



# feature



## The search for biosimilars and biobetters

Scott W. Burchiel<sup>1,5</sup>, [sburchiel@comcast.net](mailto:sburchiel@comcast.net), Rob Aspbury<sup>2,5</sup> and James Munday<sup>2,5</sup>

There has been an increasing trend toward the approval of biosimilars in the USA and the EU. The regulatory requirements for demonstration of bioequivalence with comparator and reference products are now better understood. The original goal of legislation to approve biosimilars through a fast-track process that would lead to more competition and price reductions is starting to be realized. This article updates the current list of approved biosimilars in the USA and the EU. Data are presented that outline products in development, and we discuss some of the hurdles for new entries into the market place. The availability of reference data for comparator products has been a major obstacle to drug development, forcing companies to perform their own side-by-side comparison studies, or pursue new drug development candidates as biobetters.

### Introduction

During the past two decades, many new innovative biologics have been developed by companies for the treatment of cancer and non-cancer diseases. These products include rHuDNA-derived peptides and proteins for replacement therapy of hormones, hematopoietic and other growth factors, blood coagulation products, targeted immunotherapies and humanized monoclonal antibodies. By far the largest group of therapeutic proteins that has emerged comprises humanized monoclonal antibodies for the treatment of cancer and rheumatic diseases. Based on the therapeutic and economic successes of these products, a highly competitive industry has emerged to develop biosimilar drugs [1–8]. In addition, with increased experience with biologics, major efforts are underway to make novel products that have optimized efficacy and safety prop-

erties. These products are referred to as biobetters. As shown in Fig. 1, there are hundreds of biosimilars and biobetters currently under development globally. Biobetters are regulated as new drugs and as such require full safety and efficacy testing. Biobetters have been designed to make improvements in the pharmacokinetics, bioavailability or pharmacologic actions of existing biologic drugs profile. Often, a decrease in immunogenicity for biobetters is also a key goal. This article will update the development of biosimilars currently approved by the EMA and FDA.

The EMA created a pathway in 2004 and then established overarching guidelines supporting biosimilar development between 2004 and 2006, with recent guidance updates [9] ([https://www.ema.europa.eu/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals\\_en.pdf](https://www.ema.europa.eu/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf)). In general, applications for EMA approvals have proceeded at a more rapid rate than in the USA [10–12]. The slow development of biosimilars in the USA has been attributed to several factors, including a lack of clear regulatory guidelines [13]. For example, the FDA introduced the concept of interchangeability, which added regulatory confusion [14,15]. In addition, anticompetition practices, lack of understanding about biosimilars in the medical community, the complexity of US reimbursement and medical payments, and the US legal and patent systems have all been attributed as factors impacting the establishment of biosimilar entrants, and all of these factors have probably contributed to the initially slow development of biosimilars in the USA. There are now 36 countries or regions that have a streamlined process for expedited biosimilar approvals. Biosimilars were foreseen to increase competition, thereby driving the costs

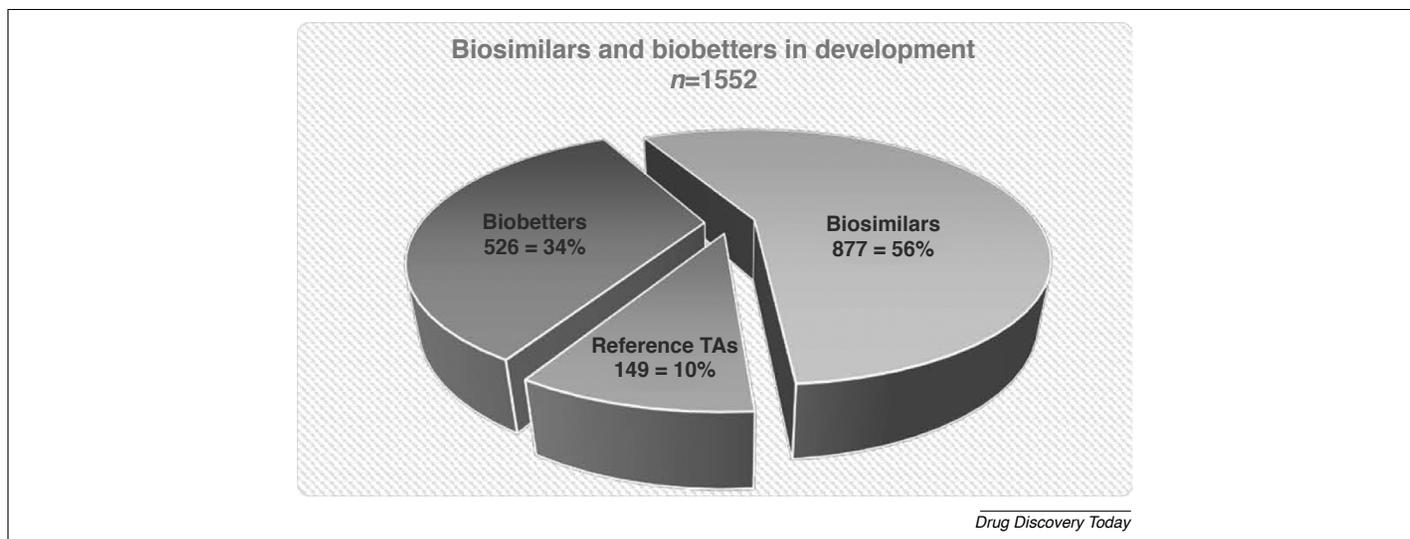


FIGURE 1

Number of products in development for biosimilars, biobetters and reference test articles (TAs) used as comparators. Adapted from Biosimilars/Biobetters Pipeline Database – courtesy of [www.biopharma.com](http://www.biopharma.com).

of these agents down, ultimately benefitting patients and consumers.

The EU has been somewhat ahead of the USA in the number of approved biosimilar products, with the first product approved in 2006. At the time of writing, there are 46 biosimilar products approved by the EMA (Table 1). The products generally fall into two categories: (i) rHuDNA-derived peptides and proteins >100 AA; and (ii) monoclonal antibodies. One key point is that several large biotech and pharmaceutical companies have already entered this market; or have formed partnerships with smaller companies. In addition, there are also several new entrants into the areas of manufacturing, drug development and testing. It is also clear that multiple biosimilar products have been approved that will compete for market share.

The Center for Biologics Evaluation and Research (CBER) within the FDA regulates a wide range of biological products, including allergenic extracts (e.g., for allergy shots and tests), blood and blood components, gene therapy products, devices and test kits, human tissue and cellular products used in transplantation, and vaccines. The Center for Drug Evaluation and Research (CDER) within the FDA regulates other categories of biological products mostly produced by biotechnology methods, including monoclonal antibodies designed as targeted therapies in cancer and other diseases, cytokines, growth factors and enzymes. Human monoclonal biosimilars are therefore regulated by the CDER through a Biologics License Ap-

plication (BLA) process. In the USA, the Biologics Price Competition and Innovation Act (BPCIA) of 2009 Section 351(k) of the PHS Act [42 U.S.C. 55 262(k)], added by the BPCIA, defined an Abbreviated Biologic License Application (aBLA) regulatory framework that would provide a pathway for the expedited process of development and marketing of biosimilars. The biosimilar development pathway with legislation passed as part of the Affordable Care Act was signed into law March 2010 [16]. However, many concerns were expressed concerning legal uncertainties and the amount of data that would be required for clinical trials, and it was predicted that the aBLA process might not be utilized by many companies [17]. Most companies have chosen the traditional BLA route for developing biosimilars, in the hope that they might prove to actually find innovative biobetters [17]. In addition, patient acceptance and physician use of biosimilars might require significant education to recognize the cost savings initially targeted by the BPCIA [18].

The first approval for a biosimilar drug in the USA occurred in 2015 under a 351(k) pathway (Table 2). However, in reality other biosimilars had been approved before this date in the USA under the 505 (b)(2) route, effectively an abbreviated NDA relying on literature and other data not generated by the applicant (e.g., insulins used this path for approval but, being <100 AA in length, they are not covered by current biosimilar legislations). Therefore, this is still a relatively new market in the USA. Eight of the 12 FDA-approved products have previously been

approved by the EMA. It is also clear that the rate of approvals in the USA is increasing.

#### Requirements for biosimilar development

The FDA and the EMA have issued many guidance documents pertaining to the development of biosimilars. Since the EU approved the first biosimilar in 2006, the EMA has played an active role in defining the regulatory framework for the development of these drugs. The EMA has defined overarching guidelines for the development of similar biological medicinal products (CHMP/437/04 Rev. 1) detailing nonclinical and clinical considerations. The EMA has also published general guidelines detailing the quality, safety and efficacy considerations for biosimilars. This should be considered in conjunction with the product-specific requirements that have been published for insulin, human growth hormone, granulocyte-colony-stimulating factor, interferons, heparin, epoietin and monoclonal antibodies. Details of relevant EMA guidelines include the following:

- European Medicines Agency: similar biological medicinal products (overarching guideline) ([https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active\\_en-0.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-0.pdf)) [19];
- European Medicines Agency: similar biological medicinal products containing biotechnology derived proteins as active substance: nonclinical and clinical issues (<https://www.ema.europa.eu/en/documents/scientific->

TABLE 1

## EMA-approved biosimilar drugs (July 2018)

	Biosimilar	Generic name	Company	Approval date
1	Omnitrope <sup>®</sup>	Somatropin	Sandoz	12 April 2006
2	Abseamed <sup>®</sup>	Epoetin alfa	Medice Arzneimittel Pütter	28 August 2007
3	Binocrit <sup>®</sup>	Epoetin alfa	Sandoz	28 August 2007
4	Epoetin Alfa Hexal <sup>®</sup>	Epoetin alfa	Hexal	28 August 2007
5	Retacrit <sup>®</sup>	Epoetin zeta	Pfizer/Hospira	18 December 2007
6	Silapo <sup>®</sup>	Epoetin zeta	Stada Arzneimittel	18 December 2007
7	Ratiograstim <sup>®</sup>	Filgrastim	Ratiopharm	15 September 2008
8	Tevagrastim <sup>®</sup>	Filgrastim	Teva Pharma	15 September 2008
9	Filgrastim Hexal <sup>®</sup>	Filgrastim	Hexal	6 February 2009
10	Zarzio <sup>®</sup>	Filgrastim	Sandoz	6 February 2009
11	Nivestim <sup>®</sup>	Filgrastim	Pfizer/Hospira	8 June 2010
12	Inflectra <sup>®</sup>	Infliximab	Pfizer/Hospira	10 September 2013
13	Remsima <sup>®</sup>	Infliximab	Celltrion Healthcare Hungary	10 September 2013
14	Ovaleap <sup>®</sup>	Follitropin alfa	Teva Pharma	27 September 2013
15	Grastofil <sup>®</sup>	Filgrastim	Apotex Europe	18 October 2013
16	Bemfola <sup>®</sup>	Follitropin alfa	Gedeon Richter	27 March 2014
17	Abasaglar <sup>®</sup> (previously Abasria <sup>®</sup> )	Insulin glargine	Eli Lilly	9 September 2014
18	Accofil <sup>®</sup>	Filgrastim	Accord Healthcare	18 September 2014
19	Benepali <sup>®</sup>	Etanercept	Samsung Bioepis UK (SBUK)	14 January 2016
20	Flixabi <sup>®</sup>	Infliximab	Samsung Bioepis UK (SBUK)	26 May 2016
21	Inhixa <sup>®</sup>	Enoxaparin sodium	Techdow Europe	15 September 2016
22	Thorinane <sup>®</sup>	Enoxaparin sodium	Pharmathen	15 September 2016
23	Lusduna <sup>®</sup>	Insulin glargine	Merck Sharp & Dohme	1 April 2017
24	Terrosa <sup>®</sup>	Teriparatide	Gedeon Richter	1 April 2017
25	Movymia <sup>®</sup>	Teriparatide	STADA Arzneimittel	1 November 2017
26	Truxima <sup>®</sup>	Rituximab	Celltrion Healthcare Hungary	17 February 2017
27	Amgevita <sup>®</sup>	Adalimumab	Amgen Europe	22 March 2017
28	Solymbic <sup>®</sup>	Adalimumab	Amgen Europe	22 March 2017
29	Rixathon <sup>®</sup>	Rituximab	Sandoz	15 June 2017
30	Riximyo <sup>®</sup>	Rituximab	Sandoz	15 June 2017
31	Erelzi <sup>®</sup>	Etanercept	Sandoz	23 June 2017
32	Blitzima <sup>®</sup>	Rituximab	Celltrion Healthcare Hungary	13 July 2017
33	Ritemvia <sup>®</sup>	Rituximab	Celltrion Healthcare Hungary	13 July 2017
34	Rituzena <sup>®</sup> (previously Tuxella <sup>®</sup> )	Rituximab	Celltrion Healthcare Hungary	13 July 2017
35	Insulin lispro Sanofi	Insulin lispro	Sanofi-Aventis	19 July 2017
36	Imraldi <sup>®</sup>	Adalimumab	Samsung Bioepis UK (SBUK)	24 August 2017
37	Cyltezo <sup>®</sup>	Adalimumab	Boehringer Ingelheim International	10 November 2017
38	Ontruzant <sup>®</sup>	Trastuzumab	Samsung Bioepis UK (SBUK)	15 November 2017
39	Mvasi <sup>®</sup>	Bevacizumab	Amgen Europe	15 January 2018
40	Herzuma <sup>®</sup>	Trastuzumab	Celltrion Healthcare Hungary	9 February 2018
41	Semglee <sup>®</sup>	Insulin glargine	Mylan	23 March 2018
42	Kanjinti <sup>®</sup>	Trastuzumab	Amgen Europe	18 May 2018
43	Zessly <sup>®</sup>	Infliximab	Sandoz	18 May 2018
44	Halimatoz <sup>®</sup>	Adalimumab	Sandoz	26 July 2018
45	Hefiya <sup>®</sup>	Adalimumab	Sandoz	26 July 2018
46	Trazimera <sup>®</sup>	Trastuzumab	Pfizer/Hospira	26 July 2018

Data from: <https://www.ema.europa.eu/human-regulatory/overview/biosimilar-medicines>.

[guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active\\_en-2.pdf](#)) [20];

- European Commission. In biosimilars in the EU: information guide for healthcare professionals ([https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals\\_en.pdf](https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf)) [21];
- European Commission: what I need to know about biosimilar medicines. Information for patients (<https://ec.europa.eu/growth/>

[content/commission-publishes-qa-biosimilar-medicines-patients-0\\_en](#)) [22].

For the FDA, guidance documents can be found on the website (<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/ucm444891.htm>) [23] and they include:

- Considerations in demonstrating interchangeability with a reference product. Draft Guidance for Industry CDER/CBER (January 2017);

- Labeling for biosimilar products. Guidance for Industry CDER/CBER (March 2016);
- Biosimilars: additional questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009. Draft Guidance CDER/CBER (May 2015);
- Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for Industry CDER/CBER (April 2015);
- Quality considerations in demonstrating biosimilarity of a therapeutic protein product to a reference product. Guidance for Industry CDER/CBER (April 2015);

**TABLE 2**  
**FDA-approved biosimilar drugs (July 2018)**

	Biosimilar	Generic name	Company	Approval date
1	Zarxio <sup>®</sup>	Filgrastim	Sandoz	6 March 2015
2	Inflixtra <sup>®</sup>	Infliximab	Pfizer	5 April 2016
3	Erelzi <sup>®</sup>	Etanercept	Sandoz	30 August 2016
4	Amjevita <sup>®</sup>	Adalimumab	Amgen	23 September 2016
5	Renflexis <sup>®</sup>	Infliximab	Samsung-Bioepis	21 April 2017
6	Cyltezo <sup>®</sup>	Adalimumab	Boehringer Ingelheim	25 August 2017
7	Mvasi <sup>®</sup>	Bevacizumab	Amgen-Allergan	14 September 2017
8	Ogivri <sup>®</sup>	Trastuzumab	Mylan-Biocon	1 December 2017
9	Lxifi <sup>®</sup>	Infliximab	Pfizer	13 December 2017
10	Retocrit <sup>®</sup>	Epoetin alfa	Pfizer	5 May 2018
11	Fulphila <sup>®</sup>	Pegfilgrastim	Mylan-Biocon	5 June 2018
12	Nivestym <sup>®</sup>	Filgrastim	Pfizer	20 July 2018

Data from: <https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm580432.htm>.

- Questions and answers on biosimilar development and the BPCI Act CDER/CBER (April 2015);
- Reference product exclusivity for biological products filed under Draft Guidance CDER/CBER (August 2014);
- Clinical pharmacology data to support a demonstration of biosimilarity to a reference product. Draft Guidance CDER/CBER (May 2014).

One of the major hurdles for biosimilar development is the availability of appropriate BioCMC data necessary to meet GMP requirements defined in 21 CFR parts 600, 601 and 610. Product specifications, such as identity, purity and stability, as well as detailed manufacturing processes and controls, must be described in a document analogous to a drug master file. The final GMP-produced test article and its associated incipient must be tested for biologic activity *in vitro* and *in vivo*. To qualify as a biosimilar, regulations stipulate that the product must be bioequivalent to the comparator or innovator (reference product). Reference products and associated data can also be a hurdle for development. Therefore, availability of reference product data to compare to the biosimilar is a key consideration and has also generated a significant amount of new work. Thus, as shown in Fig. 1, many current studies are being conducted to generate the necessary data needed for comparison between reference drugs and biosimilars.

To be considered bioequivalent, biosimilars must demonstrate pharmacokinetic profiles that are similar in humans to the reference product. The clinical dose needed for efficacy is also expected to be in the range of the reference product. Finally, the immunogenicity of the biosimilar must also be equivalent to, or no worse than, the reference product. If these criteria are met, a biosimilar can then rely upon a

more limited testing requirement for safety and efficacy in early- and late-stage clinical trials. The early-phase trials assess PK/PD and the late-stage clinical trials are generally a confirmatory comparative trial for safety, efficacy and immunogenicity. Under these conditions, a biosimilar can be approved for the same indications as the reference or comparator drug.

#### A general regulatory strategy for biosimilar development

Given the current regulatory environment and the competitive nature of the marketplace, it is obviously important that companies developing biosimilars have strategies for drug development, testing and filing with global regulatory agencies that consider timelines and expenses. It is not uncommon for a biosimilar drug to take 5 years to complete all phases of development and testing at an expense approaching US\$200 million. In developing a biosimilar drug, a stepwise approach is needed beginning with chemistry manufacturing controls (CMC) and bioanalytical (BioA) characterization. Batches of product must be developed and characterized for consistent uniformity and purity before any *in vitro* and/or *in vivo* preclinical work can proceed.

Whereas the necessary preclinical testing program will differ for each individual agent, some general characteristics can be described. Functional assessment for biologic activity will typically be performed using *in vitro* models that are known to be relevant for human clinical activity. This work will then be followed by animal testing, primarily designed to examine PK/PD activity. The requirement for animal testing varies somewhat by region. Samples can also be taken from animals (typically non-human primates, NHP) to compare immunogenicity of the reference product and the biosimilar.

Based upon satisfactory *in vitro* and *in vivo* PK and PD bioequivalence data, companies can move on to the filing of an investigational new drug (IND) application to permit patient testing in a small number of individuals in a Phase I study. Based upon the potential safety risk of the agent, these studies can be conducted in healthy volunteers or, for immuno-oncology (IO) applications, these studies are conducted in a Phase Ia proof-of-concept (POC) cohort of cancer patients designed to assess PK and safety. In the case of IO agents considered to present minimal risk to patients, some Phase I studies are still conducted in healthy volunteers. Following completion of successful clinical trials, product surveillance and batch testing must continue to ensure successful quality control and post-market surveillance. The FDA and EMA will focus on the 'totality of evidence' when considering the studies and literature used to support a BLA or European application [24]. Biosimilars must have equivalent efficacy, PK/PD, *in vitro* and *ex vivo* biological activity, highly similar immunogenicity and comparable safety to the original reference drug [25].

#### General considerations for biobetters and concluding remarks

Although this article has focused on the development of biosimilars (Fig. 1), there are also many biobetters that are currently in development. Companies are developing many novel products that are truly designer proteins with increased PD properties and increased safety. These products are tested as new chemical entities requiring full preclinical and clinical testing. There have been several recent reviews on the types of structural changes that are being made in biobetters to achieve improved biological properties [8,26–28].

Although no definitive regulatory pathway for biobetters exists, there are still significant advantages of following a biobetter route for approval. Knowing the target biology and clinical background for enabling efficacy in a disease can reduce the risks associated with drug development. This can have a significant reduction in the costs associated with drug development. The market for anti-tumor necrosis factor (TNF) $\alpha$  therapeutics is a good example of how biobetters can be developed and offer significant advantages over the originator compound. Remicade<sup>®</sup> (Janssen) was the first anti-TNF $\alpha$  monoclonal antibody approved by the FDA in 1998. This product was a murine antibody that neutralizes the effect of TNF $\alpha$  in many autoimmune diseases. Despite the good efficacy of this compound the murine structural backbone resulted in high immunogenicity rates for this compound. To

overcome the high immunogenicity rate associated with Remicade<sup>®</sup>, Abbot produced the bio-better known as Humira<sup>®</sup>. This is a human antibody with grafted murine-complementarity-determining regions that bind TNF $\alpha$  and neutralize its effects. The human structural backbone of this therapeutic resulted in a compound with reduced immunogenicity, giving patients potential benefits in treatment. With the increasing rise of new biologics on the market, the potential for new biosimilars and biobetters is a significant drive for the future of drug development.

## References

- Zalcberg, J. (2018) Biosimilars are coming: ready or not. *Intern. Med. J.* 48, 1027–1034
- Wiland, P. et al. (2018) Biosimilar switching – current state of knowledge. *Reumatologia* 56, 234–242
- Pierpont, T.M. et al. (2018) Past, present, and future of rituximab – the world's first oncology monoclonal antibody therapy. *Front. Oncol.* 8, 163
- Scheinberg, M. and Azevedo, V. (2018) The future landscape of biosimilars in rheumatology: where we are where we are going. *Autoimmun. Rev.* . <http://dx.doi.org/10.1016/j.autrev.2018.09.005>
- Gámez-Belmonte, R. et al. (2018) Biosimilars: concepts and controversies. *Pharmacol. Res.* 133, 251–264
- Cohen, H.P. et al. (2018) Switching reference medicines to biosimilars: a systematic literature review of clinical outcomes. *Drugs* 78, 463–478
- Ho, R.J. (2017) Midyear commentary on trends in drug delivery and clinical translational medicine: growth in biosimilar (complex injectable drug formulation) products within evolving collaborative regulatory interagency (FDA, FTC, and DOJ) practices and enforcement. *J. Pharm. Sci.* 106, 471–476
- Kesik-Brodacka, M. (2018) Progress in biopharmaceutical development. *Biotechnol. Appl. Biochem.* 65, 306–322
- European Medicines Agency Guidance. Available at: [https://www.ema.europa.eu/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals\\_en.pdf](https://www.ema.europa.eu/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf).
- Santos, S.B. et al. (2018) Biosimilar medicines used for cancer therapy in Europe: a review. *Drug Discov. Today* . <http://dx.doi.org/10.1016/j.drudis.2018.09.011>
- Rahalkar, H. et al. (2018) Non-clinical and clinical considerations for biosimilar monoclonal antibody development: EU, WHO, USA, Canada, and BRICS-TM Regulatory Guidelines. *Front. Pharmacol.* 9, 1079
- Ishii-Watabe, A. and Kuwabara, T. (2018) Biosimilarity assessment of biosimilar therapeutic monoclonal antibodies. *Drug Metab. Pharmacokinet.* . <http://dx.doi.org/10.1016/j.dmpk.2018.11.004>
- Konara, C.S. et al. (2015) The tortoise and the hare: evolving regulatory landscapes for biosimilars. *Trends Biotechnol.* 34, 70–83
- Sarpatwari, A. et al. (2018) The US biosimilar market: stunted growth and possible reforms. *Clin. Pharmacol. Ther.* 105, 92–100
- Dougherty, M.K. et al. (2018) Perspectives on the current state of the biosimilar regulatory pathway in the U.S. states. *Clin. Pharmacol. Ther.* 103, 36–39
- FDA Guidance. Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf>.
- Wiatr, C. (2011) US biosimilar pathway unlikely to be used: developers will opt for a traditional BLA filing. *BioDrugs* 25, 63–67
- Bakalos, G. and Zintzaras, E. (2018) Drug discontinuation in studies including a switch from an originator to a biosimilar monoclonal antibody: a systematic literature review. *Clin. Ther.* . <http://dx.doi.org/10.1016/j.clinthera.2018.11.002>
- European Medicines Agency Guidance. Available at: [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medical-products-containing-biotechnology-derived-proteins-active\\_en-0.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medical-products-containing-biotechnology-derived-proteins-active_en-0.pdf).
- European Medicines Agency Guidance. Available at: [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medical-products-containing-biotechnology-derived-proteins-active\\_en-2.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medical-products-containing-biotechnology-derived-proteins-active_en-2.pdf).
- European Medicines Agency. In biosimilars in the EU: information guide for healthcare professionals. Available at: [https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals\\_en.pdf](https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf).
- European Commission. What I need to know about biosimilar medicines. Information for patients. Available at: [https://ec.europa.eu/growth/content/commission-publishes-qa-biosimilar-medicines-patients-0\\_en](https://ec.europa.eu/growth/content/commission-publishes-qa-biosimilar-medicines-patients-0_en).
- FDA Guidance Documents. Available at: <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/ucm444891.htm>.
- Christl, L. FDA's Overview of the Regulatory Guidance for the Development and Approval of Biosimilar Products in the US. US FDA Website. Available at: <https://www.fda.gov/downloads/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm428732.pdf>.
- European Medicines Agency Guidance. Available at: [https://www.ema.europa.eu/documents/scientific-guideline/guideline-similar-biological-medical-products-containing-mono-clonal-antibodies-non-clinical\\_en.pdf](https://www.ema.europa.eu/documents/scientific-guideline/guideline-similar-biological-medical-products-containing-mono-clonal-antibodies-non-clinical_en.pdf).
- Elgundi, Z. et al. (2017) The state-of-play and future of antibody therapeutics. *Adv. Drug Deliv. Rev.* 122, 2–19
- Strohl, W.R. (2015) Fusion proteins for half-life extension of biologics as a strategy to make biobetters. *BioDrugs* 29, 215–239
- Barbosa, M.D. et al. (2012) Biosimilars and biobetters as tools for understanding and mitigating the immunogenicity of biotherapeutics. *Drug Discov. Today* 17, 1282–1288

Scott W. Burchiel<sup>1,\*</sup>,<sup>5</sup>  
Rob Aspbury<sup>2,5</sup>  
James Munday<sup>2,5</sup>

<sup>1</sup>Covance Labs, Madison, Wisconsin, USA

<sup>2</sup>Covance Labs, Harrogate, England, UK

\*Corresponding author.

<sup>5</sup>The authors are solely responsible for the content of this article.