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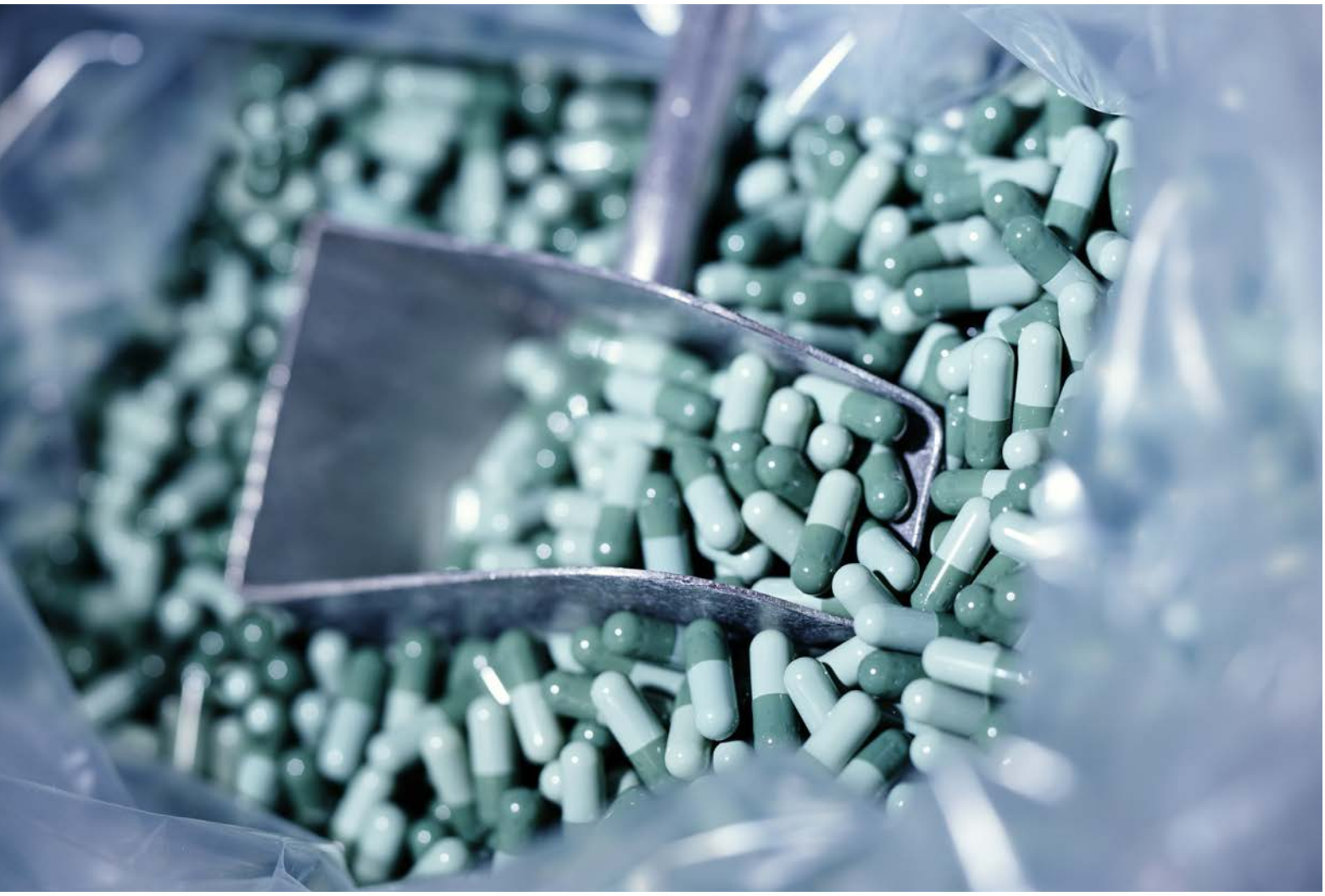

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Comparator local sourcing for clinical trials: Balancing opportunities and challenges

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Abstract

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.[1] 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.[2] The demand for reference drugs or so-called comparators is soaring as the volume, size and complexity of clinical trials reach record levels. Under pressure to source necessary quantities of these products within tight timelines and budget constraints, many supply chain managers are opting to go local. Comparators are increasingly used in clinical trials to establish that 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. On average, a sponsor spends a total of $50 million on clinical supplies, half of it for comparators, according to the Tufts Center for the Study of Drug Development.[3]

This growing demand for comparators is causing many supply chain managers to explore available sourcing options. Two out of three polled during a recent webinar by Thermo Fisher Scientific indicated that they have either gone to local markets for sourcing comparators or are considering this as an option for a future trial. Those who have already taken the plunge into local sourcing cited a variety of reasons for their decision, including product availability, timing, obstacles to importing comparators in some countries, and regulatory and clinical requirements. Half of those queried said all of these factors influenced their decision to source comparator locally.

There's no doubt that local sourcing of comparators can be a highly effective option under the right circumstances, but it's not a one-size-fits-all solution. In some cases, local sourcing may be neither the best, nor the most economical choice. 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. Furthermore, since executing any local sourcing strategy demands a high level of management throughout the trial, having the right internal resources in place—or the right partner to support local sourcing – is a crucial and often overlooked success factor. This paper examines the fundamentals of local sourcing, including the benefits and challenges of sourcing locally, and the circumstances under which local sourcing can be a sound decision. Recommendations are provided for avoiding common pitfalls in implementing a local sourcing strategy.

Examining sourcing options

There are three primary sourcing options for comparators: central sourcing, local sourcing and hybrid sourcing.

What is central sourcing?

The sourcing of a commercial drug in a single country for use in all 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.

What is local sourcing?

The purchase of a commercial drug within a single country for use in that same country. Example: A chemotherapeutic agent is sourced in Russia for use in a clinical trial that is underway at Russian investigator sites. Another version of local sourcing is known as local sourcing with export for re-import. This involves the purchase of a locally registered comparator and export of that drug to a regional hub in another country that has a GMP labeling facility. Post-labeling, the drug is re-imported back to the original country, where it is shipped to local study sites.

Emerging markets are more likely to require local sourcing of comparator drugs.

What is 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. For the same trial taking place in both major and emerging markets, a drug might also be sourced locally for emerging markets and centrally for others. Emerging markets are more likely to require local sourcing of comparator drugs. Russia and China are examples of countries with this requirement.

Sourcing considerations

Sourcing decisions should be made after considering several key factors, including:

1. Comparator

- Which comparator(s) is required for the trial?
- When is it needed?
- Is the comparator a generic?
- Where and by whom is it manufactured?
- Is it available in sufficient supply? Where?

2. Country selection

- Given the countries participating in the trial, what sourcing options are available?
- Is the comparator available in these countries?
- Are local sources for comparator reliable and trustworthy?

3. Regulatory landscape

- What are the regulatory requirements for sourcing and labeling the comparator in the designated countries?
- Do any of the designated countries mandate local sourcing?

4. Import/export complexity

- How difficult is it to import? How long does it take?
- Once imported, can it be exported? What are the requirements?

5. Protocol requirements

- What quantity of comparator(s) is required?
- Under what circumstances will the comparator(s) be used?

6. Cost considerations

- What are the financial/resource costs associated with various sourcing solutions?

When to consider local sourcing

Local sourcing of reference products can be a highly effective option for clinical trials under the right circumstances. Determining when the circumstances are right is the key.

Sourcing experts recommend that companies considering local sourcing begin by developing a simple framework that they can use to help assess whether and when local sourcing is a good choice.

For local sourcing to be successful, there must be a balance between the costs of the product and several other factors—including operational costs and capabilities, the local needs of depots and the resources required to manage.

The decision and balance of necessary variables differ from company to company, based upon available resources, subject matter expertise, network, and access and protocol complexity.

IMP	nIMP	Product	Import/regulatory
Non modified	**Medication**	**Expensive**	**Restrictions**
no repacking no blinding open label	Rescue, background co-medication and standard of care	Leverage price differences between regions/ countries and taxes	no documentation available import challenges

Sourcing considerations

1. IMP

- IMP is a good option for local sourcing when it does not require blinding, repackaging or manipulation. In this form, the product is supplied open-label.

2. nIMP

- Another good option for local sourcing, examples include rescue medications, background therapy, chemotherapy, co-medications and standard-of-care medications.

3. Cost Considerations. Keep the following in mind:

- Cost is a key factor, and there may be substantial unit cost differences locally v. centrally for comparator.
- When sourcing comparator locally, note that there may be no opportunity to shop around for a better price. In countries such as Russia, for example, the price for these drugs is set and there is no room for negotiation.
- When sourcing centrally within the EU for a trial taking place in EU countries, shopping around for a good price is possible and recommended.
- When the comparator is expensive, always investigate price differences between regions/countries and taxes to grasp the big picture.
- Consider operational costs associated with comparator. It's hard to quantify the added cost and work that locally-sourced drug will add to the resource structure. Before opting for local sourcing, understand both the product and operational cost for managing the new SKU.

4. Import/regulatory

- The regulatory landscape and import/export complexity are huge drivers in sourcing decisions. If product cannot be imported due to regulatory constraints and documentation is not available, local sourcing may be the only possible solution.

Considerations when sourcing locally: Drug availability

Once a decision has been made to source comparator locally, be prepared to encounter challenges along the way. Here are some of the most common challenges and solutions:

Product availability in small countries

Challenges

- In smaller countries, there may be only two or three manufacturing runs per year.
- There may not be sufficient product on the market to meet clinical trial requirements.
- Due to limited production runs in that market, the supply chain manager may receive resupplies bearing the same expiry date.

Solutions

- Consider make-to-order. The manufacturer may agree to run a batch of non-IMP open-label products specifically for the clinical trial.
- If obstacles are substantial, it may be possible to switch to regional or central sourcing, if permitted.
- If sourcing locally is mandatory, consider strategically planning trial resupply in conjunction with manufacturer resupply schedule. This may be the only answer.

Hospital line product availability

Challenges

- The manufacturer only delivers directly to hospital pharmacies.
- Due to a restricted supply chain, the product is not available on the open/wholesaler market.

Solutions

- The best and only solution is working through a comparator supplier to go directly to the manufacturer. Disclosing the requirements of the clinical trial may convince the manufacturer to make an exception and sell product directly for trial use.

Availability of product documentation

Challenges

- Obtaining documentation can be a substantial challenge, as it differs from country to country. How a comparator is used in a study and where it is sourced may be impacted by the availability of a Certificate of Analysis (CofA). For example, open-label studies in the U.S. may receive CofAs, while head-to-head studies may not.
- Regional differences also exist; EU-based companies have demonstrated greater willingness to provide CofAs for drugs they manufacture than U.S.-based companies.
- Documentation may be mandatory for Regulatory Affairs to prepare CTAs and for import/export purposes.

Solutions

- If planning begins early, it may be possible to work with internal peers to identify documentation that is mandatory versus nice to have. Then work with the comparator supplier to learn what is available.
- Bringing these assessments together will make it possible to decide on sourcing strategies before realizing too late that a certain difficult-to-obtain document is required to file the CTA. This misstep could lead to a late filing, necessary switch of sourcing strategies, and delayed clinical timeline.
- With respect to documentation and photos for planning decisions and filings, keep in mind the nuances of patient inserts. Some drugs are manufactured and marketed by separate companies.
- Establishing product quality, must take place before it reaches the depot. Quality, compliance, and product safety are the key objectives in the clinical network, so select a comparator supplier with an appropriate qualified and audited network in place for drug procurement.

Defining key processes for local sourcing

By now, it should be clear that local sourcing is a highly complicated process. To successfully execute a local sourcing strategy, companies would do well to establish a general framework to guide decision-making and define key processes.

This framework also makes it possible to replicate successful sourcing solutions. Otherwise, it would be necessary to reinvent the wheel each time a new study was planned, and local sourcing of comparator became an option.

Always define the strategy for local sourcing from an end-to-end perspective. This requires consideration of many factors, including:

- How will you access the product? Think hospital line, controlled sales, availability of inventory in local market.
- How will you select suppliers? Think manufacturer, local wholesaler, and authorized distributors.
- Are roles and responsibilities clearly defined among internal and external stakeholders? Who handles what?
- How will you navigate country requirements from a regulatory perspective? From an import/export standpoint?
- How will you marry the company's capabilities with local sourcing requirements? Is there a CRO? What about depots?
- How will suppliers be vetted and qualified? What about Quality Assurance (QA) standards? Traceability of source?
- What are the commercial rules? Think VAT compliance and local commercial specificity.
- Are the capabilities in place to execute a successful local-sourcing strategy?

In developing the framework, keep in mind that processes should evolve over time with the changing regulatory, supplier, sourcing, and trial design landscape.

Qualifying a supplier

Selecting and pre-qualifying suppliers is a best practice when executing a local sourcing strategy. Doing so helps ensure sustainability of supply throughout the study.

As discussed, direct sourcing from the manufacturer is almost always the preferred route of supply because it offers the shortest and most transparent supply chain.

Sometimes, however, sourcing from an innovator is neither feasible nor desirable for several reasons: The manufacturer isn't present in those countries, has no stock available within the study timelines, or the quantities of comparator required are too small. A sponsor may also not want a manufacturer to know about plans for a competitive trial.

Criteria for supplier should include reputation and referrals, licenses, capacity, pricing and benefits, economic status, and financial stability.

Under these circumstances, supply chain managers must turn to wholesalers and distributors to obtain comparators. Suppliers and sponsors are extensions of one another; given the issues described earlier, it's important to work only with suppliers who have been carefully selected and vetted through a rigorous qualification process.

The qualification process should consist of multiple parts, from a physical audit to risk assessments of both supplier and the country of sourcing. Criteria for supplier should include reputation and referrals, licenses, capacity, pricing and benefits, economic status, and financial stability.

The country of sourcing is important because some markets are "safer" than others, based upon these criteria: Level of regulatory requirement of Medicines Regulatory Authority/Drugs Regulatory Authority, such as GMP, GDP and GCP requirements, legal provisions on marketing authorization, regulatory inspection of manufacturer and distributors, import control, licensing, and sanctions for violation of codes of conduct.

One additional assessment involves the frequency with which counterfeit drugs have been documented in the country, using information from the World Health Organization (WHO) and International Medical Products Anti-Counterfeiting Task Force (IMPACT). Prescription drug counterfeiting is escalating globally, with counterfeit products having been detected in every region of the world.[4]

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.[5] Data on counterfeiting, illegal diversion and theft incidents show that incidents have soared by 60% in the past five years, climbing to 3,509 incidents in 2017 from 2,193 incidents in 2013, according to the Pharmaceutical Security Institute.[4] With 1,677 incidents of pharmaceutical crime, North America topped the list of troubled regions in 2017, followed by Asia with 768 incidents.[3]

Trusted supply sources and the capacity to confirm authenticity through testing are important safeguards for preventing counterfeit drugs from entering the supply chain.

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.

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 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 start-ups 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 to 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. Always 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?

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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. 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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