
The establishment of Biologics as Biosimilars and “Interchangeable”

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Word count: 2999

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Introduction

The Center for Biologics Evaluation and Research (CBER) is an organization within the Food and Drug Administration (FDA) that has been tasked for the evaluation of the safety and efficacy and the regulation of biologics.¹ Biologics, according to section 351(i) of the Public Health Service (PHS) act, has been defined as a “virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.”² As such, biologics are therapeutics originating from biological materials including blood, cells, tissues and with the advent of biotechnology, gene-based treatments.³

Biologics are different from the small molecules which we generally consider to be drugs or medications and which are regulated by the Center for Drug Evaluation and Research (CDER). Small molecules are chemically synthesized and have a well-defined chemical structure which can be readily reproduced under strict adherence to the respective protocols. Biologics tend to be complex and large molecule usually without well-defined characteristics observed of chemical entities.⁴ Furthermore, in cell or gene therapy, there is no one chemical or structural entity that defines the biologic therapeutic as it is a conglomerate of molecules and structural entities that encompasses the biologic in such situations.

Challenges associated with biologics

Unlike small molecule entities, manufacturing of biologics is consumed with challenges. Biologics inherently suffer from variability influenced by the physiological state of the organism or the cell from which they are extracted. Compounded by the fact that biologics are large

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complex molecules that constitute a plethora of organic molecules and structures, the control of such variability proves to be of drastic challenge.⁶

Since batch-to-batch consistency can be reasonably guaranteed with drugs, they can be readily analyzed in the laboratory prior to release for distribution. In addition, their manufacturing process can be modified, especially if establish batch-to-batch consistency can be established. However, this flexibility is not available for manufacturing of biologics. Maintaining batch-to-batch consistency is challenging for biologics since they are susceptible to alterations in cellular physiology even with minor changes in the manufacturing process.⁵ In addition, the molecular complexity makes biologics particularly difficult to analyze in the laboratory, prior to their release for distribution. The only way manufacturers can guarantee batch-to-batch consistency is by ensuring strict adherence of biologics to the manufacturing process with tight controls and adherence of protocols.⁶

Definition and concept of biosimilars

Similar to Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act) which was implemented to increase market competition through the introduction of generic drugs, the Biologics Price Competition and Innovation Act (BPCIA) of 2009 helped create a pathway for biosimilars.⁷ Biosimilars are to biologics akin to what generics are to drugs. FDA defines biosimilars as “a biological product that is highly similar to a US-licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product”.⁸ A list of currently FDA-approved biosimilars is shown in table 1.⁹ The European Medicines Agency (EMA) definition of biosimilars is on par with that of the FDA. However, unlike FDA which may

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view small biologics such as insulin and human growth hormone as semisynthetic and allow their development under the abbreviated New Drug Application (aNDA), the EMA has taken the position that these small molecules biologics are biosimilars and are to be developed as such.⁸

Table 1: List of the 31 FDA-approved biosimilars, their approval date, and the reference product against which they were developed.⁹

Name of Biosimilar	Approval Date	Reference product	
		Trade Name	Generic Name
Hulio	July 2020	Humira	adalimumab
Abrilada	November 2019	Humira	adalimumab
Hadlima	July 2019	Humira	adalimumab
Hyrimoz	October 2018	Humira	adalimumab
Cyltezo	August 2017	Humira	adalimumab
Amjevita	September 2016	Humira	adalimumab
Zirabev	June 2019	Avastin	bevacizumab
Mvasi	September 2017	Avastin	bevacizumab
Retacrit	May 2018	Epogen	epoetin-alfa
Eticovo	April 2019	Enbrel	etanercept
Erelzi	August 2016	Enbrel	etanercept
Nivestym	July 2018	Neupogen	filgrastim
Zarxio	March 2015	Neupogen	filgrastim
Avsola	December 2019	Remicade	infliximab
Ixifi	December 2017	Remicade	infliximab
Renflexis	May 2017	Remicade	infliximab
Inflectra	April 2016	Remicade	infliximab
Semglee	July 2021	Lantus	Insulin glargine
Nyvepria	June 2020	Neulasta	pegfilgrastim
Ziextenzo	November 2019	Neulasta	pegfilgrastim
Udenyca	November 2018	Neulasta	pegfilgrastim
Fulphila	June 2018	Neluasta	pegfilgrastim
Byooviz	September 2021	Lucentis	ranibizumab
Riabni	December 2020	Rituxan	rituximab
Ruxience	July 2019	Rituxan	rituximab

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Truxima	November 2018	Rituxan	rituximab
Kanjinti	June 2019	Herceptin	trastuzumab
Trazimera	March 2019	Herceptin	trastuzumab
Ontruzant	January 2019	Herceptin	trastuzumab
Herzuma	December 2018	Herceptin	trastuzumab
Ogivri	December 2017	Herceptin	trastuzumab

While the reference biologic product is filed and licensed under 351(a), biosimilars are filed as abbreviated Biologics License Application (aBLA) under 351(k), of the PHS act.¹⁰ Similar to the aNDA for generics, the intent of the aBLA is to avoid duplicative and costly clinical trials for articles whose safety and efficacy has already been established by the reference product. However, there is difference in the regulatory process between aNDA and aBLA. With respect to aNDA, the manufacturer must show that the active pharmaceutical ingredient (API) is not only chemically equivalent to that of the brand name drug but also bioequivalent.¹¹ In contrast, the constraints associated with biologics require manufacturers to demonstrate high similarity of the biosimilar with that of the reference product even with minor differences with the clinically inactive components; and without significant difference in the clinical safety and effectiveness of the product.¹²

Developing biosimilars consist of manufacturing challenges that renders it to critical regulatory oversight. Frequently, the processes and controls developed for the manufacturing of the reference product are patented.⁸ These proprietary concerns limit the manufacturer access to protocols needed in the development of the biosimilar as highly similar to the reference product. Additionally, biologics introduce considerable variables in the manufacturing process.⁵ Any minor changes to the manufacturing process may result in significant drift of the analysis of the biosimilar. This phenomenon, which is observed with the reference product also,

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may compromise the integrity of the biosimilar as a marketable product.¹³ More so, the director of CBER has the authority to request lot samples for analysis to biosimilars especially when the safety, purity, or potency of the product is called into question.¹⁴

While a biosimilar product is highly similar to the reference product, it does not necessarily imply that the product is interchangeable. There are two separate pathways created by the BPCIA: biosimilarity and interchangeability. A highly similar product can be demonstrated through comparative in-vitro tests for “purity, chemical identity, and bioactivity.”¹⁵ A biosimilar that is interchangeable needs to demonstrate, in addition, comparable and lack of clinical difference, with respect to safety and efficacy, between the biosimilar and the reference product. Substantiation of these additional requirements will deem the biosimilar interchangeable, allowing it to be substituted for the reference product without the intervention of a medical prescriber, albeit, select states prevent non-prescribers from taking such measures.¹⁵ In contrast, a biosimilar product that has not been deemed interchangeable by the FDA can only be substituted with the authorization of a medical prescriber.

Demonstrating biosimilarity with reference product

A biosimilar may not be interchangeable with a reference product, however, a biosimilar must be highly similar in order for it to demonstrate interchangeability.¹⁶ FDA evaluates the totality of evidence before deciding if the 351(k) application meets the standard of 351(a) reference standard.¹² For biosimilars, data to prove high similarity may be “derived from analytical studies, animal studies, and a clinical study.”¹² In evaluating the totality of evidence, FDA may require additional studies to ensure that the biosimilar meets the standard of the reference product. To demonstrate interchangeability, additional clinical studies and switching

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studies may be necessary.¹⁶ Further details pertaining to the necessary studies and requirements for the 351(k) application are described below.

Analytical testing

Analytical characterization of the physicochemical and biological properties of the biosimilar are required to demonstrate its similarity to the reference product with respect to identity, quantity, purity, and potency. Any difference observed during assessment should be further evaluated to understand its impact on performance in clinical setting.¹² During analysis residual uncertainties may arise due to limitations of the analytical techniques involved. Understanding these residual uncertainties and “the relationship of a product’s structural attributes and its clinical performance” is critical to the employment of the necessary testing with “adequate sensitivity and specificity to detect and characterize differences between proposed product and the reference product”.¹² In addition, all relevant assays that demonstrate the functional activity (including mechanism of action), the specific target binding properties (if applicable), and quantification and identification of impurities need to be performed. The latter being particularly important to help understand if further pharmacological or toxicological studies are needed. Also, stability profiles are necessary to not only evaluate the shelf life and storage conditions but also to “reveal product differences that warrant additional evaluations.”¹⁷

Non-clinical testing

The use of animal studies in ascertaining high similarity between the biosimilar and the reference product may be required when analytical results call into question the residual uncertainty of the biosimilar. They are included as part of the totality of evidence to help substantiate product safety and overall biosimilarity of the 351(k) application with that of the reference product.¹² Usually, animal toxicity studies can help address concerns related to

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residual uncertainties. Accordingly, “if comparative structural and functional data using the proposed product provide strong support for analytical similarity to a reference product, then limited animal toxicity data” may be needed.¹² If the analytical data calls into question the quality and safety of the biosimilar, a thorough toxicological panel may be required. In some cases, a pharmacodynamic (PD) and pharmacokinetic (PK) study may suffice to demonstrate the high similarity. When the extent of manufacturing of the biosimilar varies considerably from the reference product, or the antigenic propensity of an excipient or residue is called into question, animal immunogenicity studies may be warranted.¹²

Clinical pharmacology

To help ensure that the biosimilar product is as safe, pure, and potent as the reference product, human PK/PD studies are required to be submitted. These studies are required irrelevant of whether PK/PD studies are conducted in animals, unless the sponsor can justify that it is not needed.¹² FDA recommends that the sponsor demonstrates similar exposure of the proposed product to that of the reference product for the PK study, and similar response for the PD study. In designing the study, it is critical for the sponsor to select human subjects that fit into parameters used for the reference product to account for subjects’ intra and inter variability. This is especially true for the PK studies that evaluate the biosimilar’s absorption, distribution, metabolism, and elimination; considering that disease states, health, and genetic predispositions play a role in the PK of the product.¹² Similarly, PD studies should be designed using parameters that are sensitive, measurable, and relevant to clinical outcome. To ensure measurable and dose-related clinical outcomes, it is important for the sponsor to select “the steep part of the dose-response curve for the proposed product” so that meaningful clinical difference can be observed.¹² A strong correlation between the PK and PD data provides strong

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evidence of no clinical difference and high similarity between the biosimilar and reference product.

Clinical immunogenicity

Immunologic response to the product in the 351(k) application needs to be assessed. This assessment is required regardless of the results obtained from the animal immunogenicity studies, as they are not good predictors of immune response in humans.¹² Clinical immunogenicity assessment may be required during premarket evaluation or in combination with post-market surveillance. This discretion of the FDA is dependent on the perceived severity of the immunologic response based on prior incidences observed with the reference product. Severe clinical consequences will require extensive immunogenicity assessment, while a rare event may suffice on simple evaluation of the observed differences.¹² The type of immunogenic events that occurred with the use of reference product will also direct the sponsor on the design of the study, study population, and immunogenicity endpoints. The sponsor is expected to develop all the relevant assays needed to assess the immunogenic response, for both the biosimilar and its reference product.¹²

Clinical safety and efficacy testing

The need for comparative clinical studies is dependent on the totality of evidence submitted. If residual uncertainties are present, then FDA may request additional studies to help determine if there is no clinical difference between the product in 351(k) application and its reference.¹² Determining what type of further comparative study is needed is influenced by factors which include: the complexity of the reference product; the limitations of analytical testing in characterizing the proposed biosimilar; the degree to which analytical data, non-clinical tests, PK/PD results determine clinical outcome; and the clinical experience of the

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reference product and its therapeutic class.¹² When required, study design should generate insight into the existence of clinical difference between the proposed biosimilar and the reference product. Clinically sensitive endpoints that correlate with clinical outcome, analytical data, and mechanism of action need to be used. The study sample size and population should be adequate and reflective of the population used for the reference product; and should be designed to address the degree of residual uncertainty, and the ranges (asymmetric or symmetric) of performance of the proposed biosimilar relative to the reference product.¹²

Extrapolation of data

A proposed biosimilar submitted under the 351(k) application may seek licensure for a condition other than that indicated for the reference product, if the biosimilar is able to demonstrate high similarity with the reference product in terms of safety, purity, and potency, and is able to scientifically justify the use for such condition.¹² In demonstrating justification, the applicant must be able to provide the necessary mechanism of action for each condition for which the biosimilar licensure is sought; the PK/PD, immunogenicity, toxicity potential for the target population for which the new indication is sought. In reviewing the 351(k) application, FDA will review the totality of evidence along with the applicable scientific justification before approving the biosimilar to be used for the novel indications.¹²

Manufacturing drift

FDA requires that all lots produced to support the 351(k) application be highly similar to the reference product. Minor changes to the manufacturing process may eventually result in “drift” of the biologic and biosimilar from the characteristics and parameters that were initially part of 351(k) application.¹³ Unless, the pre- and post- manufacturing changes show comparability, analytically or clinically, FDA may request additional studies to demonstrate high

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similarity between the proposed biosimilar and the reference product. Of note, even the reference product is subject to such drifts. FDA requires lots that are used for analysis should support biosimilarity of not only those lots used in clinical studies but also for those lots being marketed.¹⁷

Demonstrating interchangeability with a biosimilar

Providing the necessary evidence from the above tests and studies will help FDA evaluate the biosimilarity of the 351(k) application from that of the reference product. FDA will approve the 351(k) evidence if all the evidence shows no residual uncertainties and no meaningful clinical difference of the proposed biosimilar from the reference product. In addition, the biosimilar must have the same route of administration and dosage form as the reference product. “An applicant may not seek approval in a 351(k) application or a supplement to an approved 351(k) application, for a route of administration, a dosage form, or a strength that is different from that of the reference product.”¹⁸ Even when the proposed 351(k) application is deemed biosimilar, it is not considered interchangeable. Interchangeability requires additional studies as described below.

Switching studies to demonstrate interchangeability

While the above may help establish biosimilarity, to demonstrate interchangeability FDA may require the sponsor to conduct additional studies, including switching studies. Switching studies are required for products that are to be administered more than once to an individual. Biosimilars that are not intended to be administered more than once are not expected to perform switching studies.¹⁶

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Switching studies are two arm studies, a switching arm and a non-switching arm. In the switching arm the reference product is switched with the proposed biosimilar during an interval in the study. The switching arm must start with the reference product, end with the biosimilar, with at least three switches (or two exposures to the biosimilar) during the duration of the study.¹⁶ Obviously, there would be no switching in the non-switching arm. The duration of the study is dependent on the clinical condition and its associated risk. It is recommended that these studies evaluate patients that are suffering from the condition that is treated with reference product or proposed biosimilar. A comparison of the primary endpoints, which include PK/PD and immunogenicity, between the switching and the non-switching arm would help determine if there is a difference in safety and efficacy. Results that demonstrate no clinical difference in safety or efficacy would deem the proposed biosimilar to be interchangeable with the reference product.¹⁶

If a proposed product in a 351(k) application has been found to be highly similar to a reference product and has no clinical difference in the safety and efficacy, the product may be approved by FDA as a biosimilar and interchangeable. No specific recommendation for labeling pertaining to interchangeable product has been published by the FDA, and according to the guidance document, *Labeling for Biosimilar Products*, it will be provided in the future.¹⁹ Current recommendations for biosimilars require that the labeling of such products should be an accurate reflection of approved labels for the reference product. Accordingly, the results of the tests and studies of the biosimilar are not meant to “independently establish safety and effectiveness of the proposed product.”¹⁹ Rather, they are a demonstration of no clinical difference between the proposed biosimilar and the reference product. Hence, FDA recommends implementing the relevant information from reference labels, applying

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modifications as necessary, but not deviating from the overall intent or scientific information of the reference labels.¹⁹

Concluding Remarks

BPCIA helped foster innovation and competition by carving out a pathway for biosimilars. Unlike small molecular drug entities, biologics and biosimilars are complex substances with high degree of variability that puts forth challenges in manufacturing and analysis. The source of biologics/biosimilars is subject to physiologic and environmental influences that makes batch-to-batch consistency particularly difficult.¹³ In respect, FDA has developed a stepwise pathway for the aBLA, 351(k) application, in order to ensure that biosimilars introduced into the marketplace are highly similar to the reference drugs and as safe, pure, and potent.¹² The stepwise pathway uses a totality-of-evidence approach in ascertaining the biosimilarity of the proposed product, as described above and summarized in Figure 1. Demonstration of “biosimilarity” does not imply interchangeability.¹⁶ A biosimilar product is interchangeable only when further clinical studies, usually done through switching studies, demonstrate that there is no difference with respect to safety and efficacy upon substituting the reference product with the biosimilar in the absence of a medical prescriber. Lastly, the routes of administration, dosage and strength must be the same, and the label must reflect that observed of the reference product in order for the product to be biosimilar or interchangeable.^{18,19}

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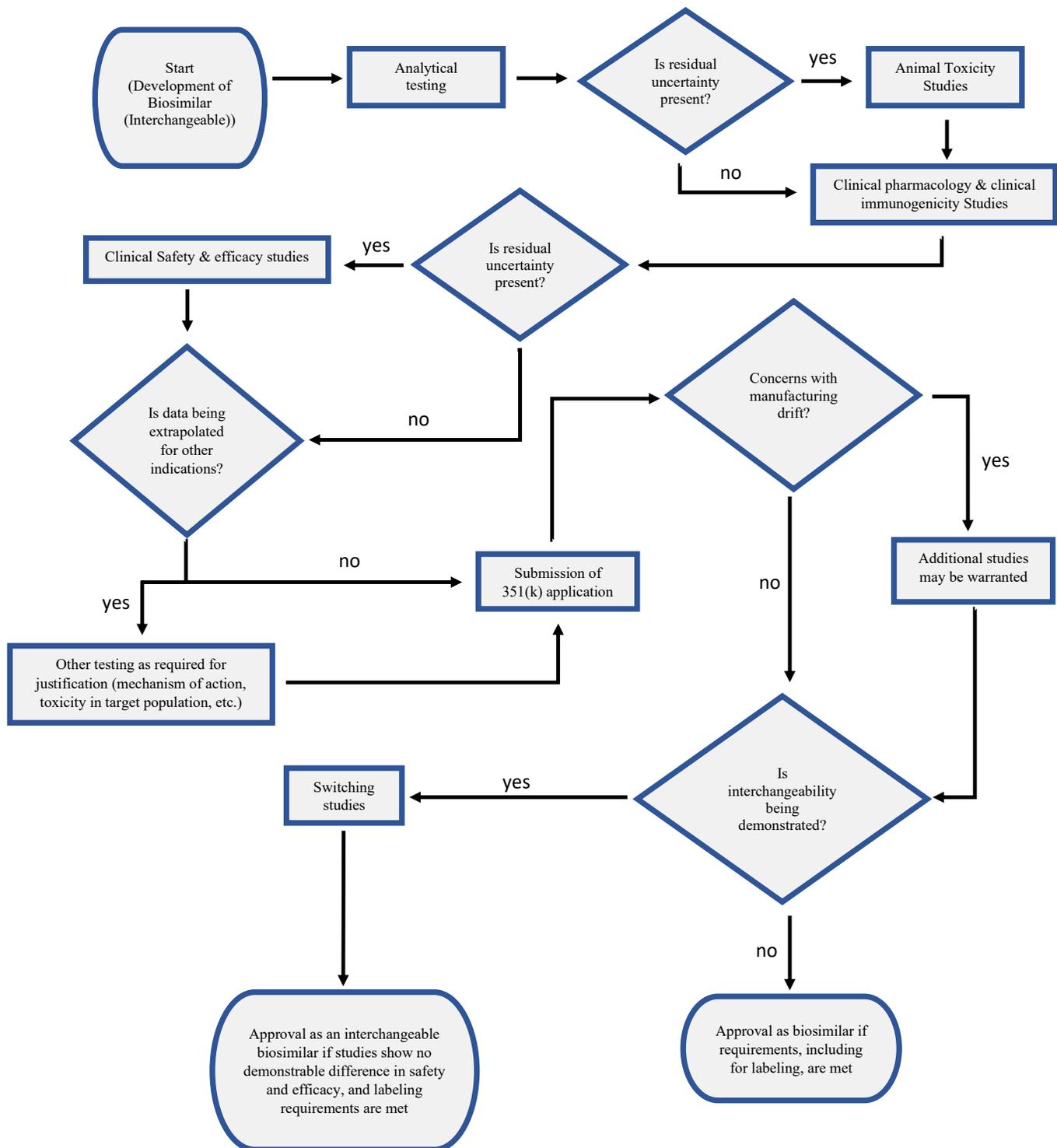


Figure 1: A flowchart showing the stepwise and totality of evidence approach in the development and approval of biosimilars and interchangeable products.

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