ThermoFisher SCIENTIFIC

TOP FOUR DIFFERENCES WHEN MANAGING CLINICAL TRIAL SUPPLIES FOR BIOSIMILARS

patheon

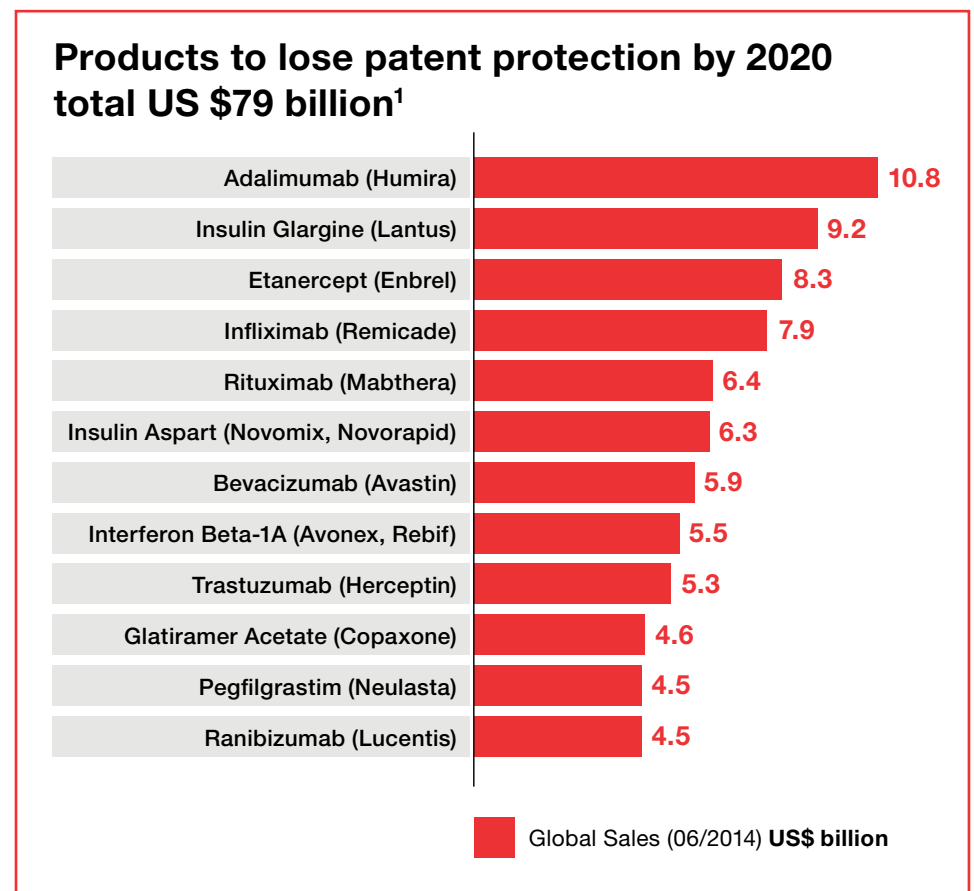
- API
- BIOLOGICS
- VIRAL VECTOR SERVICES
- EARLY & LATE PHASE DEVELOPMENT
- **CLINICAL TRIAL SOLUTIONS**
- LOGISTICS SERVICES
- COMMERCIAL MANUFACTURING

Introduction

At first glance, planning a clinical supply chain for a biosimilar trial appears like getting ready for a traditional study. As in all clinical trials the supplies team is responsible for making sure the investigational biosimilar drug makes it to the right patient, at the right time and place. Yet these studies do present some unique challenges for clinical supply chain professionals. First among these differences is the sourcing of the comparator medication. A highly strategic sourcing strategy is necessary because these trials most often target biologic medicines that are high cost and in high demand. The popularity of these successful medications brings other unique challenges when designing effective blinding methods. This eBook outlines the top 4 differences in managing clinical supplies for biosimilar trials. These challenges make biosimilar studies anything but routine for clinical supply teams.

Many years ago, there was little discussion of a patent cliff for biologic products. These large molecule drugs were considered too complex to copy. They were thought to be immune to the generic competition faced by traditional small molecule products. Today we know better.

As shown in the graph below, biologic products worth US $79 billion in 2014 revenue are facing loss of patent protection by 2020, according to an analysis by IMS Health, the largest vendor of U.S. physician prescribing data.



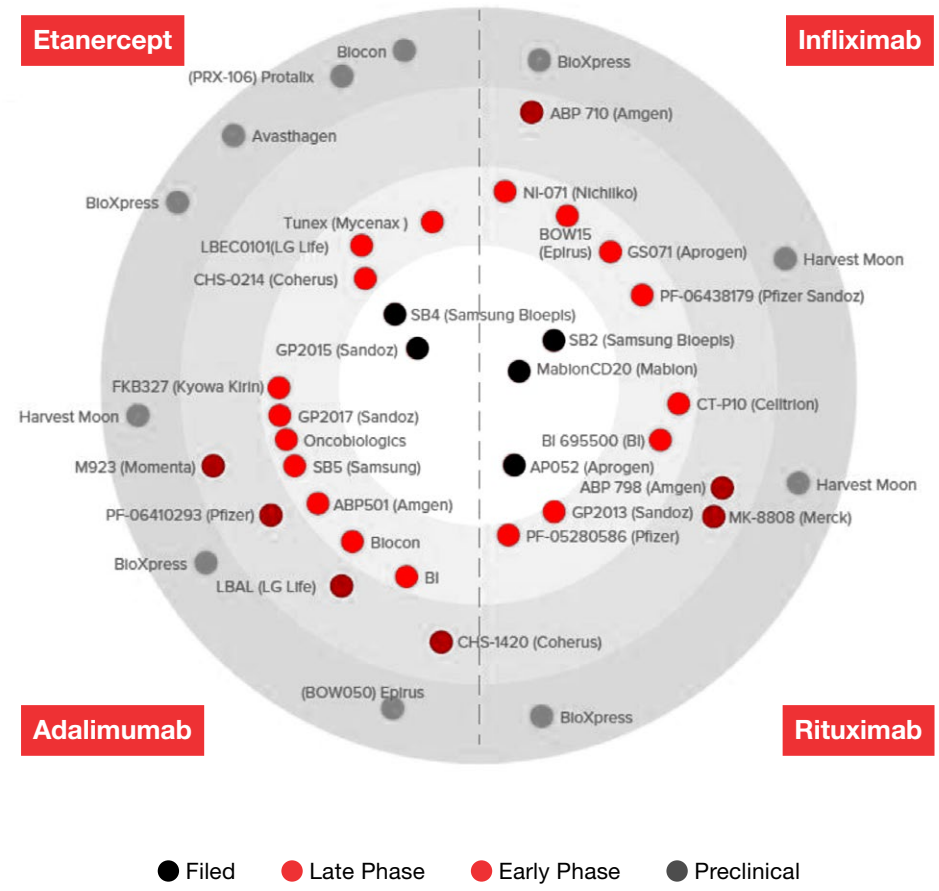
1. The Business of Biosimilars, Doug Long, IMS Health, Inc., March 2016

Biosimilars opportunity brings newcomers to clinical supplies

Biologic medicines are delivering the most revolutionary innovations in health care today. Clinical supply teams have been on the forefront of this research, supporting studies in oncology, infectious disease, neurology and many other therapeutic areas. While these breakthrough large molecule medicines often come at a high price, biosimilars promise to add new value by making this innovation more affordable.

Many companies outside the traditional ranks of drug manufacturing see the biosimilars opportunity as an attractive investment. This chart shows the industry's current biosimilars developmental pipeline. Note that Samsung and LG—companies with a foundation in consumer electronics—now mingle with top biotech and pharmaceutical companies such as Amgen Merck, and Pfizer. These new entrants are also new to clinical supplies, which is the second difference in managing biosimilar trial supplies. Samsung Bioepis, for example, claims 2 of the 5 biosimilar medicines shown as filed.

As leaders in consumer electronics, companies like Samsung realize that the supply chain can provide a key competitive advantage. Understanding the differences between commercial and clinical supply chain, some of these large firms approach supplies management like smaller biotech companies. Working with partners, like Thermo Fisher Scientific, they outsource a larger percentage of strategic planning, forecasting, inventory management, and other high level services compared with traditional large pharmaceutical companies.



Source: IMS Institute for Healthcare Informatics, Jan 2016

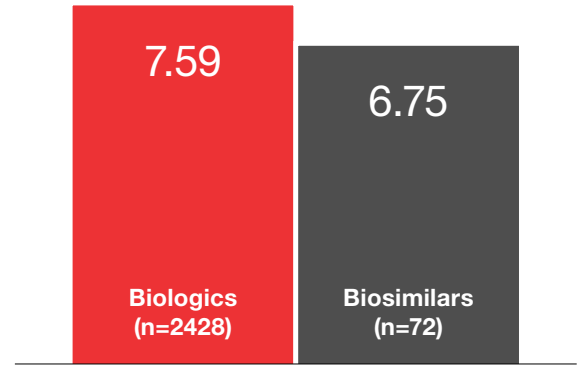
FDA pathway cuts development time, adds pressure for supply teams

The first 3 questions of most clinical trial supply programs are: How much drug will be needed, where, and by when? Knowing the total timeframe of a biosimilar trial may help you answer the latter question. The market research company Sagient Research looked at 72 biosimilar studies and found that development time for a biologic is about 7.5 years while “anticipated total” development for a biosimilar is 6.75 years—a difference of about 43 weeks. (This is a nonweighted sum of the average value of each development segment.)

In March 2010, the US Biologics Price Competition and Innovation Act (BPCIA), or 351(k) pathway, was enacted to allow an abbreviated pathway for the licensure of biosimilar therapeutics. This regulatory path has made development possible, and its impact on timelines may not appear to be significant.

But in the clinical supply chain, 43 weeks can make a world of difference. The 351(k) approval pathway enables biosimilar developers to forego Phase 2 clinical trials. They can simply move from a small Phase 1 study directly into Phase 3.

This is encouraging, but potentially frightening and brings up our third point of differentiation for biosimilar clinical supplies management. For the supplies team the compressed timeline adds pressure because it eliminates much of the traditional learning about patient enrollment and drug usage that comes in Phase 2. Supply teams working on a biosimilar trial may need to be more vigilant about drug usage at the clinical sites. On the positive side of study execution, total patient numbers are usually lower compared with trials for originator biologics.



Source: Biosimilars Special Report, Sagient Research BioMedTracker, August 2015

Survey: Non-blinded clinical staff add risk to clinical trial supplies

It comes as no surprise that the most popular targets for biosimilar developers are the most prescribed and profitable biologic medications. Humira (adalimumab) —the world's highest selling prescrition drug[2]—is leading the list.

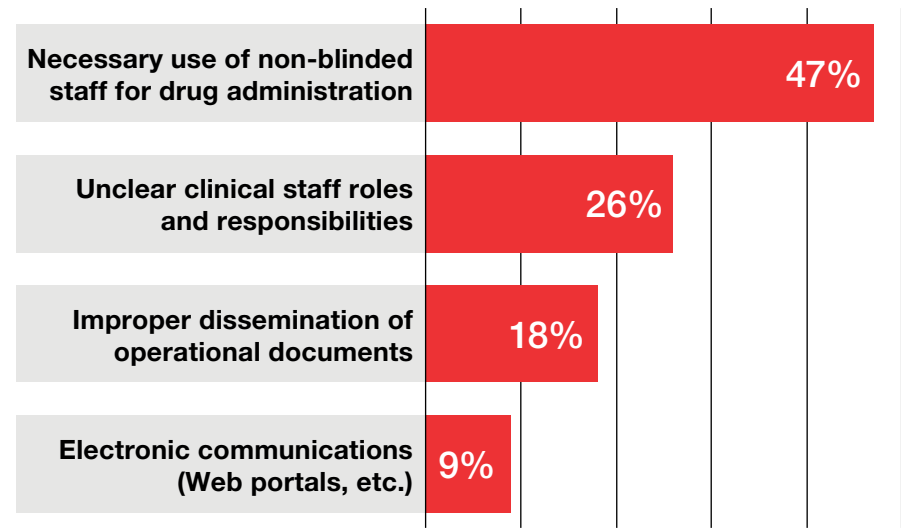
Yet from a clinical supplies perspective, the popularity of these target medications makes study design difficult when it comes to blinding the products to prevent bias. This is the fourth point of differentiation for biosimilar supplies management.

Unless working with treatment naïve patients most study volunteers will recognize the distinctive Humira pen. Building and testing an exact replica for blinding purposes is nearly impossible. That means blinded biosimilar studies may require dosing with unblinded site staff. While the patient and physician remain blinded to treatment assignment, non-blinded dosing staff can add risk to the protocol.

In a webinar, conducted by the Fisher Clinical Services team, attendees indicated that this was the biggest blinding challenge[3]. Detailed to the right, survey data show attendees also see red flags in unclear definition of clinical staff roles and responsibilities and improper dissemination of operational documents.

These more traditional blinding concerns raise the importance of communications among internal and external partners. When planning supplies for a biosimilar trial, just as in all clinical studies, it makes sense to use a RACI document or similar project management tool that clearly spells out all roles, responsibilities and accountabilities. Ensure all staff and vendor partners know who is blinded, who has the authority to break the blind in case of an emergency and what procedures to follow if this becomes necessary.

What do you see as the largest blinding challenge in biosimilar trials?



2. AbbVie Profit Tops Estimates and Sees Higher Humira Sales by 2020, Wall Street Journal, October 30, 2015

3. Biosimilars in Clinical Trials: Smart Reference Drug Sourcing and Advanced Blinding Techniques, Fisher Clinical Services, Xtalks Webinar, May 2016

Case study: Forecast averts study stock outs in biosimilar supply chain

As noted on page 4, companies developing biosimilars are coming to partners like Thermo Fisher Scientific for assistance with forecast planning. This case study shows how these partnerships are paying off.

A midsize pharmaceutical company came to us prior to launching an ambitious Phase III clinical trial for a biosimilar product. It was planning four different four-year studies at 320 clinical sites, involving about 1,500 patients suffering from chronic kidney disease.

With only three members, including a contractor, the company's clinical supply team was not confident in their own capacity to forecast supply needs and manage them on an ongoing basis. They started to feel uneasy when the time was approaching to initiate the first trials. Because it was one of the company's first biosimilar studies there was alot riding on the success of the trial.

Determining the packaging schedule was a challenge because dosing was variable and dependent on the clinical response of each patient. The Fisher Clinical Services team discussed this complexity with the sponsor and determined that the best route forward would be to create a series of assumptions based on Phase I data describing enrollment rates and patient dosing. Members of our Clinical Supply Optimization team would then fine tune these assumptions based on new data as they became available. Agreeing to this path, the sponsor released the raw data to our team then performed their own forecast calculations.

Conservative supply estimate embraced

Getting to the next step required applying statistical principles to the trial design. After just two weeks, our Clinical Supply Optimization team delivered a plan with estimates that were extremely close to the numbers the sponsor had developed. They calculated that patients would be coming to the sites for dosing three times per week on average; our figures showed that the average would be 2.8 doses per week.

Though the sponsor favored taking the more conservative route, our group was confident in its recommendation and argued against a strategy that could waste precious supply. They again emphasized that the initial estimates would be adjusted when the trial data began to accumulate.

Further discussion revealed continued uncertainty on the part of the sponsor's team who then decided to accommodate three doses per week.

Forecast meets the ultimate test

Enrollment began and the dosing data started flowing in from the 320 sites. In the early stages of the study, enrollment and dosing data were analyzed often and compared with the initial assumptions.

During weekly meetings with the sponsor, the assumptions were adjusted and the forecast updated regularly. After a few months, the Fisher Clinical Services team was able to limit drug waste and maintain a sufficient supply cushion by decreasing the inventory levels to 2.6 doses per week.

A short time later our supply forecast met the ultimate test. We learned that the sponsor had rejected two batches of study drug due to quality issues. This was bad news because it meant throwing away a large amount of biologic at a crucial time in the trial. To make matters worse, the batches failed the sponsor's certificate of analysis during the holiday season when most everyone was out of the office.

Fortunately, our team was able to bring calm to the storm when they showed the sponsor that there was plenty of stock in the supply pipeline to keep the trial on track. Though we had saved money by lowering the forecast to meet a weekly schedule of 2.6 doses, the team retained enough slack in the supply chain to cover extreme conditions like this one. Despite losing the rejected bulk, there were no stock outs due to the lack of drug at the depots.

With that emergency behind them, the sponsor was more comfortable with their supply strategy. They moved meetings with the Fisher Clinical Services Clinical Supply Optimization team to a monthly schedule, down from weekly at study start. And now they can focus on their core competencies. "We really don't worry about the fate of our drug supply," the sponsor's team leader said. "We know we have a handle on it."

Strategic sourcing options outlined for comparator supplies in biosimilar trials

Direct Sourcing	Open Market
Directly from the innovator	Sourcing from wholesalers

Sourcing Strategies

These 2 options above can be applied geographically as follows:

Central sourcing

Sourcing one presentation / formulation in one single country for all countries involved in the trial

Local sourcing

Sourcing a commercially available product in a given country, for use in the same country

Hybrid solution

Eg. EU for EU, USA for USA

Advantages of Direct Sourcing

- Safest and shortest supply chain
- Full documentation for submission and logistics
- High volumes and best possible shelf-life
- Possibility of providing matching placebo
- Price stability during the trial
- No interruptionin the supply
- Price stability during the trial
- No interruption in the supply

Advantages of Open Market Sourcing

- Not disclosing Phase 1 study data
- Short lead-time
- Price
- Originator not willing to supply directly

Top 15 companies by biologics sales[4]	
No.	**Manufacturer**
1	Roche
2	Amgen
3	Novo Nordisk
4	AbbVie
5	Sanofi
6	Johnson & Johnson
7	Pfizer
8	Merck & Co.
9	Lilly
10	Biogen Idec
11	Merck KGaA
12	GlaxoSmithKline
13	Bristol-Myers Squibb
14	Novartis
15	Bayer

The Fisher Clinical Services team facilitates biosimilar trials with direct supply from 13 of these companies.

4. Top 15 companies by biologics sales, Pharma Live, http://www.pmlive.com/top_pharma_list/biologic_revenues, Accessed 23 June 2016

Survey: Access to documentation most concerning in biosimilar trial sourcing

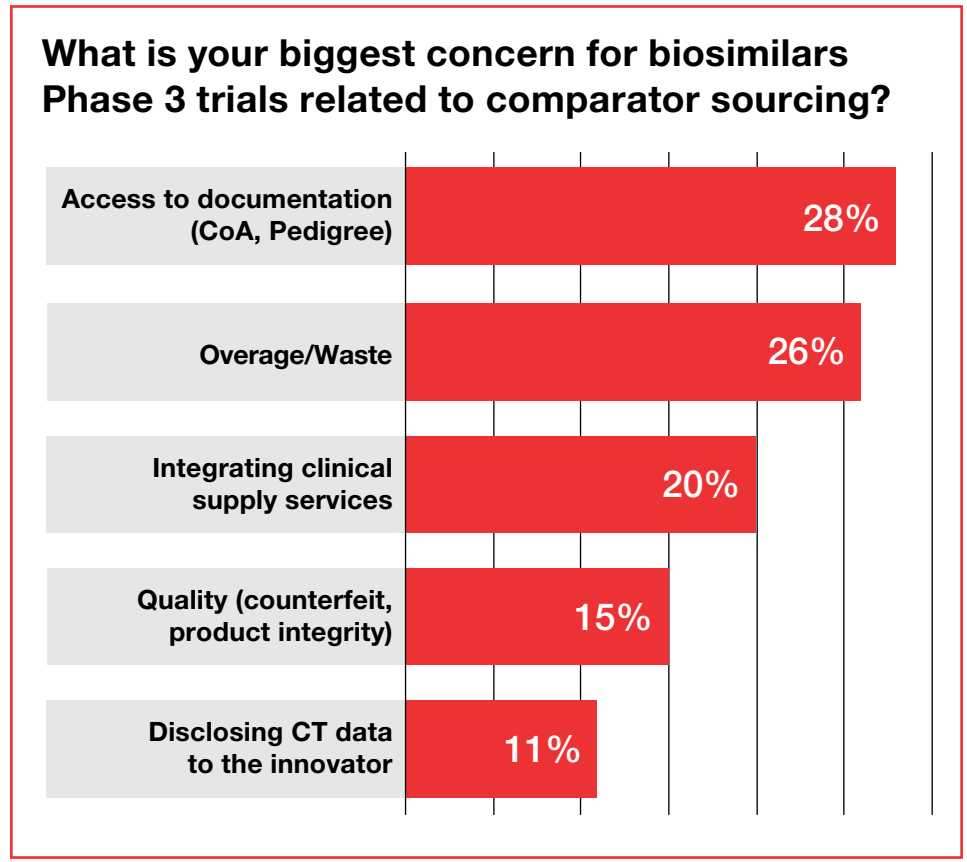
As noted in the graph to the right, attendees at a Webinar on biosimilars classified the main risks in comparator sourcing[3]. Responding to a survey during the presentation, 28% said their biggest concern about comparator sourcing in a biosimilar Phase 3 trial was access to documentation.

When sourcing from the open market these documents, including Certificates of Analysis and Pedigree, are not readily available. Yet there are advantages to the open market strategy, such as price and short lead times for small quantities. To make the most out of an open market strategy while reducing risk, consider working with a strategic partner that has better access to all key markets.

The attendees came from a range of small, medium, and large pharmaceutical, biotech, and biosimilar companies. This diverse audience revealed that there is a high level of interest across a broad segment of the industry.

The survey respondents identified overage and waste as the second most concerning aspects of sourcing comparator drugs in a biosimilar trial. This concern is prominent due to the high cost of comparator biologic medications. According to a Tufts University study, half of the typical clinical supply budget is spent on comparator drugs and co-therapies[5]. However, this cost can be alleviated through the use of demand planning, lean inventory management, and other clinical supply optimization techniques as illustrated in the case study on page 7 of this eBook.

Concerns about packaging, labeling, and distribution—integrated clinical supply services—were the group's third most concerning issue. This was followed by quality and finally by disclosing clinical trial data to the innovator. This last issue can be mitigated in Phase 1 through the use of an open market strategy.



5. Tracking Trial Cost Drivers: The Impact of Comparator Drugs and Co-Therapies, Kenneth A. Getz, May 01, 2013, Pharmaceutical Executive, Accessed August 3, 2016

How biosimilar comparator sourcing needs differ by development phase

Phase	Needs	Challenges	Key Success Factors	Additional Tips
Pre-Clinical	• Multiple different batches and expiry dates	• Limited number of new batches with different expiry dates released on the markets	• Constantmonitoring of the market in terms of available batches • Access to key markets & global market intelligence • Access to newly launched products	• Begin prior to the start of development and manufacturing activities
Phase I	• Fast supply • Limited quantity	• Optimal to use only one batch in the PK/PD study • Additional complexity due to blinding strategy	• Access to open market in key countries • Access to samples	• Anticipate early sample ordering for blinding strategy development
Phase 3	• Robust long term supply • Large quantities	• Expiry dates vs. trial duration • Cost due to number of units • Multiple site / depots / countries = import/export challenges	• Secure uninterrupted supply with supportive documentation for import / export	• Direct sourcing through originator and supply chain optimization

Case study: direct sourcing strategy enables speedy resolution of temperature excursion

A leading biosimilar company was running a Phase 3 trial with a drug for the treatment of Rheumatoid Arthritis. The Fisher Clinical Services team was in charge of the comparator sourcing, packaging, labeling and distribution for the trial.

The packaging and labeling of the IMP and the reference medicinal product was done in a walk-in refrigerator so that the drugs remain at a consistent temperature.

Defective Refrigerator Chills Study Progress

The storing and transportation to the individual clinical sites were performed as scheduled within the required temperature range. But unfortunately one clinical site had a defective refrigerator for 34 minutes and the drugs were stored between 8°C and 12°C. If these medicinal products are exposed to temperature outside their approved range of 2°C to 8°C (up or down), they can, at best, lose their effectiveness and, at worst, aggregate into particles that can cause serious reactions in patients.

Our Quality Assurance (QA) Team investigated immediately to find out if the reference product could still be used even though it had been stored outside the required 2°C to 8°C range. However, for this product there was no published stability date in either the electronic Medicines Compendium or FDA database.

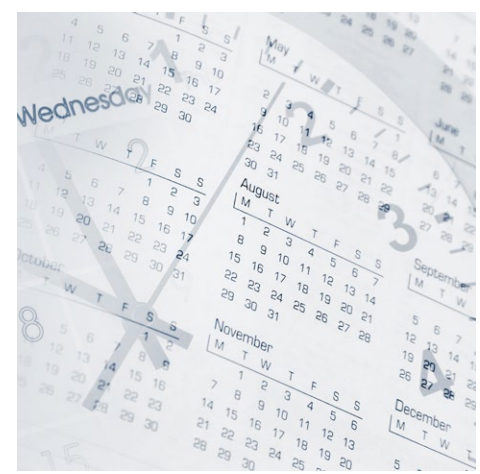
In order to get clarification, the QA Team contacted the manufacturer. Thanks to the excellent direct-sourcing relationship with the manufacturer and the fact that the product was sourced directly from one of its warehouses (with no intermediary) a response to the request and the assessment of the excursion was provided quickly. Consequently the QA team was able to issue a “Fit for Use” document on the same day.

In parallel, the biosimilar sponsor informed the clinical site that the IMP could still be used, according to its stability profile. After receiving this confirmation, the clinical site was able to continue with the trial and avoided the time intensive and expensive resupply scenario.

Result: Clinical site was able to continue with the trial and avoided the time intensive and expensive resupply scenario.

Approaches to biosimilar sourcing for clinical trials

	Samples	Phase 1	Phase 3
Sourcing Strategy	**Open market**	**Open market** • Protects confidentiality • Alternatively direct sourcing	**Direct sourcing** • Alternatively open market
Leadtime	• 24–72 hours in EU • 48–96 hours in US • Multibatch request longer lead time	**Open market** • 5 days up to 2–3 months • Variables: medication, multiple lots, quantity & country **Direct Sourcing** • 5–20 days from stock • 3–6 months production on demand • Study Approval 48 hours up to 2 months	



How to assure supply when not sourcing direct from manufacturer

Question	Answers
How do we assure comparator drug availability from Phase 1 to Phase 3 trials when not sourcing it directly from manufacturer?* 	Phase 1 -> Attempt sourcing in a large country; Secure one single batch for PK/PD studies
	Phase 3 -> Source from an international network of multiple qualified wholesalers
	Anticipate shortages and proactively communicate with clinical team to mitigate consequences
	Ensure robust cold chain supply to limit wastage
	Improve supply flexibility by increasing the number of packaging runs
	Consider Clinical Supply Optimization Services to keep overage to the absolute minimum

*As noted on page 8, the Fisher Clinical Services team facilitates direct sourcing with 13 of the top biologics manufacturers. Though direct sourcing is the most secure route, a network of qualified wholesalers provides open sourcing when needed.

The reasons for open sourcing can ude:

- timely availability of stock
- small quantity required
- local sourcing needs
- sponsor not willing to disclose clinical trial data.

Take this short quiz to test your biosimilars comparator knowledge

	True or False	Statements
1		Most manufacturers will block the supply if I disclose trial data.
2		Open market is sometimes cheaper than going direct to the manufacturer, but disruption risk is higher.
3		I can run my trial all the way through in full confidentiality.
4		I need good market intelligence to better secure the supply.
5		Low comparator unit price is the only way to reduce costs and savings.
6		A wholesaler can guarantee the same competitive price and supply over the coming year.

Comparator quiz:
Answers and explanations

	True or False	Statements
1		Most manufacturers welcome any knowledge that will help them plan production.
2		Sometimes the open market is lower priced but it raises risk of disruption when sourcing open market rather than direct from manufacturers.
3		Due to study registration rules, manufacturers will know you are running a trial using their drug as early as Phase 3.
4		Because the market is so dynamic, consistent and reliable market intelligence is needed to secure supply.
5		Unit price is important but there is more assurance of savings with clinical supply optimization
6		It is difficult for wholesalers to guarantee long term supply.

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