Navigating the complexities of biologics

The stakes are high when it comes to supply chain management of large-molecule products. **Dr Sean Smith** and **Dr Timothy Oostdyk** explain why comprehensive project management is so important

Clinical trials involving biologics have accelerated in recent years. Trials of large-molecule therapeutics and vaccines are growing at double-digit rates. The number of monoclonal antibodies entering into clinical trials has tripled in the last decade. And all this is happening as trials of small-molecule drugs near stagnation.

At the same time, more and more trials of biologics are being conducted overseas, as cost concerns and the ability to effectively recruit patients make foreign trials more attractive. The number of trial sites in China is growing by 47% a year, trial sites in Russia are rising by 33% a year, and Argentina's year-over-year growth is nearly 27%, while the share of trials being conducted in the US is dropping.

The collision of the skyrocketing growth of biologics with the trend of increasing globalization of clinical trials means an emerging set of challenges for trial sponsors. Unlike small-molecule drugs, which can usually be shipped at room temperature in easy-to-pack, easy-to-store blister packs, glass vials filled with biologics require a great deal of care. The sensitive nature of proteins means that such products must be held and transported in the cold chain, with superb analytical characterisation and monitoring needed to ensure that only effective products reach the bedside.

These complexities have driven a boom in outsourcing of supply chain management of clinical trials. Large pharmaceutical companies have long used such outsourcing as a way to effectively manage the costs of international operations. Small biotechnology companies, at the other end of the spectrum, have increasingly come to rely on outsourcing firms to give them access to experts in the logistical and regulatory challenges of global supply chain issues. Here at Fisher Clinical Services, more than a quarter of projects involve products that must be shipped in the cold chain, and we have seen a steady growth of 35% to 40% in the market with no signs of a slowdown.

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Because of the challenges implicit in dealing with sensitive large molecules – a product that has been 'out of environment' for even a few minutes may be rendered useless – comprehensive project management may be the most critical element of global biologics outsourcing. Each project needs a point person who can map out the proper procedure to ensure that a product departs the packaging facility investigator site without allowing potency-destroying temperature excursions. This is not a simple process for even domestic trials, but the logistics involved in getting a refrigerated shipment halfway across the world – to China, for example, or Russia or Brazil – by plane and truck, across roads of questionable quality, are downright staggering.

But project management means more than simply tracking a given shipment. A tremendous amount of planning must be done to ensure that the proper import licences are issued at exactly the right time, to keep biologics from sitting on the tarmac of a foreign country. Experienced project managers are aware of every logistical challenge they may face and have intimate knowledge of the peculiarities in each country and the unique risks that sensitive product may face in each of those environments.

Global biologics outsourcing requires a marriage of excellent know-how with top-rate facilities that are conveniently located near investigator sites. Given the difficulties of bringing biologics from production to investigators when the supply chain stretches thousands of miles, sponsors will need to find partners who have the ability to support sites through facilities near or in the region. A large global trial will ideally have this sort of support on five continents. And while it is well understood that dealing with vials of product in the cold chain means refrigerators and freezers, the difference between success and failure goes beyond simply keeping biologics on ice. A proactive planning approach must be in place to ensure that unforeseen problems will not place thousands of doses – and millions of dollars – at risk and product must be validated to provide additional confidence that trials are conducted with well-characterised therapeutics.

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Monitoring is critical to ensure that vials have been kept at the proper temperature throughout the storage and shipment process and have not degraded. Analytical characterisation measures product stability to evaluate whether a product has changed in any way during transport or storage. The analytical characterisation of biologics requires a much higher level of laboratory expertise than do small-molecule products, as well as multiple techniques. Mass spectrometry, in particular, becomes a very important tool in the analysis of biologics.

Managing the complex and on-going monitoring process is also critical to ensuring that only stable products enter into the system. While some still painstakingly record such information in written logs, we believe that this is an area where using best-in-breed information technology is necessary. Written records are difficult to read, difficult to access remotely and easy to alter, undermining efforts to ensure that the product at the investigator site is uncompromised.

And the future could make for even better storage and distribution. Although many trials are already using interactive voice response systems, tomorrow's trials will go beyond phone and web support and will incorporate the next generation of technologies, including radio-frequency identification (RFID) chips and GPS tracking devices to further expand monitoring capabilities.

There are now more than 400 biologics and vaccines in clinical trials, representing possible new weapons for 200 different diseases. Successful products will go through a development process that takes somewhere between eight and 15 years and costs $1.2 billion – development costs that are $400 million higher than the average small-molecule drug.

That means that the stakes have never been higher when it comes to supply chain management of large molecules. Breakdowns in the system may prevent investigators from having trial medication exactly when they need it – in addition, missteps and errors during the cold-chain storage and distribution process could mean that even if the right product arrives, it is degraded to the point at which it is no longer usable. In an era where life science companies have no margin for error – either financially or clinically – when conducting trials, proper management at every stage of the process is absolutely necessary.

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