CMC considerations for US biosimilars development

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KEYWORDS

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ABSTRACT

The US Biologics Price Competition and Innovation Act of 2009 (BPCI Act) provides an abbreviated licensure pathway for biosimilar products. This pathway brought the hope of lower cost biologics, perhaps similar to what was accomplished by generics for small molecule drugs. Twelve years have now passed since the BPCI Act and experience continues to be gained with biosimilars development. With this experience comes the knowledge of the essential CMC-related considerations for development that may be overlooked by those who are new to this product type. This paper discusses: the importance of Chemistry, Manufacturing and Controls (CMC) data in the biosimilar application; what is meant by an 'abbreviated' licensure pathway; the role of the reference product; the preparation for biosimilar inspections; and how careful timing of manufacturing changes can lead to faster approval without sacrificing process optimisation.

Introduction

Biologics are used to treat serious and life-threatening diseases. Most biologics are used to treat cancer, but they have many other indications, such as diabetes, monogenic diseases, and enzyme replacement therapies. They are complex macromolecules, with even more complex manufacturing processes encompassing cell banking, upstream process in bioreactors, multi-step downstream process to purify the active substance and complex formulation to allow product integrity. All this complexity leads to higher costs and lengthy development times. In the US, spending on biologics represents 40% of total sales of prescription drugs. Currently, the US is experiencing success from the use of the 1984 Hatch Waxman Act, which established an approval pathway for generic drugs, facilitating competition between generic drugs and their corresponding brand-name drugs to make healthcare savings. Specifically, the US has achieved healthcare savings of close to US$2.2 trillion in the past decade owing to the use of generics, with US$313 billion saved in 2019 alone. Policymakers believed they could reproduce the success that they had with generics with biosimilars. In 2018, Mulcahy et al estimated that biosimilars would lead to a reduction of US$54 billion in direct spending on biologic drugs, or about 3% of total estimated biologic spending, between 2017 and 2026. Policymakers, regulators and biosimilar drug developers all hope that the savings can be increased as more biosimilars enter the market.

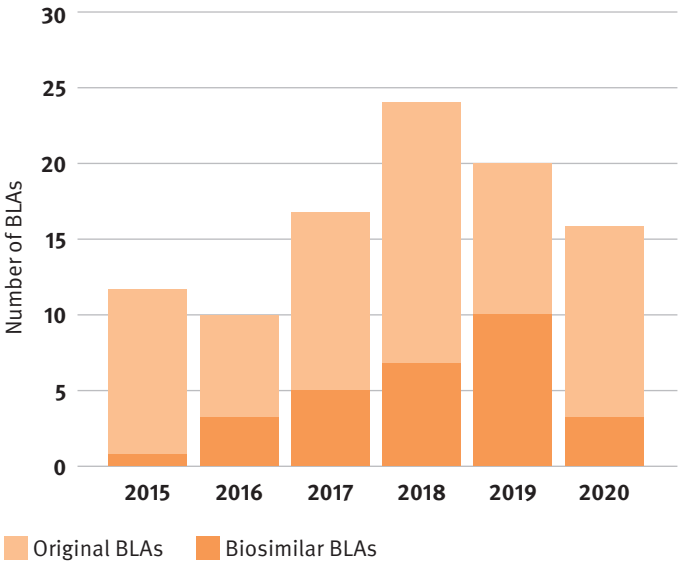
The BPCI Act established an abbreviated licensure pathway for biologic products that are biosimilar to an FDA-licensed reference product. Using the biosimilar licensure pathway, sponsors must demonstrate biosimilarity based on a totality of evidence from analytical studies, animal studies (if applicable) and clinical studies. To be deemed biosimilar, the biologic product must be highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and there must be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency.

One of the factors that could impact the approval of biosimilars is that we are still learning how to develop, manufacture and regulate biosimilars. Although some may see similarities between biosimilars and generics, a biosimilar is not simply a 'biologic generic'. Small molecule drugs can be made with high levels of homogeneity via chemical processes, whereas biologic drugs are inherently heterogenous because they are made from living host cells. Moreover, biologic drugs are much more complex macromolecules, often with multiple elements contributing to its mode of action in vivo. These differences make biosimilar development more challenging and approaches that have previously been successful for generic drugs may not be as successful for biosimilars. The new biosimilar licensure pathway was established in 2009; however, it was not until 2015 that the FDA published 'Scientific considerations in demonstrating biosimilarity to a reference product', the first biosimilar guidance describing considerations for the development of biosimilars. Also in 2015, the first US biosimilar product, Sandoz's Zarxio, was approved. As of November 2021, only 31 biosimilars have been approved (see Table 1), with the number of biosimilar approvals typically lagging behind the number of originator Biologics License Application (BLA) approvals per year (see Figure 1). As the field continues to acquire regulatory experience, it is becoming clear that the path to the successful approval of a biosimilar product has important differences compared with the approval of an original product.

CMC data underpin biosimilar applications

One main difference between the development of an originator product and a biosimilar product is that the CMC work is 'front-loaded'. Typically, resources for originator products are focused on clinical development in the early phase for originator products. On the other hand, the first step in biosimilar development focuses on understanding the physicochemical and biological characteristics of the reference product via a comprehensive and robust analytical characterisation, as well as a review of publicly available information. Then, the biosimilar product's process is designed to manufacture a product that is highly similar to the reference product. Next, the sponsor should perform a robust comparison of the reference product and biosimilar product to identify any differences and determine

Figure 1 **FDA biologics licence application approvals by year**



Since the approval of the first biosimilar in 2015, a larger number of original BLAs are typically approved within a given year, compared with biosimilar BLAs. Data for this table was compiled from the Purple Book Database of Licensed Biological Products. Available at: https://purplebooksearch.fda.gov/ (accessed 18 November 2021)

the impact of these on clinical performance. The quality attributes tested as part of the comparison should be based on what is known about the physicochemical and biological characteristics of the reference product. An example of quality attributes and methods that could be included in the comparison is listed in Table 2. It is important to complete an adequate comparative analytical assessment because these data inform the amount and type of animal and clinical data that will be needed to fully support development.

When designing the comparative analytical studies, it is important to consider that this assessment is not the same as a comparability assessment that is performed to support a manufacturing change. For a manufacturing change, the process is well-controlled and supported by the sponsor's extensive product and process characterisation data. On the other hand, the biosimilar sponsor will need to independently acquire product and process characterisation data. For originator product development, comparability studies supporting any process changes often include side-by-side comparisons of both drug substance and drug product. One of the main challenges of biosimilar development is the lack of access to the originator drug substance, creating a need to design comparability plans that are supported by solid analytical methods, that can characterise and compare in parallel the drug substance and the drug product. The biosimilar sponsor is also likely to use a different host cell, manufacturing process, manufacturing site, test methods and raw materials than those used for the originator product. Therefore, although elements of 'ICH Q5E: comparability of biotechnological/biological products subject to changes in their manufacturing process' can be applied to biosimilars development, it is important to understand that a demonstration of biosimilarity is more complex than a demonstration of comparability after a change is made by the same manufacturer.

Abbreviated 351(k) pathway

The next consideration is that the CMC and regulatory standards are the same for originator and biosimilar products. Too often, the abbreviated nature of the 351(k) pathway is mistaken as a lower drug approval standard. The need for a robust and adequately controlled manufacturing process, as well as the standards for safety, are consistent among originator and biosimilar products. When the 351(k) pathway is described as abbreviated, this refers to the ability of the applicant to leverage previous FDA determinations for the reference product (ie, determinations of efficacy from clinical data). This approach could facilitate a shorter and less costly drug development programme. In addition, the need for a strong narrative and coherent storytelling within the application remains of utmost importance. In the urgency to create a biosimilar product, the applicant may neglect the need for compelling writing to clearly state scientific rationales and to link the data to regulatory requirements. In these cases, applicants may opt to provide study reports, with no accompanying narratives. Instead, applicants should ideally invest resources in the writing to ensure that the data, information and scientific rationale are presented as clearly as possible.

Comparing to the reference product

The reference product is the single biological product licensed under section 351(a) of the Public Health Service Act, against which the proposed biosimilar is evaluated. Therefore, the reference product must be a US product that currently holds a license and cannot be, for example, an EMA-approved product. Of interest, FDA regulations allow an applicant to leverage non-clinical or clinical data obtained using a non-US-licensed comparator, with appropriate bridging. With this approach, comparative data from the proposed biosimilar, US-licensed reference product and the non-US-approved comparator must be provided to support the 'three-way bridge' from a clinical and analytical perspective. In this instance, there is still only one reference product – the US-licensed product. This can be an attractive approach when there is a limited supply of the US-licensed reference product, or if the applicant is considering global commercialisation.

Preparing for inspections

Preparations for the current Good Manufacturing Practice (cGMP) pre-licensing inspection (PLI) are a common part of BLA planning and should form part of plans for a 351(k) BLA. For both 351(a) and 351(k) BLAs, the cGMP PLI will include inspectors with a range of experiences and backgrounds. Applicants should expect the inspection team to include the same product quality, microbiology and facility reviewers that are assessing the BLA submission. Compared with surveillance inspections, which focus primarily on compliance with cGMP, these PLIs tend to be more technical as the subject matter experts reviewing the BLA are also part of the FDA inspection team. Generally, the PLI is scheduled in advance as the product must be scheduled for manufacturing during the inspection.

In addition to the PLI, 351(k) BLA applicants should expect scheduling of a biosimilar inspection. The purpose of the biosimilar inspection includes confirmation of the accuracy of the data provided in the 351(k) BLA, and that the comparative analytical data were collected using suitable assays, with adequate controls and that all the data supporting the 351(k) BLA are appropriately documented. Since so much of the 351(k) BLA hinges on the CMC and comparative analytical data, the outcome of the biosimilar inspection is a vital component of the FDA decision. The location of the biosimilar inspection depends on where the critical comparative analytical data were collected. Sometimes, the biosimilar inspection occurs in parallel with the drug substance and/or drug product manufacturing site inspections if the sites are close geographically. In other instances, a standalone biosimilar inspection will be scheduled, or multiple biosimilar inspections may be scheduled. As with the PLI, the biosimilar inspection is scheduled in advance as the site is expected to have all the necessary

Table 1 List of current US biosimilar approvals*

Biosimilar			Reference product	
Trade name (non-proprietary name)	**Sponsor**	**Approval date**	**Trade name**	**Sponsor**
1. Zarxio (filgrastim-sndz)	Sandoz	6 March 2015	Neupogen	Amgen
2. Inflectra (infliximab-dyyb)	Celltrion	5 April 2016	Remicade	Janssen Biotech
3.Erelzi (etanercept-szza)	Sandoz	30 August 2016	Enbrel	Immunex Corporation
4. Amjevita (adalimumab-atto)	Amgen	23 September 2016	Humira	AbbVie
5. Renflexis (infliximab-abda)	Samsung Bioepis	21 April 2017	Remicade	Janssen Biotech
6. Cyltezo (adalimumab-adbm)	Boehringer Ingelheim Pharmaceuticals	25 August 2017	Humira	AbbVie
7. Mvasi (bevacizumab-awwb)	Amgen	14 September 2017	Avastin	Genentech
8. Ogivri (trastuzumab-dkst)	Mylan Pharmaceuticals	1 December 2017	Herceptin	Genentech
9. Ixifi (infliximab-qbtx)	Pfizer Ireland Pharmaceuticals	13 December 2017	Remicade	Janssen Biotech
10. Retacrit (epoetin alfa-epbx)	Hospira	15 May 2018	Epogen / Procrit	Amgen
11. Fulphila (pegfilgrastim-jmdb)	Mylan Pharmaceuticals	4 June 2018	Neulasta	Amgen
12. Nivestym (filgrastim-aafi)	Pfizer	20 July 2018	Neupogen	Amgen
13. Hyrimoz (adalimumab-adaz)	Sandoz	30 October 2018	Humira	AbbVie
14. Udenyca (pegfilgrastim-cbqv)	Coherus BioSciences	2 November 2018	Neulasta	Amgen
15. Truxima (rituximab-abbs)	Celltrion	28 November 2018	Rituxan	Genentech
16. Herzuma (trastuzumab-pkrb)	Celltrion	14 December 2018	Herceptin	Genentech
17. Ontruzant (trastuzumab-dttb)	Samsung Bioepis	18 January 2019	Herceptin	Genentech
18. Trazimera (trastuzumab-qyyp)	Pfizer Ireland Pharmaceuticals	11 March 2019	Herceptin	Genentech
19. Eticovo (etanercept-ykro)	Samsung Bioepis	25 April 2019	Enbrel	Immunex Corporation
20. Kanjinti (trastuzumab-anns)	Amgen	13 June 2019	Herceptin	Genentech
21. Zirabev (bevacizumab-bvzr)	Pfizer	27 June 2019	Avastin	Genentech
22. Ruxience (rituximab-pvvr)	Pfizer	23 July 2019	Rituxan	Genentech
23. Hadlima (adalimumab-bwwd)	Samsung Bioepis	23 July 2019	Humira	AbbVie
24. Ziextenzo (pegfilgrastim-bmez)	Sandoz	4 November 2019	Neulasta	Amgen
25. Abrilada (adalimumab-afzb)	Pfizer	15 November 2019	Humira	AbbVie
26. Avsola (infliximab-axxq)	Amgen	6 December 2019	Remicade	Janssen Biotech
27. Nyvepria (pegfilgrastim-apgf)	Pfizer	10 June 2020	Neulasta	Amgen
28. Hulio (adalimumab-fkjp)	Mylan Pharmaceuticals	6 July 2020	Humira	AbbVie
29. Riabni (rituximab-arrx)	Amgen	17 December 2020	Rituxan	Genentech
30. Semglee (insulin glargine-yfgn)	Mylan Pharmaceuticals	28 July 2021	Lantus	Sanofi-Aventis US
31. Byooviz (ranibizumab-nuna)	Samsung Bioepis	17 September 2021	Lucentis	Genentech

*The information in this table was compiled from the Purple Book Database of Licensed Biological Products Available at: https://purplebooksearch.fda.gov/ (accessed 18 November 2021).

documents and subject matter experts immediately available for inspection and questions on the FDA team's arrival. It is important for applicants to be aware of the need for a biosimilar inspection and for them to prepare their team according to the specific needs of a biosimilar inspection.

Timing of manufacturing changes

Typically, drug manufacturing processes are optimised and scaled up several times prior to the BLA submission. In order to leverage early CMC development data (eg, stability data) to support BLA submission, applicants routinely provide comparability data to bridge the product from all stages of development to the proposed commercial product. For a biosimilar BLA, the comparisons to the reference product are often made early in the development of the biosimilar product. In this case, the comparisons must be expanded to include the commercial product for the 351(k) BLA.

After biosimilar approval, the FDA draft guidance, 'New and revised draft Q&As on biosimilar development and the BPCI Act' (Revision 2; December 2018), indicates that post-approval manufacturing changes for a licensed biosimilar should follow the principles outlined in ICH Q5E, but does not state that additional comparative analytical assessments to the reference product must be performed. Comparability studies to support post-approval changes should ensure no drifts in product quality with respect to batch-to-batch variability and the similarity to the reference product. Therefore, planning of submissions (ie, the initial 351(k) BLA versus subsequent supplements) should consider what is required for commercialisation (should be prioritised for the initial 351(k) application), the type of change, the number of batches that would be required to support biosimilarity at the time of the initial 351(k) approval versus to support a post-approval change, and whether an additional inspection may be needed to support

Table 2 Example of quality attributes and methods for comparison of the biosimilar to the reference product*

Quality attribute	Methods
Primary structure	• Reduced and non-reduced peptide mapping with ultraviolet (UV) and mass spectrometry (MS) detection and various enzymes • Amino acid composition analysis • Intact molecular mass (LC-MS and/or electrospray ionisation time-of-flight MS, ESI-TOF-MS) • Reduced and deglycosylated molecular mass (LC-MS) • N- and C-terminal sequence (peptide mapping with LC-MS/MS) • Molar absorptivity and extinction coefficient calculation
Protein content	Concentration (UV280)
Higher order structure	• Near UV circular dichroism • Fourier transform infrared spectroscopy (FTIR) • Liquid chromatography coupled with mass spectrometry (LC-MS) • Ellman's assay (disulfide bond characterisation) • Differential scanning calorimetry (DSC) • Disulfide bond analysis by native and reducing peptide mapping (LC-MS)
Size variants/aggregates	• Size exclusion chromatography (SEC) • SEC with multi-angle light scattering (SEC-MALS) • SEC with static light scattering (SEC-SLS) • Analytical ultracentrifugation sedimentation velocity (AUC-SV) • Field flow fractionation (FFF) • Dynamic light scattering (DLS) • Reduced and non-reduced capillary electrophoresis sodium dodecyl sulphate (CE-SDS)
Charge	• Capillary isoelectric focusing (cIEF) • Ion exchange chromatography (IEX)
Post-translational modifications	Deamidation, oxidation, N-terminal glutamine and C-terminal lysine (peptide mapping)
Glycosylation**	• N-linked glycan analysis (high performance anion exchange chromatography with pulsed amperometric detection, HPAEC-PAD, and/or LC-MS) • Hydrophilic-interaction liquid chromatography (HILIC) • Sialic acid content • Monosaccharide composition analysis (HPAEC-PAD) • Glycation analysis by reducing intact mass analysis
Potency/biological activity***	• Cell based assay • ELISA binding assay • SPR binding assay

*The quality attributes used to compare a particular biosimilar with its reference product should be based on the physicochemical and biological characteristics of the reference product. The quality attributes listed in this table are examples and may not be relevant for all biosimilars. The information in this table was compiled from FDA Oncologic Drugs Advisory Committee Briefing Documents, available at https://www.fda.gov/media/106528/download (accessed 18 November 2021).
**Glycan analyses are only relevant for products expected to have glycans.
***Typically, many more potency/biological activity assays are included in the comparative analysis. The types of potency and biological activity assays used for a particular biosimilar comparison are directly linked to the mechanism of action and biological properties of the reference product. Cell based and binding assays are generally included in most biosimilar programmes and are listed here as examples.

the change. Depending on the CMC changes and timing of implementation, the resource and time commitments could differ, and it is recommended that some changes are staggered in order to gain licensure faster. Therefore, one strategy may involve requesting licensure of an 'intermediate' manufacturing process, for which all the data/information required for licensure are readily available. Then, the applicant could continue to collect additional data in parallel and submit a supplement to request approval of perhaps a larger-scale/more commercially viable process immediately after licensure is obtained. This approach could reduce the burden of resources needed to obtain licensure, while allowing for additional manufacturing capacity to be implemented soon afterwards.

Conclusion

Biosimilars bring the promise of more affordable biologics by paving the way for an abbreviated licensure pathway. However, it is already apparent that there are differences in the technical and CMC regulatory strategy that should be applied to biosimilars development. Just six years after the first US biosimilar approval, the field – including both drug developers and regulators – is still learning the best way to develop and license biosimilars. The US, with a tally of 31 licensed biosimilars as of November 2021, still lags behind the EU, which has more than double that number of approved biosimilars. Considering the number of biosimilars approved by the FDA versus the EMA, there are noted similarities in biosimilar development across the Atlantic. For example, both the US and EU allow the use of a reference product not approved in their region if supported by adequate three-way bridging data. It will be interesting to follow the development of biosimilars regulation in the US compared with the EU as the field matures.■

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Additional resources

1. FDA draft guidance: development of therapeutic protein biosimilars: comparative analytical assessment and other quality-related considerations (May 2019)
2. FDA guidance: guidance for industry scientific considerations in demonstrating biosimilarity to a reference product (April 2015)
3. FDA draft guidance: new and revised draft Q&As on biosimilar development and the BPCI Act (Revision 3) (September 2021)
4. ICH Q5E: comparability of biotechnological/biological products subject to changes in their manufacturing process
5. FDA guidance: quality considerations in demonstrating biosimilarity of a therapeutic protein product to a reference product (April 2015)