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BEYOND PROCUREMENT

TAKING A STRATEGIC APPROACH TO COMPARATOR DRUG SOURCING

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Introduction

The escalating volume and complexity of global clinical trials have been accompanied by a corresponding increase in the demand for reference medicinal products or so-called comparator drugs. Active comparators are used in clinical trials as a means of establishing that drug candidates are substantially better than established treatments. In the highly competitive biopharmaceutical industry, demonstrating such differentiation is crucial for the market success of new products and a prerequisite for formulary listing, and, in some cases, for successful licensure.

As the market for comparators grows, so do the challenges facing study sponsors and the clinical supply chain industry. Among them: Securing large volumes of comparator for multisite studies taking place in every corner of the world, complying with evolving import requirements of markets where clinical sites are poised to begin enrollment, addressing the special handling needs of temperature-sensitive biologics, and accommodating the higher costs associated with the use of comparators instead of less costly placebos – all while taking the precautions necessary to prevent counterfeit product from entering the supply chain.

Effectively overcoming these obstacles demands a strategic—rather than a tactical, or procurement driven—approach to reference medicinal product sourcing. At a time when Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) are more closely linked than ever before, an integrated and strategic team approach is required for a successful clinical trial. Failure to take such a strategic approach could have costly consequences down the road, including the delay or halt of a clinical trial. It has been estimated that biopharmaceutical companies stand to lose between $600,000 and $8 million for each day clinical trials delay the development and launch of a drug.[1]

Extensive global experience has enabled Fisher Clinical Services, by Thermo Fisher Scientific to develop best practices in supply chain management, including the creation of customized comparator sourcing plans for clinical trials. This ebook discusses a strategic approach to comparator sourcing and provides recommendations for biopharmaceutical companies that are planning clinical trials involving comparators.

The key to a successful clinical trial is an integrated and strategic team approach to comparator sourcing

1 Reprioritizing Investigator Meetings - Accelerating Clinical Trials through process improvement.

Using a comparator instead of a placebo

Placebo-controlled clinical trials have long been considered the gold standard in biomedical research, but for ethical reasons, not all clinical trials may use a placebo as a control. Studies involving comparator treatments are conducted when placebo-controlled trials are considered unethical.

When testing drugs for life-threatening diseases such as cancer, it is unethical to deny patients established treatments. In these cases, established treatment known as a comparator is given to a control group of study subjects. In these trials, clinical investigators compare the performance of the drug candidate or Investigational Medicinal Product (IMP) against that of the comparator or established treatment.

The objective is to determine which of the two treatments offers better efficacy, tolerability or, preferably, both.[2]

In these resource-constrained times, containing costs—through well-planned sourcing, integrated efforts, and minimizing waste and overages—is imperative.

2 Clinical Trials: World Market 2010-2025; Visiongain 2009

3 "Trends, Charts and Maps." Clinicaltrials.gov. U.S. National Institutes of Health, accessed 21 June 2018. https://www.clinicaltrials.gov/ct2/resources/trends

4 "Tracking Trial Cost Drivers: The Impact of Comparator Drugs and Co-Therapies." PharmExec.com. Pharmaceutical Executive, accessed 21 June 2018. http://www.pharmexec.com/print/203238?page=full&id=&sk=&date=&=&pageID=3

The growing importance of comparators

The value of showing superiority is the primary driver behind the growing use of comparator drugs in clinical trials.

There are several reasons why the market for comparators is growing:

- For one thing, more clinical trials are being conducted today than ever before and more of those trials are using active comparators. According to ClinicalTrials.gov, the registry of clinical trials underway in the United States and around the world, 47,448 studies of the 276,190 studies registered on the site were recruiting participants in mid-2018. By contrast, the total number of registered studies in 2008 was 35,742.[3]
- The proportion of studies using comparators and co-therapies has also skyrocketed. An estimated two-thirds of clinical trials today involve the use of comparators and co-therapies.[4]
- Many of these trials are taking place in emerging markets of Asia, Eastern Europe and Latin America The inclusion of emerging markets in clinical trials has served to increase the size and complexity of clinical trials, particularly from the standpoint of sourcing comparator.
- In conducting comparative studies, biopharmaceutical companies are also responding to a growing chorus of demands from patients, healthcare professionals and payers for demonstrably better treatments for diabetes, cancer, Alzheimer's disease and other serious medical conditions.
- Demonstrating medical differentiation through comparative studies is crucial for the success of new pharmaceutical products. In fact, demonstrating the differentiation of a drug candidate is becoming a prerequisite for formulary inclusion, healthcare reimbursement and, in some cases, successful licensure.

Comparators are by definition more expensive than placebos, making them a significant line item in development budgets.

Options for sourcing comparators

Sponsors and supply chain managers rely upon four suppliers of comparator drugs for clinical trials. They are:

Biopharmaceutical companies: Individual drug companies may negotiate directly with other companies, agreeing to supply comparator drugs for each other's clinical trials and those of partner firms.

Pharmaceutical wholesalers: Although pharmaceutical wholesalers are reliable sources for comparator drugs, their role is strictly that of supplier. They are generally unaware and insensitive to the challenges of conducting global clinical trials, such as managing expiry dating and securing resupplies.

Sourcing specialists: While these companies specialize in obtaining drug supplies for clinical studies and have a general understanding of clinical supply chain, many are relatively new to the industry. Often small and privately owned, they may not offer the security and service level desired by most sponsors.

Clinical supply chain specialists: Because comparator drugs have grown more important to the success of a clinical study, many sponsors now rely on vendors that make comparator sourcing an integral part of their overall supply chain services. Dedicated vendors, such as Thermo Fisher Scientific, provide fully integrated clinical supply chain management that includes the full range of services—comparator sourcing, clinical ancillaries sourcing, clinical supply optimization service, blinding, packaging, labeling and distribution. This approach ensures the comparator is managed properly and makes the entire supply chain more efficient, saving time and costs.

There are three primary sourcing options for comparators. They are:

Central Sourcing: The sourcing of a commercial drug in a single country for use in all of the countries participating in a particular clinical trial. Example: A drug that is manufactured in the United Kingdom is shipped to a labeling facility, where a global booklet label is applied. The drug is then distributed to all of the countries in which the trial is being conducted.

Local Sourcing: The purchase of a commercial drug within a single country for use in that same country. IMP is a good option for local sourcing when it does not require blinding, repackaging or manipulation. In this form, the product in the local language is supplied open-label. IMP is another good option for local sourcing, examples include rescue medications, background therapy, chemotherapy, co-medications and standard-of-care medications. Example: A chemotherapeutic agent is sourced in Russia for use in a clinical trial that is underway at Russian investigator sites.

Hybrid Sourcing: A commonly used combination or blending of local and central sourcing, such as sourcing a drug in one European Union (EU) country for use across the EU. Example : A drug is sourced in the UK, where it is packaged, labeled and shipped to all EU countries that are participating in a clinical trial.

Seven common missteps in comparator sourcing

Often unaware of regulatory and other requirements regarding the transportation and use of comparator drugs, sponsors inexperienced in sourcing comparators may make incorrect assumptions and costly missteps. Here are some examples:

1. **Taking a tactical approach by focusing exclusively on cost:** Although cost is a key factor in clinical development, the cost of a clinical study is assuredly more than the price-per-milligram of comparator drug. At a time when Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) are more closely linked than ever before, a strategic, fully integrated team approach is required for a successful trial. Such an approach requires taking all key factors into account, such as expiry dates and resupply requirements. The ultimate goal is effectively managing the clinical supply chain from day one through trial completion. Failure to think long-term could result in study delays, or even cause a trial to grind to a costly halt. The notion of the procurement department acting independently to source comparator at the lowest price possible can be both short sighted and risky.

2. **Failing to consider all viable sourcing options:** While sourcing comparator drug from the United States for a U.S. study is an intuitive choice, it may not be the only—or the best—strategic option. Out of habit, many sponsors neglect to consider other viable options, such as the possibility of sourcing comparator for a U.S. study from the European Union. European drugs are often identical and typically less expensive, which may make sourcing comparator from Europe a cost-effective option. Using drug from Europe for a U.S. study requires either accompanying documentation to assure pedigree or confirmatory testing to establish that the product is identical.

3. **Making assumptions about the availability of comparator drugs:** For commercial and regulatory reasons, every drug may not be available in ample supply in every market. Even if a comparator is available in a particular country, it may not be possible to source or use it in a clinical study. Sponsors may find that the best laid plans to acquire comparator require adjustment. Some real-life examples:

   - Plans to source the entire comparator supply for a global trial from Portugal changed upon learning how difficult it is to export pharmaceuticals from the country
   - Sufficient quantities of comparator for a multi-country trial were not available in Italy, which had been identified as the preferred single source of the product
   - A wish to import comparator to Ukraine for use at clinical sites was scuttled when it was discovered that the country requires in-country drug sourcing for studies

4. **Requesting comparator from multiple sources:** A series of simultaneous requests to wholesalers and suppliers for supplies of comparator can be counterproductive. Such requests inevitably make competitors aware of plans to mount a comparative trial, often leading them to block or at least delay access to comparator. Prolonged delays often compel a sponsor to abandon plans for use of that comparator, threatening the entire development strategy.

5. **Overlooking other necessary trial components:** It's important to note that sourcing comparator may also involve the sourcing of co-medication or background medication, rescue medication, and ancillary supplies such as needles, tubing and IV bags for biologic comparators.

6. **Expecting one size to fit all:** If the globalization of clinical trials means only one thing, it would be that one size most definitely does not fit all. Even though the same comparator may be available in multiple markets, its presentation, strength, packaging, trade name and price may be different in each. If repackaging and relabeling of comparator are required, as they frequently are, it's critical to be aware of local regulations with respect to translation and relabeling.

7. **Bringing a vendor aboard late in the game:** All too often, a sponsor engages with a provider of comparator drugs late in the development process and after key details have been finalized. At that point, there is little opportunity for the supply chain manager to offer recommendations that could increase the efficiency and cost-effectiveness of the trial.

Anticipating challenges of comparator drugs

As planning begins for trials involving comparators, it pays to anticipate and address potential stumbling blocks as early in the process as possible:

Inaccurate forecasting: A common pitfall is variation in comparator demand. It's difficult to project the pace of recruitment in large trials involving dozens of countries and hundreds of sites. Recruitment that occurs faster or slower than anticipated impacts the delivery of comparator supplies, which may be required sooner or later than scheduled. It's important to secure adequate supplies of comparator in advance, while using modeling tools to constantly adjust the forecast.

Problems with placebo production: Trials may require a matching placebo for comparator. The easiest way to obtain a matching placebo is from the company that manufactures the comparator. It comes as no surprise, however, that biopharmaceutical companies willing to manufacture placebos for studies evaluating new doses or indications of their own drugs are unlikely to do so for studies being conducted by competitors. Generic manufacturers may be another potential source of matching placebos. Whatever the circumstances, manufacturing a matching placebo requires procurement of identical components, whether the placebo takes the form of a tablet, capsule, prefilled syringe or inhaler device. This process can be highly complex if the comparator differs in presentation from market to market.

Failure to meet blinding requirements: Comparator drug requires the same level of attention as investigational drug, and if blinding is required it may require more attention. Failure to manage blinding properly could jeopardize the entire trial. Depending on the dosage form, there are multiple options with respect to blinding:

- Sourcing unlabeled comparator from a manufacturer is without a doubt the most direct option. Another option is sourcing bulk comparator, which can be used to produce blinded comparator.
- Filling areas of engraving or over-coating a tablet is usually successful, but it may still be possible to see through to the engraving or printing below. Filling engraved areas may also add weight, affecting the dissolution rate. Many of these trials are taking place in emerging markets of Asia, Eastern Europe and Latin America. The inclusion of emerging markets in clinical trials has served to increase the size and complexity of clinical trials, particularly from the standpoint of sourcing comparator.
- De-inking uses ethanol to wipe printed inscriptions, such as commercial logos and identifiers, from capsules. This must be done carefully, however, since alcohol may also remove the capsule coating, revealing the core tablet beneath.
- Over-printing with confusion text to obscure the original printing on a capsule can also work. Here again, care must be taken to over-print with precision in order to prevent trial participants from being able to discern the original text.
- Over-encapsulation—a highly customized process of concealing tablets, capsules or other solid dosage forms inside a hard gelatin capsule shell -- is the most common choice in blinding solid dosage forms.
- De-labeling and relabeling involve the removal and replacement of labels, a process that is frequently used in blinding liquids, vials and syringes.

Anticipating challenges of comparator drugs (continued)

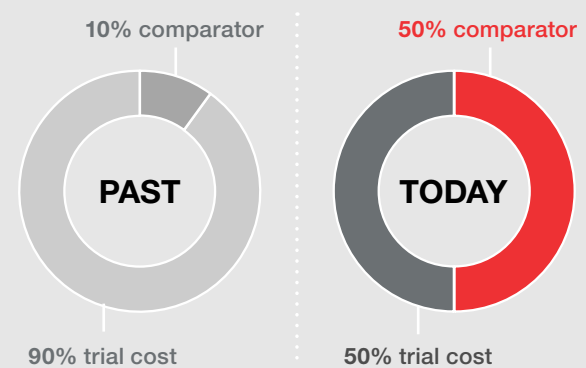
Changing regulatory environments: Regulatory requirements differ from market to market. Furthermore, they can evolve and continuously change without notice, particularly in emerging markets, where the volume of clinical studies is escalating. Understanding the regulatory environment for every country in which a clinical trial is taking place safeguards against errors that can cause delays.

Customs delay: Suffice to say that no one wants to see a supply of comparator perish on the tarmac should a customs official take issue with product declarations and delay clearance for a week. Most customs issues boil down to three causes: incomplete/inaccurate documentation, bureaucratic process or inexperience. In emerging markets where clinical studies are being conducted for the first time, a combination of all three may come into play. Remaining vigilant and informed about evolving customs requirements is mandatory.

Counterfeiting: Prescription drug counterfeiting is escalating globally, with counterfeit products having been detected in every region of the world.[5] In a 2017 report, the World Health Organization (WHO) said that one in 10 medications in low- and middle-income countries are either substandard or counterfeit.[6] Data on counterfeiting, illegal diversion and theft incidents show that incidents have soared by 60 percent in the past five years, climbing to 3,509 incidents in 2017 from 2,193 incidents in 2013, according to the Pharmaceutical Security Institute.[6] With 1,677 incidents of pharmaceutical crime, North America topped the list of troubled regions in 2017, followed by Asia with 768 incidents.[5] Though no precise figure for the extent of counterfeit medicines is possible, the problem tends to be greatest in developing countries where regulatory and legal oversight is weakest. Trusted supply sources and the capacity to confirm authenticity through testing are important safeguards for preventing counterfeit drugs from entering the supply chain.

Expense and availability of biologics: The substantial increase in the number of studies for temperature-sensitive biologic products, which require cold-chain storage, packaging and transportation, makes comparators highly expensive and logistics challenging. By 2020, for example, more than half of best-selling drugs will be cold-chain products. A major contributing factor is the growth of the global biosimilars market, which could reach $35 billion by 2020.[7] Continued strong growth in vaccines is also driving growth. In 2017, 264 vaccines were in development to prevent and treat diseases, according to the Pharmaceutical Research and Manufacturers of America (PhRMA).[8]

Clinical supply costs



Cost of comparator
Up to 50% of total clinical supply cost can be spent on the comparator drugs[9]

5 "Total Number of Incidents" and "Incidents – Regions of the World". Psi-inc. Pharmaceutical Security Institute, accessed 21 June 2018. http://psi-inc.org/incidentTrends.cfm http://psi-inc.org/geographicDistributions.cfm

6 "1 in 10 medical products in developing countries is substandard or falsified." who.int. World Health Organization, accessed 21 June 2018. http://www.who.int/en/news-room/detail/28-11-2017-1-in-10-medical-products-in-developing-countries-is-substandardor-falsified

7 "Enhanced Cold Chain Capabilities." Clinical leader.com. Clinical Leader, accessed 21 June 2018. https://www.clinicalleader.com/doc/enhanced-cold-chain-capabilities-0001

8 "2017 State of Vaccines." PhRMA.org. Pharmaceutical Research and Manufacturers of America, accessed 21 June 2018.https://catalyst.phrma.org/new-report-and-event-examine-the-new-era-of-vaccines

9 Tufts CSDD Comparator and Co-Therapy Sourcing Study, Ken Getz

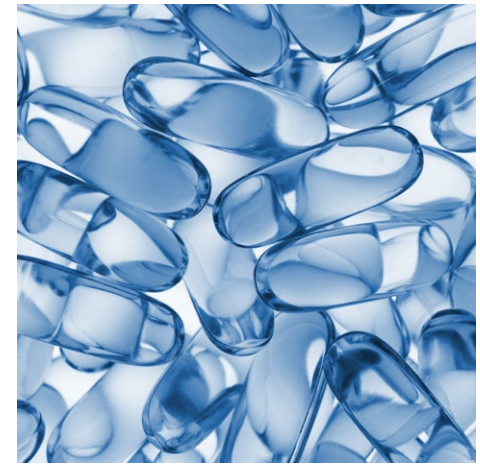
Case study: Supplying the EU from Asia

Through a combination of global market research and the ability to leverage its considerable network of contacts, Fisher Clinical Services Comparator team is often able to offer clinical trial sponsors innovative solutions to sourcing challenges. One large study recently conducted by one of our EU-based trial sponsors gives new meaning to the term ‘creative sourcing’.

The sponsor required EU product as comparator for the study, but had established the goal of paying less than the price set in the EU. Our research identified two potential alternative supply sources in major markets—the United States and India. The U.S. drug differed so significantly from the EU product that it was deemed not to be a viable option. As it turned out, India actually used EU product, which was available at a 20 percent savings compared with the cost to purchase it in the EU.

Ultimately, the Fisher Clinical Services comparator team sourced the product from India. Working with a local regulatory authority in Europe, our Qualified Person (QP) confirmed the requirements for releasing the imported drug so that it could be used in an EU clinical trial. Lancaster Laboratories in Ireland then conducted reduced analytical testing. The testing successfully completed, we arranged for QP release and the drug from Asia was ready for use in the EU.

This product required cold chain (2°C to 8°C) handling and had to reach clinical sites. The comparator team engaged the logistics team within Thermo Fisher Scientific Pharma Services organization to transport the comparator product. The sponsor received temperature tracking data from point of shipment release to delivery until all deliveries were complete.



Getting it right: Five essential elements of successful comparator sourcing

1. Begin planning well in advance.

Begin planning a comparator sourcing strategy in Phase 2 for a Phase 3 trial, for example, or when the protocol is in development. Advance planning provides maximum flexibility and options.

2. Identify relevant facts.

For planning purposes, it's necessary to identify key details about the study—including the number of sites and subjects, duration, strength and maximum volume of comparator—in order to accurately predict supply needs and conduct the market research necessary for reaching optimal sourcing solutions.

3. Take a strategic approach.

Sourcing comparator for clinical studies is not merely a tactical or procurement issue. Taking a strategic approach involves taking every factor into consideration to create a customized comparator sourcing plan that includes multiple options. Remember, the ultimate goal is managing supply chain from day one through the conclusion of the trial.

4. Select a known, trusted and experienced partner.

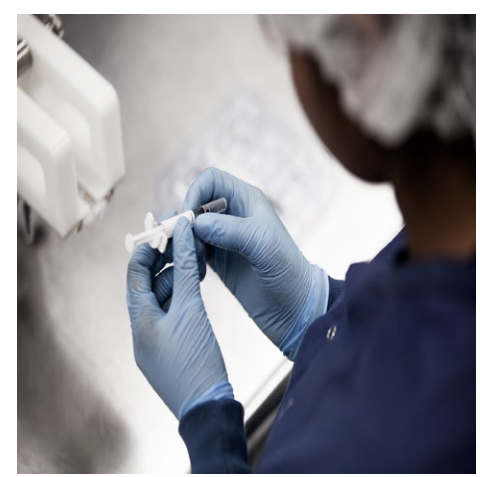
The rule to follow is a simple one: The fewer the handling points when conducting a comparator trial, the better. Through its Thermo Fisher Scientific Fisher Clinical Services℠ offerings, Thermo Fisher Scientific provides a fully integrationed approach to supply chain management—including sourcing, blinding, packaging, labeling and distribution—making the process time- and cost-efficient.

Clinical trial sponsors can experience a de-risked supply chain through:

- Our unmatched geographic footprint, with the capabilities and capacity for central and local sourcing, regulatory support and transportation management in Asia, Latin America and Eastern Europe, as well as the United States and European Union
- Our established sourcing network, including trusted industry relationships that enable it to source product directly from innovator companies at optimal pricing, thereby reducing both costs and the risk of counterfeit product
- The financial strength necessary to support procurement activities in an efficient way that limits financial risk

5. Maintain an open mind.

Depend upon a knowledgeable and experienced partner to make strategic recommendations about sourcing comparator that can offer the advantage of time- and cost-savings. That's a true win-win.



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

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