White Paper

Accelerating Biosimilar Drug Development Using Bayesian Methods

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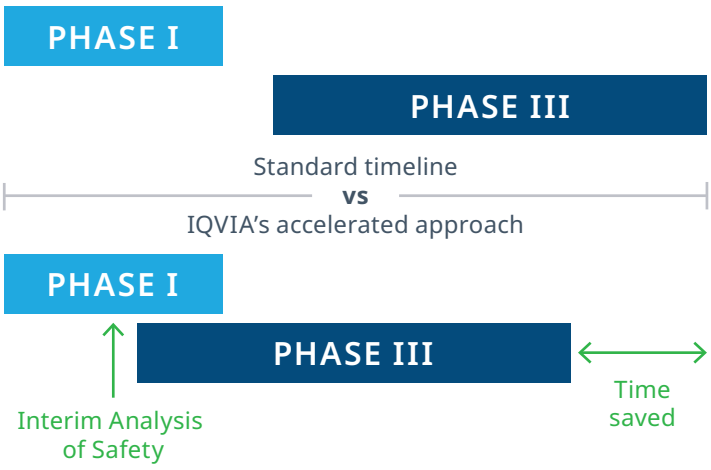
Executive summary

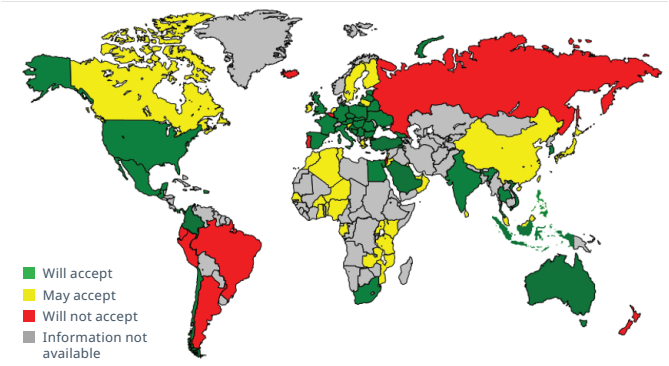
Over the last decade — since biosimilar sponsors tackled the first wave of innovator biologics coming off patent — biosimilar drug development has become increasingly crowded and complex. Biosimilar sponsor strategies now include novel R&D approaches to combat ever-changing innovator tactics. For example, sponsors of newer biosimilars may change the formulation of the biosimilar when compared with the reference product, such as the use of subcutaneous (SQ) vs. intravenous (IV) administration for biosimilars of trastuzumab.

With this growing competition, there is a need to develop novel trial designs to shorten biosimilar drug development timelines and gain cost-effectiveness. In 2015, the IQVIA Biosimilars Center of Excellence developed an accelerated approach to biosimilar drug development *(Figure 1)*. This involved staggering the biosimilar Phase I (PK) and Phase III (confirmatory) trials, such that the biosimilar sponsor garnered enough interim safety data in the Phase I trial (if the drug was amenable to being studied in a healthy volunteer population) for regulators to feel comfortable to proceed with the Phase III trial while the Phase I study was ongoing.[1]

Figure 1: IQVIA's Phase I/III Accelerated Solution



- Interim Safety Report including data from 10-20 subjects/arm, 14-21 days post-dose
- Demographics, safety (AEs, SAEs) and clinically relevant laboratory findings. No PK data included.
- Analysis by an independent team; reviewed by Principal Investigator; results are masked to prevent bias. Analysis is only descriptive.



Consider regulatory acceptance of interim Phase I data if implementing an accelerated Phase I/III solution

In the first real-world use of this novel accelerated model, IQVIA was able to demonstrate a nine-month time savings when compared with the timeline for sequential drug development starting with a healthy volunteer population.

This strategy saved time, but did not decrease the number of patients required to assess efficacy and safety in a confirmatory Phase III trial.

In 2019, IQVIA proposed using real-world data to augment insulin biosimilar clinical trial data, effectively decreasing the number of patients enrolled in a biosimilar insulin trial by using matched, real-world patients.[2]

Herein, we present a biosimilar case for leveraging historical data — utilizing Bayesian methods — in order to shorten the Phase III timeline and potentially use a much smaller number of patients for the confirmatory registration trial. We discuss borrowing information about the reference product from published data from pivotal trials from when the reference product was approved, through a Bayesian "power prior" technique. We propose that the parameter of power prior could be evaluated and estimated during the conduct of the Phase III trial.

IQVIA was able to demonstrate a nine-month time savings when compared with the timeline for sequential drug development starting with a healthy volunteer population.

Introduction

Biological medicines are large, complex molecules produced by living organisms and used for disease prevention or treatment. Their introduction into clinical practice has revolutionized healthcare in many challenging therapeutic areas, especially where effective treatments did not previously exist. Biological medicines have extended the lives of patients with certain cancers, reduced disability for patients with multiple diseases, such as rheumatoid arthritis, and provided life-saving replacement proteins for patients with certain rare genetic diseases.

According to Informa Pharma Intelligence, biologics are the leading growth engine of global medicines spending.[3] The biosimilars field is one of the fastest growing pharmaceutical sectors globally, largely because many blockbuster biologics will reach patent expiration in the next few years. Globally, IQVIA has forecast that U.S. biologics spending will grow from $165bn in 2017 to $320bn in 2023.[4]

Increasing numbers of biopharmaceutical companies — including those originally committed to developing innovative drugs only — are eager to take advantage of the opportunity presented by biosimilars. The success of companies aspiring to develop biosimilars is related not only to the timing of expiration of the originators' patents, but also to the companies' technical and financial ability to manufacture sufficiently comparable products. Considerable resources are required to finance the necessary studies and protect the biosimilar sponsor during patent litigation.

Evolution of biosimilar novel trial designs

The biosimilars market continues to expand. In the United States, the 2019 fiscal year ended with a record number of approvals *(Figure 2)*.

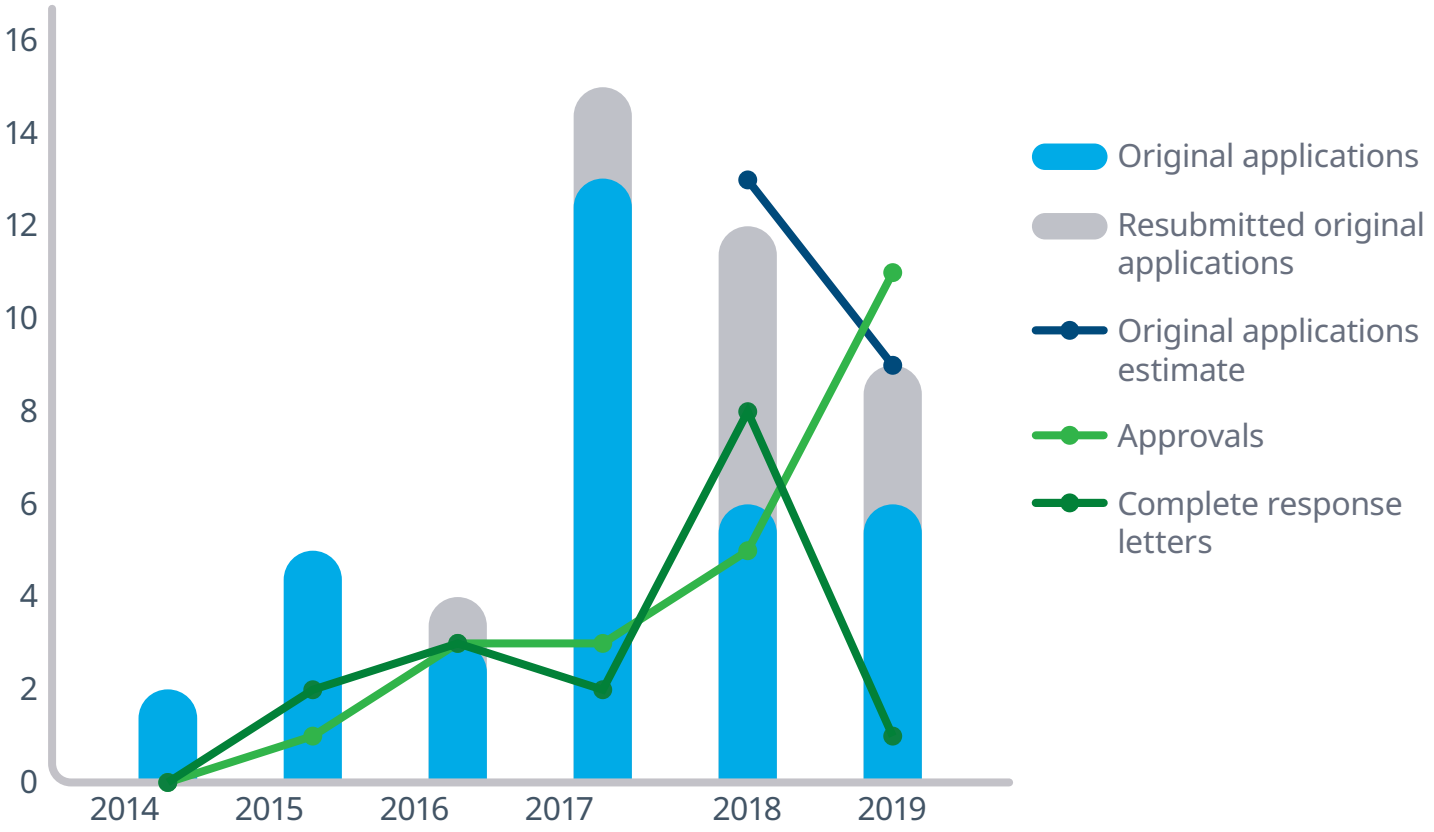
At IQVIA, we have utilized several models designed to either decrease the drug development time (as with the accelerated solution developed in 2015, described in *Sidebar 1*) or reduce the usual number of patients with a given indication needed to treat in the clinical trial setting.

A review of the medical literature with respect to the use of Bayesian methods to streamline biosimilar Phase III drug development, revealed more than 25 different examples of Bayesian methods being utilized in ongoing clinical trials[6] (see *Sidebar 2*).

IQVIA examines an approach that not only has the potential to shorten the timeline, but also to reduce the number of patients required for the confirmatory Phase III trial. Our Bayesian technique approach provides a strategy for borrowing information from the reference product from published pivotal trials of the reference product.

Figure 2: U.S. Biosimilar Approvals: 2014 to 2019[5]

The FDA has received a total of 35 original 351(k) applications since the biosimilar user fee program's inception.



There were no original application submissions in FY 2013, the first year of BsUFA.

SIDEBAR 1: THE ACCELERATED SOLUTION (2015)

Speed is important to biopharmaceutical sponsors seeking a competitive advantage in biosimilars drug development. Given the potential for first mover advantages, as well as for regulatory exclusivity, which acts like patent protection in the U.S. if the biosimilar is deemed to be interchangeable, sponsors of biosimilars are looking for innovative and new ways to shorten their clinical development programs.

Biosimilar drug development is unique because it is possible to initiate the Phase III (confirmatory safety and efficacy study) trial prior to the completion of the Phase I comparability trial with the use of interim safety data from the Phase I trial, although interim safety data from a Phase I study may not be acceptable in all countries. Due to the ever-changing regulatory landscape, it is best to perform a feasibility study to ensure countries of interest to the sponsor will accept interim safety data to initiate the Phase III study before completion of the Phase I study. *Figure 1* illustrates how the interim analysis allows the Phase III trial to commence earlier.

SIDEBAR 2: PRECEDENT FOR THE USE OF BAYESIAN METHODS IN CLINICAL TRIAL DESIGNS

Bayesian methods have been used in exploratory analysis in drug development for more than three decades.[7] One advantage of Bayesian methods is that they provide a natural mechanism for incorporating information from external sources (e.g., other trials) and adaptive modification of trials based on information learned up to a given point in time. These methods are actively employed in clinical trials. For example, in January 2020, a search of clinical trials using Citeline's Trial Trove database revealed 28 ongoing trials that were using Bayesian techniques to develop adaptive designs to shorten drug development timelines, elucidate or optimize dosing or optimize pharmacokinetics. Trials were broadly spread across various therapeutic areas; however, no biosimilar programs using Bayesian methods were identified that led to registration and no ongoing biosimilar studies were identified that were using Bayesian methods.

As for all therapeutic areas, the control of Type I error (e.g., "false positive") is a potential concern for biosimilar Phase III studies, but statisticians appear to have a solution to rectify this problem.[8] The Bayesian use of historical data of the reference product is one approach to biosimilar drug development, though data from the reference product can also be replaced by meta-analyses.[9] One biosimilar approach, described by Psioda et al. (2018), involves using Bayesian methods to analyze data from concurrent trials in multiple therapeutic indications, with Rituxan® (rituximab) as an example. Computer simulations (Monte Carlo-like) are used to gauge the usefulness of alternate approaches.

Support for a Bayesian concept

Bayesian methods — which offer a formal calculus (Bayes' Theorem) for combining prior and current information during design, conduct, and analysis of clinical trials[10] — are explicitly encouraged in recent U.S. legislation and regulatory guidance.

For example, the 21st Century Cures Act (2016)[11,12] seeks "broader application of Bayesian statistics and adaptive trial designs" (sec. 2061).[13] The Prescription Drug User Fee Act (PDUFA VI), incorporated as part of the FDA Reauthorization Act of 2017 (FDARA), also highlights the goal of facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs.[14] FDA is conducting a Complex Innovative Trial Design (CID) Pilot Meeting Program to support this goal, offering selected sponsors the opportunity to meet with Agency staff to discuss the use of CID approaches in medical product development. In a 2019 paper, former Director of the Office of Biostatistics in the Center for Drug Evaluation and Research (CDER) Lisa M. LaVange describes "significant advances in the acceptance of Bayesian methods for drug development" over the past year and a half.[15]

Bayesian approaches are also mentioned a total of 24 times in the FDA's November 2019 *Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry*. In the guidance, the agency notes that "the term *Bayesian adaptive design* has been used to refer to a wide variety of clinical trial designs that use Bayesian statistical reasoning and/or calculations in various ways."[16,17] FDA lists several examples of Bayesian adaptive design features:[18]

- **Use of predictive statistical modeling**, possibly including information external to a trial, to govern timing and decision rules for interim analyses
- **Use of assumed dose-response relationships** to govern dose escalation and selection
- **Explicit borrowing of information from external sources**, such as previous trials, natural history studies, and registries, via informative prior distributions to improve the efficiency of a trial
- **Use of posterior probability distributions** to determine trial success criteria.

The Bayesian concept explained

"Bayesian statistics is an approach for learning from evidence as it accumulates," according to the FDA.[19] "In clinical trials, traditional (frequentist) statistical methods may use information from previous studies only at the design stage. Then, at the data analysis stage, the information from these studies is considered as a complement to, but not part of, the formal analysis. In contrast, the Bayesian approach uses Bayes' Theorem to formally combine prior information with current information on a quantity of interest. The Bayesian idea is to consider the prior information and the trial results as part of a continual information stream, in which inferences are updated each time new data become available."

A Bayesian approach has particular potential to supplement biosimilar clinical programs, where sponsors may have access only to study-level data from the literature, rather than to patient-level data. Statistical details of how the Bayesian approach is implemented are beyond the scope of this white paper, but potential efficiencies in biosimilars programs are discussed in the literature.[20,21,22,23,24,25]

Biologic drug development programs generate rich data sets to support regulatory approval. For biosimilar developers, these data are typically available only at the study level, based on what is in the public domain, either in peer-reviewed journal papers or in the summary of the regulatory data package.

While patient-level data are particularly valuable, it is nonetheless possible to derive deep insights into the properties of originator biologics from study-level data. In the Bayesian approach, these insights can form the basis of the prior distribution for the reference product. One example is the "power prior" developed by Ibrahim and Chen, 2000.[26,27] The power prior enables information to be borrowed in a fixed manner or adaptively, as prespecified in the protocol. Both fixed and adaptive borrowing power priors are reviewed in the paper by Ibrahim et al., 2015.[28]

In the rarer cases where patient-level data are available, patients can be more accurately matched based on important demographic and disease-related factors, making information borrowing by Bayesian prior more precise.

IQVIA examines an approach that not only has the potential to shorten the timeline, but also to reduce the number of patients required for the confirmatory Phase III trial. Our Bayesian technique approach provides a strategy for borrowing information from the reference product from published pivotal trials of the reference product.

In the 2010 guidance, FDA lists potential benefits of using Bayesian methods as including:[29]

- **Additional information for decision-making:** Current trial findings are augmented and precision may be increased by using prior information in a Bayesian analysis.
- **Sample size reduction via prior information:** In some cases, use of prior information may reduce the need for a larger trial.
- **Sample size reduction via adaptive trial design:** Adaptive designs use accumulating data to inform decisions on trial design based on a pre-specified plan. Such designs may enable a reduction in trial size by stopping early. In some cases, adaptive designs can be easier to implement using Bayesian rather than frequentist methods.
- **Flexibility for midcourse changes to the trial design:** With appropriate planning, a Bayesian approach can offer flexibility for midcourse changes to a trial. Options may include dropping an unfavorable treatment arm or modifying the randomization scheme.
- **Other potential benefits:** These may include exact analysis, flexibility to deal with missing data, and the ability to make multiplicity adjustments.

Potential challenges to using the Bayesian approach identified by FDA include the need for:

- **Comprehensive preplanning:** Planning the design, conduct, and analysis of a Bayesian trial is especially crucial, involving pre-specification of an agreement with regulators on both the source of prior information and the model for how the information is incorporated into analysis of the new trial data.
- **Extensive model-building:** Elements may include:
  - » Probability distributions selected to reflect the prior information

- » Relationships between sources of prior information
- » Influence of covariates on patient outcomes or missing data
- » Sensitivity analyses on the model choices.

- **Specific statistical and computational skills:** These may include the use of computational algorithms to analyze trial data, check model assumptions, assess prior probabilities at the design stage, carry out simulations to evaluate the probabilities of various trial outcomes, and estimate sample size.
- **Justification of choices regarding prior information:** It is important to be able to justify choices of prior information both clinically and statistically. Sensitivity analyses can help confirm model robustness to different choices of prior distributions.
- **Taking account of the fact that preplanned Bayesian and frequentist approaches may yield different conclusions**, each of which may be scientifically valid, however, FDA recommends against switching between frequentist and Bayesian analyses once a trial has been initiated.

It is important to note that, although the FDA Guidance was developed for medical devices, the fundamentals of Bayesian methods can be applied to both biologic and small molecule drug development.

Bayesian clinical trial safety considerations

In common with other biosimilar clinical trials, those using a Bayesian approach are not powered for safety.

Biosimilar clinical development programs aim to compare the proposed biosimilar with its reference biologic in terms of pharmacokinetics (PK) and pharmacodynamics (PD), efficacy, safety and immunogenicity. These studies are not designed to demonstrate the safety and efficacy of the biosimilar *per se* as these parameters were already established adequately by the originator company for the reference product. Clinical studies for biosimilars are typically powered to demonstrate equivalence with the reference biologic. There is no need or expectation to power the studies for safety and immunogenicity endpoints.

Although the FDA Guidance on Bayesian statistics was developed for medical devices, the fundamentals of Bayesian methods can be applied to both biologic and small molecule drug development.

A comprehensive battery of physiochemical assays constitutes the most critical component in the evaluation of biosimilars. These are far more sensitive than *in vivo* clinical studies in patients, where multiple confounding factors could conceal a potential difference or show a difference when none exists.

The ideal initial candidates for biosimilar trials using a Bayesian approach are ones where there is:

- **A high degree of biosimilarity** demonstrated in terms of physicochemical assays, including state-of-the-art orthogonal methods, *in vitro* assays of biological activity and clinical PK endpoint studies.
- **A well-established safety profile** for the reference product and extensive clinical data on the reference product.
- **A low risk of immunogenicity for the reference product**, i.e., a low propensity for formation of unwanted anti-drug antibodies (ADA) and no significant clinical consequences in case of ADAs.

Conclusion

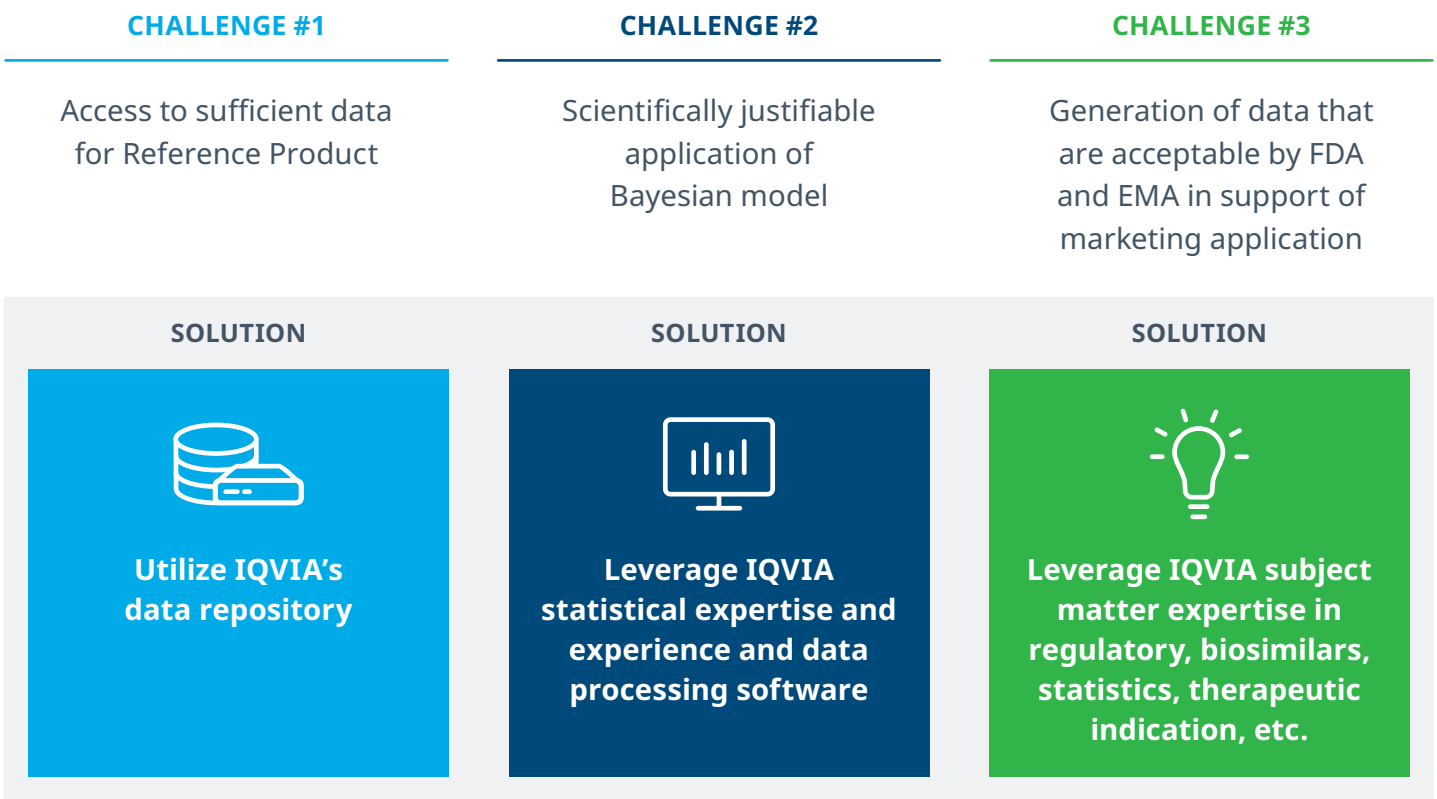
BAYESIAN STATISTICS HAVE POTENTIAL IN A VIABLE PHASE III BIOSIMILAR CLINICAL TRIAL DESIGN

Now that many of the Wave I biosimilars are entering international markets, key questions going forward include: "Can they remain on the market?" and "Can leaner models enable sponsors to take more biosimilars to the marketplace?"

As a result of protracted biosimilar patent disputes in the U.S. and uncertainty around how biosimilars of orphan drugs will be approved (among Wave II products, defined here as biosimilars targeting originator biologics with patent expirations in the 2020 to 2026 timeframe), biosimilar sponsors indicate that only the leanest clinical trial designs will be acceptable in the future.[30] Therefore, it behooves these sponsors to discuss novel trial designs with the agencies regarding the potential to limit the amount of clinical data required for approval, while continuing to protect patient safety.

We support the biostatistical rationale for utilizing Bayesian methods for clinical trials, including biosimilar programs. However, it will be important to keep in mind the tension over unacceptable Type I error rates. While borrowing up to 50% of the information for the comparator arm might be acceptable based on careful, scientific selection of the source for the prior, a figure of 20-30% may be more realistic.

Figure 3: Challenges with the Bayesian approach to Phase III biosimilar drug development
Adaptive borrowing of data from a reference product could reduce sample size for up to 50% in a reference arm.



Our decision science team approach to shorten biosimilar Phase III drug development includes utilizing a Bayesian approach that tackles three key challenges *(Figure 3)*:

1. The first challenge involves **borrowing sufficient data from the reference product** to understand the originator's efficacy data. Sufficiently robust data could be obtained from sources including study-level summaries from publications, the U.S. product label, the EU summary of product characteristics (SmPC), or the ICH regulatory package used for the originator product approval. Patient level data, typically considered proprietary, would also be helpful, but could probably only be leveraged if the biosimilar sponsor was also the originator. It is important to note that only a few of the largest biosimilar sponsors will fit into this category.

2. The second challenge includes **scientific justification** (addressing the power prior) of the Bayesian model under consideration. Regulatory agencies are increasingly utilizing Bayesian methods in clinical development for adaptive designs as well as dose optimization. The Bayesian biosimilar scenario needs to address the amount of data to be borrowed, with planning to include medical knowledge of the most sensitive patient population. This would allow statistical augmentation of the borrowed data from that patient population into the overall Phase III clinical trial design that increase the statistical power of the biosimilar study. Complex computer simulations could be performed and prepared ahead of time to justify the use of the borrowed data. Statisticians with expertise in using Bayesian methods would need to be employed to design the model and perform the modeling simulations.

3. The third challenge involves **combining the "borrowed" data with the data collected** during the clinical trial and presenting this information to the regulatory agency in the market of interest.

Given the novel nature of the Bayesian approach in biosimilar trials, we recommend – as with any new clinical trial design – that the biosimilar sponsor review the program with the appropriate regulatory agency prior to implementation.

In conclusion, the objective of biosimilars is to make biologics more accessible for patients. It is therefore important to contain costs and reduce timelines to the extent scientifically possible. A Bayesian approach has promise here.

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IQVIA's Decision Sciences Team

Decision Sciences is a department within IQVIA's Data Sciences, Safety, and Regulatory business unit, composed of experts in biostatistics, pharmacometrics, psychometrics, clinical trial simulations, statistical data mining, and operational and commercial analytics who combine their expertise to enhance biostatistical and statistical programming services through innovative solutions and unique perspectives to clients.

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