Operational Challenges Associated with Biosimilar Drug Development

This article examines the current operational landscape of biosimilar clinical drug development and identifies opportunities to decrease the risks associated with increasing competition. With an emphasis on European Union and United States’ markets, it gives an overview of some of the challenges and issues that need to be considered by researchers in this increasingly crowded environment.

Introduction
The introduction of biologics to healthcare has had a tangible effect on patients, especially in cases where they have provided the only available treatment for a disease. The success of biologics and their spiralling costs, timed with patent expiries, have led biopharmaceutical companies to develop biosimilar products. Biosimilars have the potential to increase access and provide lower-cost options for treatment of several conditions. Due to the structural complexity of biologics and their manufacture, in addition to non-clinical analytical and functional comparability data, regulatory authorities may request clinical trials to provide additional evidence of the similarity of a biosimilar product to the reference product. Although there are multiple possible routes to biosimilar approval depending on a biologic’s mechanism of action (MoA) and the jurisdiction’s views, the current typical development paradigm utilised for the European Union (EU) and the United States (US) includes a Phase I pharmacokinetics (PK) study and a Phase III confirmatory similarity study. It is possible that, over time, this development paradigm will shift to increase or decrease requirements.

As there are an increasing number of biosimilar products in development, the existing competition for the requisite patient populations, and for qualified investigators interested in conducting the research necessary to get these drugs to market, is intensifying. This article examines the current operational landscape of biosimilar clinical drug development and identifies opportunities to decrease the risks both for development and commercialisation purposes.

Differences in Biosimilar vs Innovator Biologic Development
Biosimilar drug development is considered unique for many reasons. In contrast to innovator biologic development which normally proceeds from Phases I to II to III, in a biosimilar development programme, the extent of clinical evaluation required is dependent on the assessment of the non-clinical analytical data package. If a clinical programme is recommended by the applicable regulatory authority, clinical Phase I and possibly Phase III studies would be performed to obtain regulatory approval. Phase II dose-ranging trials are not considered required for biosimilars because it is assumed that similar efficacy will be demonstrated with the same dose regimens for the biosimilar as for the innovator biologic. A Phase I biosimilar study would be focused on demonstrating PK, and pharmacodynamic (PD) if applicable, equivalence between the biosimilar and innovator biologics as well as the initial safety of the biosimilar. If a Phase III study is required, as it is currently in many countries, our experience indicates the Phase III trial may be initiated once interim Phase I data demonstrate sufficient safety. The Phase III study typically targets a similar patient population utilised to file for an indication for the innovator biologic, although exceptions exist as described subsequently. At the time of the biosimilar’s submission for registration, if a clinical programme has been conducted, usually fewer patient years of exposure are required for a biosimilar in contrast to the large safety databases for an innovator biologic; the limited safety profile obtained for the biosimilar should appear similar and is typically associated with that of the innovator biologic.

It may be possible for a biosimilar to obtain extrapolation to other indications for which the reference product is approved without a specific study being performed in those indications, provided that proper scientific rationale is provided for each indication for which extrapolation is requested. If an indication is studied, the primary indication chosen for evaluation is usually one that is considered sufficiently sensitive, and often it is the one considered most sensitive for evaluation, i.e., for the innovator biologic, has demonstrated the greatest effect size. It is not always practical to use the most sensitive indication for study if investigators are not willing to use the drug in their patients and data obtained from the study will not resonate with clinicians using the drug for a different patient population. In other situations, the most sensitive indication may not be clearly delineated.

For example, for a tumour necrosis factor inhibitor (TNFi) drug, per our analyses, the most sensitive indication has often been psoriasis. Infliximab, however, is used less commonly than other biologic agents for psoriasis treatment, so infliximab biosimilar development to date has not utilised the psoriasis indication. Similarly in oncology, for trastuzumab in breast cancer, adjuvant and neoadjuvant disease have been seen as the most sensitive settings for study. In contrast, for rituximab, the most sensitive indication has not been as clear as lymphomas are not homogeneous. There is evidence from clinical trial registries, e.g., ClinicalTrials.gov, that rituximab development is proceeding as monotherapy in
untreated low tumour burden follicular lymphoma to show similarity. In such cases, though the study might help support the approval of the rituximab biosimilar, the data would not allow the biosimilar to obtain the indication since not approved for the innovator biologic.\textsuperscript{15, 16, 17} Such a trial may serve, however, to provide data to providers and patients that the biosimilar would be effective in the treatment of off-label indications where there may also be significant use of the innovator.\textsuperscript{18}

Consideration also needs to be given to the selection of endpoints in biosimilar studies which may be conducted to evaluate an indication. In these cases, some regulatory agencies may request use of sufficiently sensitive endpoints.\textsuperscript{9, 10, 11} Biosimilar trial primary endpoints do not have to be the same as those used for clinical trials of the innovator, and currently may be selected to facilitate the detection of differences between innovator and biosimilar products. Should different primary endpoints be used than those that would be most sensitive or were used for the innovator biologic pivotal studies, secondary endpoints may be recommended by some regulatory authorities to include some common endpoints as those used for the pivotal trials of the innovator biologic to ensure more complete evaluation of clinical efficacy.\textsuperscript{11}

For oncology, as overall survival endpoints are not considered adequately sensitive, biosimilar trastuzumab and rituximab clinical trials have used objective response rate (ORR) as primary endpoints. This may raise concerns in terms of biosimilar efficacy with clinicians, as ORR may not always correlate sufficiently with survival.\textsuperscript{19, 20} Pathological complete response (pCR) has been used as the most sensitive endpoint in a neoadjuvant setting, though again may not be predictive of overall survival.\textsuperscript{14, 21, 22}

In autoimmune diseases, endpoints based on continuous measures rather than dichotomous measures are also considered more sensitive; e.g., in rheumatoid arthritis (RA), focus may be placed on the Disease Activity Score (DAS) results rather than American College of Rheumatology 20\% (ACR20) response rates, or in psoriasis, on the mean Psoriasis Area and Severity Index (PASI) results rather than achievement of a PASI 75\% response rate.\textsuperscript{23, 24} Data analysis should also focus on the steep part of the response curves rather than the plateau in biosimilar development as differences between reference and biosimilar products may be more apparent.\textsuperscript{9, 10} Requirements to achieve an interchangeability designation for the US may also influence trial designs and endpoints. Seeking early engagement with the regulatory agencies is essential to agree the most appropriate balance in a biosimilar’s development pathway.

Phase I Programmes

Phase I biosimilar trials may entail enrolment of large numbers of subjects if conducted to demonstrate three-way equivalence between US- and EU-sourced innovator biologics and the biosimilar to support global development. Usually, fewer subjects are needed in first-in-human and multiple-ascending-dose Phase I studies of innovator drugs as the primary focus in these settings is to demonstrate safety of a single drug. Phase I clinical units, typically designed to house smaller numbers of subjects, may be overloaded both in terms of recruitment capabilities and available beds for scheduling when conducting a biosimilar Phase I study. To complete a Phase I biosimilar PK study, it is not uncommon for a sponsor or subcontracting entity to stagger multiple groups of subjects through a Phase I unit or to involve multiple sites to increase subject capacity to obtain the required numbers. The conduct of biosimilar studies, while guaranteeing business for the Phase I unit, may jeopardise innovator or other biosimilar development timelines if designated Phase I units have no capacity for extended periods of time. It is important to keep one’s options open regarding securing Phase I unit capabilities.

Phase I biosimilar trials, like many innovator trials, are typically conducted in healthy volunteers. This has not been considered possible for rituximab biosimilars as safety risks associated with rituximab exposure are not considered acceptable for healthy volunteers. Rituximab biosimilar Phase I studies are often conducted in RA patients,\textsuperscript{13} because the RA patient population is considered easier to recruit and tends to be a more homogeneous population for PK determinations than cancer patients. The RA patient population studied may not always be in line with the indicated use of rituximab; while rituximab is indicated for patients who have failed TNFi treatment, the RA population studied for a rituximab biosimilar Phase I study might allow TNFi-naïve patients.\textsuperscript{25} In order to support patient recruitment against other studies, including innovator studies competing for the same patients, expectations exist to provide treatment for this population for at least one year. Clearly, this potentially increases the costs of Phase I study conduct substantially. Rituximab biosimilars also pose potential hurdles for ethics and regulatory committees regarding the acceptability of interim Phase I safety data in RA patients to initiate Phase III studies in cancer populations, as rituximab differs in the doses used as well as the immunogenicity profile for RA vs cancer patients.\textsuperscript{17}

Country and Site Selection and Recruitment

Country selection strategies for Phase III programmes are typically based on balancing high enrolment potential, start-up timelines and business strategic needs. The basis for initial country and site selection is to focus on countries with shorter regulatory start-up timelines and previously high-enrolling sites for the indication being studied. High enrolment potential is also influenced by regional prevalence and incidence of disease. Though the expectation is that previously high-enrolling countries and sites will perform similarly in future studies, there may be differences in the recruitment patterns for a biosimilar versus a novel drug.
Limitations in access and variations in reimbursement criteria are important considerations in choosing countries. Access to biologics may be highly variable and in RA, for example, patients may have to meet requirements for disease duration, certain levels of disease activity or the number of previously failed traditional therapies to gain access to biologic therapy. Just as for innovators, the focus for biosimilars is often on those countries, e.g., Eastern Europe, to recruit studies where start-up timelines are relatively fast and there are large numbers of untreated patients who for financial reasons cannot get access to an innovator. Similarly, although countries in Southeast Asia or Latin America generally have somewhat longer start-up timelines than Western Europe and North America, they may recruit more quickly due to high numbers of biologic-naïve patients and poorer access to innovators. Investigators might be further motivated by opportunities to gain access overall or earlier than payer guidelines allow to the most effective biologic therapy for their patients by enrolling them in a biosimilar trial. Co-payments, co-insurance for innovators, standard of care treatment as well as income level may also influence patient participation in clinical trials in certain countries.

Biosimilar studies, generally, because they do not typically involve a placebo treatment arm, may be initiated more quickly by posing fewer concerns for ethics committees and institutional review boards. As with any situation, exceptions exist, e.g., European Medicines Agency (EMA) has requested a short placebo arm for interferon beta biosimilar studies. While lack of a placebo arm may influence patient recruitment, enrolment may also be impacted by the known efficacy and safety profile of the innovator biologic. In autoimmune disease and breast cancer studies, recruitment rates may be higher for biosimilar studies than innovator studies as all patients obtain a form of active therapy, i.e., the innovator biologic or biosimilar, known to be or presumed to be, respectively, efficacious. In contrast, for non-small cell lung cancer (NSCLC), discussed further subsequently, recruitment might be slower, possibly due to the innovator biologic’s perceived modest efficacy profile and multiple opportunities to participate in novel drug studies. Overall patient recruitment rates may still be affected by similar restrictive inclusion and exclusion criteria as used in the innovator programmes.

Business strategy for a biosimilar product development influences country selection, often to ensure that regulatory requirements of countries of interest are met. There are a number of countries which currently require that the biosimilar drug be studied in their patient population in order to seek approval, e.g., Mexico, Russia, China; these requirements are often in line with their regulatory requirements for innovator development, and may change with time. As it is conceivable that some studies could complete enrolment prior to initiation of a ‘required’ country, it is difficult to predict the success of a single country and site selection approach to meet all strategic needs. There may also be a desire to allow investigators in a target country to gain experience with the biosimilar product prior to market approval. As a result, sponsors may plan to conduct additional trials to meet their anticipated needs. Many regulators will require post-approval requirements to evaluate late occurring safety events for biosimilar products. Such studies may provide the opportunity to include additional countries to meet business strategic needs. Sponsors may also focus efforts in certain countries, especially if they themselves are based in those regions.

Managing the Competitive Environment

Per ClinicalTrials.gov, the number of Phase III trials for biosimilars aimed at the treatment of RA and other related autoimmune conditions has increased significantly in the last five years, with 80% of the Phase III studies having been or planned to be started from 2013 onward. A similar scenario exists for oncology. The situation therefore exists where virtually identical studies are running with overlapping timelines. As site capacity for running competing trials is finite, historically high-enrolling sites will ultimately become saturated. Some companies are looking for new territories and sites as a potential way to broaden their access to patients for biosimilar trials. Even so, expectations regarding recruitment rates may need to be modified as this bulus of studies progresses through the clinics.

Many of these studies are focused on drugs with the same mechanism of action, e.g., TNFi agents, targeting similar patient populations, and, therefore, similar investigators. Novel drugs may also be competing for the same patient populations. This is exemplified in NSCLC trials where multiple bevacizumab biosimilars are competing directly for investigator site resources against innovator therapies. In these situations, the risk of competition from novel drug trials that may offer compelling opportunities for improved efficacy and survival should be evaluated, despite the risk of receipt of placebo (including standard of care with or without active control) in the innovator study. Such trials may threaten the enrolment of biosimilar trials, so it is important to have a clear understanding of the competitive landscape at the local level. As with any clinical trial, investigators should be supported with tools that reduce the risk of enrolment delays. Recruitment practices vary by specialty and country, so should be designed and implemented to support the needs and preferences of investigators, as well as to be culturally appropriate and acceptable to ethics committees/institutional review boards and regulatory authorities. In a global survey conducted by Quintiles in 2012, less than 45% of investigators who conduct trials in haematology-oncology, rheumatology, and dermatology reported having adequate patient numbers at their sites. Referrals from other physicians were cited as the most effective method to supplement recruitment across these specialties globally, though advertising was preferred by more than 65% of rheumatologists and 70% of dermatologists in the US.
Regulatory

Utilising education to inform investigators regarding biosimilars may be successful in gaining their involvement in a biosimilar study where they may have previously dismissed participation due to lack of scientific interest. According to a survey of EU specialists conducted by the Alliance for Safe Biologic Medicines, over half claimed to have only a basic understanding of biosimilars and nearly one-quarter could not define or previously had not heard of biosimilars. Comparable results exist from other similar efforts. Based on these results, education is needed to explain biosimilars, the unmet need for biologics to treat disease, and regulatory requirements to ensure non-clinical analytical and functional comparability to the innovator biologic before clinical testing. The importance of sponsors investing in developing relationships and instituting education earlier rather than later with investigators cannot be underestimated from the perspective of delivering on development needs for both innovators and biosimilars. These interactions might also serve to reshape standards of care and eventually prescribing patterns.

As more biologics have come into the marketplace for RA, treatment paradigms are advocating for patients to be treated sooner and more aggressively, which may make trial recruitment more difficult. Many RA Phase III biosimilar studies focus on recruiting biologic-naive patients, or for rituximab, TNFi failures, as these were the target populations for the innovator biologic pivotal studies. Previous biologic drug exposures may also disqualify a patient from participation in subsequent innovator or biosimilar studies. Patient recruitment may become more difficult over time as the availability of additional therapies continues to improve access.

Currently, biosimilars require the collection of immunogenicity and safety data for at least one year if planning to market in both the EU and US. Biosimilar studies rarely extend beyond this duration. Innovator Phase III studies usually involve longer-term extensions to build safety databases. As competition for patient populations increases, sponsors need to give consideration to extending treatment periods to compete not only with recruitment for innovator trials, but also with other biosimilar trials.

To appeal to patients and investigators, minimising trial complexity is important. Thought should be given to the minimum clinical and laboratory data needed and collected in a case report form, and whether or not 100% source data verification is recommended based on the risk-based approach to monitoring. The burden of patient travel to sites should be reduced as much as possible. For example, for biosimilar studies in RA or psoriasis, visits should ideally be no more than monthly after the initial four weeks from randomisation, excepting more frequent visits expected by the regulators when evaluating switch or transition between innovator biologic and biosimilar products. Allowance should be made for home injection, if applicable, for interim doses. For oncology biosimilar trials, provision of backbone chemotherapy by the sponsor must be considered to alleviate any potential burden and inconsistency within the supply chain throughout the trial.

For companies that provide full pharmaceutical and clinical trial services such as contract research organisations (CROs), it is critical to establish the timing of its sponsor’s clinical trials. This is not only important to determine potential business conflict of interest issues upfront to maintain firewalls between teams as needed, but also to determine “roll on/roll off” of studies sequentially to keep high-enrolling sites continuously active and to identify site resource constraints and potential site and country saturation issues. CROs often see many biosimilar and innovator trials in a short timespan, receiving more frequent regulatory feedback related to biosimilar and innovator development than most sponsors in the same period. Therefore, CROs are in a position to provide more ‘real-time’ evaluation of issues to inform current development and operational execution. CROs may also be able to support investigator engagement with educational materials, including proprietary websites where investigators can learn more about the role of biosimilars in a particular disease and the status of biosimilars in their region.

Investigational Product Considerations

Other issues that may arise unique to biosimilar trials are related to use of the innovator biologic as a comparator. Similar to providing active controls in studies, obtaining the innovator product can be problematic for many reasons. Careful planning and attention will need to be given to sourcing innovator product. It is critical to arrange for adequate supplies of the reference product at study onset to ensure supply continuity, but with appropriate expiration dates to avoid clinical drug supply wastage. The optimal strategy should include obtaining large supplies of reference product from the same lot, if at all possible, as lot-to-lot variation can become an issue. Blinding may also cause concern, especially with the different packaging configurations often associated with subcutaneous innovator biologics, including prefilled syringes and auto-injectors, as compared to those planned for the biosimilars. Blinding strategies need to be planned, including identifying whether the need exists for an unblinded monitoring team. Third-party clinical supply vendors can assist with sourcing as well as blinding needs.

The costs and ease of sourcing of biologics from different regions may vary depending on regional supply and pricing of the innovator. The current environment is such that if either EU- or US-sourced product is being used as a sole comparator in a Phase III study, its use will need to be scientifically justified. This justification can include analytical and functional similarity data between the chosen reference comparator and the reference product approved in the country/region of interest. Both the EMA and FDA allow use of non-EU or US-sourced references, with the key risks being comparability across the biosimilar products and variability among regions.
non-US reference product, respectively, as a comparator in a confirmatory clinical Phase III study once a scientific bridge has been built between the EU/US and non-EU/US reference product from an International Conference on Harmonisation (ICH) country.9, 11 Although this bridge may be built non-clinically, currently, the bridge clinically is built via the Phase I programme. Furthermore, at this time, for interchangeability assessments in the US, data will need to be provided with US-sourced reference as a comparator.

Many injectable innovator products have an auto-injector presentation, and biosimilar sponsors may provide an auto-injector to be on par for marketing against the innovator and other biosimilars where the drug is approved for self-injection. For arthritic patients specifically, sponsors should be aware that the US FDA currently requires PK evaluation in a representative patient population with the auto-injector vs. prefilled syringe to ensure adequate delivery of the drug as well as the usual human factor studies that are required for both innovator and biosimilar compounds.10 Therefore, for an injectable TNFi biosimilar, consideration should be given to evaluating the auto-injector in the subset of psoriasis patients with psoriatic arthritis and/or in RA patients with manual dexterity issues to garner the requisite PK data and patient usability data.

Other issues to consider are provision of a certificate of analysis for all investigational products in accordance with ICH guidelines and, in the EU, a qualified person to certify release of investigational product.41, 42, 43 For pharmacovigilance, appropriate adverse event reporting for the innovator itself to the respective sponsor should be implemented.

Commercial and Reimbursement Challenges

Lastly, commercial and market access issues need to be considered in biosimilar development programmes.

Marketing needs may drive the conduct of biosimilar trials in more than one indication. As regulatory requirements for biosimilars continue to evolve and clinicians remain still relatively unfamiliar with them, providers may be unwilling to use biosimilars without data in the actual indications for which they see patients, e.g., a gastroenterologist may not use a TNFi biosimilar for the treatment of Crohn’s disease (CD) if the only data available for the biosimilar are in RA.35 This attitude may change over time as clinician awareness of biosimilars increases and they gain actual experience with biosimilar products.14, 18

The potential for biosimilars to reduce overall healthcare costs has led to stakeholder and payer support for biosimilar development among various countries, including the US and Western Europe.44 Market uptake of biosimilars also has not always been as significant as expected and may not be solely driven by pricing.3, 45 As a result, medical and payer stakeholders may drive generation of additional data or conditions required for adoption. For example, the Norwegian Medicines Agency (NoMA) is sponsoring a post-marketing switching study designed to demonstrate interchangeability with innovator infliximab.46 A key lesson for sponsors is to engage early with payers and key physician groups to determine the optimal dataset necessary for commercial uptake. Even if desired endpoints cannot feasibly be generated during Phase III studies due to time and cost constraints, discussions with commercial and reimbursement stakeholders can help sponsors proactively plan appropriate post-approval studies.

Another important market access consideration for sponsors as they pursue biosimilar development is that sponsors may currently have specific payer requirements for provision of cost-effectiveness evidence. Whether generated during clinical development or post-approval, cost-effectiveness data have been important for payers to decide to endorse or reimburse biosimilars; thus, sponsors could incorporate such assessments in development programmes. Although most payers and health technology assessment (HTA) agencies are generally aligned with regulatory requirements, some have demanded additional evidence as for innovator therapies. For example, the All Wales Medicines Strategy Group (AWMSG), an HTA agency based in the United Kingdom (UK), indicated in their assessment of biosimilar epoetin zeta (Retacrit®) that it was lacking in special population, economic and patient outcomes evidence and, therefore, did not recommend the biosimilar for reimbursement.67

Other important factors for sponsors to consider during development programmes include: stakeholder (physician, patient, and payer) educational/awareness efforts – beyond attracting investigators to biosimilar studies, prescribing physicians are more likely to adopt and encourage the use of biosimilars based on good understanding of biosimilars;14, 33, 34, 35 development of innovative, user-friendly devices (e.g., easy-to-use and convenient auto-injectors for patients) – which have the potential to differentiate biosimilars; support and value-added programmes (e.g., nurse educators or co-pay assistance) for patients who have become accustomed to such services from innovator biologic manufacturers; and forming partnerships with key payers, payer-providers (e.g., disease centres of excellence or in the US, accountable care organisations), distributors (e.g., drug wholesalers or group purchasing organisations), and patient advocacy organisations, who can all support sponsors with use of their biosimilar therapies. These are important as potential cost differentials for biosimilars may be countered for the innovator biologic.8, 49

Incorporating these considerations into biosimilar development means that commercialisation of biosimilars may be more similar to branded therapies than to generics; thus, sponsors must allocate sufficient marketing resources to these products. Such resources
include key medical, sales, and reimbursement personnel (e.g., medical science liaisons, sales reps, and managed care account representatives); medical education materials and events; and consumer advertising budgets.

Summary
Biosimilar clinical development offers many opportunities for sponsors, investigators and patients. It is an evolving landscape from a clinical trial, regulatory and commercial point of view, which increases the challenges associated with implementing a successful biosimilar development programme. As biosimilar development is still a relatively new endeavour, and as more experience is gained, countries continue to adapt to allow unique provisions for biosimilar development. New guidelines for biosimilar development have been announced already for 2015 by regulatory agencies and government advisory bodies including the US FDA and the National Institute for Health and Care Excellence (NICE) in England. Based on the experience gained in the past 10 years, EMA also have modified their thinking regarding biosimilar product development as shown by revisions not only to the overarching guidelines for non-clinical and clinical development, but also to product-specific guidelines.

To bring a biosimilar to market still requires a significant investment of money, resources and time, though currently less than that required for an innovator product. To be successful in biosimilar development requires comprehensive, in-depth planning of the entire programme, with a global outlook. Contributions to optimise planning should be obtained not only from internal sponsor representatives including clinical operations, medical, regulatory, statistics, and marketing, but also from external representatives e.g., regulatory agencies, payers, investigators, prescribers and patients. Ultimately, the goal of biosimilar development is to provide more opportunities for patients to access potentially life-changing drugs.

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