Drug Pooling in the Clinical Trial Supply Chain

Abstract
Global clinical trials require efficient and robust supply chain which can bring more transparency and can introduce risk mitigation strategies. Currently, it is following consumption-based supply chain model where all the medication kits are initially assigned with patient information and then dispatched for clinical trials from central depots. This is followed by dispatching overage supplies to the tune of 100-150 % to emerging markets. Unused patient specific medication kits coupled with unused overage supplies produce large amount of clinical trial material wastes which also include expensive comparator drugs. Drug pooling, a demand-based model, is possibly a strategic approach that could bring the clinical supply chain in parity with this evolving R&D pipeline. In this model the decision making for assignment of medication kits is brought closer to trial sites which could be initiated upon investigator's request only.

This paper provides the impact analysis of "Clinical Drug Pooling at Depots" for various clinical trials. To understand the impact of drug pooling over various segments, Beroe conducted a survey among global clinical trial supply vendors, which hold 60-70 % of the overall market for clinical trial supplies.

Introduction

Today the clinical trial supply chain is using consumption-based models. Given that the demand from the patients' side is very volatile and unpredictable; the current model is not able to manage the clinical supplies efficiently. Clinical drug supplies are planned at the start of the trial and are run accordingly, providing less room for meeting any unexpected demand. There are some big issues which need to be fixed to make the clinical supply chain more efficient.

- **Supply-demand mismatch:** Most of the clinical trial sites complain about supply-demand mismatch for clinical trial materials. Forecasting actual numbers for patient enrolment is a very challenging task. This leads to issues like customs, lead time, quality issues, etc. A study across 150 clinical studies, involving almost 16,000 sites, published by Tufts Centre for the Study of Drug Development (CSDD) in 2013 states that 11 % of the trial sites failed to enrol even a single patient, 37 % under-enrol, 39 % meet their targets and only 13 % exceed their targets. So according to this study only 39-40 % of sites met targets whereas the remainder, 60-61 %, of sites were either not performing or they were exceeding the targets, both of which are issues for the clinical trial supply chain.
- **Least flexibility:** If there is a change in the study or if the forecasted supply varies with the actual need of supply this can lead to high overage and wastes, creating high wastage in investment for R&D. CTS (clinical trial supply) vendors generally follow a fixed protocol for supply chains, leaving less room for on-time changes required in supply of clinical materials. Secondly medication kits labelled with patient information can't be used for other patients, which is again a sign of rigidity in supply chain process.

Drug pooling is a comprehensive strategy to fix many of the current clinical supply chain issues. It connects various segments of the clinical trial supply chain and makes the whole system more automated, dynamic, and forecasting-based. Here IMP or non-IMP supplies for different clinical trials are sent through a single window in a planned manner. The approach takes care of both over-supply and under-supply situations by maintaining periodic buffer stock of clinical trial materials.

Drug pooling can be implemented at various levels of the clinical supply chain according to the requirements. It will assist the R&D supply chain in the following manner:

Drug Pooling at Various Levels

Currently there are three different approaches for drug pooling:

• **Pooling prior to labelling:** The pooling of packaged kits or kit components is done and they can be sent to regional depots to take care of labelling and other processes. Analysis of this approach is out of the scope of this document.

• **Pooling at depots (unlabelled):** One can send unlabelled packaged kits or kit components to regional or country-level depots. At depot level the pooling can be done, which takes care of the requirements of each clinical trial site which comes under its geographic scope. In this approach the kits are received at depots without any protocol number, which is mentioned only after receiving a request from the principal investigator from the clinical trial site. This is useful for a variety of different simultaneous clinical trials running under same program. Drug pooling at depots can be applied in two different scenarios which are discussed as follows:

- **Same sponsor:** The following are the criteria for this scenario:
  1. One sponsor
  2. Same clinical trial site
  3. Multiple clinical protocols but similar medication
- **Different Sponsors:** This scenario is based on the following criteria:
  1. Different sponsors
  2. Same or nearby clinical trial sites
  3. Similar clinical protocols or protocols using similar medication

• **Pooling at sites (labelled):** In this approach the drug pooling is brought one step closer to the patients. Here the packaged kits are sent to clinical trial sites without any protocol number, although sometimes they do show a set of protocols, or a program code. In any case, the kits remain protocol independent, even at the clinical site, until they are dispensed. This can be a most fruitful strategy for the clinical supply chain, but currently there are many challenges which must be sorted out first to implement this step. The analysis of this segment is currently out of the scope for this document. We will discuss the impact analysis of "**Pooling at depots**" approach in more details.

Pooling at depot level is achievable and some CTS vendors are indeed applying this concept for their pharma clients but in a very limited scope. There are some vendors who suggest that they have robust systems in place for effectively implementing drug pooling for sponsors. But in reality there are many issues like regulatory issues, effective technology, trust on trial sites, etc. which need to be fully resolved before its implementation.

Clinical supply chain companies are trying hard to implement technologies and strategies to reduce drug wastages, to bring more transparency, to make the process more robust and flexible, and to make the supply chain more integrated and streamlined. These reforms, if implemented effectively, can provide direct cost savings up to 30-40 % of clinical drugs budget.

Benefits of Implementing Drug Pooling for Clinical Trials
According to industry experts, drug pooling, if implemented successfully, will definitely assist in transforming the clinical trial supply chain.

1. Cost Reduction: Almost 70 % of the respondents feel that reduction in clinical material wastes will be a significant benefit for the drug pooling approach. This is due to the fact that decision-making for shipments of clinical material will come closer to trial sites, which will help supply chain companies to deal better with demand fluctuations. According to Beroe's analysis, the approach can assist in saving 30-40 % compared to the current level of waste in IMPs or non-IMP drugs. Less waste for drugs also means that pharma companies will need to pay less for the drug destruction process.

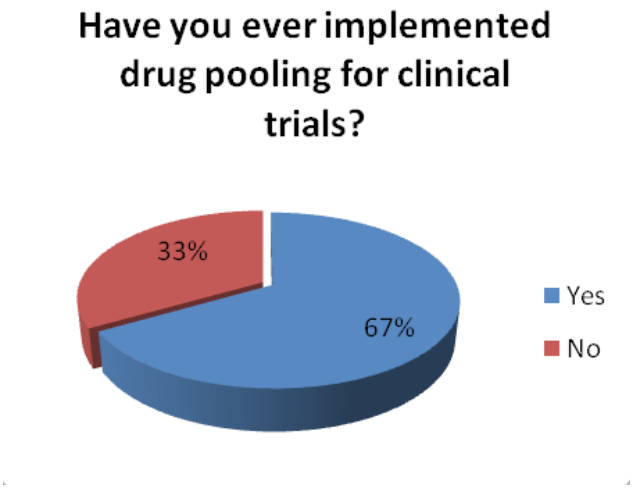


Fig 1:
Survey shows that 60-70 % of the respondents are implementing drug pooling for clinical supplies, but on a small scale.

2. More Efficiency and Transparency in Supply Chain: Drug pooling requires robust and efficient use of IVRS/IWRS, automation, forecasting, and JiT packaging and labelling technologies. For an effective and robust process, the medication kit should get dispatched within 48-72 hours after the order is placed.

3. Large Molecules: It is expected that by 2018, 45-50 % of top 100 blockbuster drugs will be large molecules, also called biologics. These molecules are very sensitive and require strict protocols for handling, storage, distribution, and administration. Current models for the clinical supply chain are just not capable of handling these molecules effectively. Due to unexpected delays these molecules often lose their nature. Depots used for the purpose of drug pooling can prove to be efficient for handling, storage and distribution purposes. In this way the exposure of these drugs out of the temperature range, 2-8°C for many large molecules, can be minimized. Drug pooling for large molecules can be a very significant approach for efficiently maintaining the stock inventory for longer time periods according to the shelf life of these biologics.

For more information on rising market share of large molecules please check the appendix

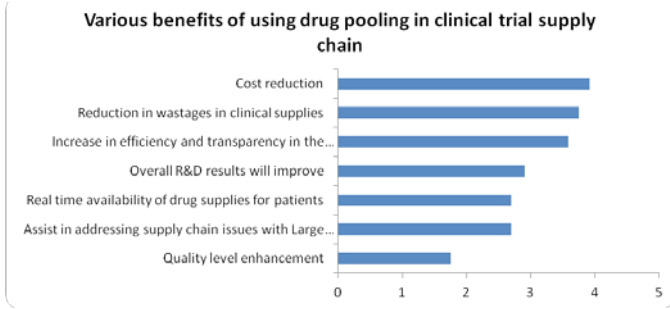


Fig 2
Survey shows various expected benefits for pharma sponsors through clinical supply pooling process, N=15; Scale used is 1-5 where 1 shows minimum impact and 5 shows highest impact.

4. Supply-Demand Harmonization for Clinical Trial Drugs:
According to industry experts, drug pooling will bring more harmonization in the clinical trial supply chain. Decision-making will become more streamlined as it will come closer to trial sites. Requests for the medication kits will be triggered by investigators; only after the analysis and prediction of patient participation in the clinical trial. This will create more collaboration and understanding between investigators and vendors responsible for supplies of trial materials.

5. Overall R&D Results will Improve:
According to the analysis it is expected that drug pooling on a big scale will impact the overall R&D outputs. This is due to the fact that the clinical supply chain will become more streamlined and robust. Drug availability to patients will become easy and can assist pharma companies in getting more accurate results for different titrations on a particular patient sample size.

Challenges and their Solutions for Implementing Drug Pooling:

1. JiT Labelling and Packaging:
Medication kits sent to regional-level or country-level depots need to be labelled with protocol number, patient information, etc. only after a request from the investigator. This needs a robust Just-in-Time clinical packaging and labelling process. Once the investigator requests a medication kit, the team at depot level should be able to process and dispatch it within 48-72 hours. This will bring more flexibility in the supply chain process and will also bridge the gap between demand and supply of clinical trial materials. JiT labelling and packaging becomes a very integrated part of the drug pooling process. Many vendors

involved in the clinical supply chain don't have efficient JiT infrastructure in place. Some clinical packaging companies offer JiT facilities for clinical supplies and CTS vendors need to collaborate with such companies on a regional basis to have the required level of resources.

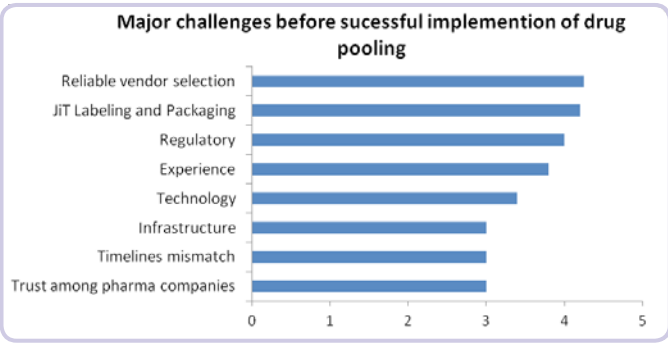


Fig 3
Survey shows major challenges which arise during planning and implementation of drug pooling strategy

2. Reliable Vendor Selection:
This is the biggest issue in the industry and many pharma companies want to engage with the best supply chain vendor for their service requirements. On the other hand many CTS vendors say that they do have the necessary resources for providing streamlined clinical supply services and that they can support drug pooling as well. But many of them may not have the required experience of handling such requests. Selection of the most capable vendors should be strictly based on criteria like service requirements, their operational capabilities, operational KPIs, etc. Some of the basic factors that go into supplier selection criteria are mentioned in Table 1:

In such a scenario it becomes very significant on the part of sponsors to have very comprehensive know-how about supplier landscape on a global as well as a regional basis.

Suppliers' strength and weakness analysis on a regional basis is very significant for pharma sponsors.

3. Technology Adaptation and Integration:
Developed markets like North America and Western Europe provide technological and infrastructural advantages. But in emerging markets it is still a big issue. Adaptation and integration of technologies like IRT, IVRS/IWRS, etc. are expensive tasks for vendors.

Global vendors along with local players can provide a good technological base as well as their experience in global clinical trials. A good and integrated network of technology platforms will provide leverage to the vendor for a better prediction and decision-making process in the clinical supply chain.

4. Country-specific Pooling Strategy:
One can't implement drug pooling in all countries due to region-specific issues. For instance, implementing drug pooling is easier in the US as compared with India and China, whereas Russia

Challenges	Description
Global vs. regional supplier selection strategy	Pharma companies need to understand every geography's supplier landscape, which is very significant for them to take decisions regarding supplier engagements like depot network, logistics players, drug destruction, etc. ✓ In LATAM, including Brazil, one will find more involvement of 3PL players in the overall clinical supply chain. ✓ In Russia local companies don't have adequate infrastructure capabilities and global-local vendor partnerships are relevant. ✓ China and India both provide a hybrid model of clinical supply chain where global CTS vendors have good collaborations with local players.
Experience	Drug pooling needs good experience in managing the overall clinical supply chain. Many companies may not have experience in the overall supply chain process.
In-house infrastructure	Most of the companies subcontract some clinical supply services to third-party vendors.
Flexibility	Often CTS vendors may not be flexible in terms of the requirements for effective drug pooling. This increases the overall waste in the clinical supply chain.
KPIs	Many times sponsors don't have KPIs for effective supplier selection. Eligibility criteria can be segmented into operational and functional KPI requirements.
cGDP compliance	The visibility for cGDP compliance decreases when engaging with many vendors globally in a centralised engagement model.

and Brazil are still tough countries for an effective clinical supply chain itself. Singapore is a logistics hub for the APAC region. A regional depot in Singapore can be used to directly send the trial supplies to trial sites in countries like Malaysia, Philippines, Taiwan, etc. whereas in countries like India and China one can adopt a model of in-country depot. This depot can be used for proper management of clinical trial supplies for drug pooling. In these regions some companies are already using pooling for ancillary supplies and clinical drug materials for locally procured marketed products.

5. Regulatory Know-how

For import approval process of clinical trial materials, the NOC (No objection certificate) and import license need to be protocol-specific. But drug pooling is a concept where drugs are required to bring closer to clinical trial sites without putting protocol number. In-country depots can play a vital role in this process.

Still, experienced clinical supply chain vendors can manage drug pooling in this environment. Generally the protocol number provides information on various aspects like the phase of the clinical trial, therapeutic area, FDA or EMA, trial site, patient identity, clinical trial site, etc. One can import the container of medications without putting the patient's identity number which can still be done at depot levels. This provides leverage and a window of opportunity for CTS vendors to implement drug pooling in respective countries.

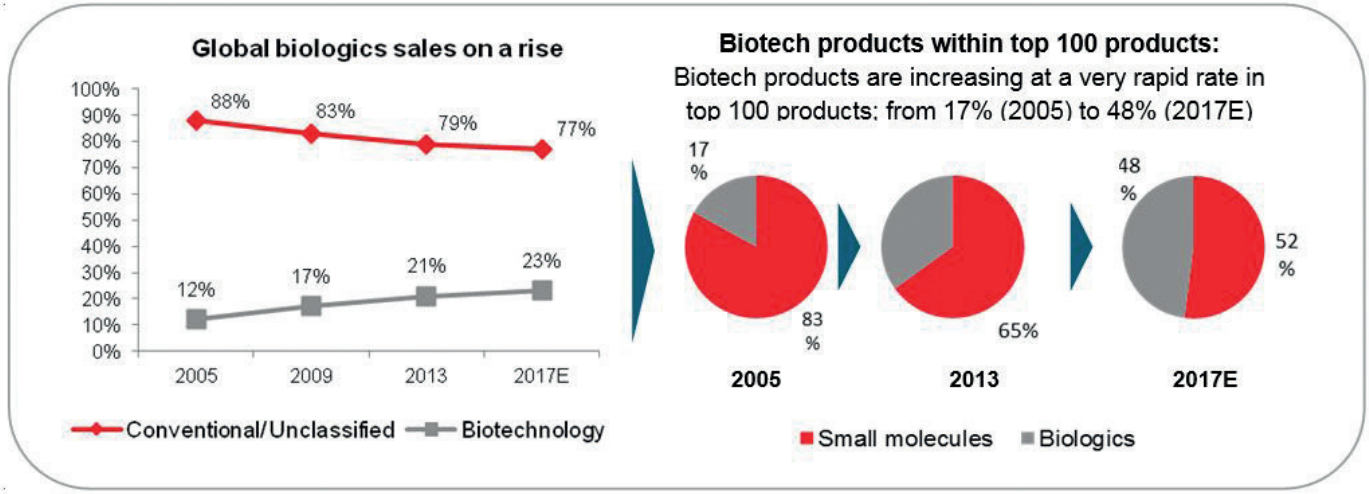
Scope for Drug Pooling – An Evolutionary and Tough Task

Since drug pooling is expected to become one of the comprehensive strategies for the clinical supply chain, the overall scope is also expected to increase its horizons. Currently drug pooling is done for various trial protocols for the same pharma company. In future drug pooling for multi-sponsor clinical trials could be a possibility. Different pharma sponsors can combine their supplies for same medication for similar programs.

This needs to have many complex systems in place, e.g.-

1. Robust clinical supply chain: Industry needs to decimate most of the current issues in the clinical supply chain and must make technology, regulatory and cGDP a must and an integrated part of the overall system.

2. End-to-end services: Currently we have different types of players in the system, i.e. logistics provider (3PLs), depot provider, packaging service provider, CTS vendor, etc. Among these CTS vendors are the most experienced players with good technical know-how of managing the overall clinical supply chain. They can develop more in-house resources either by developing in-house infrastructure or by collaborating with service providers for end-to-end services. This is followed by 3PLs which are expanding their service portfolios in remote areas like Africa, LATAM and in developing markets like MENA (Middle East and North America).



Appendix - Emerging state of bio-pharmaceutical products

3. Pharma collaboration: This is the most complex part to deal with. But some time back the industry witnessed a group named TransCelerate Biopharma, a consortium of the top 10-15 pharma companies, which talked about working together for sourcing comparator drugs for their comparator trials. Based on these lines we can also expect this consortium to come up with a collaborative model for a strategy like drug pooling to streamline and consolidate the overall clinical supply chain. There are many issues like sharing confidential information with each other and working together on these lines. But this discussion is currently out of the scope of this document.

This practice requires a huge investment in the form of infrastructure and technology development. For the purpose of understanding the feasibility of pharma collaboration on evolving clinical supply chain we asked the experts for their analysis and thoughts. For significance of pharma collaboration for inter-pharma drug pooling they agreed on 3.5-4 on a scale of 5, which is again very significant.

Expert:
"Clinical supply chain service providers are understanding the evolution of clinical R&D and so they are working on bringing new innovative models for a more efficient clinical supply chain."
Director, clinical supply chain organisation

Procurement manager:
"We are using drug pooling for some part of the clinical supply chain and indeed it is a good system for consolidating the supply chain process. In future we do expect expansion of this strategy on a global scale."
Independent drug supplier

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