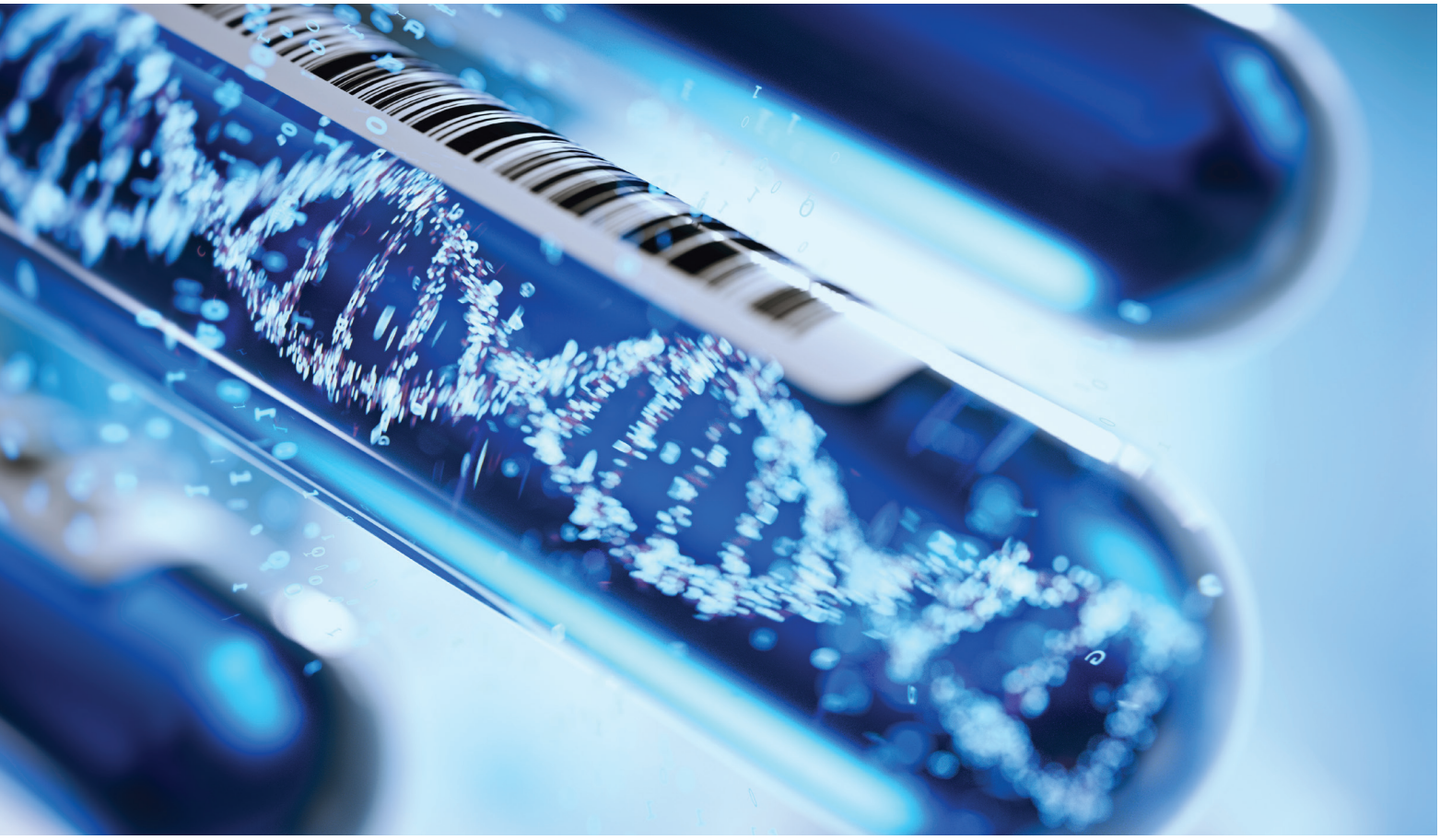
ThermoFisher SCIENTIFIC



SOLVED WITH

TECHNOLOGY & TRUST

WHITEPAPER

Comparator sourcing: Leveraging the Bolar exemption to accelerate market access for generic and biosimilar products

Executive summary

Comparator sourcing for clinical trials has always been challenging, requiring a robust supply chain, advanced forecasting operations, and logistics expertise. In recent years, the advent and rapid growth of the biopharmaceutical market and the increasing market demand for biosimilars have intensified these challenges by an order of magnitude.

Biopharmaceuticals, or biologics, have a more complicated structural character than small molecules and are significantly more time-consuming, challenging, and expensive to produce. The complexity and high production costs translate into high market prices, supply limitations, and a desire on the part of manufacturers to protect their investment for as long as possible. These are all barriers to market access for developers of biosimilars who are racing to file their drug for regulatory approval as soon as possible after the reference drug's patent expires, while also staying within their development budgets.

The manufacturers of the original biologics have no real interest in facilitating research and development for new entrant drugs and will not compromise on drug pricing for use in future competitors' clinical trials. Therefore, during the period of patent protection, development companies have no alternative but to allocate more of their budget to comparator sourcing and pay the cost of sourcing the original drug.

The cost and access landscape changes when the original patent expires. Market competition through new biosimilars creates price erosion, and a variety of sourcing options become available. In particular, biosimilar manufacturers are often willing and eager to supply their newly marketed products for clinical trials because doing so can enhance their own market penetration and brand recognition. This can reduce comparator supply costs significantly. Importantly, it also establishes collaborative relationships that can be leveraged before the originator's patent expires under a research exception to patent infringement called the Bolar exemption.

This whitepaper provides insight into the changing comparator sourcing landscape, focusing specifically on the instrumental role the Bolar exemption plays in the shift away from dependence on innovators for clinical supplies. The key elements of the report include:

- The specificities and challenges of pharmaceutical patents
- The definition and patent implications of the Bolar exemption
- Regional differences in Bolar and Bolar-like provisions
- Strategies for leveraging these exemptions to accelerate market access for generics and biosimilars

Introduction

In 2021, research and development spending in the pharmaceutical industry totaled nearly $212 billion (US) globally, driven in large part by the expanding global disease burden and the explosive growth of the biologics sector as a major source of new treatments to address it.

In the biopharmaceutical space, many of today's top-selling biologics will be coming off patent in the next decade, creating a huge opportunity for biosimilars.

Because the costs to research, develop, and ultimately manufacture biologics on a commercial scale are significantly higher than those associated with small molecules, biopharmaceutical manufacturers are under pressure to bring innovative products to market and recoup their R&D investments by charging monopoly prices during the period of market exclusivity afforded by patent protection. When patent protection ends, lower-priced competitors can enter the market and drive down prices. In the biopharmaceutical space, many of today's top-selling biologics will be coming off patent in the next decade, creating a huge opportunity for biosimilars.[1] By 2030, the global market for biosimilars is expected to grow to $88 billion, up from $15.5 billion in 2021.[2]

Bringing biosimilars to market is time-consuming and expensive and involves a rigorous approval process—all of which can delay market access and potentially compromise return on investment. Although manufacturers of biosimilar medications can rely on the safety and efficacy data of the reference medication, they must first demonstrate biosimilarity to the reference product in clinical trials. This requires being able to source the innovator product in large enough quantities for comparator trials within a desired time frame. Various samples of different batches of the innovator product are needed to understand the range of allowed variability in analytical properties, a process known as analytic characterization.

In order to source enough comparator product in an increasingly stretched global supply chain, trial sponsors are allocating more of their budgets to sourcing efforts. To be successful, it is incumbent upon sponsors to define a comparator strategy early on. This means identifying sourcing partners who meet certain criteria. These include having global reach to support the trend toward clinical trial globalization, and creating and nurturing robust supplier and manufacturer relationships. In addition, sourcing partners must have compliance and regulatory expertise to help sponsors navigate the protections associated with patents that can impact market access.

The following sections focus on the relevant patent considerations and the application of a critical patent exemption, called the Bolar exemption, which can be seen as a solution to patent-related sourcing issues. The Bolar exemption is a regulatory exception that allows the use of a copy of a patented product for the purposes of providing the clinical trial and experimental evidence required for regulatory approval. The legislation is named after a US law that overruled a court ruling that did not allow for a research and development exemption to infringement.[3]

Under the Bolar exemption, manufacturers have the opportunity to develop a generic or biosimilar drug that is still under patent, as well as start clinical trials prior to the patent expiry, significantly reducing the time to enter the pharmaceutical market. By submitting test data to related regulatory authorities before the patent expires, companies are allowed to launch their biosimilar product immediately after the patent term expires.

The Bolar exemption can also be seen as a solution to patent sourcing issues. Depending on the legislation in each country, the Bolar exemption can allow sponsors to have a commercial transaction to import, for clinical trial use, a generic or a biosimilar drug that has market authorization for clinical trial use, even though the originator product is still under patent in the importation country.

Patent specifics and challenges

A patent is an exclusive right granted on an invention over a specific period. In the pharmaceutical industry, a patent is generally active for 20 years from the patent filing date. The harmonization of the patent term across national laws was provided by the implementation of the WTO's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS).[4] The purpose of the patent system is to provide some guarantee of return, but it is also designed to balance the interests of inventors and the public.

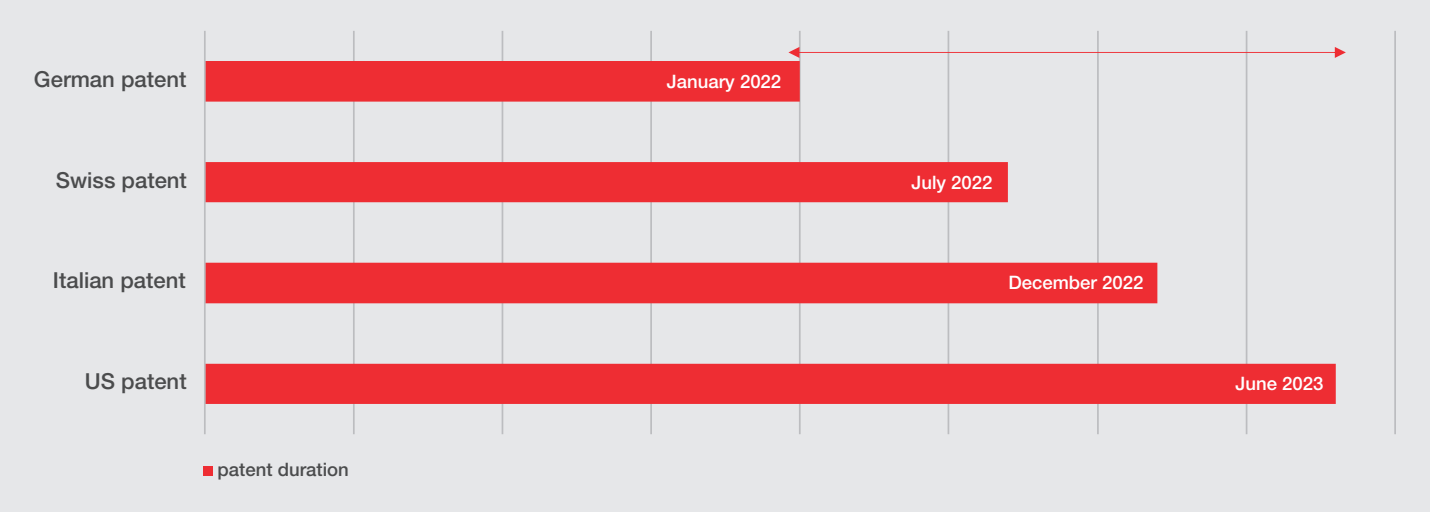
In addition to these pharmaceutical patents, there is also a Supplementary Protection Certificate (SPC) that allows the owner of a patent to extend the rights of a pharmaceutical product for up to five years from the expiration of the patent. The SPC duration depends on how long it took for the market authorization to be issued. More precisely, it corresponds to the time between the filing of the patent application and receipt of the authorization. The patent could last for up to 25 years if the maximal duration for the SPC is obtained.

Another consideration is the data protection patent, which protects the observations and data that were collected to obtain the market authorization. The data protection patent runs in parallel with other pharmaceutical patents but is very important in case of weak, expired, or unfiled patents. The data protection is limited to a period of five to 10 years depending on the country in which marketing authorization is obtained.

The purpose of the patent system is to provide some guarantee of return, but it is also designed to balance the interests of inventors and the public.

These timelines—particularly the regional differentiation—are critical considerations with respect to the Bolar exemption because the total patent durations are not the same from one country to another, as shown in Figure 1. As the graphic illustrates, the patent legislation in each country creates different windows of opportunity for applying the Bolar exemption. In this example, a biosimilar or a generic drug can enter the market in Germany because the patent has expired. Sponsors in the United States can buy the product in Germany at a lower cost than the originator and have it shipped to the US for clinical trial purposes.

Figure 1



Global differences in the Bolar exemption

Many nations have some version of the Bolar exemption in place, although the nature and scope of the provisions vary from country to country. The different interpretations globally have created different levels of protection, which must be taken into consideration before applying the exemption as part of a sourcing strategy. Following are some of the key differences by country and region.

In the United States, US legislators introduced the Hatch-Waxman Act in response to the US Court of Appeals' Federal Circuit 1984 decision in Roche Products Inc. v. Bolar Pharmaceutical Co., Inc., stating that the experimental use doctrine did not protect the "limited use of a patented drug for testing and investigation strictly related to US Food and Drug Administration (FDA) drug approval requirements."[5] The Hatch-Waxman Act states that "it shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention … solely for uses reasonably related to the development and submission of information for regulatory purposes."[6]

A later interpretation of the legislation came in the US Supreme Court decision in Merck v. Integra Life Sciences, which held that the Hatch-Waxman Act includes acts that are reasonably related to the making of submissions for the purposes of obtaining regulatory approval for generic medicines. The disparity between the various member states' treatment regarding the use of the Bolar exemption is a specific challenge related to this country.

Under the Bolar exemption in Europe, a generic or biosimilar sponsor can conduct the necessary studies in support of its application in order to be ready for market entry as soon as possible after the 10- or 11-year period of market exclusivity and the relevant patent expiry. However, within the EU, countries have not adopted a uniform approach to the implementation of the exemption into national law, which means that its scope is uncertain. Therefore, the interpretation and the possibilities linked to the Bolar exemption are variable. For example, some countries, such as Belgium and Ireland, authorize the use of the Bolar exemption only for the activities related to obtaining authorization to market generic drugs, not biosimilars. Other countries, such as France and Spain, exempt more broadly to all acts necessary for obtaining marketing authorization, including acts relating to innovative medicines.

A change in the comparator buy/sell paradigm

In this new environment, the buyer/seller relationship is shifting toward a real collaborative approach between partners that will benefit from acting before the expiration of any relevant patents to prepare for a market launch.

For example, a generic/biosimilar marketing authorization holder is eager to compete as soon as possible with the patent owner. Being able to access the market as soon as the patent expires is a must, but the launch phase is highly competitive due to the high number of generic/biosimilar sponsors getting ready to enter the market. By supplying clinical trials under Bolar, the marketing authorization holder will gain a strong competitive advantage by being visible as reference treatment before commercial launch and get in a top position for future market share penetration.

Another example is a research-based company that may have an entirely new product in the pipeline whose development can be impacted or delayed by the complexity and cost of original reference product sourcing. With the sourcing olution described above, this company can see a 30% to 40% cost savings relative to the originator price, while still having the necessary documents to conduct the clinical trial thanks to a collaborative generic/biosimilar market authorization holder that has an interest in selling its own product to the market before the patent cliff of the original reference product.

The enablers for leveraging the Bolar exemption for this innovative sourcing solution are:

A marketing authorization holder available for the generic or biosimilar product delivered by the competent authority for a specific country

Wide coverage and interpretation of the patents and legal factors globally enabling the Bolar case feasibility evaluation by the marketing authorization holder

Given the complexity of patent protection and the legal landscape surrounding application of the Bolar exemption, conducting a thorough investigation for all countries involved in a trial is imperative. Sponsors should also allow a significant and drastic diminution of the risk associated with application of the Bolar exemption to run a clinical trial prior to a patent cliff.

Thermo Fisher expertise around the Bolar exemption

Thermo Fisher Scientific is a client-focused service company with strong expertise in bridging the gap between the commercial and clinical supply chains.

With a team of more than 70 experts dedicated to comparator sourcing, we facilitate sourcing activities by handling the communication and coordination between customers and manufacturers while analyzing and discussing customers' needs.

In order to leverage the Bolar exemption and obtain early access to generic/biosimilar drugs, our team has developed proactive market intelligence to identify key products and players. By analyzing new market authorization submissions of future biosimilars and the clinical landscape regarding usage of the original products, we have targeted and built relationships with top biosimilar companies that have relevant products in their development portfolios.

Our team proactively proposes those innovative alternative sourcing solutions and facilitates communication regarding the feasibility evaluation for specific trials. This feasibility requires a deep understanding of how the reference drug will be used and the relevant patent claims in each country. Therefore, our team supports the clinical trial sponsor's full evaluation and transparent sharing of information to build a strong solution that limits the risk of originator claims regarding patent infringement.

After a successful feasibility evaluation, our team also supports the coordination between clinical demand planning, aggressive and condensed over time, and the production capabilities at an early-phase industrial process to de-risk the supply chain.

Case study

Navigating the Bolar exemption

Our customer required access to an original product that is the gold standard for a specific oncology indication in order to perform clinical trials in 2020. The planned recruitment was 300 patients, each requiring a yearly treatment cost of $120,000 (US).

On top of this cost challenge, access to the Standard of Care through the originator was restricted and required a heavy contracting phase either in the EU or in the United States.

The Thermo Fisher Comparator Services team advised the customer of a potential alternative solution they wanted to explore with them, as the original product patent was set to expire in the EU in December 2024.

In November 2019, a generic company successfully received a marketing authorization in the EU for a generic version of the original product of interest, well in advance of the patent expiry. Obtaining a marketing authorization confirmed that the generic version complied with all Current Good Manufacturing Practice (CGMP) regulations.

Because of the time lag prior to being able to launch its product commercially, the generic manufacturer was eager to supply its product for clinical trials under the Bolar exemption. The price of the generic product was approximately 50% lower than that of the original product.

Thermo Fisher engaged the sponsor to disclose information including a detailed synopsis and a list of countries engaged in the clinical trial. This information was necessary to evaluate how the Bolar exemption could prevent a potential lawsuit for patent infringement regarding use of the generic drug before the original drug patent cliff.

Assessment of the Bolar exemption, performed in cooperation with the generic company and involving patent law expertise in each country participating in the trial, confirmed that the Bolar exemption could be applied to the sponsor's trial.

Using a generic under the Bolar exemption greatly facilitated the contracting process, which accelerated product access and enabled the sponsor to reduce its costs by more than $18 million.

Through a combination of global market research and the ability to leverage its considerable network of suppliers and manufacturers, the Thermo Fisher Comparator Services team was able to offer our customer an innovative solution, bringing savings in development costs and considerably advancing the study start date through a de-risked approached.

References

1 Patel, U. "The Coming Wave of Biosimilar Medications." Evernorth. June 2021. https://www.evernorth.com/articles/the-coming-wave-of-biosimilar-medications

2 Reports and Data. "Biosimilars Market Size, Share, Trends, By Product Type (Recombinant Non-Glycosylated Proteins, Recombinant Glycosylated Proteins, Recombinant Peptides), By Disease Type (Oncology, Blood Disorders, Chronic Disease, Infectious Disease), and By Region Forecast to 2030." May 2022. https://www.reportsanddata.com/report-detail/global-biosimilars-market

3 Justia US Law. *Roche Products, Inc. v. Bolar Pharmaceutical Co., Inc.*, 733 F.2d 858 (1984). http://law.justia.com/cases/federal/appellate-courts/F2/733/858/459501

4 Article 33 of the TRIPs Agreement.

5 *Roche Products, Inc. v. Bolar Pharmaceutical Co., Inc.*, 733 F.2d.858 (Fed.Cir.1984) at 863.

6 835 U.S. Code § 271 – Infringement of patent.

About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics, and commercial manufacturing to customers through our Patheon brand. With more than 65 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services, and commercial manufacturing and packaging. Built on a reputation for scientific and technical excellence, we provide pharma and biotech companies of all sizes instant access to a global network of facilities and experts across the Americas, Europe, Asia, and Australia. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. Our Quick to Clinic™ programs for large and small molecules help you balance speed and risk during early development so that you can file your IND quickly and successfully. Digital innovations such as our mysupply Platform and Pharma 4.0 enablement offer real-time data and a streamlined experience. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

+1 919 226 3200 • thermofisher.com/patheon • pharmaservices@thermofisher.com

Published 10/22

ThermoFisher SCIENTIFIC