Minimising Risk and Maximising Efficiency by taking a Strategic Approach to Comparative Trial Supply

Widely acknowledged to be a prerequisite for formulary listing and even successful licensure, comparator drugs and co-therapies are used within an estimated two-thirds of clinical trials[1] and provide sponsors with the ability to demonstrate a study drug's enhanced efficacy and tolerability over the best performing, commercially available alternative.

A core driver for the growing popularity of comparative trials is the increasingly competitive global drug development marketplace, which in recent years has seen a surge in new drug launches and a marked decrease in the average time to market[2].

Factors contributing to this growth are the rise of co-therapies for diseases like HIV, which have previously responded poorly to single therapies, and the increasing complexity of protocols for sophisticated therapies that allow several experimental drugs to be tested at once.

While comparative trials offer unquestionable benefit, they bring with them the burden of additional risk.

So, what can sponsors do to effectively minimise these added risks, while maximising efficiency so that patients receive the right drug, at the right time, with the right expiry, in the right place and under the correct conditions?

Examining the Supply-based Risks Synonymous with Comparative Trials

Before methods can be assessed to optimise comparative trial supply, it's important to apply appropriate scrutiny to the added risks present in comparator product supply chains. It's vital that this activity doesn't become an afterthought once other aspects of the clinical trial operation are already in place. Instead, strategic risk assessment and forward planning should take place at the earliest opportunity. This way, hot spots can be appropriately identified, and sponsors empowered to adapt with speed, agility and precision to implement effective mitigations that safeguard supply and support bigger-picture programme success.

Some of the more obvious risks associated with conducting comparative trials include the increased difficulty of accurately forecasting demand, given the global scale and complexity typical of many comparative trials.

Inaccurate forecasts can have a detrimental impact on comparator sourcing activity, risking stockouts or wastage depending on which way the balance tips. This risk is amplified against the context of global comparator drug shortages and makes calculating clinical supply/demand over time, simulating a range of supply/demand scenarios, and closely monitoring patient enrolment data even more vital.

Placebo matching is another core challenge sponsors of comparative trials commonly encounter. Given the commercial sensitivity around conducting comparative trials, securing an appropriate placebo, which encompasses identical components to 'match' the comparator drug can be almost impossible, especially if the presentation of the drug varies across markets.

With an estimated 10% of all medicines sold worldwide classed as counterfeit[3], with 'higher prevalence in regions where drug regulatory and enforcement systems are weakest'[4], comparative trial sponsors have a leading role to play in tackling the wider problem, while protecting their own interests.

To mitigate the risk of propagating substandard and falsified drugs in comparative studies, supply sources need to be trusted and regularly audited, and drug supply traceability known. The ability to authenticate comparator products and provide corresponding documentation is necessary to prevent counterfeit products entering the supply chain and posing a risk to patients.

Several other risk hot spots need to be appropriately assessed before comparative studies commence. These include, but are not limited to, the enhanced difficulty of upholding blinding protocols, managing country-specific regulation, nuances surrounding import/export activity, maintaining safety and efficacy of biologics-based comparator products, and managing potentially lengthy bulk supply lead times.

Developing a Strategic Comparator Sourcing Approach

The added complexity and risk that comes with managing comparative trial supply places greater emphasis on the importance of adopting a 'strategic' approach to managing the sourcing, procurement and supply of commercialised products for use within comparative studies.

To successfully minimise risk and maximise supply efficiency, comparator product sourcing should not be treated as a bolt-on exercise but as a vital component of the overall clinical supply chain operation. When it comes to comparator sourcing, the ethos must be 'plan early and revisit often'.

To design a fit-for-purpose source & supply strategy, a thorough comprehension of key regulatory requirements and appropriate analysis of core aspects of comparator sourcing are required. Both must be informed by a comprehensive understanding of the technical side of supply chain management and complemented by trial-specific knowledge.

For instance, recent updates to the EU Falsified Medicines Directive (FMD) have increased compliance pressure on sponsors / CROs & CMOs operating comparative studies involving sites and patients located in the European Union. Designed to bolster existing legislation and ensure medicines supplied in the EU are safe, the new 'safety features' aspect of the FMD requires use of unique identifiers (UI) and anti-tampering devices (ATD) on drug packs. UI data must be uploaded by the marketing authorisation holder onto the central European Medicines Verification System (EMVS). However, once packs are removed from the marketed product supply chain and enter into the clinical supply chain, responsibility for decommissioning packs from the relevant EMVS must be appropriately assigned.

Likewise, in the US, the Drug Supply Chain Security Act (DSCSA) places similar pressure on comparator trial sponsors to play an active role in protecting consumers and patients 'from exposure to drugs that may be counterfeit, stolen, contaminated, or otherwise harmful'[5]. Failure to meet these key regulatory requirements can not only result in penalties and reputation damage, but also have a negative impact on study timelines and outcomes.

Regulation aside, there are several other core aspects of developing effective comparator sourcing strategies that warrant close attention. Again, at the earliest opportunity, sponsors should consider some important questions such as the types of drug and ancillaries needed, whether centralising sourcing is feasible, what documentation may be required for drug import or export and the likelihood of encountering availability constraints.

The answers to these questions will help sponsors and CMOs create and develop strategic source & supply solutions, as required, to challenges that arise throughout the lifecycle of the project and facilitate smart decision-making.

By taking a bigger-picture approach to comparator sourcing, through awareness of key regulatory requirements, and by asking the right questions during the planning stages of a clinical trial, risks can be identified early and effective strategies implemented.

Defining the Best-fit Sourcing Strategy

Once risk hot spots have been assessed, regulatory requirements understood and core questions thoroughly considered, an appropriate sourcing strategy will begin to take shape. At this point, sponsors may have to weigh up the pros and cons of a central, local or hybrid sourcing strategy. Selecting a best-fit approach will be dependent upon a myriad of factors but access to the required commercial drug product is ultimately what will determine the route sponsors take. Forward planning is essential in order to avoid a domino effect that threatens overall programme performance.

While drug availability will ultimately determine the sourcing route sponsors take, it's important to understand the nuances associated with the different sourcing models available.

For example, a central sourcing approach refers to the procurement of a comparator product from a single country for subsequent packaging / labelling and distribution within all countries participating in the clinical trial. Although central sourcing is typically used for larger studies and is often best suited to trials involving countries with straightforward import processes, limited access to comparator products can mean central models are not always feasible. When supply is plentiful in a single country, central sourcing can reduce the risk of overstocking local depots; minimising the risk of wasted supplies. Central sourcing is also typically less complex to plan, and requires lower set-up, storage and management fees, in comparison to a local model. However, a central approach may increase freight costs and courier fees. Weighing up the pros and cons of a central model at the earliest opportunity will help to keep timelines and budgets on track.

If comparator products are more difficult to procure, or desired quantities aren't available in a central supply model, a local sourcing approach may offer an ideal solution. Local sourcing model refers to the procurement of comparator drug product in an individual country for use within the same country. This approach can also be used when import processes are long or cumbersome, as it removes the need to ship drugs across borders and is therefore a lower-risk option, especially for temperature-controlled supplies. Returns can be sent to local depots, which also eliminates equally drawn-out, resource-intensive export activity. While a local sourcing approach may deliver lower freight costs and courier fees, higher set-up, storage and management fees are likely. Understanding drug availability constraints early in the process will therefore help sponsors to select a model tailored to the specific criteria of their comparative studies.

Central and local sourcing models offer a number of benefits to sponsors, depending on their exact needs and the availability of the comparator product in question. Yet, many sponsors prefer to 'pick 'n' mix' from both the central and local approach to create a hybrid sourcing strategy that has the potential to offer the best of both worlds. This model combines specific aspects of both a central and local sourcing approach to provide a bespoke solution able to meet a global study's unique requirements. A hybrid sourcing approach can be particularly beneficial for more complex studies, particularly when recruitment outperforms projections and gaps in supply need to be urgently filled.

Weighing Up the Business Case for Strategic Comparator Sourcing

It's all too easy to approach comparator sourcing as an afterthought and to take a cost vs value approach to procurement and management.

Procuring comparator drugs from wholesalers may initially seem like a value-for-money proposition. Yet, while wholesalers may reliably supply comparator products, they rarely offer the guidance and support most sponsors need in order to effectively balance overall study risk and cost, manage expiry dating issues and ensure all necessary documentation is available.

Taking a best-practice approach to comparator sourcing requires timely planning and in-depth research to capture a study's unique requirements, identify potential challenges and design appropriate sourcing strategies and processing protocols. It requires cultivating relationships with manufacturers, suppliers and wholesalers within a vast, global marketplace to define and deliver best-fit supply strategies. It also requires in-depth expertise to identify suitable comparator materials, the optimal source to procure them, available options, market limitations, and supply lead times.

For most sponsors, maintaining this niche specialism in-house is commercially unviable. It is, however, still possible to achieve comparator sourcing best practice through partnerships with clinical supply chain specialists. Through these partnerships, sponsors can obtain visibility over what is available in each market, based on the different formulations, presentations, strengths, and brands, and create enhanced insight over access and availability, including expiration, lead times and licensing.

In a fiercely competitive market, where drug availability issues have been compounded by disruptions caused by the global Coronavirus pandemic, it has never been more important to plan early and adopt a strategic comparator sourcing approach that minimises risk, safeguards supply, and promotes timely, cost-effective trial completion.

REFERENCES

1. Tracking Trial Cost Drivers: The Impact of Comparator Drugs and Co-Therapies. PharmExec.com. http://www.pharmexec.com/print/203238?page=full&id=&sk=&date=&=&pageID=3
2. The Changing Landscape of Research and Development: Innovation, Drivers of Change and Evolution of Clinical Trial Productivity. The IQVIA Institute for Human Data Science. April 2019.
3. Fighting fake drugs: the role of WHO and pharma. Lancet. 2011 May 14; 377(9778):1626.
4. World Health Organization. Medicines: spurious/falsely-labelled/falsified/counterfeit (SFFC) medicines 2012. http://www.who.int/mediacentre/factsheets/fs275/en/
5. https://www.fda.gov/drugs/drug-supply-chain-integrity/drug-supply-chain-security-act-dscsa#:~:text=The%20Drug%20Quality%20and%20Security,distributed%20in%20the%20United%20States

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