints, study duration, statistical analysis, efficacy, and safety are critical considerations in phase III biosimilar clinical studies [37].

2.5.2. Pharmacovigilance study

A pharmacovigilance study is needed for the post-safety approval monitoring of biosimilars [63]. Even though biosimilars have no clinical difference compared to their reference biologic, it is important to evaluate adverse effects that might appear when administer to real patients [64]. Therefore, spontaneous reporting systems (SRS) and active surveillance (AS) systems are applied to monitor product quality changes and product safety, respectively. For this purpose, healthcare professionals and patients play an important role in providing traceable safety in post-marketing biosimilars data profiles [23].

3. Economic prospects and beyond

The availability of biosimilar products in the biological medicine market increases significantly, together with expiring patents and the new implementation of regulatory pathways. This condition is predicted to influence the sustainability of the pharmaceutical business. The Biologic Price Competition and Innovation Act (BPCIA) is responsible for the biologic and biosimilar price controls. Due to this market battle, biosimilars offer a price reduction of about 10% to 40% lower than biologic reference products. Consequently, some innovator biologics such as Erythropoietin and Infliximab reduce the price by up to 33% and 70%, respectively. This price competition is beneficial for the customers or ends users, as they have more options and possibilities for replacement therapy instead of a unique innovator biologic [23,65].

4. Conclusions

Biosimilars era started few years ago and the future market of

Table 3
Analytical methods preference for biologics similarity assessment.

Categories	Quality attributes	Methods
Physicochemical Characterization		
Primary structure	Molecular weight	LC-ESI-MS/MS
	Amino acid sequence	Peptide mapping by LC-ESI-MS/MS (a combination of digestion enzyme)
	Methionine oxidation, deamination, C-terminal and N-terminal variants	Peptide mapping by LC-ESI-MS/MS
	Disulfide linkage mapping	Peptide mapping under non-reducing condition
	Free sulfhydryl group	Fluorescence detection kit
Higher-order structure	Protein secondary and tertiary structure	Far- and near-UV CD Spectroscopy
		FTIR
		ITF
		Antibody conformational array
	Thermodynamic stability	DSC
	Extinction coefficient	SEC/UV/MALSS/RI
Glycosylation	N-linked glycosylation site determination	LC-ESI-MS/MS
	N-glycan identification	Procainamide labelling LC-ESI-MS/MS
	N-glycan profile analysis	2-AB labelling, HILIC-UPLC
	O-glycan profile analysis	MS
	Glycan heterogeneity	MS
Fragmentation /size heterogeneity	High molecular weight	SEC
		SEC-MALLS/RI
		SV-AUC
	Low molecular weight	CE-SDS, SDS-PAGE (non-reducing/reducing)
		DLS
		MFI
Charge heterogeneity	Acidic and basic variants	CEX-HPLC, icIEF
Isoform	Distribution	IEF, CZE
Impurity	Oxidation, Nick-form	RP-HPLC
Quantity	Protein content	UV/VIS 280 nm
Biological Characterization		
Fab-related biological activity	TNF neutralization activity	NF-kB reporter gene assay
	TNF binding activity	FRET
	Apoptosis activity	Cell-based assay
	Transmembrane TNF-α binding assay	FACS
Fc- related biological activity	FcRn binding	AlphaScreen®
	FcγRIII (V/V type) binding	SPR
	ADCC	Cell-based assay
	CDC	Cell-based assay
	C1q binding	ELISA
	FCγRIa binding	SPR
	FCγRIIa binding	SPR
	FCγRIIb binding	SPR
	FCγRIIIb binding	SPR
Efficacy	EPOR binding	SPR
	In vitro cell proliferation activity	Cell-based assay

This table shows quality attributes as part of similarity assessment for SB2 vs Remicade® (infliximab) (Hong et al. 2017), LBDE vs NESP® (darbepoetin alfa) (Jeong et al. 2018) and SB5 vs product Humira® (adalimumab) (Lee et al. 2018), including the analytical methods preference. *ADCC* antibody-dependent cell-mediated cytotoxicity, *CD* circular dichroism, *CDC* complement-dependent cytotoxicity, *CE-SDS* capillary electrophoresis-sodium dodecyl sulfate, *CEX-HPLC* cation exchange-high performance liquid chromatography, *CZE* capillary zone electrophoresis, *DLS* dynamic light scattering, *DSC* differential scanning calorimetry, *ELISA* enzyme- linked immunosorbent assay, *FACS* fluoresence-activated cell sorting, *FcRn* neonatal Fc receptors, *FRET* fluoresence resonance energy transfer, *FTIR* fourier transform infrared, *HILIC* hydrophilic interaction, *icIEF* imaging capillary isoelectric focusing, *ITF* intrinsic and extrinsic spectroscopy fluorescence, *LC-ESI MS/MS* liquid chromatography electrospray ionization mass spectrometry, *RP-HPLC* reversed-phase high performance liquid chromatography, *SEC* size exclusion chromatography, *SEC-MALLS/RI* size exclusion chromatography-multi angle laser light scattering/refractive index, *SDS-PAGE* sodium dodecyl sulfate polyacrylamide gel electrophoresis, *SPR* surface plasmon resonance, *SV-AUC* sedimentation velocity analytical ultra-centrifugation, *TNF* tumor necrosis factor

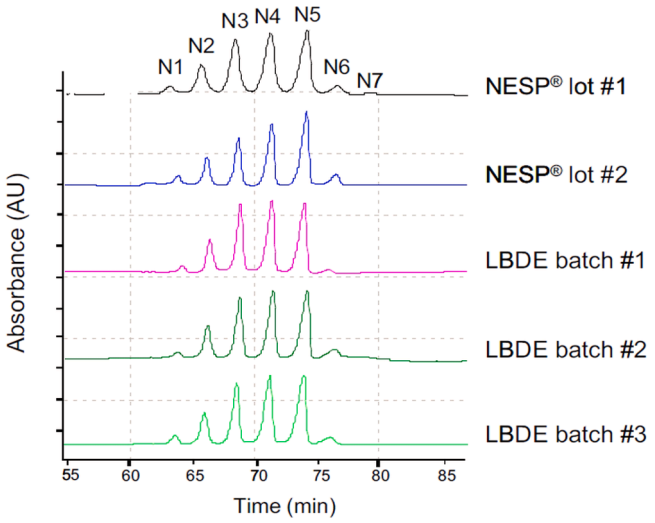

Fig. 4. Comparison of electropherograms of proposed biosimilar darbepoetin alfa, LBDE and NESP® by CZE. Isoforms were labelled from N1 to N7 in the direction of basic to acidic regions. The isoform distribution was regarded as a critical quality attribute that affects the efficacy. LBDE showed a highly similar isoform distribution to NESP®. Reprinted with permission from [50].

biosimilars is still promising. Several diseases have been treated with biological products as a first line therapy such as cancer, diabetes, and autoimmune diseases, thus the demand for these medications will be increasing dramatically. The rapid growth of biosimilars and bio-betters' sciences in the field of therapeutics is expected to reduce healthcare cost and improve patient access to these biologics, assuming clinicians determine the degree of their utility in practice. Biologics and similar products are highly complex in nature therefore, the similar product -not the exact biomolecule- is the intended product with the addressing of non-effective minor alterations during the manufacturing process. In this context, the effective regulatory guidelines that have been adopted by various regulatory agencies worldwide reflect the global concerns about the safety, efficacy and quality of biosimilars. Although the established EMA and USFDA regulations led to clear guidelines for biosimilar development and approval, products interchangeability remains an issue in pharmacy practice. This is due to the different definitions and governing frameworks among these regulatory agencies.

A step-by-step evaluation approach is involved during product development including characterization, pre-clinical, and clinical studies to prove its similarity to the reference biologic regarding safety and effectiveness. Moreover, immunogenicity studies and pharmacovigilance studies are employed as monitoring tools of quality and safety profile when administered to real patients. Characterization of the primary and higher-order protein structure of these biologics is a critical step in their development and registration. Therefore, using highly sensitive and versatile analytical tools such as high-resolution mass spectrometry is widely utilized during both development and quality control processes.

Additionally, the successful biosimilars can provide affordable alternative medical treatments in the market and encourage biologic manufacturers to improve manufacturing process development. This would give rise to biobetters and next-generation biopharmaceuticals.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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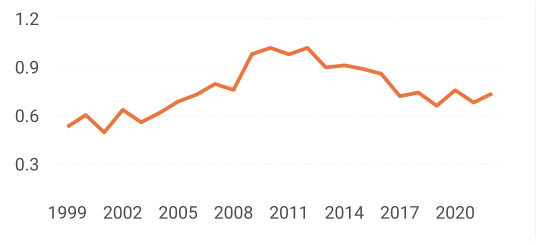

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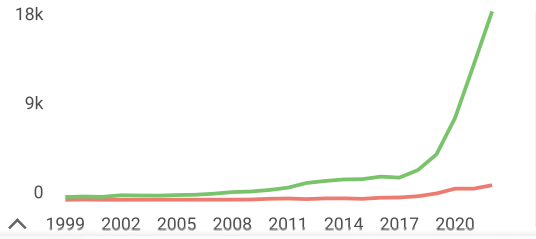

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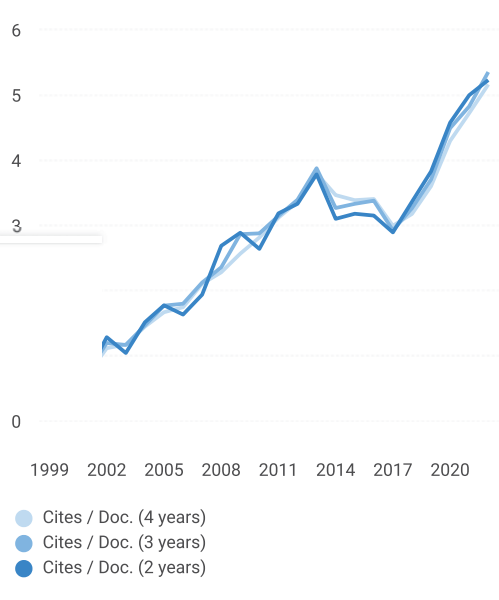

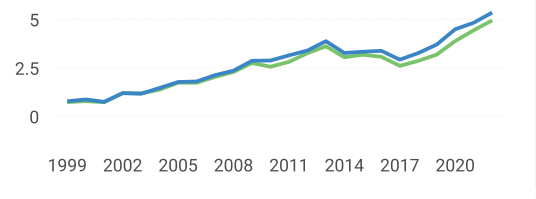

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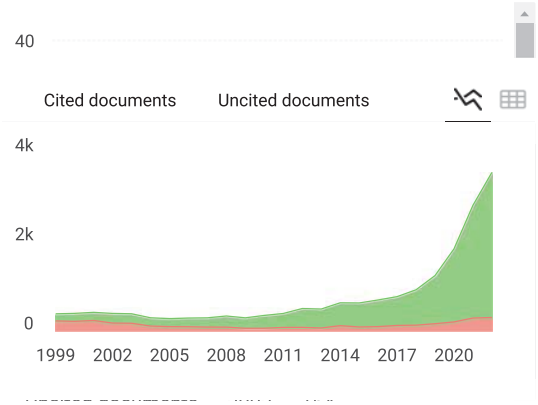

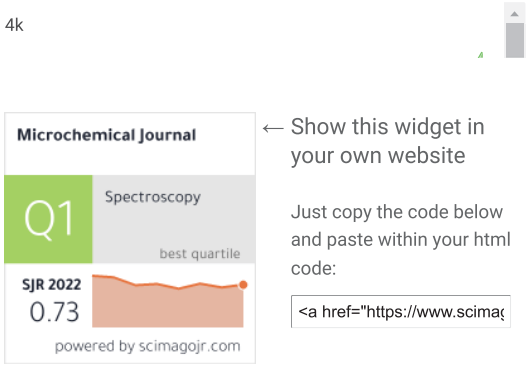

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