

Clinical Supply Chain Logistics of Small Molecules vs. Biologics – A Provider’s Perspective

by Timothy S. Brewer

Introduction

A clinical supply chain that carefully considers the critical differences between small and large molecules is critical for ensuring a sponsor’s maximum return on investment. Complex, fragile, and more difficult and costly to manufacture, large molecules require a sophisticated approach and special handling to sustain viability. That includes careful planning and support to package, store, and transport to investigator sites, including 24/7 monitoring for potency-destroying temperature fluctuations.

This *Knowledge Brief* gives a provider’s perspective overview of and considerations in:

- the differences between clinical supply chain logistics of small molecules versus biologics
- a comprehensive project management approach to supply chain planning
- managing appropriate import licenses
- ensuring stability through continuous monitoring

Small Molecules vs. Biologics: Differences in Form and Supply Chain Logistics

Biotechnological applications in healthcare encompass prophylactic agents, in vivo diagnostic tools, and therapeutic products. Advances in this field are rapidly turning Western medicine inside out. *Datamonitor* predicts 60% of revenue growth forecasts will come from therapeutic proteins and monoclonal antibodies by 2010.¹ But with the promise of innovation and potential breakthrough medical therapies comes complications not encountered in the traditional manufacturing of small molecule therapies. Developing the most effective supply chain strategy that takes into account the special considerations of biologics is critical for ensuring a sponsor’s maximum return on investment.

Small molecule medical therapies are typically administered by mouth and tend to work inside the cells of the body. They typically consist of pure chemical

substances that are easily analyzed after manufacture to determine safety, purity, potency, and effectiveness. However, biologics are protein-based, large molecules that are typically injected into the bloodstream and interact on the surfaces of cells once inside the body. Derived from living matter or manufactured cells, biologics are complex, fragile, and more difficult and costly to manufacture. These delicate substances or cells are sensitive to heat, light, and agitation (when being shaken in liquid form), and are easily susceptible to contamination. As such, they require careful planning and support to package, label, store, and transport to investigator sites.

While small molecule therapies today can be shipped at room temperature in easy-to-use, easy-to-store blister packs, most large molecules have to be transported and stored under specific refrigerated conditions in a glass vial. They also must be monitored continuously for potency-destroying temperature fluctuations. Hardly a simple process for domestic trials, the complexities increase exponentially when transporting an expensive, refrigerated investigational therapy in a fragile container to multiple locations around the world using multiple, and frequently unpredictable, transportation systems and highly variable regulatory approaches.

In addition to offering both greater value and greater risk protection of large molecule therapies, the right outsourced provider must offer a complete supply chain strategy that is proactive, takes into account risk mitigation planning, and ultimately successfully navigates the complexities of international distribution.

Protecting an Investment through Comprehensive Project Management

When planning for clinical supply distribution starts *after* sites are selected and patient recruitment has started, clinical teams can be caught unprepared by the impact on their budget and on

their timelines when they have to adjust their approach to accommodate the import/export requirements and other obstacles. Often, it is too late to do anything, but run over budget. Since multiple work streams are required to get the right drug to the right patient at the right temperature and the right time, comprehensive project management of the supply chain – especially for large molecules – is one of the most important first steps.

Considering supply change management as part of an overall clinical development solution allows sponsors to identify and explore any challenges with patient or investigator populations *before* site or patient population decisions are implemented. By incorporating clinical supplies planning as part of comprehensive project management from the outset, sponsors can ensure that the clinical plan has incorporated the impact of import and export and logistic requirements into their timelines.

An integrated clinical and clinical supplies project management approach also delivers specialized skills early in the planning stages to design efficiencies into: pack configuration, multilingual labeling solutions that ensure investigator *and* patient compliance, smarter inventory control, compliance with all regulatory and customs requirements, and the most effective on-the-ground approach logistics – especially in countries plagued by limited infrastructure. Working with a provider that has experience with large multinational trials and thousands of protocols every year across all therapeutic areas, offers access to the latest and best practices.

Managing Appropriate Import Licenses

When countries are selected without consideration of the import requirements for investigational drugs, it is no wonder that trials of any type of investigational drug run into distribution problems and trials run over budget. With the higher cost of manufacturing, packaging,

storing, and transporting large molecule compounds, budget implications are exponentially multiplied. Complex layers of policies and regulations can lead to jurisdictional disputes over paperwork between national to regional to local government authorities. Without the proper import licenses issued at the right time, shipments of temperature-sensitive biologics can be delayed as long as a year in some parts of the world – and arrive completely out of stability.

Given the considerably higher production costs of large molecules, as well as the environmental impact of waste, it is critical to have access to experts who understand the continuously changing regulations and customs requirements of countries where products are targeted for development. Careful consideration of the unpredictable nature of drug distribution across multiple borders while navigating a multitude of continuously changing regulatory requirements prevents product wastage. Additionally, using centralized and regional distribution centers improves distribution and logistics efficiencies and limits the times when trial drugs must pass through customs.

Even more important is having a project lead well-versed in FDA, EMEA, and other specific government regulations. Well-documented regulations, which are very specific in detailing the clinical supplies requirements, require meticulous advance planning followed by flawless execution. Successful project execution in that environment requires a thorough logistical understanding, knowledge of risk assessment and mitigation planning, multi-cultural awareness, and leadership competences that include strategic analytical skills, detail-orientation, and strong verbal and written communication skills. Instituting a study plan using proven project management methods to identify all milestones of a shipment also helps establish expected timelines for Import Licenses, the number of days for transport, expected customs clearance, and other critical items.

Ensuring Stability through Continuous Monitoring

A dramatic shift expanding clinical work into Asia, Latin America, India, and Sub-Saharan Africa has brought a greater volume of treatment-naïve patients along with even greater distribution and logistics challenges. Ensuring that a refrigerated large molecule arrives within stability (and remains stable) at an investigational site in emerging markets present unique challenges for handling and distribution of biologics under special temperature, light, shear force, and chemical phase conditions. Even one unexpected delay in transit can mean missing a treatment window due to potency-destroying temperature fluctuations. The latest technologies preserve and monitor – in real-time – the conditions of clinical trials materials.

The use of technology in managing the supply of materials to investigator sites is focused on enhancing access to tools that allow continuous monitoring and on-the-ground analytical characterization to ensure that supplies arrive at the right temperature, light, and motion parameters. Regardless of the location, technology solutions provide the sponsor and clinical teams peace of mind through access to real-time tracking.

Conclusion

As the application of biotechnology in health care continues to grow, the number of clinical trials involving large molecules on multiple continents will require even stricter controls and monitoring. Development of large-molecule products incorporating a proactive and integrated approach to the supply chain of these therapies requires planning for risks and taking measures to address destructive temperature, shear force, chemical phase, and light variables before the start of any trial to best protect a sponsor’s investment in such innovative therapies. These are the trials that will be most likely to succeed and will leverage other innovations in technology to support rigorous and trustworthy monitoring of all variables.

Reference

1. Big Pharma Turns to Biologics for Growth to 2010: Financial and strategic segmentation of the ‘Big Pharma’ sector by drug technology, Datamonitor, May 2006.

For Further Information

For more detailed and related information, the following ISPE resources are available:

Technical Document:

- ISPE Good Practice Guide: Development of Investigational Therapeutic Biological Products, August 2007
<http://www.ispe.org/goodpracticeguides>

Publications:

- “Building a Flexible, Cost-Efficient Global Supply Chain,” by Simon Kaye, *Pharmaceutical Engineering*, Sept/Oct 2009, Volume 29, Number 5, pp. 72-76.
<http://www.ispe.org/pharmaceuticalengineering>

Online Course:

- Operational Economics (Supply Chain Management)
<http://www.ispe.org/onlinelearning>

Recorded Webinars:

- Investigational Products: Balancing Risk and Costs to Optimize the Clinical Supply Chain – A Step Beyond Simulation
- Investigational Products Series: Reduce Supply Availability Time by 70% - Remarkable Changes in Operations Management (Fundamental)
- Investigational Products Series: Reduce Supply Availability Time by 70% - Remarkable Changes in Operations Management (Intermediate)
- Investigational Products Series: Reduce Supply Availability Time by 70% - Remarkable Changes in Operations Management (Advanced)
<http://www.ispe.org/onlinelearning>

Investigational Products (IP)

Community of Practice (COP):

- Visit our IP COP on the ISPE Web site for the most current and up-to-the-minute discussions on the topic discussed in this *Knowledge Brief* and other related topics.
<http://www.ispe.org/communitiesofpractice>

About the Author

Timothy S. Brewer is Global Vice President, Logistics, at Fisher Clinical Services. Formerly Chief Executive Director of Clinical Trial Services (CTS), Brewer has more than 15 years of experience in the pharmaceutical industry. He established CTS, a pharmaceutical packaging firm, in December 1996 where he was responsible for providing executive leadership, managerial direction, and client development. Brewer attended the United States Military Academy at West Point where he majored in chemical engineering, and Alvernia College where he received a BS in business administration and management. He is a member of various professional organizations, including the Drug Information Association (DIA), Association of Clinical Research Professionals (ACRP), ISPE, AAPS, and others. ●