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WHITEPAPER

Comparator local sourcing strategies: Leveraging advantages and avoiding common pitfalls for clinical trials

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Abstract

Comparators are increasingly used in clinical trials to establish whether an investigational drug is more effective than an existing product, a differentiating factor that can be a prerequisite for licensure, formulary listing and healthcare reimbursement.

This growing demand for comparators is causing many supply chain managers to explore available sourcing options. Savvy supply chain managers say deciding to source locally requires weighing factors that include the preferred comparator, the countries in the trial, and the requirements of the protocol.

This whitepaper will focus on local sourcing. Local sourcing is the purchase of a commercial drug within a single country for use in that same country. This paper elaborates on alternative local sourcing strategies, including advantages and disadvantages of local sourcing.

Local sourcing strategies

Local sourcing may sound simple, but it is far from it. Supply chain professionals have a menu of local sourcing strategies from which they can choose, depending on the circumstances in addition to the true local sourcing explained above.

Product without registration

In this case, comparator is sourced in a country where it is registered and shipped to another country where it is not registered—but the countries share a common language. An example is comparator purchased in Russia and shipped for use in neighboring Belarus, where Russian is one of the two official languages.

Local presentation

This strategy involves centrally sourcing local presentation, or product designated for use in several specific countries, directly from a manufacturer. The product is usually produced with a long lead time only once or twice per year and delivered directly to a regional depot. Recently, for example, Thermo Fisher Scientific helped a client source open-label product from a generic manufacturer in Austria; the manufacturer labeled the product in Spanish for use at investigator sites in five South American countries. Of course, the ability to source directly from a manufacturer depends upon the relationship with the supplier.

Combined presentation

The production of international packs is an originator option when the market need in individual countries is too small. International packs are generic in nature, produced without marketing authorization numbers and approved for use in multiple countries. The labels on international packs are printed in English. Example: Central sourcing of one international pack approved for use in three countries in Asia—Hong Kong, Thailand, and Philippines—from a manufacturer in Switzerland.

Weighing advantages and disadvantages

Assessing the pros and cons of all sourcing options is critical. Once actionable sourcing options have been identified, supply chain professionals should review these options with all stakeholders to lay the groundwork for informed decision-making.

Advantages of local sourcing

Minimal or unnecessary labeling. An auxiliary label is often the only addition necessary for investigational (IMP) or non-investigational (nIMP) medicinal product that stays within a country. This depends upon the regulatory requirements of the sourcing and destination countries.

Simpler Clinical Trial Application (CTA). The content of the CTA that must be submitted by Regulatory Affairs may be less complex, since the reference product is sourced locally, open-label and not being manipulated. In some cases, it may not even be necessary to include a reference product in the CTA, an advantage that Regulatory Affairs is likely to appreciate.

Since product is not being imported, paperwork requirements are reduced.

Minimal paperwork with potential freight and tax savings. Since product is not being imported, paperwork requirements are reduced. Also, reduced use of distribution networks and the elimination of depot-to-depot or multiple depot transfers yield freight and possible tax savings.

S**peed of supply.** In most countries, product sourced locally can be available in two weeks or less. While product sourced from another country or region may take more than a month to arrive, pass through customs and reach a depot enroute to trial sites.

Local language advantages. It's difficult to overstate how advantageous it is to supply reference drugs in the local language to clinical trial sites and participants. Doing so enables all parties concerned to read the product/patient insert, rather than rely on ancillary documents such as the protocol or booklet label to understand how to use the drug properly.

Disadvantages of local sourcing

Intense lifecycle management required. For all stakeholders, local sourcing requires a great deal of attention and ongoing management from the beginning to the end of a study. Local sourcing can increase depot complexity, packaging and labeling activities, batch records to be completed and reviewed by the sponsor, and distribution networks to be managed. There is also the operational and reconcilation work at the end of the study. Local sourcing requires managing a sponsor's Investigational Medicinal Product (IMP) plus several new stock keeping units (SKUs) of comparator drug in the network, while applying the same parameters to both.

Expiry management/lot transitions requirements. The IMP being evaluated in many clinical trials have short expiry dates. In some early-stage oncology trials, for example, clinical drugs may expire after only 12 months. Managing these lot transitions is a labor-intensive task for the investigator sites, clinical research organization (CRO), monitors and the development team. Adding these same requirements for managing expiries and getting lot transitions before locally sourced reference products expire or run out significantly increases the workload.

Scrap risk. When sourcing comparator locally, there is less flexibility than with central sourcing because it is not possible to reallocate locally sourced comparator for use in another country. As a result, there is a heightened risk of scrap.

Administrative burden. Obtaining multiple quotes, managing multiple invoices and generating multiple payments is a labor-intensive undertaking for Procurement, Logistics and Finance staff.

Foreign product & language. It is obviously more difficult to manage a foreign product in a foreign language from an operations standpoint. This makes sense when you consider that staff being unable to read the product insert must use translation vendors, adding time to the process. This makes getting an early start important.

CASE STUDY I

Balancing resources in local sourcing

This complex case study sheds light on the considerations involved in local sourcing. It involves the sourcing solution — in this case, solutions – chosen by a large pharmaceutical company that effectively balanced the cost of product and resources.

The clinical trial

The sponsor managed nine different SKUs for two oncology open-label studies using the same comparator. The trials involved 74 sites in eight regions. Services involved comparator procurement, ancillary labeling and product storage, and distribution to clinical study sites upon CRO request. The company opted for three different local sourcing solutions:

Solution 1: Export for re-import

Reference drug was purchased in Romania and Poland. Two SKUs were shipped to an EU hub in Germany for labeling because there were no packaging facilities in Romania and Poland. To ensure GMP-compliance for the auxiliary labeling, product was stored at the German labeling facility for the duration of the study, with clinical study direct-to-site shipments going from Germany to Romania and Poland in response to manual shipment request.

Solution 2: Classic local sourcing

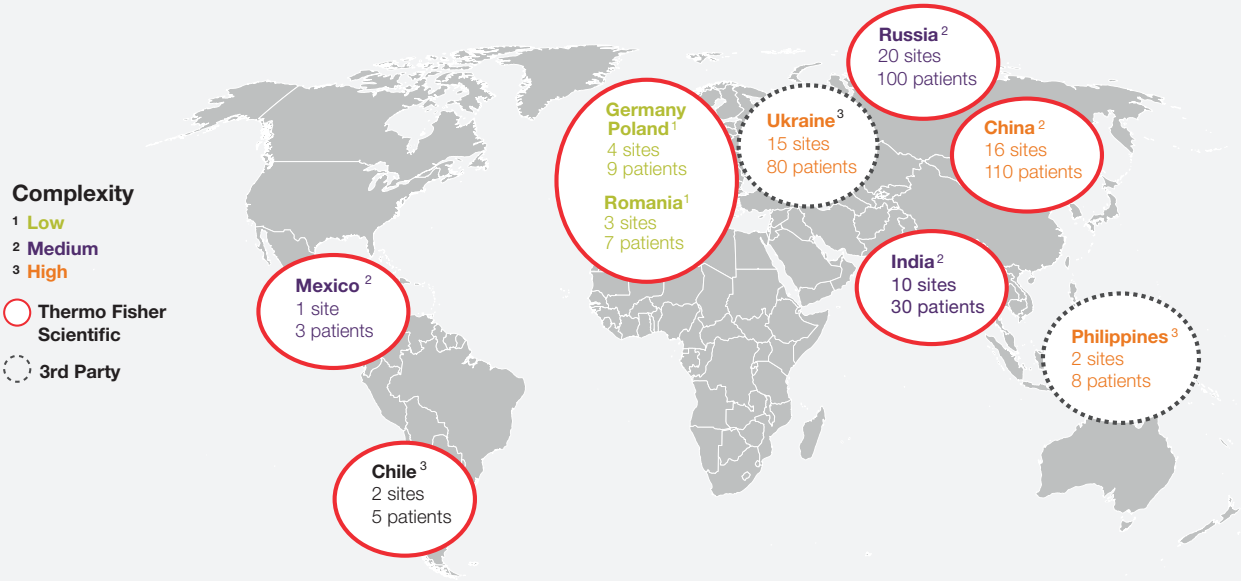
A total of six SKUs were purchased, one in each of the following countries—Russia, Ukraine, Mexico and Chile (for Latin America), and India and China (for Asia). The product went to the local depot in each country, where it was auxiliary-labeled if needed and shipped to study sites upon request.

Solution 3: Another type of export for reimport

One SKU was purchased in the Philippines and sent to a Singapore hub for GMP labeling. After labeling, the product returned to the local depot in the Philippines, where shipments were fulfilled at CRO request.

The bottom line

In this case study, blending a variety of local sourcing solutions enabled the sponsor to balance the costs of product and resources, while optimizing patient supplies.



CASE STUDY II

Cost of local versus hybrid sourcing

Cost is a perennial issue in clinical development. Although local sourcing has the potential for significant savings, it can be more expensive than other sourcing options, as this second case study illustrates.

The clinical trial

This was a Phase II trial with rescue and co-medications taking place in Russia, Israel, U.S., Canada and 10 EU countries. The cost of comparator using a classic local sourcing strategy was estimated at EUR 1.15 million, deemed too expensive for a 14-country trial. As a result, the sponsor chose hybrid sourcing.

Hybrid sourcing solution

- Sourcing in the UK for the 10 EU countries.
- Sourcing locally in Russia, Israel, U.S. and Canada to reduce costs and time, and to procure product with local language labels.
- Final cost was 0.95 million EUR, representing a savings of 200,000 EUR or 17% over the classic local-sourcing strategy.

The bottom line

As this case study demonstrates, a strict local sourcing strategy can be more expensive than other options, so it may be cost-effective to take a hybrid approach. Importantly, always consider the operational costs of local sourcing vs. central sourcing.

Initial costs to purchase comparator may be higher, but one must also factor in reduced operational costs—in this case, the reduced costs of transportation and lower labeling expenditures, thanks to product bearing labels in local languages for open-label trials.

Caution required: Compliance with GMP and GDP

Local sourcing decisions require compliance with Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) standards. This can be a challenge in some markets due to local interpretations of these standards and regulatory issues.

While it may appear counterintuitive, GMP and GDP standards—established for the purpose of ensuring consistency—may be interpreted differently from country to country. Meanwhile, new and changing regulations pose further challenges.

A good example of a farreaching new regulation is the Drug Supply Chain Security Act (DSCSA) in the U.S. The purpose of the DSCSA is to establish a nationwide drug track-and-trace system to prevent counterfeit or illegitimate medications from entering the market.

Each stakeholder in the supply chain, from the original manufacturer to the end distributor, is required to keep track of the product coming into and out of its possession, allowing the product's route to be traced by federal regulators. The first of the DSCSA requirements became effective in 2014 with others phasing in through 2023. The DSCSA applies to manufacturers, re-packagers, wholesale distributers and dispensers.[1,2] Regulations such as the DSCSA underscore the importance of qualifying wholesalers and distributors before partnering with them.

Sponsors and comparator suppliers must understand not only their own country requirements, but the requirements —and interpretation—of all countries involved in the clinical trial. Unfortunately, GDP is not a standard in global use. For example, EU GDP must be followed only in Europe. Certain regions and countries, therefore, have different standards.

For example, wholesalers and distributors in Japan do not monitor the temperature during shipments of ambient products, nor do they monitor the temperature of products that must be maintained at 2-8°C.

One possible solution when purchasing comparator from wholesalers is to arrange for product pick-up directly from the innovator through the comparator specialist, thus observing more restrictive foreign GDP guidelines and'eliminating uncontrolled handling.

Compliance with taxes and local laws

Executing any local sourcing strategy requires complying with taxes and other local laws. This includes everything from local taxes, import taxes and Value Added Tax (VAT) to value declarations, all of which can be complicated when sourcing locally.

To avoid tax headaches, it's always best to seek the counsel of a local subject matter expert. One topic bound to arise is that of VAT, because of wide differences from country to country and not merely in the rate.

VAT must be paid on locally sourced comparator that does not leave the country.

VAT must be paid on locally sourced comparator that does not leave the country. However, VAT rates and rules differ by countries. For instance, VAT is 6% in Australia v. 17% in Israel. In some countries, local registration is required for VAT compliance and reimbursement; in other countries, a legal entity is required for a VAT transaction.

Another key issue is that of currency. Some Asian, Latin American and European countries have restrictions on the use of foreign currency, while others have restrictions on the use of local currency.

Some examples:

- In China, local sourcing is permitted only from Chinese legal entities and payment must be made in the local currency, the renminbi/Yuan.
- Comparator may be purchased in Brazil as long as an entity outside the country is invoiced for it. It should be noted that exporting locally sourced comparator out of Brazil is a complex process.
- For comparator sourced and used within the country, Russia requires invoicing in its local currency, the ruble. For locally sourced comparator that is exported from Russia, however, invoicing must be in foreign currency. Exporting locally sourced comparator out of Russia is possible, but can be difficult.

Finally, it's best to treat suppliers of comparator as an extension of the company. For a company to be fully compliant, its suppliers must be as well.

Seven best practices to follow

Thermo Fisher is a leading provider of clinical supply chain services. With a network of cGMP (Current Good Manufacturing Practice) facilities strategically located across the globe, we offer a worldwide presence for all aspects of clinical supply management, including comparator sourcing. Our knowledgeable staff includes a team of experts exclusively dedicated to identifying sustainable comparator sourcing solutions.

This team serves a broad range of clients, from startups to multinational firms that conduct trials of every size and level of complexity. Currently, 15 of the top 20 pharmaceutical and biotechnology companies use Fisher Clinical Services℠ comparator sourcing and strategy services.

Here are seven best practices that the Comparator Center Of Excellence recommends you follow when adopting a local sourcing strategy:

1. **Start early.** The earlier you learn that comparator sourcing is required, the more time there is available to make informed sourcing decisions, taking all elements—timing, protocol, budget, and stakeholders—into consideration.
2. **Purchase samples to test, translate and understand.** If a comparator supplier offers samples, buy one of each, ship them to a local depot or facility, and conduct hands-on analyses of all of them. Translate labels and instructions completely so you understand the product thoroughly and have pertinent information for all necessary documentation.
3. **Strategize internally and externally.** Work closely with all stakeholders in order to choose the best comparator and sourcing solution for that clinical study design.
4. **Understand all regulatory, quality, operational and clinical requirements.** All functional stakeholders must understand what is required and the associated challenges before executing the study with the comparator being considered.
5. **Consider all potential sourcing solutions and the impact of each on the commercialization strategy, the global study, and all stakeholders.** Engaging a supplier offering the full breadth of comparator sourcing options—central, local and hybrid—leads to a tailored and disinterested sourcing solution.
6. **Strengthen your own compliance.** Have a fully compliant network internally and externally. Remember, suppliers are extensions of your company. You cannot be compliant if your suppliers aren't compliant.
7. **Put patient safety and product quality first.** Bear in mind that there is a patient at the end of everything we do. Make it personal: If you were a patient, would you want to receive that drug?

References

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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. We give pharma and biotech companies of all sizes instant access to a global network of facilities and technical experts across the Americas, Europe, Asia and Australia. Our global leadership is built on a reputation for scientific and technical excellence. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. As a leading pharma services provider, we deliver unrivaled quality, reliability and compliance. Together with our customers, we’re rapidly turning pharmaceutical possibilities into realities.

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