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CROs and OIP development

Why you may want to integrate a contract research organization into the development process for your orally inhaled product (OIP)

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Bringing any new pharmaceutical product to market presents many different challenges in meeting technical and regulatory expectations for demonstrating safety and efficacy over the course of the development process. As combination products with a significantly greater number of variables than solid dosage forms, orally inhaled products (OIPs) place major demands on developers and require highly specialized knowledge and equipment.

The development of OIPs presents significant technical challenges in that OIPs must overcome the patients' natural defenses designed to prevent small particles from entering the lungs. The variability introduced by the use of a delivery device that provides an interface between the patient and the formulation offers further challenges, requiring extensive characterization of the device/formulation combination. Numerous additional variables, ranging from raw material particle size distribution to environmental conditions, affect product performance.

Significant delays in product development can occur during the characterization process due to the need to solve scientific problems or because of resource limitations when staff or equipment requirements exceed what the sponsor site has available. As a result, a pharmaceutical company investigating a new orally inhaled drug (the drug's sponsor) may benefit by integrating a contract research organization (CRO) into the development process to supplement the basic analytical expertise available in the sponsor laboratory. The spectrum of offerings from various CROs encompasses the entire range of activities for OIP product development, and sponsors also have the option of working in parallel with a CRO on various activities.

Early phase formulation development

The first step of formulation development requires the sponsor's understanding of the target patient population, the site of action (local or systemic delivery), and the drug's physicochemical properties prior to consideration of formulation approaches. At the very early phases of development, the sponsor may not have a clear idea of which inhalation dosage form will prove ideal for the product.

Sponsors often prefer to formulate drugs as aqueous solutions for nebulization for the purpose of proof of concept studies since these formulations offer easy preparation with minimal equipment requirements. However, extended dose delivery times and issues with nebulizer portability make solutions for nebulization relatively unpopular with the target patient population, so the sponsor may find a pressurized metered-dose inhaler (pMDI) or dry powder inhaler

(DPI) easier to market. Having the ability to test formulations for all three delivery forms in order to determine which form represents the best therapeutic benefit with the best marketability requires a significant investment in laboratory equipment, particularly for pMDI filling (Table 1).

When the sponsor lacks the specialized equipment and/or the expertise to perform the necessary studies, a CRO can be an ideal partner, providing both technical guidance to navigate the complexities of these formulations and the equipment for preparation. Even if a sponsor has full capabilities to prepare multiple dosage forms, conducting the necessary formulation screening studies to identify a lead and a back-up formulation for a compound can generate a large number of samples, placing a large workload on a small group of formulators/analysts. Engaging a CRO to participate in this process can greatly increase the number of formulations prepared, analyzed, and evaluated following short term storage.

In addition, utilizing a well-staffed CRO in early stage development eliminates the potential for multi-lab variability while providing sufficient analytical resources to support expanded formulation development activities in later stage studies. In many cases, where analytical methods have not been optimized, which is often the case, results are likely to vary between laboratories. Testing a related series of formulations in a single laboratory provides assurance that any differences in method performance between formulations are relative, and sponsors can further evaluate those formulations that best meet target profile requirements in their own laboratories.

Product characterization studies

Regulators require a number of characterization studies for inclusion in the regulatory dossier as a product moves through early phase development to clinical trials. For OIPs, as for any pharmaceutical product, this work includes stability studies for the drug substance as well as for the formulated product to understand the impact of storage under stressed conditions. Additionally, guidance documents for European, US, and Canadian registrations require studies to understand the product performance over a number of patient- and device-related variables (Table 2). These additional studies reflect the potential effect on product performance of factors such as misuse and cleaning scenarios, as well as environmental exposure factors.

Sponsors may find it difficult to justify the cost of obtaining the required equipment and experience to conduct one-time characterization studies. For example, the purchase, qualification, training, and maintenance costs for a laser imaging system to evaluate the plume geometry of the emitted aerosol from a nebulizer or pMDI will likely cost many times more than the cost of contracting with a CRO to develop and validate a method and to complete sample analysis. In addition, some studies, such as a patient simulation study or bioequivalence studies for generic drug development require a substantial commitment of resources, and the sponsor laboratory may have difficulty staffing this work among other internal project priorities.

CROs have the ability to accurately budget and schedule characterization studies, which are gener-

Table 1

List of standard equipment for development of OIP dosage forms

Analytical equipment for OIP testing	Formulation equipment for OIPs
Inertial cascade impactor	Crimper, circulation pump, and pressure filler for pMDIs
Airflow controller as described in USP <601>	Blender for powder mixing
Laser diffraction instrument	High shear mixer for suspension mixing
Dose uniformity sampling apparatus described in USP <601>	Dispenser for powder metering
Plume geometry and spray pattern system	Pressure vessels for formulation
Calibrated airflow meters	Glovebox to accommodate potent API work
Photomicroscopy for formulation and component analysis	Pressure burette for small scale formulation
Breath simulator for nebulized products	Lab scale micronizer and/or spray dryer for particle size reduction/formation

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ally well defined, and they can provide sponsors with feedback on the state of the analytical methods, identifying areas in the methodologies that might require optimization or further development, which may be especially valuable for sponsors without OIP experience. The CRO may provide guidance, for example, on the selection of a cascade impactor for aerodynamic particle size testing. Developing proper analytical methods at this point in the process, while sponsors still have time to make changes before final validation, will prove invaluable.

In particular, extractables and leachables characterization, which has received increased attention in recent years, requires specialized knowledge and understanding of regulatory acceptable analytical approaches and objectives, making it ideally suited for a contract laboratory that routinely performs this type of development. For these studies, analysts must first perform controlled extraction studies of critical device components for volatile, semi-volatile, and non-volatile extractables to identify which extractables to monitor as potential leachables in the drug product. At that point, analysts must develop and validate leachable methods, which are then used to monitor leachables throughout the expected shelf life of the product.

Late phase studies

Most sponsors lack sufficient analytical staff and the necessary equipment to perform the stability testing required for OIPs. For starters, aerosol testing at the 3-, 6-, and 12-month timepoints may require as many as 10-15 experienced analysts. Furthermore, testing for some OIPs requires temperature- and humidity-controlled rooms that provide critical reductions in variation and/or bias in results due to fluctuations in laboratory conditions that can affect particle/droplet size characteristics of the emitted aerosol. A single room providing space for four test stations costs about $100,000 plus operating costs.

Stability testing of OIPs also requires a relatively large amount of storage chamber space compared to traditional dosage forms. A typical pMDI package, for example, measures 1.5” x 2.5” x 4”, so a registration stability study for 3 lots of this product, stored in two orientations at 3 standard temperature/humidity conditions would require more than 56 cu ft of chamber space at stability initiation. For comparison, a registration stability study for a solid oral dosage product, such as tablets contained in 30 cc bottles, would

Table 2

Characterization studies for OIP products

MDI	DPI	Products for nebulization
Dose proportionality■	Dose buildup and flow resistance■	Photostability●
Effect of varying flow rates■	Dose proportionality■	Drug delivery rate and total drug delivered from nebulizer●,▲,*
Microbial challenge■	Effect of orientation■	Particle/droplet size from nebulizer●,▲,*
Plume geometry■	Effect of patient use■	Performance after temperature cycling●,▲,*
Accessory drug deposition■,▲,*	Photostability■	Preservative effectiveness●,▲,*
Cleaning instructions■,▲,*	Priming■	Compatability▲,*
Performance after temperature cycling■,▲,*	Cleaning instructions■,▲,*	Shaking requirements▲,*
Resting time, priming, re-priming■,▲,*	Device robustness■,▲,*	
Profile near exhaustion■,▲,*	Effect of moisture■,▲,*	
Effect of moisture▲,*	Effect of varying flow rates■,▲,*	
Fine particle mass with spacer▲,*	Fill weight■,▲,*	
Low temperature performance▲,*	Profile near exhaustion■,▲,*	
Minimum fill▲,*	Accessory drug deposition▲,*	
Robustness▲,*	Single dose fine particle mass▲,*	
Shaking requirements▲,*		
Single dose fine particle mass▲,*		

■ = See reference 1
● = See reference 2
▲ = See reference 3
* = See reference 4

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require less than 1 cu ft of chamber space.

The actual volume necessary would include additional volume for storage containers and for air flow allowances in stability chambers, as well as room for reserve samples for confirmatory testing. Additionally, study designs defining more than two storage orientations and/or more than one packaging configuration will require even more storage space, requiring a significant investment.

For pharma companies with a large number of respiratory products in their pipelines, investing in the specially equipped laboratories and personnel with the required scientific knowledge base necessary for development of OIPs may or may not be cost effective. For smaller companies, the cost of in-house development is likely prohibitive. In either case, engaging a CRO with established OIP capabilities for any or all of the development work can reduce costs while ensuring access to the most up-to-date analytical techniques and equipment.

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