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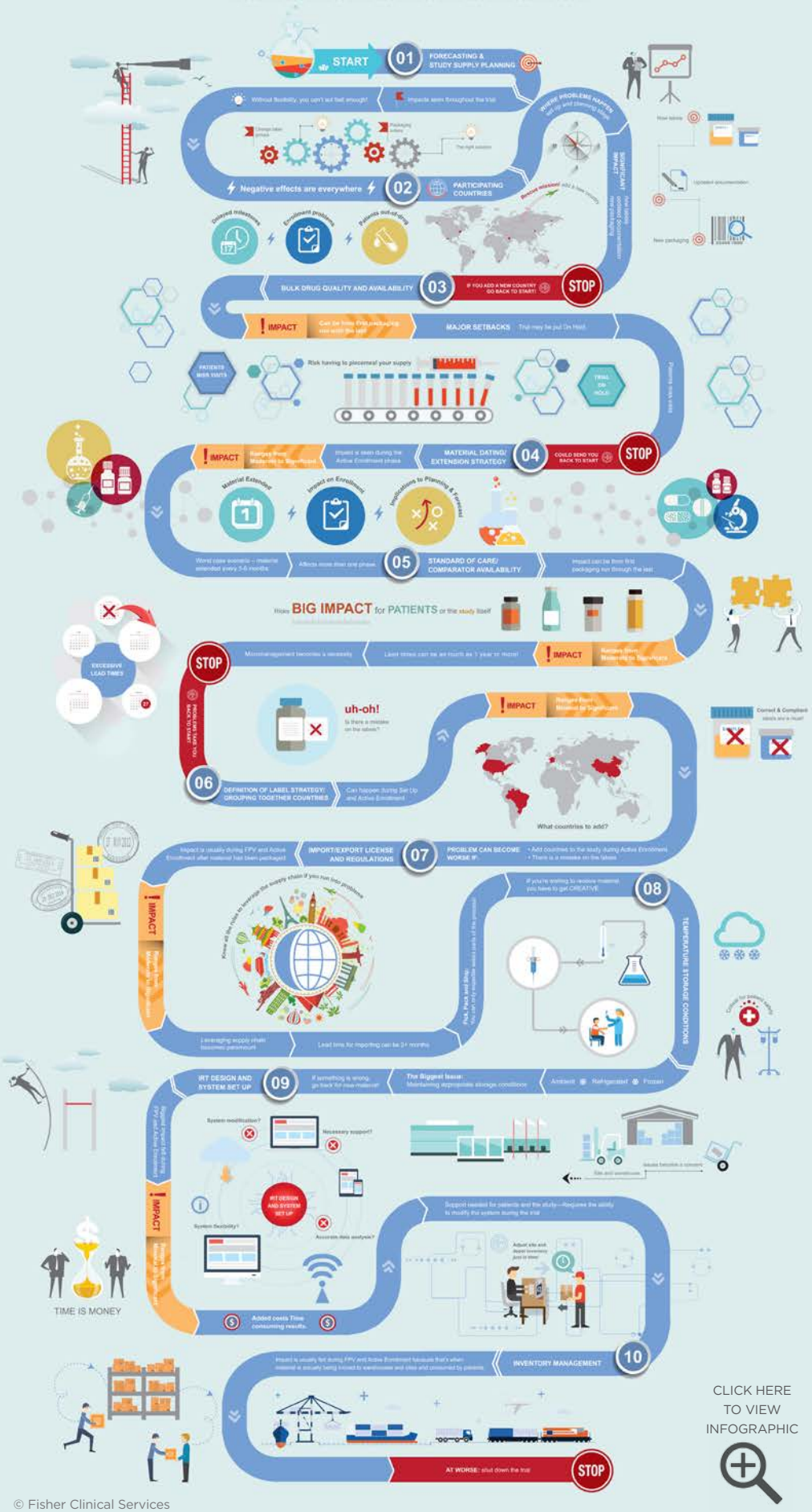
If you took a look at the pharmaceutical headlines from the past few years, the stories read like sensationalist media. "Companies Losing Patent Fights." "Phase III Trial Data Misses the Mark." "Companies Struggle to Rebuild their Pipelines." These and similar headlines and the continuing trend of challenges facing our industry, is creating a sense of urgency to drug development and operational performance of many organizations. The data behind the news is quite striking:

- In 2000, www.clinicaltrial.gov had a mere 5,648 trials registered. By 2011, that number soared to more than 119,000 and covered every major therapeutic area.
- Over the last 2 decades, approvals for new medicines remained essentially flat. Many of the approvals that were granted were for duplicate therapies that will compete with products already approved.
- According to research done by The Tufts Center for the Study of Drug Development, it is estimated only 20% of new drugs that enter clinical testing will receive US marketing approval.
- In 2000, the cost of developing

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new drug therapies was roughly $800 million. That figure ballooned to $1.3 billion in 2005. Now, depending on drug type, costs have been estimated at $3 billion or more.

Not exactly these metrics that inspire confidence amongst those in pursuit of new drug development and research.

However one aspect of clinical trial planning and execution that often gets overlooked is the critical role that the Investigational product itself plays. Or as one of our investigator sites told us, "I can work with a difficult or complex protocol even when I wasn't well trained. If a study is slow to enroll, I can figure out ways to increase our enrollment, but the one thing I can't work without is the drug itself. If there is no IMP, the study cannot go forward."

How does this impact clinical supply professionals? Sponsors are increasing the number of countries participating in global trials, and they're actively seeking new countries where patients are drug naïve but logistics and distribution is difficult. In the countries that are selected, there are increasing numbers of locations and study subjects. There are logistical issues with shipping and managing material while controlling the temperature ranges. The Regulatory environment is also ever-evolving and constantly changing in many countries. Finally, the timeline from Protocol approval to First Patient Visit is being constricted. All of these challenges affect the ability to effectively supply drugs.

Many clinical teams consider the drug supply planning a fairly straightforward process, like an equation, Essentially you take the number of patients and multiply by the number of sites for all countries and then multiply that by the number of dispensing doses and essentially you reach your conclusion, which is the quantity of drug required for the trial. However as we have already realized, drug development has gotten increasingly complicated and that also affects how and when we consider drug supplies.

In today's environment, minimally, you have to consider the following:

- Enrollment speed
- How fast milestones are attained
- Material dating and need for extension

## ARE YOU OVERWHELMED AND DON'T KNOW WHERE TO START?

Instead of hitting the panic button, imagine sitting in an airplane on a sunny, cloudless day at 30,000 feet and see the view of what is possible and the opportunity to create something new and potentially life changing. Then get to work!

To help you get started, here's a list of my 5 favorite supply planning tips:

- **Waste isn't always a bad thing.** I've had many clients request that overages for comparator purchases be as minimal as possible, which is pretty reasonable. After all, who wants to throw money down the drain? However, instead of using a base percentage as an overage (i.e. 10% of patient demand), consider thinking about where that overage is needed. Maybe you need it to seed sites all over the globe or maybe to seed your 10 warehouses. Don't spread the material so thin that you struggle to meet patient demand in execution.
- **Know the rules** with respect to regulatory requirements, import licenses and other rules to avoid surprises that can derail a timeline. In a recent situation, an import license filed in one country included the lot numbers for only new lots of product. The old import license was about to expire, but the lots of product included on it still had good dating. Subsequently, there was a delay in approving and releasing the new lots. Because the new import license included only the new lots and the old import license had expired by then, no material could be shipped to the country 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 you can.
- **Allow sufficient time** for supply forecasting, sourcing comparator, blinding solid dosage forms, filing import licenses and other critical pre-study activities. If materials are in short supply and must be sourced globally, 6 months or more of lead time might be required.
- **Get out of the box!** It is easy to approach supply planning and forecasting as a mathematical exercise because of the amount of number crunching that is required. However, life happens and it creates situations where your best options require some creativity in their approach. For example, if you ran out of a package type, could you dispense a similar package type instead until the supply was reestablished? If you had material at a site that never enrolled a patient, but limited supply at a high enrolling site and at the warehouse, could you move material from site to site? Sometimes you have more options that you think.
- **Good supply planning and execution is like the old adage of Measure Twice, Cut Once. Repeat as necessary.**

- Bulk drug availability
- Blinding needs
- Package design and dispensing plans
- Numerous dosages, forms, sizes and shapes
- Comparator needs
- Label design and groupings
- Storage conditions and Cold Chain Management
- Distribution systems
- IRT usage
- Site and warehouse inventory quantities
- Regulatory requirements

Sound supply planning and forecasting at its foundation is dependent on a well thought out plan that takes all of the specific variables in to consideration and attempts to balance risks with mitigations. Good supply planning and forecasting can be compared to the old adage of "Measure Twice, Cut Once" and repeat as necessary.

## HOW DO YOU REALLY BUILD A DEMAND PLAN FOR CLINICAL SUPPLIES?

In some ways, the work of clinical supply planning is a lot like what a landscaper must do. You draw your design, outline a budget, chart weather fluctuations and temperature zones, even model growth rates over time. At some point in your project, however, you are going to need to get out in the yard.

Two important elements to planning clinical supplies go hand-in-hand: Determining the packaging design and dispensing plan for the trial. In making decisions around packaging design and dispensing plan, considerations should include (but are not limited to):

- The indication being studied
- The dispensing visits in the study schedule
- Number of packages per drug type to dispense per dispensing visit
- The dosing information chart & diagram
- Stability information for packaging drug, including the allowable fill range
- Cost of bulk drug and/or commercial comparators
- The enterprise supply chain (i.e. manufacturing locations → packaging locations → warehouses → countries → sites → patients)
- Ease and flexibility of managing supply throughout the study

Every decision has a downward effect on the success and ease of managing the IP supply.

Another decision that is made in the initial supply planning phase is determining label groupings. For some trials, this process may be fairly straightforward. For other trials, this decision is more complex. The key point here is to consider a label strategy that yields the most flexibility for your supply.

For a large global trial, the choices could include:

- U.S. – Single panel, Outside the United States / Rest of World (OUS/ROW) 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

If there are so many options, how would a team make an informed decision? Here are some important factors to think about when developing your strategy for label groups:

- When will First Patient Visits (FPVs) occur?
- Distribution network and inventory management complexity
- Label text requirements and label generation lead times
- Supply flexibility
- Frequency of regulatory changes
- Country specific regulatory requirements
- Country specific extension dating requirements

Like starting your landscaping project, don't try to transform everything overnight. Start small and break it down into the different parts. Think about the foundational requirements first, and then work out the details from those major decisions.

It is important to keep it in perspective. The reality is that sometimes, despite our best planning and execution, life happens. The gardeners out there know that a season of unexpected high or low temperatures can wipe out some of their prized perennials. In the last few years, we have seen an increase in the number of catastrophic events—from natural disasters to drug shortages and everything in be-

tween—that have impacted the clinical supply chain. While you can't foresee every disaster, you can plan effectively and proactively to minimize the effects of events that are out of your control.

## 10 CRITICAL STEPS FOR SUCCESSFUL CLINICAL SUPPLY CHAIN MANAGEMENT

There are many ways that your project can be delayed and often these are managed in real time rather than proactively on the front end where they can be most effectively controlled and minimize the impact to timelines and enrollment or even actual study conduct. If you don't know where to start, here are 10 important factors to think through:

1. **Allow sufficient time** for supply forecasting, sourcing comparator, blinding solid dosage forms, filing import licenses and other critical pre-study activities. If materials are in short supply and must be sourced globally, 6 months or more of lead time is required.
2. **Maintain constant communication** between the operations and supply team for more effective study planning and prompt fixes to problems as they arise.
3. Know the rules with respect to regulatory requirements, import licenses and other rules and regulations to avoid surprises that can derail a timeline.
4. Be inclusive on paperwork, particularly import licenses to provide a buffer against mid-trial supply shortfalls.
5. Avoid unnecessary risks and don't make the mistake of assuming that commercial product will be available when needed. As one seasoned supply chain professional once put it, supplying a global clinical trial "is not like going to the local drugstore pulling the drug you want off the shelf."
6. Be realistic as well as economical. No sponsor can afford to waste resources, but having some overage is better than having patients out of drug or stopping the trial enrollment because there's no more comparator in the cupboard.
7. Expect the unexpected & factor in "what ifs" by ensuring that the supply plan reflects options in the event of a strike, tsunami, super storm or other emergency that could prevent material from reaching sites when it's needed.
8. **Consider collaboration and partnering.** Clinical supplies is a complex function that really can enable success or failure of your trial. We have come a long way as a function, but there is more to do. Collaborators or partners can have the knowledge and experience necessary to guide sponsors through the thorniest supply planning challenges.
9. **Measure twice, cut once. Repeat as necessary.** A forecast is established on a set of assumptions at a specific period of time. Keep reviewing the data and make adjustments as appropriate.
10. **Remember that patients are the top priority.** At the end of the day, every trial, every supply plan, all the execution and challenges (hopefully) go toward supporting a new therapy to change the lives of patients. We get to participate in providing improved options, better outcomes and a brighter future. Quite possibly the best reason to drive clinical supplies excellence!


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