ThermoFisher SCIENTIFIC

MADE WITH
PROTOCOLS & PASSION

WHITEPAPER

Factoring the “what ifs” into supply forecasting: Why building a durable supply chain around a protocol is critical

Abstract

Clinical supplies have historically been considered part of the execution phase of clinical trials, instead of a key component of the planning process. Now, growing urgency in the biopharmaceutical industry to speed new products to market is leading to greater appreciation for supply forecasting as a strategic and highly complex success factor. A supply shortfall can delay the start of a clinical trial or cause an ongoing one to grind to a halt. At the same time, clinical supplies overage can be equally costly. Recent studies have shown that as much as two-thirds of the materials packaged and shipped were not actually dispensed to a patient.[1]

Although seemingly simple, supply forecasting is surprisingly complex. Relying exclusively on a standard mathematical formula for forecasting supply needs, however, fails to factor in all that can go wrong to disrupt a supply chain at a time when sponsors can least afford costly missteps. Escalating trial costs reflect a steady increase in the volume, length, breadth, and scope of clinical studies. The complexity of trials is also accelerating, thanks in part to a spike in studies of biologics requiring special handling and those targeting especially challenging problems such as Alzheimer's disease, diabetes, and cancers. With such high stakes, clinical trial professionals must take every precaution to prevent the supply chain from unraveling. In addition to modeling, this includes factoring a host of "what ifs." Defined as anything that could jeopardize the supply chain, "what ifs" include everything from natural disasters to shortages of commercial drugs used as comparator or standard of care.[2]

Effective supply planning requires decision making that strikes a balance between what's known and unknown, risk and budget, the needs of the trial and those of patients. The ultimate goal is ensuring that the right patients receive the right drugs at the right time. Otherwise, sponsors, investigators, patients, and society at large stands to lose. This whitepaper discusses the aspects to consider when developing a supply plan, the influence of early decisions and impact on outcome as a trial progresses, and how decisions can put patients and the trial at risk.

Table of contents

Drug development challenges escalate

Pressure on biopharmaceutical companies to deliver new products faster and more efficiently is driving a heightened sense of urgency and amplifying already considerable operational and strategic challenges.

That urgency is accelerating as companies struggle with an array of obstacles. Among them: The latest round of patent cliffs, increasing demands prior to licenser from regulatory authorities, and sluggish R&D output amidst pressure from investors demanding financial returns.

Today, only 12% of investigational drugs win marketing approval in the U.S.[3]

Despite herculean efforts to hold the line on drug development costs, the average price tag for developing a drug has climbed to $2.6 billion, while the success rate has declined. Today, only 12% of investigational drugs win marketing approval in the U.S.[3]

Just when it seemed that clinical trial professionals couldn't possibly be under greater pressure, they find themselves facing a host of challenges.

- **Growth of clinical trials:** The sheer number of trials is huge and growing. In 2018, for example, there were 277,000+ trials registered at ClinicalTrials.gov, the registry of clinical trials in the U.S. and around the world, compared with 101,000+ registered trials in 2010.[4]
- **Logistical complexity:** Thanks to the industry's embrace of globalization, over half of all clinical trials are now conducted offshore. As of July 2018, trials were underway in 204 countries, with only 35% exclusively in the United States. Asian, Latin American, and other emerging nations comprised 28% of total registered studies.[4]

The migration of studies to every corner of the globe has been a success, but supplying such trials is a highly complicated undertaking. In many countries, the supply chain must be closely managed.

Take India, for example. Although this nation of over 1.3 billion people is a top-ranked location for clinical trials, its climate and infrastructure pose substantial challenges, particularly for trials of biological products requiring cold-chain handling.

- **Shifting research:** Double-digit growth in clinical trials of biological products has been transforming the clinical trial environment. The success of biologics is fueling explosive growth in the global biosimilars market as potential biologics, worth over $70 billion, are set to lose their patent exclusivities during the period 2016 to 2020.[5]
- **Volume of investigators & clinical sites:** The number of clinical investigators and sites are at an historic high. From 2013 to 2016 there were approximately 34,000 active investigators in the US alone.[6] By 2016 over 32,000 sites were involved in sponsored Phase III studies, with 54% of these outside the US.[7] In many countries, clinical sites are located hundreds of miles from major cities and airports, increasing supply issues.
- **Patient recruitment challenges:** In addition to the rising number of trials, more patients are enrolled in trials today than a decade ago. Larger-sized studies reflect requirements by regulatory bodies to ensure products' safety and efficacy prior to licenser.The larger the trial, the greater the patient recruitment burden. Consider that 47,300 of the 277,000+ trials registered in 2018 were recruiting patients.[4]

Unfortunately, about 80% of pharma clinical trials do not meet enrollment deadlines, resulting in an average loss up to $1.3 million per day for a given drug candidate.[8] Recruitment rates substantially impact supply forecasting for global trials, since supplies bound for one country cannot be redeployed to another without relabeling to accommodate language and regulatory differences.

- **Differing regulatory & customs requirements:** Many countries, mainly those considered to be emerging markets, are evolving and developing regulatory requirements. These ongoing changes significantly impact supply chain issues, such as the phrases used in labels, Investigational Medicinal Product (IMP) dating restrictions and eligibility for drug to be extended.

In addition, despite substantial progress toward global regulatory alignment, customs requirements also continue to evolve and may differ dramatically amongst even neighboring countries. The greater the number of countries participating in a trial, the greater the pressure from a supply standpoint.

- **Compressed development timelines:** Tight timelines, which reflect industry-wide efforts to boost R&D productivity, increase that pressure further.

- **Shorter study start-up timelines:** Shrinking timelines also mean shorter study lead times, resulting in the need to squeeze critical tasks—from obtaining import permits and training investigators to manufacturing, blinding, packaging and shipping supplies—into a narrower time window, with little room for error.

It's obvious that there is no shortage of challenges facing clinical trial professionals.

Clinical supplies demand new attention

If one imagines a clinical trial as a stool, its three legs would no doubt be sites, subjects and supplies. While sites and subjects have always gained significant attention, supplies were typically taken for granted largely because they were inexpensive and readily available. That is, until now.

As the industry struggles with escalating R&D costs, it is focusing new attention on the cost of clinical supplies, a subject that was of little concern 20 years ago. Then drugs cost pennies per tablet and sponsors were unconcerned about overproduction and wastage. In fact, production of as much as 500% of the drug or drugs necessary for a clinical trial was commonplace and acceptable.

Once averaging just 4% of overall trial costs, clinical supplies have become big-ticket items and a major clinical trial expense.

Clinical trial professionals say supplies are now responsible for a minimum of 10% of trial costs, a proportion that continues to increase. In studies involving biologics, for example, the proportion may be substantially higher.

Once averaging just 4% of overall trial costs, clinical supplies have become big-ticket items and a major clinical trial expense.

What's certain is this: Applying old assumptions to the cost of clinical supplies as a percentage of trial costs could result in projects running excessively over budget. Here are some reasons why:

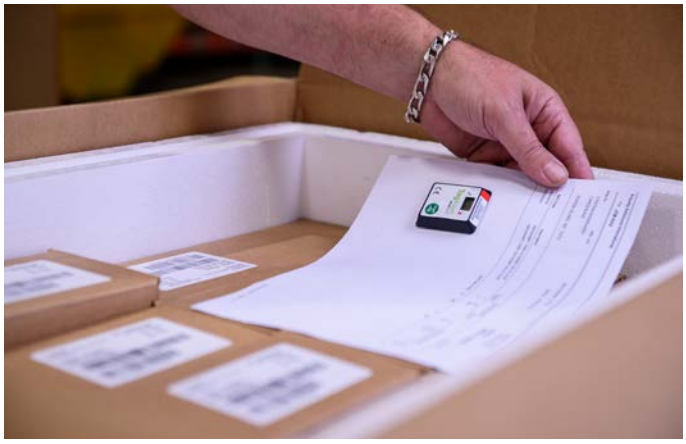
Impact of biologics: Biologics have been heralded for making possible giant leaps forward in the treatment of a host of serious diseases, from cancers and diabetes to rheumatoid arthritis and multiple sclerosis.

Their success has fueled the growth of biologics trials, impacting supply chains and development costs. Today, more than a third of projects within Thermo Fisher Scientific's clinical trial business involve biologics.

Due to their complexity to manufacture, biologics are expensive and often available in limited quantities during development.Because they are produced from living organisms, biologics must be stored, transported and maintained at controlled temperatures in a "cold chain," a strict system of temperature and stock control to assure their potency and safety.

Cold-chain compliance requires careful documentation, tracking of biological products at every level, and adherence to strict temperature requirements at all times.

To ensure temperature control, special handling of biologics is necessary. Packaging and shipping, for example, are frequently more expensive than those for small molecule drugs. These additional precautions ensure the biological product maintains its integrity, permitting a trial to proceed on schedule. Without them, product will likely require replacement, impacting patient and causing critical trial delays.



Global trial complexity: The biopharmaceutical industry embraced globalization in pursuit of cost-savings and the rapid recruitment of new patients, a gamble that has paid off. Another benefit of global trials has been that of gaining a marketing foothold in countries such as China and Japan, which may require local trials before licensing new drugs and vaccines.

Offsetting these substantial benefits are the expense and effort of supplying trials underway in thousands of locations across the world. Obstacles include the resources necessary to navigate evolving government regulations for drug importation, unravel jurisdictional disputes over paperwork that can delay the start of a trial, and manage the logistics of supplying multi-site trials in countries with inadequate infrastructure.

Growing demand for comparator: The volume and complexity of global clinical trials have been accompanied by an increase in the demand for commercial drugs used as comparator or standard of care and the challenge of obtaining them.

Securing large volumes of comparator, meeting the high costs associated with the use of comparators instead of placebos, and taking precautions to prevent counterfeit product from infiltrating the supply chain are among the issues facing supply chain professionals.

Once comparator has been sourced, the need to blind solid dosage forms can also stress efforts to meet aggressive clinical timelines. Effective supply planning must strike a balance between sourcing sufficient clinical supplies vs. having an oversupply that could go to waste.

How difficult can supply planning be?

To assume that supply forecasting is a matter of multiplication is understandable, but that's merely a starting point in a highly complex process aimed at managing risk. Of course, a standard forecasting formula can work—assuming, of course, that everything goes according to plan. But how often does everything go perfectly?

Today, sophisticated simulation software tools can be used to test multiple scenarios. These solutions use quantitative methods that better predict what will happen over the course of a study. When used early on, they can also influence the protocol design.

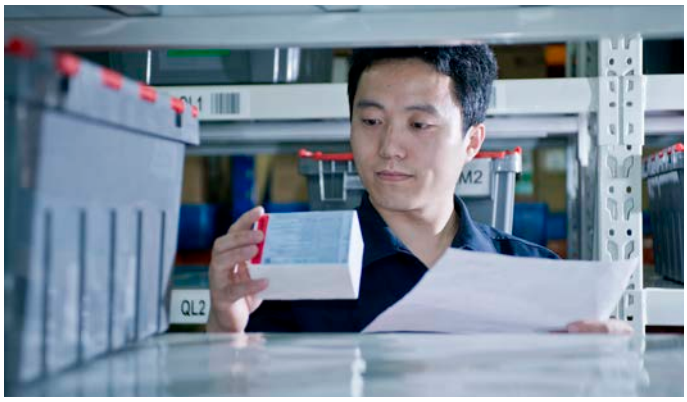
Effective forecasting requires fully informed decisions that take multiple factors into consideration, including every imaginable complication that could derail a supply chain. Among the considerations:

Enrollment speed: Speed and location of enrollment impacts the volume of supplies needed. If enrollment speed differs from what is anticipated, an all too common problem, it can increase the difficulty in supplying the study.

Milestone attainment: Every supply chain has lead times that can be inconsistent with the development milestones for a study or molecule. This can understandably result in friction between Clinical and the supply chain management team. Example: Clinical traditionally establishes milestones such as protocol approval, country and patient allocation, and first-patient visits (FPVs).

If for whatever reason, finalization of the protocol or the list of participating countries is delayed and a corresponding adjustment in FPV timing is not made, there may be insufficient time to create labels or complete packaging. This can jeopardize both FPV attainment and that of future study milestones.

Dating & extensions: Ensuring that there are sufficient supplies with good dating prevents problems with potential stockout should the study or the resupplies be delayed. In addition, some countries permit only a prescribed period of drug dating until real-time stability is established. This impacts how material is supplied to these countries.



Material availability: Drug shortages are commonplace and can significantly impact lead times. Supply chain managers may have to obtain sufficient supplies of comparator drugs from many different sources, when sourcing from the originator is not an option. The issue of availability is not limited to comparators; Sponsor-provided Investigational Medicinal Product (IMP) can also be in short supply if the molecule is new or the active pharmaceutical ingredient (API) is available in limited quantities.

Blinding: Supplies must be sourced early enough to permit blinding, since a delay in the latter could prevent a study from starting on time.

Distribution systems: Having an extensive global footprint of qualified distribution and packaging facilities provides needed flexibility for supplying trials, especially in the event of crises. A regional hub-system provides flexibility to adjust to regional patient enrollment changes.

Numerous dosages, forms, sizes & shapes: It stands to reason that the greater the quantity of dosages, forms, sizes and shapes, the greater the complexity of supplying the study.

Key considerations in supply planning

Every supply forecasting decision impacts the protocol. Here we examine three specific factors—Package Design, Dispensing Plan and IMP Label Grouping—and the impact of decisions about each on the supply chain. Of course, these are not the only factors that impact planning and forecasting. Individual factors and situations vary and an experienced supply chain manager must assess their impact on the supply chain.

Factors 1 & 2: Package design & dispensing plan

- Though separate, these two factors are intertwined and for that reason are addressed together. Prior to decision making about package design and the dispensing schedule, it's necessary to know the following:
- The dispensing visits in the study schedule
- Amount of drug in a primary package (i.e. tablet count per bottle or blister card)
- Number of packages per drug type to dispense per dispensing visit

In making decisions, considerations should include, but are not limited to:

- The indication being studied
- The dosing information chart & diagram
- Stability information for packaging drug, including the allowable fill range
- Cost
- The enterprise supply chain page (i.e. manufacturing locations → packaging locations → warehouses → countries → sites → patients)
- Ease of managing supply throughout study

Every decision has a downward effect on the success and ease of managing the IMP supply. Consider, for example, a decision to have a low number of package types for dispensing in a variety of combinations for all dispensing visits versus a specific package configuration for each dispensing visit.

Similarly, consider a decision to have regular dispensing visits versus dispensing at every other visit or doubling up at one visit so the next visits can be skipped.

Factor 3: IP label grouping

One of the first steps in building a supply plan is determining the country label groups. For a global trial, the choices could include:

- U.S.: Single panel, Outside the United States /Rest of World booklet
- Regional booklets: North America (NA), European Union (EU) and Asia Pacific (AP)
- Global booklet: Inclusion of all countries
- Alternative: That of developing a customized solution, as example using an eLabel with supplemental information via 2D barcode.
- Decision making considerations should include, but are not limited to:
- First Patient Visits (FPVs)
- Distribution network and inventory management complexity
- Label requirements and label generation lead times
- Supply flexibility
- Frequency of regulatory changes

The following chart illustrates the effects of package design and dispensing plan decisions on the supply chain.

Decision	Impact	Supply chain challenge
Low number of package types	• Decreased demand forecasting complexity • Increased flexibility in supply management • Decreased overages • Decreased packaging lead times and/or instances • More efficient use of storage space (warehouses and site) • Less complex Interactive Response Technology (IRT) • Fewer number of site shipments	• Operational communications • Lead times • Forecasting complexity
Regular dispensing visit intervals	• Decreased demand forecasting complexity • Less complex IRT forecasting and set up • Fewer resupply shipments • Few site monitor visits for drug return	• Operational communications • Forecasting complexity

When "what if" becomes reality: Managing supply crisis

Even the most meticulously planned trials can and do go awry. From acts of nature to acts of terrorism, life can intervene to jeopardize a trial. It's the responsibility of the supply chain manager to ensure that a trial continues uninterrupted and that supplies keep flowing, regardless of what happens to ground flights, closed roads, cut off power or shut down sites.

The following examples focus on two of the most common threats to trials—natural disasters and drug shortages—and the real-life solutions savvy supply chain managers implemented to prevent trials from going off the rails.

Natural disasters

Natural disasters and weather patterns—from earthquakes, floods and superstorms to tornadoes, tsunamis, volcanic ash clouds and everything that falls in between top the list of threats that can have a material effect on supplies.

Consider some recent examples:

April 2010: An ash cloud from the eruption of Icelandic volcano Eyjafjallajokul closes European airspace for a week, grounding 100,000 flights in the biggest air travel disruption since World War II.[8]

March 2011: A 9.0 magnitude earthquake hits Japan, triggering tsunamis that kill 28,000 people, washing away entire villages, and prompting a nuclear crisis. It becomes the most expensive natural disaster in world history.[9]

September 2017: Hurricane Maria devastates Puerto Rico, knocking out electrical power and phone service, while flooding resulted in deadly mudslides. In 2016 Pharmaceuticals made up 72% of Puerto Rico's exports (25% of total U.S. pharmaceutical exports).[10]

In similar circumstances, the strategies described here have enabled supplies to keep flowing to patients:

Shipping some supplies, warehousing the rest: Remember the idiom about not putting all one's eggs in one basket? In this case, the supply chain manager had taken the precaution of shipping a portion of the material from a packaging campaign to one warehouse, while retaining the remainder at the warehouse where packaging took place.

This limited the exposure of clinical supplies to the crisis and permitted quick access to back-up material. Meanwhile, a review of the supply forecast was conducted to determine whether the next resupply should be expedited.

Assessing the protocol for visit flexibility: Occasionally, a solution may be as close at hand as the protocol. In this situation, the supply chain manager worked in collaboration with Clinical Operations and the Regional monitoring groups to determine whether the protocol allowed for flexibility in the visit windows.

Protocols usually specify a target visit interval, but allow for minimum and maximum visit intervals as well. In the event of a crisis, it's important to assess the risk of having patients run out of study drug and the sites' inventory status.

The solution was to have the sites reschedule patients for the maximum visit interval, permitting time to assess the inventory or for new material to arrive. Of course, there may be instances in which material cannot be shipped in a timely fashion or patients cannot make a return visit in time. The supply chain manager and Clinical must develop a plan for dealing with these situations.

Qualifying multiple packaging locations: Qualifying multiple packaging locations as a precaution in the event of a crisis is the supply chain equivalent of having insurance. When the entire inventory was wiped out in a particular disaster, a network of locations in the affected area stood ready to spring into action and package new supplies. This solution required considerable preparation before any packaging was required, including:

- Ensuring that additional bulk material and packaging components were available for a new packaging campaign.
- Checking to be sure that regulatory documents reflected all possible facilities capable of packaging material.

- Confirming that all affected countries would accept material to and from the back-up facilities.
- Reviewing labels to determine whether they contained any facility-specific information.
- Networking with other facilities to determine if they had the capacity and appropriate tooling capabilities necessary for packaging.

Drug Shortages

Expanded use of commercial drugs in clinical trials as comparator or standard of care is occurring just as drug shortages impact supply chains and patients in general.

In 2017, 146 medications experienced a new shortage—in addition to any that may have remained on shortage prior to January 1.[11] The drug classes often affected included electrolytes, antibiotics, CNS medications, cardiovascular and chemotherapy. Shortages are primarily due to manufacturing issues affecting medication quality, supply and demand imbalances, or shortages of raw materials needed to manufacture the medication.

Shortages of commercial drug product can impact a trial in a variety of ways, such as:

- Extending the lead time for sourcing.
- Requiring sourcing from multiple suppliers in multiple countries.
- Increasing complexity and time to the packaging process when materials received are packaged differently than expected—e.g. different dosage format. Additionally, multiple batches are received with different lot numbers. which results in a higher complexity during the packaging runs and management of different expiry dates at each site.

The following are successful supply planning strategies that have been used to address drug shortages.

Sourcing globally: When shortages for U.S. commercial drugs that are standards of care appear on the FDA website, supply managers have to act quickly in order to head off a potential supply crisis. They can source materials outside the U.S., then import to the U.S. for use in trial there.

This strategy requires that the drug be included on the FDA shortage list. Procurers face a series of hurdles, among them obtaining a sufficient quantity of material with appropriate dating in a usable form from credible sources. To accomplish all of this may require a lengthy lead time of six months or more.

Once the materials are acquired, importing it to the U.S. requires updated regulatory filings, notifications to Ethics Review Boards (ERBs), and the agreement of study patients in the Informed Consent. Study teams, monitors and sites also require additional training. This strategy impacts the availability of material on a global level.

Waiting it out: Some teams have opted for the risky approach of micromanaging their clinical supplies to the last vial or blister pack while they anxiously await new material from their current manufacturer. In choosing this strategy, it's important to have a back-up plan for obtaining the material from an alternative source or via alternative means.

This could entail reimbursing sites for material they have in stock. Of course, the greatest danger is that new supplies fail to arrive in time, leading to a treatment delay or halt in enrollment, and consequent impact on the development timeline.

Practicing good supply chain management

The best way to prepare for the unexpected is by maintaining the fundamentals of good supply chain management at all times. So what constitutes good supply chain management?

Clinical trial professionals define good supply chain management as planning effectively, considering a multitude of variables from a variety of sources, and creating a plan that's flexible enough to withstand unexpected events.

They constantly monitor, evaluate and adjust when necessary. Here we'll discuss two tough lessons learned when faulty judgment during the planning process led to disastrous conclusions.

Weighing cost vs. overage: An investigational drug was in a head-to-head global trial with an expensive commercial product. To avoid wasting resources, the supply plan allowed for ordering and packaging the minimum quantity needed of the commercial drug. Enrollment was so rapid that all commercial material was depleted within a matter of weeks. Therfore, further enrollment was put on hold for six months while more materials were sourced and packaged, extending the timeline of the trial and the development program.

Lesson learned: Overage isn't necessarily an indication of wasteful planning. Running out of materials can be more costly than investing in some overage at the start of a trial. Avoid being penny wise and pound foolish.

Knowing import license requirements: As the supply chain for clinical trials continues to extend beyond the U.S. and the European Union (EU) to emerging markets, strong distribution plans and a keen understanding of import license requirements are critical. For example, in a recent study, the current import license was about to expire, but the listed product lots still had acceptable dating. The newly filed import license included only new product lot numbers, but there was a delay in their release. When the old import license expired, no material could be imported because the new license had omitted the former lots that were still acceptable, and patients ran out of drug.

Lesson learned: It's worth considering the inclusion of all lots with good dating on the import license if that the new material is not released on time.

References

1. CenterWatch: Assessing the strategic impact of supply chain management, June 2017
2. U.S. Food and Drug Administration, “Drug Shortages”
3. DiMasi JA, Grabowski HG, Hansen RA. Innovation in the pharmaceutical industry: new estimates of R&D costs. Journal of Health Economics 2016; 47:20-33
4. U.S. Food and Drug Administration ClinicalTrials.gov
5. Global Biosimilars Market 2016 – 2020; Technavio
6. Non-Commercial Clinical Trial: An Underappreciated Source of Clinical Investigators; Applied Clinical Trials, January 22, 2018
7. The US and the Location of Clinical Trial Sites; Applied Clinical Trials, February 05, 2018
8. “How the 2010 ash cloud caused chaos: facts and figures;” The Telegraph, October 13, 2011
9. “Japan Earthquake, Tsunami: Moments of Destruction,” ABC World News, March 9, 2012 10. “Hurricane Maria shutters much of Puerto Rico’s pharma manufacturing,” FiercePharma, September 26, 2017
10. Drug shortages statistics. American Society of Health-System Professionals website.

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.

+1 919 226 3200 • thermofisher.com/patheon • pharmaservices@thermofisher.com

Published 07/21

ThermoFisher SCIENTIFIC