Outsourcing inhalation product development

Why companies are looking for product development partners, how the process works, and what to look for in a CRO.

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Until fairly recently, most large, fully integrated pharmaceutical and biotechnology companies liked to keep all aspects of product development and manufacturing in-house, under direct control of the company. Today, however, we estimate that the industry spends nearly one dollar out of every five on outsourced services, and Big Pharma has joined smaller companies in turning to contract development. In some areas of development and manufacturing, as much as two thirds of all of a company's expenditures on an inhaled product may go towards outsourcing. And with the substantial growth of specialty, emerging, and virtual pharmaceutical and biotechnology companies, partnering for mission critical expertise and services has become the rule rather than an exception.

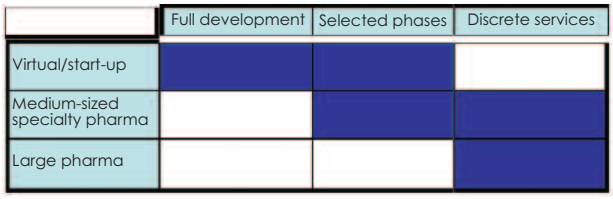
Why are more and more pharmaceutical companies turning to outsourcing partners for inhalation development and manufacturing? One reason has to do with the diversification of the market for inhalation products in recent years. Since its introduction, inhalation therapy has mostly focused on the topical delivery of drugs to the nasal and pulmonary airways for the treatment of diseases such as asthma, chronic obstructive pulmonary disease (COPD) and seasonal/allergic rhinitis. By 2006, according to reports from Frost & Sullivan and Datamonitor, the value of product sales in this market segment exceeded $25 billion, and continued growth is forecasted.

Much of that continued growth is taking companies beyond their well-established expertise in drugs for the treatment of pulmonary diseases. After the 1987 Montreal Protocol, pharmaceutical companies devoted nearly two decades to the long and arduous journey through the transition from the use of CFCs to HFA as a propellant for MDI products. Development work focused mainly on what were essentially line extensions of existing products. Now, with the transition to HFA nearly complete, companies are turning their attention to other treatment areas. Although the development and production of several inhaled insulin products has now been dropped, the approval of Pfizer and Nektar's Exubera in 2006 demonstrated the potential for successful development of inhaled products in new areas. Clinical trials are underway for inhalation and nasal products to treat conditions as diverse as obesity, breakthrough pain in cancer patients, and Alzheimer's disease.

Despite the substantial interest in the use of inhalation and nasal delivery platforms for a variety of drugs, few pharmaceutical and biotechnology companies today have the in-house expertise or intellectual property necessary for timely and cost effective development. Whether they involve new chemical entities (NCEs) or existing drugs reformulated for delivery with an inhaler or spray pump, these products generally present much more complicated development challenges than do solid dosage forms, injectables, and even the standard inhalables like salmetrol and fluticasone. Depending on the size of the pharmaceutical company and its experience with inhaled products, it may turn to a contract research organization (CRO) for help with one aspect of development or complete development all the way from feasibility studies to commercialization (Figure 1).

Figure 1

Typical outsourcing demographic



In addition to traditional development and manufacturing considerations, inhaled products also require device characterization and selection. In many cases, an entirely new device must be designed, or an existing platform must be modified to work with a specific formulation. Optimization of product and process, process scale-up and generation of a submission-ready regulatory package can also require skills and knowledge not available at traditional oral or injectable product development organizations. With development of inhalation products for NCEs taking about 5-6 years and costing millions of dollars, a pharmaceutical company's relationship with the CRO it works with is critical.

By choosing the right outsourcing partner, companies can often gain access to valuable expertise and experience across a broad range of inhaled dosage forms, allowing parallel development or format optimization for the target disease state and patient population. A drug delivery company looking to develop products around its technology in addition to out-licensing its intellectual property to large pharmaceutical companies may not be looking for a CRO to take the product or technology through full development to regulatory submission, but may simply seek a data package to demonstrate the technical and/or clinical proof of concept to illustrate the value of their asset. For companies looking to commercialize their own products, a CRO with the infrastructure and expertise to take a development forwards beyond very simple studies, with experience in overcoming the high regulatory hurdles, having cGMP capability, and possibly having the infrastructure for commercial manufacturing is probably the best bet.

A CRO with complete development and manufacturing capability for metered dose inhalers, dry powder inhalers, nasal spays, and solutions and suspensions for inhalation has the ability to partner with a company at any point in the development process from feasibility to commercialization (Figure 2). Services will include formulation and device screening along with the development of chemical and performance methods. Later in the process, the formulation and analytical teams will work closely with the manufacturing team to perform process scale-up and optimization, while the analytical team optimizes and validates methods and provides analytical process support. Once in production, raw materials, manufacturing, materials handling and analytical teams will work together to deliver clinical batches. The analytical and stability teams are then ready to perform the supporting stability studies.

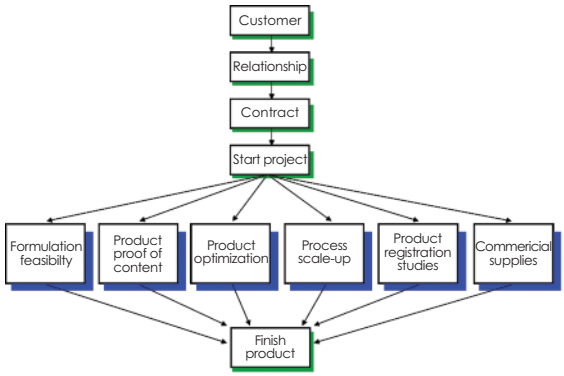
Although outsourcing any or all stages of product development to one contract facility has many advantages, including having to manage only one CRO and efficient sharing of information and technology throughout the process, customers may come to a CRO with projects at various stages of development and require the CRO to pick up their projects seamlessly and progress from there on out. As an example, customers may conduct early feasibility studies internally or with providers that ultimately do not offer the services necessary for continued development. In these cases, the CRO must be sufficiently agile to respond rapidly to both individual customer and individual project needs. The first step for the customer, therefore, is to evaluate the offerings of various CRO providers to understand how their capabilities align with the type of work being outsourced.

During the selection process, teleconferences and site visits with the CRO are valuable in assessing capabilities. These activities are typically managed through the CRO's business development groups and involve establishing some form of a mutual confidentiality agreement to allow both parties freedom to exchange the necessary information to build an effective relationship. Most often it is the business infrastructure within the CRO and working relationship between the customer and CRO that will determine the success or failure of a particular venture. That said, development is development, and even with the best laid plans the unexpected can happen. In such instances, aside from technical expertise and the experience of having seen such issues previously, the real value that the CRO can bring to such situations is the ability to effectively partner with the customer to work through any problems proactively, efficiently, and with open and honest communications to a successful conclusion.

Defining the project scope, including information such as the dosage form, the number of product strengths to be developed, the phases of product development

Figure 2

Interactivity of business and product development processes in outsourcing relationships



Stages of a typical product development project

Feasibility

Determine feasibility of developing formulation in the requested dosage form(s).

Objectives:

- Evaluate/screen formulation options
- Establish analytical methods
- Provide materials for early pre-clinical studies (if requested)

Product Proof of Concept

Establish product concept for pre-clinical and early clinical studies (Phase I and Phase IIa).

Objectives:

- Evaluate formulation compatibility with primary packaging options
- Qualify analytical methods for Phase IIa clinical studies and establish cleaning verification method(s)
- Provide materials for pre-clinical, Phase I and Phase IIa studies (as required)

Product Optimization

Product optimization—all product strengths (API, formulation, packaging) for Clinical Phase IIb studies

Objectives:

- Refine formulation and primary packaging and/or device to achieve product development targets
- Additional analytical methods qualification for Phase IIb clinical studies (if required)
- Provide materials for Phase IIb studies (as required)
- Verify timing of Phase III readiness

Process Scale-up

Commercial-scale process defined for Clinical Phase III/registration batch production

Objectives:

- Validate analytical methods with final product(s)
- Optimize production process
- Scale-up manufacturing process to not less than 1/3 commercial batch size
- Validate cleaning methods for process equipment
- Provide materials for Clinical Phase III/registration studies

Product Registration Studies

Generate supporting data and write product dossier

Objectives:

- Conduct Registration stability studies
- Conduct Developmental Pharmaceutics studies
- Prepare Registration Dossier including stability package
- Validate Full-Scale Manufacturing Process-if required for EU
- Complete validation of cleaning methods for process equipment
- Provide materials for registration stability

Commercialization

Preparation for product launch

Objectives:

- Respond to regulatory deficiency questions and support PAI
- Process validation/Produce commercial launch supplies

requiring support, the development strategy, and timelines will help the CRO to identify the appropriate technical experts needed for development of the contract or quotation for the desired work. In some instances, the CRO can provide technical experts right from the beginning of the process to assist the customer in defining this scope. Once both parties have agreed on a scope, the CRO will generally prepare a proposal for the work that details the key deliverables and the costs associated with each deliverable.

To avoid delay in starting work with a CRO, it is important to get a start on completing the necessary documents early in the business development stage. With all work, standard terms and conditions will require agreement and, in some cases, negotiation between the two parties. With outsourced projects where production of clinical supplies is involved, additional documents such as Clinical Supplies and/or Quality Agreements may be required. For work involving cGMP studies or production of clinical supplies, it is also advisable, where possible, to perform a Quality Assurance (QA) audit of the facility being evaluated to ensure that there are no regulatory concerns about placing work with the selected CRO.

Once the quote is signed and all other necessary legal agreements in place, the CRO will assemble a project team and outline the key program objectives, deliverables, and milestones. They will then establish a project timeline in preparation for project initiation. Following a kick-off meeting with the customer to finalize agreements on the program objectives and project timelines, the actual laboratory work can begin. In planning for success, it is key that both parties agree upon an effective development process that encourages teamwork and a coordinated cross-functional development path for the program, while providing a forum for addressing and correcting any issues within the program as early in the development cycle as possible.

The objective of a well-designed product development process is to facilitate good business decisions and timely management oversight throughout the program lifecycle; to provide the customer with assurance that required tasks, deliverables, and documentation will be completed prior to program maturity; and to provide an essential gating mechanism such that program budgets and resource allocation needs can be examined in a timely manner. By relating functional responsibilities to key program activities, horizontal integration of vertically organized functions is encouraged, resulting in a unified team approach to development.

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