An Executive Summary

The Product Development Superhighway: Leveraging End-to-End Solutions for Market Success

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How early collaboration between pharmaceutical scientists and clinical-supply services teams lays the foundation for development program success.

Overview

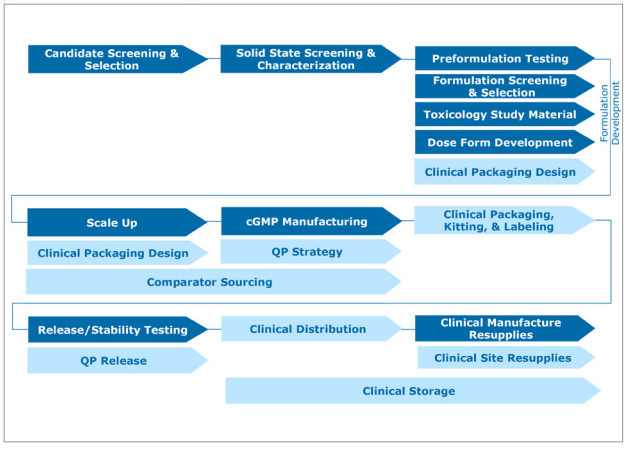
Formulating drugs for optimal stability and bioavailability is fundamental to the development of new pharmaceutical products. Once developed, these products must then be delivered to patients in the clinic. Since pharmaceutical scientists often work in isolation from the supply chain and clinical operations personnel responsible for clinical packaging and delivery of patient kits, there is an ever-present risk of potentially foreseeable and avoidable problems occurring further down the line. This article explores the benefits of a more integrated approach in which the chemical, manufacturing, and controls (CMC) teams and clinical teams work together at an early stage to achieve greater success for both the development program and patients.

Drug Development Overview

Figure 1 outlines typical stages in a development program for a new chemical entity (NCE) small-molecule oral formulation and illustrates that the process is not only about making the best and most stable formulation, but also about getting the finished product to the patient. It is important to invest in the right product to maximize the chance for success in clinical trials, in addition to having a path to market that will deliver meaningful impact for the patients.

Achieving these goals efficiently requires close working relationships between all the teams involved. Consideration is given to aspects of a development program that must be examined alongside early formulation. These include clinical packaging design, cleaning strategy harmonization between production sites, early involvement of a qualified person (QP), and supply-chain execution. The benefits of a harmonized approach are illustrated in examples of successful collaboration as well as experiences of working with a

Figure 1: An integrated view of drug development.



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Clinical Packaging Design

Drug product characteristics are a critical consideration when developing the clinical packaging strategy and patient kit design. The clinical packaging design itself may equally influence formulation development. Companies that specialize in clinical supply and offer a full range of formulation development, manufacturing, and packaging expertise are able to bring together the most appropriate subject matter experts from the start of the process. These companies may also offer access to a wider range of container, closure, and packaging options—an added benefit and capability not typically available within non-integrated organizations. Two circumstances that illustrate the importance of this level of integration are, firstly, when dealing with the presence of a moisture-sensitive API and, secondly, where there is a need for easy dosing of pediatric formulations.

Hygroscopic APIs or formulations that draw in moisture can be highly detrimental in a final product, resulting in problems such as chemical degradation, destabilization, and loss of bioavailability through crystallization of amorphous drugs. For example, there may be physical issues as well when water is drawn into a tablet, resulting in increased friability. One approach to addressing this problem is to apply a moisture-proof coating, but this can add an unsupportable degree of time and complexity to the overall project when trying to get materials into a Phase-I study. This approach also introduces the possibility of chemical incompatibility between API and coating. Furthermore, the capsule formulations often preferred for Phase-I trials are not good candidates for coating.

Instead of using complicated barrier coatings, an alternative approach is to work with the clinical supplies team to consider a physical solution rather than a chemical solution. A coated tablet may be developed at a later stage, but the first imperative is to get viable drugs to the clinic. To do this, blister packaging of a capsule formulation, for example, may be an option that provides greater protection to the drug product.

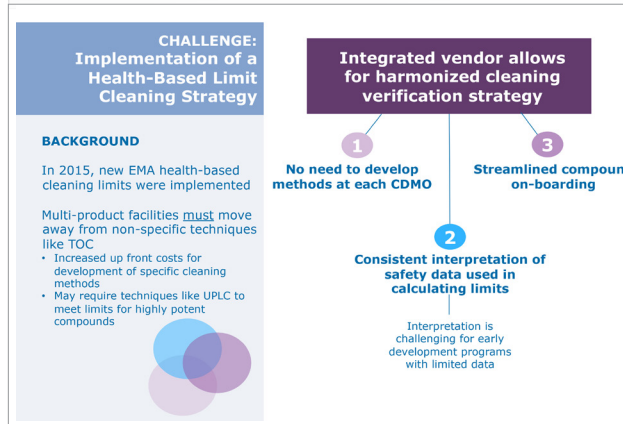
When it comes to pediatric formulations, ease of administration is key. Collaboration between the sponsor and development partner can enable the early evaluation of different formulations, such as granules or mini-tablets that are added to food using stick-pack pouches, as an alternative to taking the more traditional elixir route.

Packaging at the Manufacturing Stage

Staying with clinical packaging design but moving further along the drug development program, it is useful to consider what an integrated offering delivers at the manufacturing scale-up stage and how this can reduce complexity in preparing for an expanded clinical program.

While some contract manufacturing organizations (CMOs) can support small-scale packaging for single-site early studies, there are increasing demands for more complex presentations, especially for accelerated programs. At this stage, the need to engage another supplier to accommodate increased packaging requirements and distribution requirements can absorb significant time and effort. When formulation development, clinical manufacturing, packaging, and supply-chain capabilities are integrated, it paves the way for a more efficient workstream. For example, there is less need for separate service and quality agreements or for separate safety assessments. Once safety information is provided, it can be used across the network and redundant information is not requested multiple times. Integrated operations can also minimize the shipping delays that result from quarantine requirements because packaging operations can begin while awaiting the results of analytical testing. Similarly, streamlining of retained samples delivers savings for costly and potentially scarce APIs while maintaining regulatory compliance. In addition, costs connected with non-harmonized cleaning are reduced, as described below.

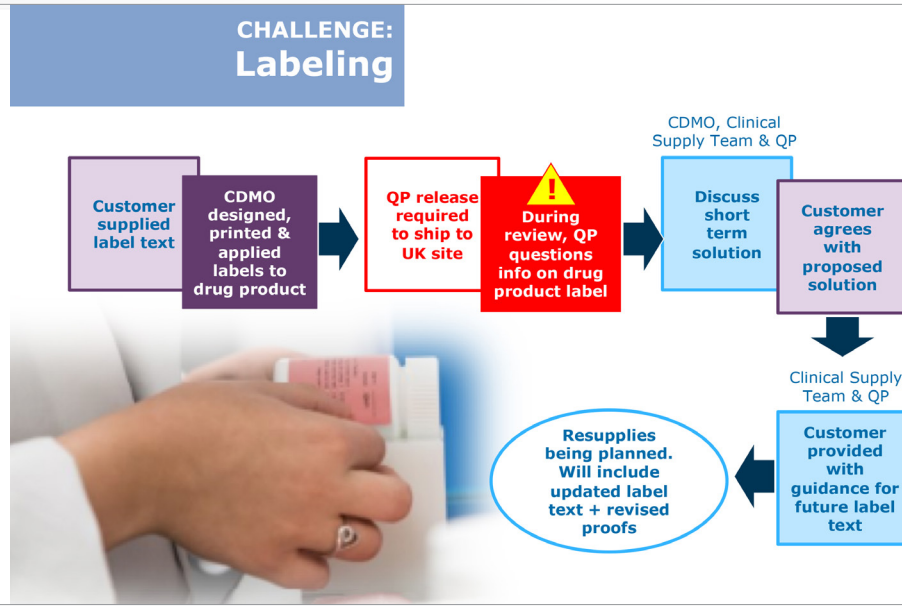
Figure 2: Clinical packaging design at scale-up.



Cleaning Strategy Harmonization

The introduction of health-based cleaning limits in 2015 presented a significant challenge for contract manufacturers and multi-product facilities (see **Figure 2**). Up to that point, most were using non-specific measures such as total organic carbon (TOC), for cleaning verification and validation. Health-based limits demand a much more sensitive analytical approach that requires the development of high-performance liquid chromatography-based methods or even ultra-high-performance liquid chromatography methods for highly potent compounds. Establishing these limits involves longer lead times and more upfront cost.

Figure 3: A real-life example of why a qualified person (QP) should be involved in early consultations.



Using an integrated vendor offers practical benefits by avoiding the need to develop methods in two different companies. This not only saves time and cost, but streamlines the compound onboarding process, which is challenging in the absence of toxicology data in early phase development. The reliance on animal data demands a clear understanding and interpretation to set the acceptable permitted daily exposure (PDE) levels and to establish the cleaning limits. Hence, consistency is key.

Early Involvement of a Qualified Person

Certain countries, including the United Kingdom and countries in the European Union (EU), require QP release before pharmaceutical materials can enter the clinic. A QP is legally responsible for certifying that each batch of a medicinal product is suitable for release and will be named on the manufacturer's authorization. When performing a final clinical release, the QP will review the entire process, including API manufacturing, packaging, and labeling. Having QP input throughout the process—not just at the end—is critically important as the following real-life illustrations suggest.

The first case describes a situation involving a labeling challenge that occurred when the QP was not involved in early consultations (see **Figure 3**). The customer had supplied the label text for the drug product when the study was in early-stage Phase I and open label. Labeling requirements were not complex, and the contract manufacturer was able to design, print, and apply the labels to the drug product. Since the study was UK-based, it required QP release. However, the QP was not engaged until after the product had been packaged and

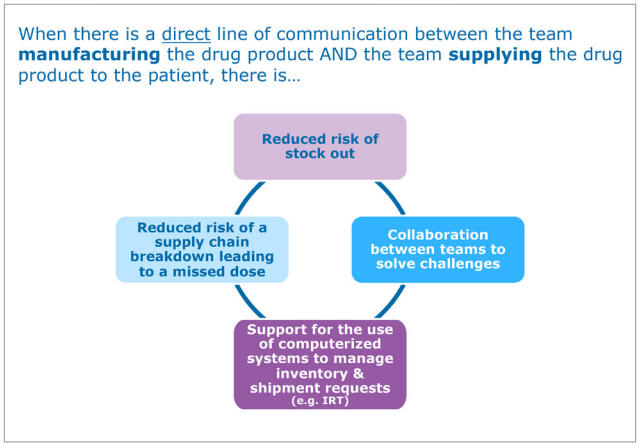
Figure 4: Clinical packaging, labeling, and kitting.

labelled, and during the review, questioned some of the information in the label text.

Fortunately, the integrated project team, including manufacturing and clinical supply, succeeded in collaborating on a short-term solution, while the clinical supply team and the QP provided guidance to the customer on how to revise the label for future use. The extra work and delay could have been avoided had the QP been engaged at an earlier stage in the project and been able to provide input into the development of the label text.

The second case examines the importance of QP input in early phase clinical manufacture (**Figure 4**). This case involves an early-phase GMP production using a non-validated process,

Figure 5: The benefits of direct communication between manufacturing and supply teams.



which had to be paused when an unexpected observation was made. In this situation, the customer, scientists, and manufacturing team came together to discuss how to proceed. This led to the proposal of two possible routes forward. Since the product was going into the EU as well as the US, the decision was made to also consult a QP. Of the two possible routes, the QP approved only one.

By taking the approved path, the product was released in a timely manner without delays. Had the QP not been consulted and the other path chosen, then the result might have been quite different, incurring significant delays or, in the worst case, requiring another production run to generate clinical supplies for Europe.

Clinical Packaging, Kitting, and Labeling

Phase-I packaging and labeling is relatively simple with a small number of clinical sites. However, complexity can quickly escalate, and there is a need to plan for subsequent stages and ensure that appropriate support is in place. At this point, the advantages of working with an integrated supplier stem from the fact that the relationship between customer, manufacturer and clinical supply is already established, with the whole team engaged in the success of the project, which positions them to proactively collaborate. Some of the synergies provided through using an integrated supplier are shown in **Figure 4** and, drawing on Catalent's experiences, following successful collaborations for packaging, kitting, and labeling reinforce these.

The first example focuses on the development of a pediatric formulation and illustrates how the clinical supply services group supported the manufacturing organization during production of a liquid formulation in a bottle. In this instance, the customer had contracted a secondary vendor to undertake the packaging, labeling, and shipping. When it was close to production time, that vendor provided example inserts for the cartons and it became clear that these would not protect the product from breakage. Thanks to the close relationship between manufacturing and clinical supply services teams, they were able to quickly source new and more robust packaging and complete the production on time. This direct communication between the manufacturing site and packaging experts allowed production goals to be met.

The second example involves a labeling challenge where a customer required primary packaging and labeling of a small quantity of drug product to support early-phase clinical trials. Given the small scale, the manufacturing site could easily fulfil the packaging requirements, but the labeling requirements were more complex. Because the drug product manufacturer had a relationship with the clinical supply services team, the manufacturer was able to reach out to the clinical supply team to assist with label design and printing, which enabled labels designed and printed in clinical supply to be shipped to the manufacturing site. The ability to leverage the integrated clinical supply team meant that everything was completed in time to meet customer and clinical timelines. This also allows the clinical supply team to develop a relationship with the customer early in the clinical life cycle, which can assure the customer that they have a supplier capable of delivering further support as the trial becomes more complex with additional labeling needs.

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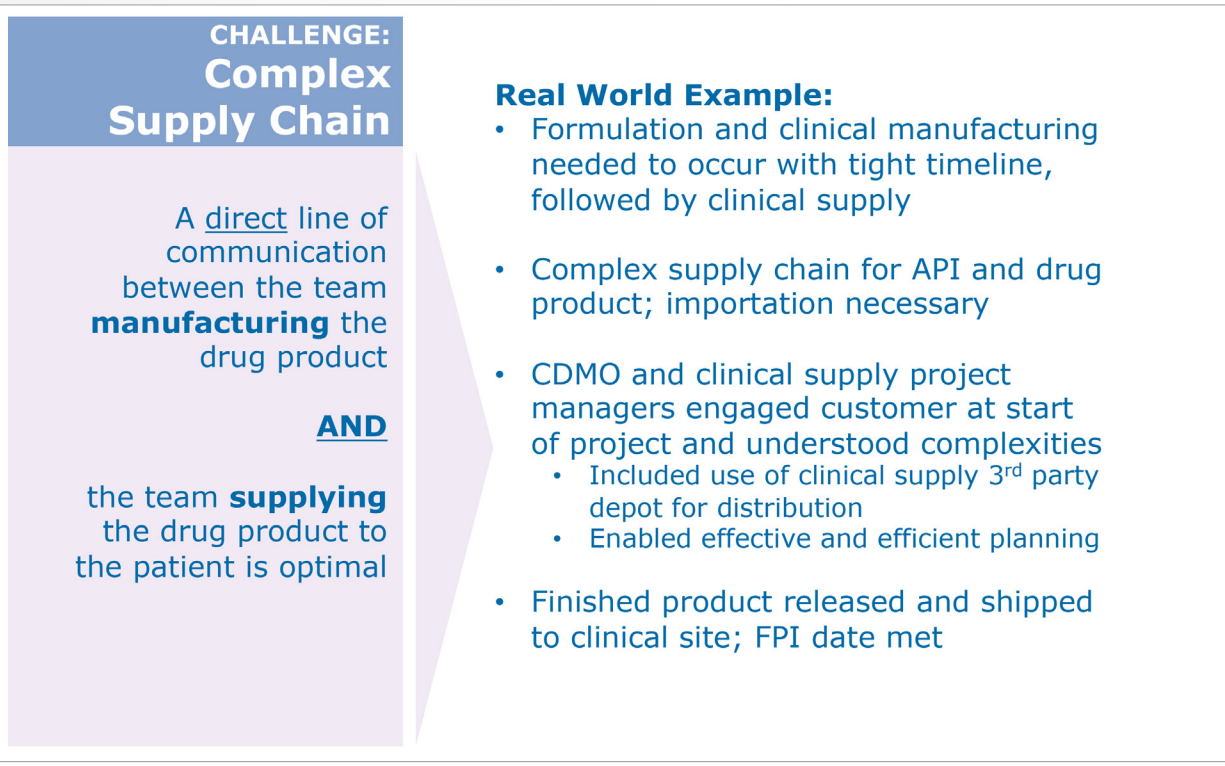
Clinical Supply Chain Execution

The storage and resupply part of the development lifecycle should not be overlooked, even though this comes at the end of the process of getting the drug to the patient. If an integrated team has been established with visibility of the manufacturing resupply schedule and ongoing clinical supplies, then it becomes easier to plan efficiently to ensure appropriate supplies are ready for patients as a program progresses through its clinical lifecycle, regulatory approval, launch, and eventual commercialization (see **Figure 5**).

Figure 6: Successful clinical supply-chain execution.



Clinical supply chain execution can be critical in meeting customer and clinical milestones. The example in **Figure 6** shows how an integrated project team with direct communication between drug product manufacturing and clinical supply was key to success. The project managers for manufacturing and for clinical supply were engaged with the customer from the start. Their efficient working together resulted in product being released and shipped to the clinical site in time to meet the important milestone of first patient initiation.

Conclusion

The importance of taking a holistic view of product for the clinic is clear, and there is an evident need to engage subject matter experts throughout the development process. Different viewpoints can produce very different solutions, so all parties must communicate and collaborate early and often.

An integrated group with established interpersonal relationships provides the necessary expertise and support while helping to streamline operations, avoid over-complication, and minimize handoffs. Often, it is the small details that cause the biggest problems down the road and integration is key to reducing overall risk. Building strong relationships now delivers a personally invested team to shape future development.