Whitepaper

Where has my clinical supply budget gone?

Part 1: Why?

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I have worked for clinical supply service providers since 1996. It didn't matter how big or small my employers have been, or how robust their financial reporting systems were, the most common challenges I have received from clients over the years are around budgetary over-spend. In this paper I will look at some of the reasons behind this. In Part 2 of this article, which we will aim to publish in the near future, I will present some ideas we can all implement to help overcome this key challenge.

Forecasting the unforecastable

While trial simulation tools have evolved over the years, allowing the implications (including cost) of different scenarios to be evaluated, over-spend against budget remains a major challenge. In my early days in the industry, this wasn't such an issue – every site received X blocks of medications, shipped in a planned number of shipments so we could budget accordingly. Great from a budgeting point of view. A disaster from a cost management and sustainability perspective. How much of this drug would be wasted? How much extra drug would we need to produce or procure for comparator trials, to cover wasted medication? Estimates from clients at the time ranged from 100-400% of extra drug would need to be produced/procured for each trial...expensive in the days when products were mostly oral small molecule drugs, unsustainable with today's biologic innovator drugs and comparators.

With the advent of IRT, Clinical Supply Management and demand-led packaging/distribution services, drug overages have been slashed. However, the very nature of these new supply chain management tools and approaches has introduced a new challenge. How do we budget a demand-led supply chain more accurately, when we don't know where or when our demand will come? Nobody has a crystal ball.

Simulation tools can improve the probability of budgets being in the right ballpark. However, these are still based on assumed scenarios, and until a trial starts, we don't know which of these scenarios is most likely to happen in reality. Furthermore, if reality does start to deviate from our initial assumptions, do we change our plans accordingly or just continue working to

plan and hope things will sort themselves out? How often do we really go back and re-forecast, even when it becomes clear that reality is deviating significantly from our initial assumptions. Even if we do this from an inventory management perspective, are we applying this knowledge to our budgets, and requesting revisions from our internal clinical supplies' teams or Vendors? In my experience, the answer to this is, more often than not, 'no'.

The reality I have seen is that both parties, Vendor and Sponsor, remain oblivious to potential over-spends until after they happen. This can lead to significant problems:

- Diversion of funds from other projects, delaying development of potentially important new therapies. Money doesn't grow on trees – if we overspend on one project, and feel it is sufficiently important to complete, we need to get the funding from somewhere.
- Breach of contract by Vendors. Many MSAs include terms that any spend in excess of budget will not be covered by the Sponsor without prior written approval. If neither party is tracking their actual spend vs budget, how do we know this has happened until it is too late? Moreover, even if a Vendor has over-spent…do they simply stop work until a new budget is approved, regardless of patient need? Sponsors and Vendors take a patient-first approach and will continue to supply patients/sites in lieu of budget extension approval. However, strictly speaking, a Vendor is in breach of contract if they do this, which can damage Sponsor-vendor relationships. In extreme cases, I have even seen these disputes settled in the courts. Earlier identification of risk of overspend gives both parties the ability to re-assess budgets before they are on the critical path.
- Increased Sponsor administration, or as we used to call it in a previous company 'Death by Change Order'. Even when over-spend is identified, change orders are often raised/approved reactively – to deal with the immediate over-spend, rather than reviewing any additional scope to the end of the project. As a result, multiple short-term change orders can be required to complete a project. No joke – I have seen the number of change orders hit three figures on some projects in past companies.
- Career considerations. I don't like going to my boss to ask for more money for a project. Nobody does. If I am doing this on a regular basis, how is my boss going to view my performance?

Before we can fix the problem, let's take a look at the key areas we should focus on to identify potential over-spend and put plans in place to mitigate against this.

Distribution Budgets

Without a doubt, Distribution is the area where I have seen most over-spend over the years. This can arise for multiple reasons.

Lack of information up-front. Clinical supply budgets are often calculated long before factors impacting distribution costs have been fully established. For example:

- Which countries (planned core and contingency) will the trial take place in? If my country list changes, do I have a process to trigger a request for a revised budget from my Vendor?
- How many sites per country? Patients per site? Direct-to-site or depot distribution? If initial estimates prove to be wrong and more of my patients are in long-haul (more expensive) countries, do I have a process to trigger recalculation of courier, and possibly depot, fees with my Vendor?

- If we are assuming particular shipment patterns (fewer larger shipments vs regular smaller shipments) in our budget, has this information been shared by all parties – especially with the IRT Vendor who will be generating shipping requests? Is there a plan to re-evaluate IRT ordering triggers if our initial assumptions prove invalid. If we need to change IRT settings, for example to preserve limited inventories, are the budgetary implications of this being worked through with the distribution Vendor? Communication between all parties is essential!
- Does the budget allow for realistic estimates of shipment size/cost? This can be challenging, as distribution budgets are often set long before pack designs/sizes have been finalised, which in turn can lead to under-estimates of shipper sizes and costs, the number of shippers required for each shipment, and ultimately courier fees – a major component of distribution costs.

- Are we being realistic? I have seen this on both the Vendor and Sponsor side of the table. In a previous company, in the absence of all other information, we defaulted to 'one shipment per site per quarter' when estimating the number of shipments to budget for. Over the years it became clear that this was an under-estimate, so we evaluated our historic shipping data and calculated that the actual figure for a large phase III project was closer to 2-3 shipments/site/quarter (depending on a range of parameters). When we started introducing these more realistic estimates into our budgets, we saw resistance internally and externally. Our own BD team felt that this would make our proposals too expensive and we should reduce the number of shipments to remain competitive. Our clients gave similar feedback when they read our quotes…or awarded work to alternative Vendors, who had grossly underestimated shipment numbers, on grounds that their quotes were cheaper. If we're ever going to get realistic budgets, Vendors and Sponsors need to work together on these assumptions, ensure all Vendors are quoting realistically, and take away the temptation for Vendors to lowball.
- Courier selection. Budgets are often set based on a Vendors preferred courier strategy. For example, using lower cost integrators for 'easy' shipments (e.g. domestic US and intra-EU shipments) and reserving premium couriers for long haul shipments and those crossing international customs borders. Once a trial starts, I have seen courier selection deviate from this plan, often with over-use of premium couriers for domestic destinations. Based on the price differences between courier types, this can have a huge impact on distribution spend.
- Inflation. Global inflation reached double digits following the COVID-19 pandemic. While some Vendors chose to share the pain of this, and honour prices quoted for projects awarded before inflation struck, others implemented inflationary price rises as soon as the implication of rising costs on their margins became apparent. Bearing in mind inflation did not only hit direct Vendors but could also impact on indirect service providers (couriers, third party depots), inflation has had a significant impact on budgets set before the recent surge in inflation.
- Have we allowed for everything? Many Vendors do not include estimates of pass-through charges such as duties and taxes in their budgets. Even those that do tend to under-estimate these. There are a whole host of reasons for this, but if they do not know where shipments will go, value per shipment, the number and value of medications going into each country, and they have no control over local changes to tax rates, how can they ever accurately estimate these? The Vendor's view on this is that providing this information gives

the Sponsor another 'guesstimated' cost to hold them to, so avoids including these. These charges can be considerable, and if no allowance (even a rough estimate) is included in the budget.

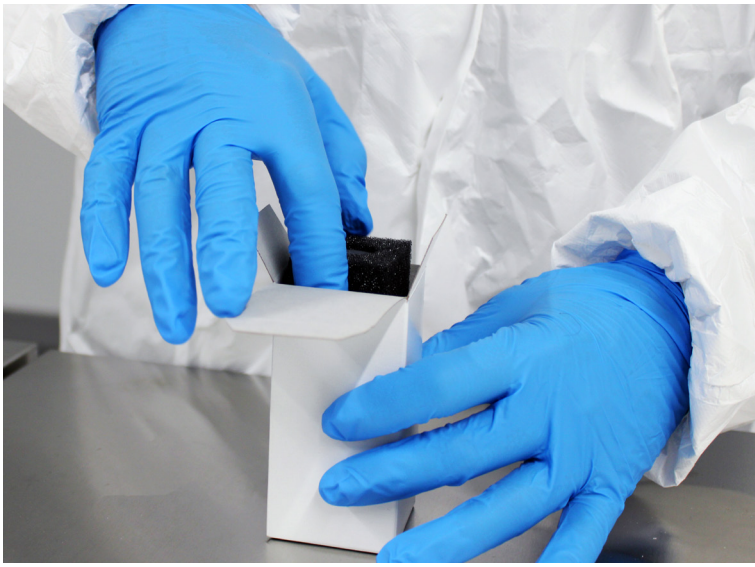
- Other unexpected fees. Some Vendors charge expedite fees to process orders in faster-than-contracted turnaround times. While there are undoubtedly occasions when this is necessary (e.g. replacement for a lost or damaged patient medication kit), are expedite fees always being charged for the right reasons? If you are seeing an excessive number of these on your invoices, it is always worth exploring root causes.

Packaging Budgets

Generally, these are easier to calculate accurately for 'build to stock' style packaging strategies – we know up front what we are producing. Some deviation from budget can still occur.

- Splitting planned large packaging campaigns into smaller campaigns to expedite availability of start-up or resupply medication, accommodate faster supply to 'early start' countries, or to accommodate increases in the number of bulk batches of product. Regardless of run size, all Vendors have fixed costs they need to cover for each packaging operation – batch records generation/completion/review, material picking and checking, room and equipment set ups, reconciliation, clean down and area clear checks – so splitting large jobs into smaller individual operations will increase costs. This is compounded for complex clinical trial supply projects, where multiple treatment groups and pack types can incur significant numbers of additional fixed fees.
- Expiry updates can also lead to additional packaging campaigns and costs. It is not unusual in clinical trials to start work with a short expiry product, and for shelf life to be extended as new data become available. While this can be less problematic in the US, where expiry date does not need to be included on clinical labels, it can create additional cost and time if the trial is running in countries where this is a requirement.
- can significantly add to costs if clinical supplies have been packed to stock and are labelled only with originally planned country/language text. Addition of new countries can lead to re-ordering of booklet labels, and potential re-packaging campaigns to add new language labels to existing packs. Even if repackaging can be avoided or minimized by creating additional inventory items that can only be used in new countries, the extra inventory/supply chain management workload created can impact on trial budgets.
- While minimal in context of total clinical trial supply spend, materials such as blister/wallet cards, cartons and labels often need to be budgeted before final pack designs are complete. As a result, Vendors often estimate these, only to discover at the time of order that their estimates were over optimistic. While some Vendors will absorb these additional costs, others will pass these on causing deviation from budget. Further over-spend can result from Vendors assuming all materials would be ordered up front, then deciding to order in smaller increments. Like clinical supply Vendors, material suppliers also have fixed costs every time they set up their equipment!

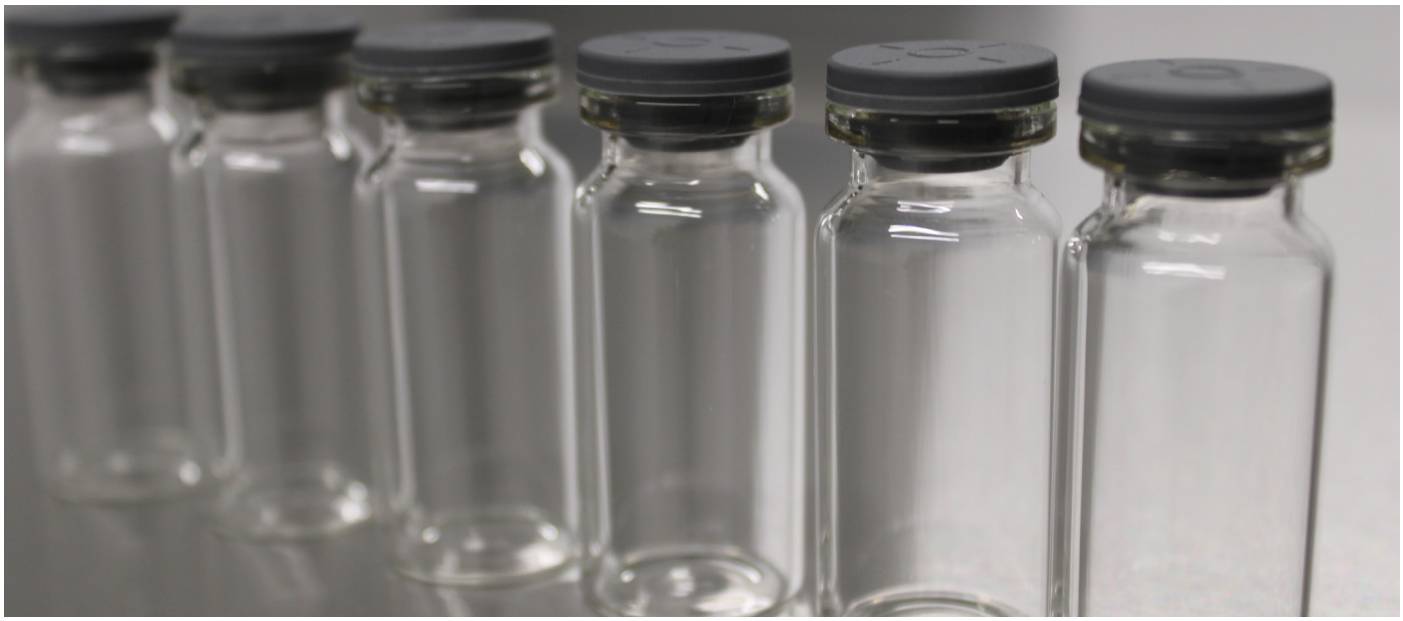
Adopting demand-led or just-in-time packaging strategies can help mitigate against factors such as repackaging of drugs if expiry dates change or new countries are added to a trial. However, bear in mind that these approaches are not cheap – even if fixed costs can be minimised for small, discreet demand-led approaches, there will still be a lot more of these incurred over the course of a project. From a budgeting perspective, since packaging orders are driven by actual patient demand, budget for demand-led approaches can be subject to much of the same variability experienced with distribution budgets.



Comparator/Co-Medication/Rescue Medication Sourcing

With the advent of high value biologic drug classes, this is becoming a major part of clinical trial supply budgets, with spend on commercial drug products often being in the $millions for later phase studies.

- Sourcing strategies can have a significant impact on budget accuracy. Ordering all commercial product to be available on day 1 of a project because enrolment projections indicate that, expiry date permitting, all drug will be used before it expires. Bearing in mind that most trials over-run, this can be an expensive assumption!
- Timing and product availability. Pricing for budgets is often sought months before a trial is due to commence, and orders for commercial products can be confirmed. In market-based sourcing (as opposed to buying directly from the manufacturer), most sourcing Vendors will provide their best price based on sourcing from a low-cost market. Unfortunately, many low-cost markets have limited quantities of drug available. For popular comparators, there is also competition between trial sponsors for these products. This can mean that a price obtained when a budget was set is no longer available if Vendors have to revert to larger, and often higher priced, markets. A few percent difference in price can be hugely significant for high value products.



Budgeting for Time-Based Activities

Most Vendor budgets include time-based fees. Examples include Project Management (PM) and storage charges. As stated above, most clinical trials over-run and do not complete when anticipated. PM services are required, and bulk material needs to be stored, for weeks/months before the trial itself begins. Also, material is never fully reconciled and destroyed the day a trial finishes, and storage charges will continue to be invoiced until material is finally removed from the Vendor's site. In RxSource we usually add 6 months to study durations to estimate the number of months these activities will be charged. For example, for a 24-month study we will budget for 30 months of storage and PM activities. We are often asked to reduce these estimates back to 24 months, creating inaccuracy.

The number of PM hours and storage locations consumed/month is also an area of inaccuracy. Some Vendors will estimate these at a low level, but then charge a significantly higher amount based on 'actual consumption'. Others will take factors into consideration that drive the number of hours/locations up such as:

- Number of packaging runs and estimated number of shipments
- Number of countries
- Number of third-party depots
- Client's preferred way of working (if known) – for example, some clients may have limited PM headcount internally, so require great support from Vendor PMs. Others may require less support.

This can result in higher, but realistic, estimates. I have worked in companies with both approaches. My preference is that we are realistic up-front and create an accurate budget – I am still amazed by the number of requests I see for PM fees in budgets to be reduced to match Vendors I know will quote a low price but invoice a much higher price.

Conclusion – Are we chasing an impossible dream?

There are so many variables in clinical trials, and as a result in the clinical supply chain, that it is easy to give up and just accept the status quo. While I don't think we will ever get to trial budgets being 100% accurate, there are things we can do to make substantial improvements to where we are today. In Part 2 of this paper, I will describe approaches that will help us get to a better place and hopefully more realistic clinical supply budgets. Sponsors and Vendors need this!

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