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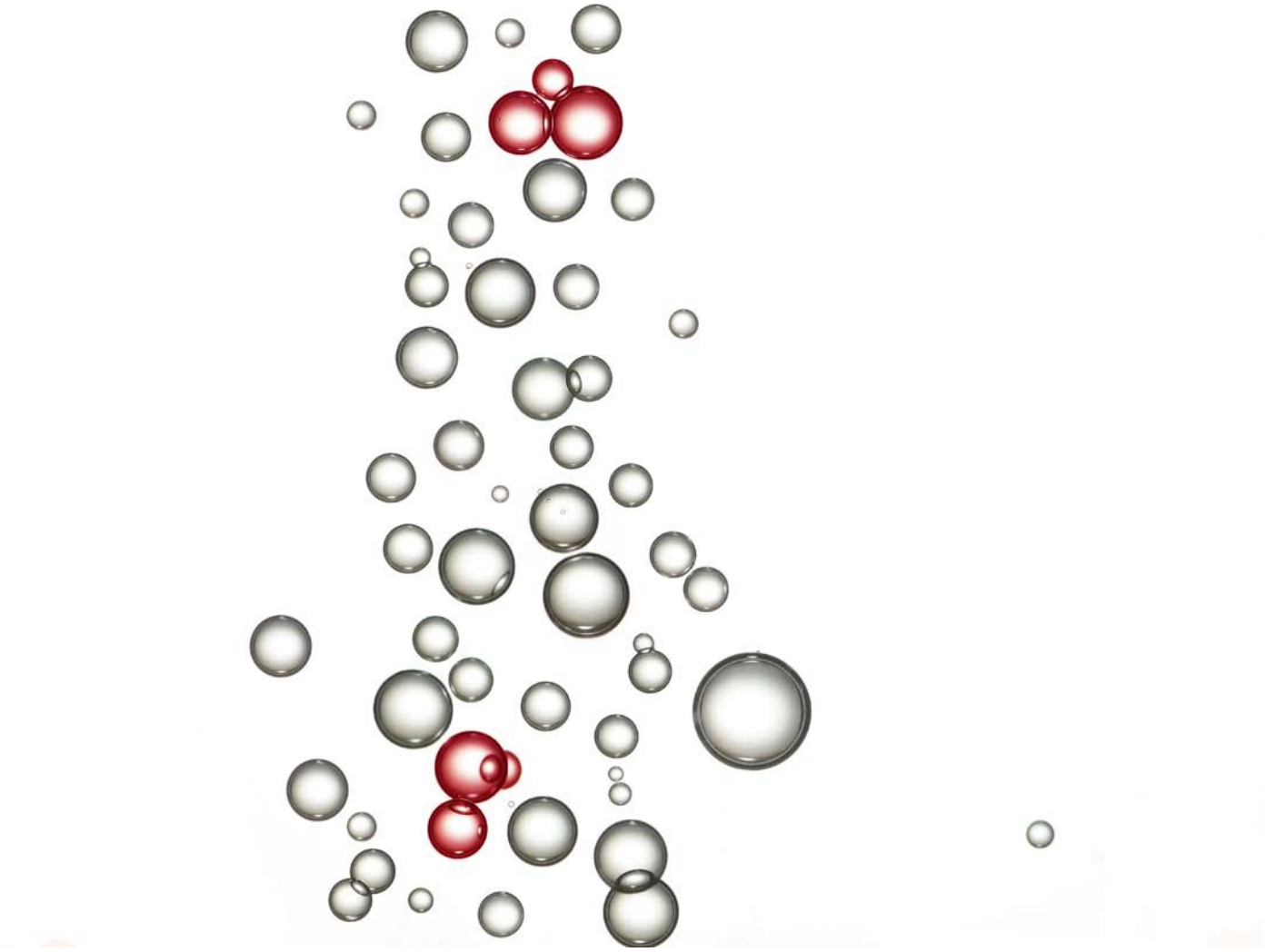

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WHITEPAPER

How explosive growth in biosimilars presents new challenges in the clinical trial supply chain

Abstract

With patent protection for many innovator biological drugs expiring within the next few years, the early 21st century may well be remembered as the dawn of the Biosimilar Era, and for good reason. Biologics are a resounding success story for the biopharmaceutical industry, credited for making possible giant leaps forward in the long-term treatment of diabetes, rheumatoid arthritis, cancers, kidney failure, multiple sclerosis, orphan, and other diseases.

Roughly $79 billion of these biologic products will become susceptible to biosimilar competition by 2020.[1] The expiry of patent protection for these medicines is creating a biosimilars market expected to be so lucrative that generic manufacturers, emerging market firms, large pharmaceutical and biotechnology companies, and even businesses with no drug experience whatsoever are competing for a share of it. In fact, so many players are targeting for a slice of the biosimilars market that they are facing off in a fierce development race. This whitepaper provides an overview of the biosimilars market and learn more about the amazing potential of these newly developed medicines and how they are altering the economics of healthcare.

Introduction

Numbers tell the story. Currently 40 recombinant proteins are blockbuster drugs with sales greater than $1 billion a year, and another 18 have sales between $500 million and $1 billion. It's no surprise that the race to capture a share of this market has grown increasingly intense.

While hugely successful, biologics have come at a high price. The economics associated with their complexity means that biologics have market pricing as much as 1,000 times per dose more than traditional small-molecule therapies. Equally challenging are the costs and complexity of supplying medications for worldwide biosimilar clinical trials. Overall, product development costs are projected to range between $75 million and $250 million per compound[2].

This expense can escalate by tens of millions of dollars due to the high price of marketed products used as comparators in clinical trials. Yet, as we will show later, comparator costs are one expense that biosimilar developers have the power to control.

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Of course, high development costs for biologics have resulted in high market prices. These prices, combined with the exceptionally high usage rates of biologics, have strained healthcare budgets in developed countries. Faced with aging populations, a rising incidence of disease and global economic pressures, health systems are struggling to control rapidly expanding medicine costs. They are looking to biosimilars as a means of increasing the availability of more affordable medicines.

For years, unclear regulatory guidance delayed market introduction of biosimilars, but that's now changing. Under pressure from health systems seeking wider adoption of biosimilars, regulations governing market approval of these products are evolving around the world. Still, the absence of uniform licensing requirements for biosimilars poses a challenge to companies pursuing a foothold in the market.

How the many market contenders manage these and the other challenges of the Biosimilar Era will undoubtedly impact the fortunes of the biopharmaceutical industry, both in the coming decade and for decades to come.

Thermo Fisher Scientific, a global leader in clinical supply chain management, has been involved in the development of biosimilars since its earliest days. With a distinct focus on the broad therapeutic coverage provided by biologics other than vaccines, this paper discusses the opportunities and challenges of biosimilars and the impact they will have on the clinical trial supply industry of the 21st century.

Biosimilars in brief

While biosimilars are frequently described as the generic versions of biological drugs, this characterization is misleading. In fact, it's impossible to duplicate a biological drug in the manner that generics companies manufacture copies of small molecule medicines. Biosimilars are actually newly developed versions of biological medicines that are produced after patents for the innovator biological drugs expire.

Depending on the market, biosimilar products are known by different names. A few examples: Biosimilars are referred to as "similar biological medicinal products" by the European Medicines Agency (EMA), "follow-on protein products" or "follow-on biologics" by the U.S. Food and Drug Administration (FDA); "subsequent entry biologics" by Health Canada; and "biocomparables" by Mexico's Federal Commission for the Protection Against Sanitary Risks.

As with the names, the definition of a biosimilar also varies somewhat from market to market. Put simply, however, a biosimilar is a biological product that is highly similar to an original biologic medicine that was licensed, approved or authorized by a regulatory body.

Biosimilars must be equivalent to the original biological medicine—known as a reference product—in purity, safety and potency. Due to the complex nature of biological drugs, regulatory agencies have designated specific biosimilar development pathways to establish bio-equivalence with reference products. In the United States, regulators established the 351 (k) approval pathway and have released numerous guidance documents over the past several years.

The U.S. FDA defines biosimilarity as being "highly similar to the reference product not withstanding minor differences in clinically inactive components" and lacking "clinically meaningful differences" with respect to safety, efficacy and potency.

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As required in the U.S., biosimilar active agents (those involving recombinant proteins) must be identical in primary sequence with their reference products. Analytical and comparative bioequivalence/pharmacokinetic (PK) clinical testing must support a lack of significant differences—particularly in efficacy and safety—between the biosimilar and the reference product. Such rigorous testing is not required of traditional generic drugs. Thus, the development time necessary for a generic medicine is about three years, compared to an estimated six to nine years for a biosimilar drug.

Like generic drugs, biosimilars cost less than reference products. However, the price differential between biosimilars and innovator biologics is not expected to be as large as that seen to date between small molecule generics and original innovator drugs.

Example: The prices for small molecule generics in countries such as Germany, the UK and the U.S. are about 80% less than those of reference products. In Europe, where more than fifty biosimilars are already available, biosimilar prices are about 30% less than those of reference products. This pricing for biosimilars reflects higher R&D costs offset by production process efficiencies, the reduced costs of a streamlined development program and, of course, competition.

From the standpoint of managing clinical trial supplies, both biologics and biosimilars present similar challenges in cold chain processing. However, the risk of a temperature excursion may be greater in a biosimilars trail if developers are forced to ship reference product without stability data. If this information is not provided by the drug innovator, then the biosimilar developer will need to stay within labeled restrictions. Without this detailed stability data, the company may need to destroy the reference product if it exceeds labeled excursion limits. This could lead to huge amounts of expensive waste.

Biological product classes

These products belong to the following key classes of biologic drugs.

Product	Class
Monoclonal antibodies (mAbs)	In use since the mid-1980s, mAbs are the leading biological drugs. More than 30 are currently in use in developed markets. Monoclonal antibodies are most commonly used in treating cancers and autoimmune diseases, including rheumatoidarthritis, and began losing patent protection in 2013.
Fusion proteins	Fusion proteins are commonly used in the treatment of rheumatoid arthritis and plaque psoriasis, although one product is indicated to treat cutaneous T-cell lymphoma (CTCL). The first fusion protein to be approved was Amgen/Pfizer's top-selling Enbrel®(etanercept), which became available in 1998.
Insulin	Insulin, a hormone produced by the pancreas, has been used to treat diabetes since the 1920s. Synthetic insulin was first marketed in 1982 and is now used extensively throughout the world. Three companies—Novo Nordisk, Sanofi and Eli Lilly—account for 80% of the market. Insulin was the leading class of biosimilars in 2011 interms of revenue.
Interferons (IFN)	Interferons (IFN), which have been in use since the early 1990s, are used in the treatment of immune disorders and viral diseases, including hepatitis B and C and multiple sclerosis. In 2011, an interferon from Merck was approved for the treatment of melanoma.
Human Growth Hormone (hGH)	Human Growth Hormone (hGH) was first extracted from the pituitary gland and used for therapy in 1958. In 1985, the synthetic hormone somatropin was introduced. Today it is used to treat growth failure, growth hormone deficiency and HIV-related weight loss. Notably, biosimilar somotropin—marketed by Sandoz as Omnitrope®—was the first to be approved in the EU in 2006 and in Japan in 2009.
Erythropoietin (EPO)	Erythropoietin (EPO) is a hormone that controls red blood cell production in bone marrow. Recombinant EPO, known as epoetin, is used to treat anemia in patients with kidney failure, as well as anemia associated with chemotherapy and HIV infection. The first EPO entered the market in 1989.
Granulocyte Colony-Stimulating Factor (G-CSF)	Granulocyte Colony-Stimulating Factor (G-CSF) is used to treat neutropenia, a blood condition resulting in a deficiency of the most common white blood cells. Neutropenia is common among cancer patients undergoing chemotherapy. The first commercial product, Neupogen® (filgrasatim) was launched in 1991 by Amgen.
Although the above constitute the major categories of biologic and biosimilar drugs today, there are several other classes.	
Interleukin-2 (IL-2)	Interleukin-2 (IL-2) is an immunomodulatory agent used to treat metastatic renal cell carcinoma.
Blood factors	Blood factors are enzymes that induce coagulation or clotting. They are used to treat patients with hemophilia or hemorrhage.
Fibrinolytic agents	Fibrinolytic agents, commonly known as clot-busting drugs, are used to treat heart attack patients. Examples including streptokinase and reteplase.[4,5]

Rapid market expansion

To describe the biosimilars market as one of enormous potential is not an exaggeration. Between 2006 and 2014 there were 19 approvals granted for EU. In 2015 US FDA approved its first biosimilar and, since then, 55 approvals have taken place in EU and US (through April 2019)[3]. Patent expiries beginning in 2013 for a number of top biologics are fueling the growth. Biosimilars of some medications are already available in several countries.

Comparator drugs: High prices and limited access

The Biosimilar Era indicates major change for the bio-pharmaceutical industry, not the least of which is the emergence of new competitors, some of them complete newcomers with no drug experience. As noted above, what may come as a shock to these newcomers is the high price of comparator biologics and the high degree of difficulty in sourcing these important competitive assets. But again, this is an area where improved trial efficiency and cost savings can be had with the appropriate strategic approach.

An important step is to consider conducting a comparator sourcing initiative with a clinical supply partner that has established relationships in most innovator companies. These relationships are critical for two reasons.

First, it may be difficult to secure affordable access to the most lucrative drugs without a connection to the sourcing leadership and knowledge of innovator pricing policies. With this pricing knowledge, it is possible to save a few percentage points on the multi-million-dollar comparator purchases.

The second advantage to having a partner with strategic connections is that reference products may have to be shipped without stability data unless this closely held information is made available, as noted above. Without this data, any temperature excursion during cold chain shipment would automatically trigger a rejection by quality assurance (QA) professionals. However, a strategic partner with ties to innovator QA groups can obtain this stability data in some cases, improving excursion management and thereby reducing waste and keeping the biosimilar trial on track.

Drawn by the prospect of a rapidly growing market and handsome returns, leading Asian electronics and imaging firms have tossed their hats into the biosimilar ring alongside those of traditional generics manufacturers, emerging market companies, Big Pharma and biotech companies. An early indication of exactly how heated the biosimilars market is likely to become is the impending patent expiration for a leading mAB, a blockbuster cancer and arthritis treatment with annual sales over $6 billion. As many as 20 companies indicated that they plan to produce a biosimilar version after patents for the product began expiring in Europe in 2013.

Here's a brief look at the competitors queuing up for a share of the biosimilars market.

Traditional generics manufacturers. As expected, the lead players are traditional generics companies. They dominate, especially in Europe, where biosimilars are already available. Among the companies in this category are Teva Pharmaceutical Industries, the world's largest generic manufacturer; Watson Pharmaceuticals Inc., one of the world's top generics companies; Sandoz Ltd., the generic pharmaceuticals division of Novartis; Mylan Inc., another leading generic manufacturer; and Hospira, Inc., the leading provider of injectable drugs and infusion technologies.

Emerging market companies. Following closely on the heels of the generic manufacturers are many drug companies in emerging markets, among them China, India and South Korea. Such countries as China and India, with a combined population of 2.5 billion, have a great deal to gain from access to biosimilars.

In China, the world's most populous country, more than 30 companies are producing or planning to produce biosimilars. Poised to be a significant force in biosimilar manufacturing and production, Chinese companies are developing biosimilar monoclonal antibodies, human insulin and interleukin products, as well as biosimilar vaccines.

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Chinese interest in biosimilars should come as no surprise since the Chinese biopharmaceutical industry has always focused on generics rather than innovation. Today, in this country of 1.3 billion people, generic drugs dominate the health economy and comprise 95% of the Chinese drug market. Domestic biosimilars have been available for more than 20 years. Shenyang Sunshine/3SBio has emerged as a leading company in China's active biosimilars market, particularly in EPO.

Like China, India has a well-deserved global reputation for leadership in the production of generic drugs. Already, 10 Indian drug companies are marketing dozens of biosimilars in this country of 1.2 billion people. Among them: Dr. Reddy's Laboratories, Zydus, Cipla and Ranbaxy, which is majority-owned by Japanese drug maker Daiichi Sankyo.

With nearly 50 million people, Korea is scarcely as populated as China or India, but that hasn't prevented Korean companies from plunging into the global biosimilars market. Seoul-based Celltrion received approval from the Korea Food and Drug Administration (KFDA) for Remsima, a biosimilar version of the mAB Remicade (infliximab), for the treatment for rheumatoid arthritis, ankylosing spondilitis, Crohn's disease, ulcerative colitis, and psoriasis. Remsima was one of the first mABs approved by EMA, and Celltrion said it also plans to market the drug in Asia and South America.

Big pharma. Multi-national biopharmaceutical leaders, which ironically view biosimilars as a means of helping to fill revenue gaps left by patent expiries and sluggish R&D productivity, are preparing to give traditional generic manufacturers a run for their money. So significant is the biosimilars opportunity perceived by Big Pharma that Pfizer, Eli Lilly and AstraZeneca, among others, have stated their intentions of carving out a share of the world biosimilars market.

Biotech companies. Small biotech companies are behind much of the interest in developing "biobetters"—essentially follow-on versions of a biologic that have been improved in some way but are based on the same original molecule and follow the same mechanistic pathway.

The improvement may be through an improved dosing schedule or route of administration, such as oral insulin, or by improving the safety of the product. Biobetters enter a market with existing demand but face the challenge of competing with the original biologic drug as well as biosimilar medicines.

The newcomers. Among those planning to enter the drug industry for the first time via biosimilar production are familiar names from another industry, that of global electronics and imaging. In an effort to compensate for their biopharmaceutical inexperience, several have established joint ventures with industry veterans.

One example is Samsung Bioepis Co., Ltd., a joint venture established by Samsung Biologics, a new division of Korean electronics firm Samsung, and Biogen Idec to develop, manufacture and market biosimilars.

Similarly, Fujifilm Corporation of Japan has partnered with Kyowa Hakko Kirin Co., Ltd., a Japanese specialty pharmaceutical company, to form Fujifilm Kyowa Kirin Biologics for the same purpose.

The newcomers have been matter-of-fact about their absence of biopharmaceutical experience, choosing instead to point to their strengths in building superb manufacturing facilities.

Development strategies awaited

As a fierce development race heats up, competitors' ability to identify and implement winning biosimilar strategies will be critical. Most companies have understandably declined to share their plans as they watch and wait to see what direction others take.

All eyes are on the companies that are most exposed with respect to pipeline. It remains to be seen exactly how they plan to safeguard their pipelines against the biosimilars market.

Such innovators are in the driver's seat with respect to their original compounds. Post patent expiration, for instance, they have the power to provide the product and simultaneously drive down its price—hurting the prospects of the many companies waiting in the wings for a piece of the biosimilar franchise.

Based on indications to date, competitors will go in a number of different directions. Some, namely Big Pharma, are likely to target the global market. Others, among them some of the Asian companies, will probably focus on providing biosimilars in that region, home to 20% of the world's population. Still others, including some of the smaller firms that have largely domestic business in emerging markets, are likely to adopt local and regional strategies.

Guidelines provide framework

In both developed and emerging markets, regulatory agencies are acting to expand access to biosimilars. For many cash-strapped health systems around the world, biosimilars may spell the difference between their ability to provide life-saving biologics or not.

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In the United Kingdom, for example, questions have been raised about whether the National Health Service (NHS) is capable of continuing to pay for Herceptin® (trastuzamab) without having to reduce its spending on other drugs.

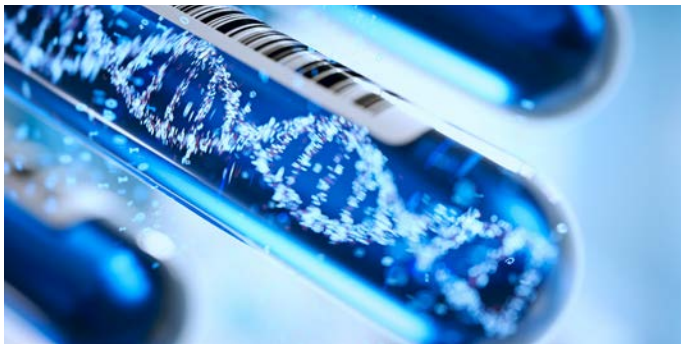
Herceptin, a monoclonal antibody, is used for the treatment of some types of breast and stomach cancer. Women who are prescribed Herceptin for breast cancer, for example, must continue to take the drug for life.

Patent protection for Herceptin expired in US in 2019 and it has been off-patent in Europe since 2014. US sales were just over $2.9 billion last year, and globally they were nearly $6.8 billion. As of mid-2019 there are five approved biosimilars (trastuzumab), the first of which was approved in 2017.

While legal patent-protection cases are still pending, once these biosiimilars are adopted it will certainly impact ongoing revenue for the branded drug—lifetime sales of $49.4bn.

- **European Union.** The European Union (EU) took the early lead on establishing regulations for biosimilars, including a directive outlining the process by which these products could win regulatory approval. Its initiative made the EU a testing ground for biosimilars, which first became available there in 2006.

Today, with over 55 EU drug approvals, biosimilars are on the market in several major EU countries. Biosimilar penetration differs by country, with Germany and France accounting for half the biosimilars by value. Uptake in Spain and the UK is on the increase. It's no surprise that the first three biosimilar drugs to win EU approval—hGH, EPO and G-CSF filgrastim—initially launched in Germany, Europe's largest generics market. Germany's receptivity to generics, driven by strong payer pressure, created a favorable climate for biosimilars.



Germany is another example of how biosimilars can shrink healthcare costs. The introduction of biosimilar EPO in Germany resulted in EUR 60 million in annual savings, or a reduction of more than 17%, in its first year on the market.

- **"Pharmerging markets".** So-called because they are emerging markets targeted by the pharmaceutical industry due to their potential for growth, these include China, India, Brazil and Mexico. Early on, most of these countries have developed their own regulatory pathways for approval of biosimilars. While they often drew on the EU biosimilar framework, they generally set a lower barrier in terms of approval requirements. This leveled the playing field for local manufacturers and potentially provided a lower cost entry point for other companies. Biosimilars are already available in China, India and Korea.
- **United States.** Among the latest to act, the characteristically cautious FDA has issued draft regulatory guidelines spelling out clinical development requirements for biosimilars. In fact, in May 2014 the agency unveiled a new biosimilars guidance that explains how to use clinical pharmacology data to show similarity to a reference product.

The current FDA guidelines and others to follow are expected help the drug industry develop these follow-on products. While the EU may be the leader with respect to biosimilars today, it can be argued that the U.S. offers the greatest opportunity for the biosimilars industry.

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In addition to being the world's largest market for biologics, the U.S. is a strong adopter of generic drugs: In 2010, 78% of the four billion prescriptions filled were for generic drugs, according to IMS Health, the pharmaceutical market intelligence firm. Although as of 2015 only one biosiimilar had been approved in the U.S., 16 additional approvals have taken place through April 2019.[3678]

Distinct development pathway

Although regulatory requirements differ from market to market, there are common elements and issues with respect to development pathways for biosimilars.

Compressed phases of development

Regardless of the market, biosimilars are required to follow a development path that differs significantly from those of traditional compounds and generic drugs. The key difference is that biosimilars do not progress through the usual phases of development: Phase I, Phase II, Phase III, Phase IV.

Instead, the development path prescribed by most major regulatory authorities requires protocols that combine Phase I and Phase II. This early phase typically involves several hundred subjects with an interim data analysis that focuses on pharmacokinetics (PK) and pharmacodynamics (PD).

Following the completion of Phase I and a favorable analysis, the number of subjects enrolled increases to approximately 1,000-2,000 globally for the remainder of the trial. As with many clinical trials for innovator biologics and traditional small molecule drugs, atient enrollment from emerging markets is a key focus in biosimilar development.

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Required use of reference compounds

Comparative clinical trials are required in order to demonstrate clinical comparability between a biosimilar in development and a reference product. This makes the selection of a reference product—and the ability to source it—key steps in obtaining regulatory approval.

Selection

The selection of a reference product against which to compare a biosimilar in development depends upon individual circumstances. For example, if a sponsor is developing a biosimilar of a leading mAB poised to begin losing patent protection in 2015, the answer is an easy one and the reference product in the study must by necessity be that mAB. By contrast, if a sponsor is developing a biosimilar interferon beta 1a for the treatment of multiple sclerosis, it can choose between two reference products on the market.

Once selected, however, the same reference product must be used for the complete comparability exercise. Though similar, current guidelines regarding selection of reference products frequently differ in detail:

- In Europe, the EMA guidelines require that a biosimilar developer demonstrate the similarity of its product with respect to quality, safety and efficacy in comparison to a reference product licensed in the EU.
- In the U.S., the Biologics Price Competition and Innovation Act (BPCI act) of 2009 states that the reference product must be licensed in that country under a full biologics license application (BLA). More recently, FDA 351K permits biosimilar products to use a drug delivery system different from that of the reference product.
- Meanwhile, the World Health Organization (WHO) Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs) outlines that the reference product must have authorization in the country/region in question, while pointing out that a product authorized and widely marketed in a highly regulated country is a suitable alternative.

Comparator sourcing strategies

Given the role of reference products in obtaining regulatory approval for biosimilars, the ability to source reference products for comparative clinical trials is a top priority.

Thermo Fisher has a Fisher Clinical Services℠ Comparator ‘Center of Excellence’ to source reference products from innovators, generic manufacturers, and authorized local distributors. The Center of Excellence accomplishes this by purchasing small batches of product, accompanied by necessary documentation, from a variety of sources in multiple regions.

This sourcing strategy is ideally suited to the development of biosimilars. Unlike traditional development programs in which a minimal number of batches are preferred due to difficulty in tracking, multiple batches offer a distinct advantage in biosimilar development.

The use of multiple batches demonstrates to regulatory bodies that compounds are of the same purity and maintain the same safety and efficacy profiles. A few sourcing strategies are detailed below.

From innovators. Thermo Fisher sources a large percentage of reference compounds directly from innovator companies—among them Abbott, Amgen, Astellas, Astra Zeneca, Bayer, Celgene, Eli Lilly, GSK, Johnson & Johnson, Pfizer, Novartis, Novo Nordisk, Roche and Sanofi-Aventis—instead of sourcing specialists or wholesalers.

The use of multiple batches demonstrates to regulatory bodies that compounds are of the same purity and maintain the same safety and efficacy profiles.

It establishes supply agreements with such innovator companies as a means of ensuring continuity of supply with good rest shelf life, as well as price stability. The absence of an intermediary also guarantees the pedigree of the product, which is accompanied by full documentation. For protocols requiring it, on-demand manufacturing of a special batch of product, unlabelled material or matching placebos can be arranged. Doing so, however, requires disclosure of study details, such as protocol number, and the countries where clinical sites are located.

From generic manufacturers. The Comparator Center of Excellence also sources product from all of the leading generic manufacturers, among them Teva, Watson, Sandoz, Mylan and Hospira. While the easiest way to obtain a matching placebo is from the company that manufactures the comparator, it's no surprise that innovator companies are frequently unwilling to provide them. Generic manufacturers are another potential source of matching placebos and one that has often been used successfully.

From authorized local distributors. Fisher Clinical Services℠ Comparator Center of Excellence can source reference products in 45+ countries across five continents. As one might anticipate, there are advantages and disadvantages to local sourcing. Among the advantages are price, which is usually 5-15% lower than the cost to purchase such materials from innovators.

Depending on the country, local sourcing often means the purchase of limited quantities; this can be advantageous because the purchase often remains 'under the radar.' Though the materials have a clear pedigree, there is no assurance of documentation; this, however, can depend upon the distributor and its relationships. Often, neither are assurances of optimal rest shelf life.

Need for blinding

The challenges for blinding, packaging and labeling in biosimilar studies are similar to those of studies for traditional Investigational Medicinal Products (IMPs). However, because many biologics come in marketed devices that are easily recognizable such as the Humira® pen the blinding strategy presents unique challenges to biosimilar developers.

While there is no consensus, some regulators have expressed preferences about appropriate blinding. The EMA, for example, is prescribing two clinical trials of randomized, double-blind crossover or parallel design. Notably, many current development programs are using unblinded pharmacists at clinical sites, which potentially could lead to additional questions from regulatory agencies at submission.

Thermo Fisher has considerable expertise in blinding, having developed and patented innovative blinding techniques. These solutions include over-encapsulation, blinding of vials or syringes, de-printing or de-inking to remove printed inscriptions, such as commercial logos and identifiers.

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Using a proprietary, patented solution for vial blinding enables the blinding of products of different colors, while preserving vial transparency. Shell color and transparency are selected depending upon the products being blinded and cold-resistant solutions are available. The application process is fully automated.

Syringes can be blinded through the use of blinding shells or the application of specially-designed labels. Here again, selection of color and transparency are based upon the products to be blinded. It's possible to use freeze-resistant materials; minimum temperature must be assessed on a project-by-project basis.

Critical issues in biosimilar development

Because the development of biosimilars is new to most companies in the industry, and the biosimilar development path is distinctly different from that of other compounds, it's critical to understand what it takes to succeed in the Biosimilar Era. Thermo Fisher has been involved in this market since the first biosimilars entered development. The company's collective experience has given it a thorough understanding of what it takes to bring biosimilars to market on time and on budget.

Global strength & experience. Focused exclusively on clinical trial supplies for more than 30 years, Thermo Fisher has the world's largest global footprint of facilities and equipment, personnel with deep knowledge of biosimilar protocol development and the expert opinion required to make the right long-term decisions for the good of clinical study volunteers and investigators.

Import/export credentials and knowledge. Both are requirements for ensuring smooth passage of costly clinical materials, wherever they are bound. The company can serve as a designated Importer of Record, a legal distinction that carries important financial responsibilities and benefits – including the ability to reclaim import duties or Value Added Tax (VAT), which can be significant. For a vial of biologic material valued at $1,000, for instance, import duties can be as high as $150-$200.

Knowledge of evolving global regulations. Some regulations are in place, while others continue to evolve. Regardless of the country, the quality team keeps a close eye on regulations governing biosimilars. The company maintains a central database that is continuously updated to reflect evolving rules in every market.

Accurate ability to forecast supply needs. Thermo Fisher's Clinical Supply Optimization (CSO) offering is designed to minimize overall drug wastage and reduce trial costs while ensuring that clinical materials reach investigators and patients when and where they are needed.

Track record in sourcing comparator and reference products. The Thermo Fisher team has a proven ability to source comparators in small or large batches and provide documentation, a distinct advantage in biosimilar development. The company's global sourcing specialists work with organizations in more than 45 countries in North America, Europe, Asia Pacific, South America and Africa.

Analytical Services. Working with a quality-approved partner, the Thermo Fisher team can offer a combination of encapsulation with analytical work and stability testing. This includes access to a comprehensive analytical comparator database, stability data generation, ID testing, dissolution, method transfer and validation.

Capability for tracking multiple batches. In conjunction with the ability to source comparator in small batches, the company has GMP batch-tracking systems that permit it to track even individual vials, so the use of multiple batches in a trial isn't a problem.

Options for packaging. While the original biologic might have been packaged in a vial for injection, the option exists for automated packaging and labeling of the biosimilar in a prefilled syringe for greater ease of use.

Blinding strategies. The Thermo Fisher project manage-ment team can guide sponsors to think about blinding options early in the planning process. This is critical, since time pressures do not permit changes later on.

'Cold chain' expertise. All biosimilars must be transported at controlled temperatures in what is known as the 'cold chain'. Over 50% of 2018 shipments required temperature management, giving the company an unmatched level of expertise in the careful documentation, tracking of clinical supplies at every level, and adherence to strict temperature requirements demanded in the development of biosimilars. The organization has a "zero excursion" mindset and protects cold chain product from time of receiving until final delivery.

Extensive global infrastructure. Thermo Fisher owns over 25 GMP/GDP-compliant facilities around the world, including five countries in Asia—in China, India, Korea, Singapore and Japan where the biosimilars market is developing quickly. Supplementing these wholly-owned facilities are over 35 partner facilities on five continents, establishing the largest global footprint of any supply chain management firm and unsurpassed capability for storage and distribution.

Flexibility and contingency planning. The Thermo Fisher team has the flexibility and experience necessary to plan for contin-gencies and accommodate special distribution requests, such as hand delivery of clinical materials to a primary investigator in Korea, for example.

Conclusion

Like any industry changing development, the dawn of the Biosimilars Era brings with it a unique set of potentially large challenges.

The most obvious of these is how sponsors seeking to tap into a market projected to surpass 69bn ($USD) by 2025[16] will follow the emerging and divergent approval pathways set down by health authorities.

Within this new regulatory climate, sponsors must also confront an array of obstacles that are unique to biosimilars—chief among them is sourcing and management of comparator medications.

While developing these novel products is a new endeavor for many drug manufacturers, many of them have increased their capacity to run the required clinical studies by partnering with an experienced supply provider.

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Published 08/21

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