

outsourcing

CMOs enter new era of expertise

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Gone are the days when clients sought help only for "commodity" activities. Today, they seek product-specific expertise, regulatory knowledge, and value-added service. This article presents examples of successful collaborations.

The pace and amount of outsourcing have grown dramatically in the last 10 years. According to a 2011 survey from Pharma IQ, 54 percent of organizations outsource less than half their global manufacturing, while 18.2 percent rely on outsourcing for at least 91 percent of their output.

Historically, contract manufacturing was viewed as a way to reduce costs, and that remains the most important consideration, according to 60 percent of the survey's respondents. But 70 percent cited lack of internal capacity, and 40 percent cited lack of internal expertise as the primary reasons for outsourcing parts of their production.

Those results underscore a trend: Pharmaceutical companies are increasingly turning to contract manufacturing organizations (CMOs) to expedite research and development or to bring products to market more quickly. Those CMOs willing to invest in sophisticated technology and to establish technical capabilities—coupled with in-depth experience in regulatory compliance—are becoming partners who add considerable value to all stages of manufacturing.

This article illustrates how contract manufacturing plays out in real life by looking at some recent projects from the CMO's perspective.

Scaling up manufacturing

A common request of CMOs is to help companies ramp up to commercial production, a job we recently performed for a client who had developed a product in-house. The client had already developed and defined a successful formulation and a blending process at the laboratory scale. The next step was to transfer that formulation and process to our facility, where we could develop it for production and validate the process to support a commercial launch.

The product contained multiple actives in amounts that most people would consider low doses or low potency. In such cases, the formulation and blending process are considered "at risk" because there is a high probability that the product would fail a test of content uniformity. We therefore had to devise a strategy to change the odds in our client's favor.

The key to success with this type of transfer is understanding the regulatory process and how it pertains to

process validation. Until January 2011, when the FDA changed the rules of the game, process validation emphasized the need to collect large quantities of data from validation batches. That information was said to provide strong assurance that a specific process would consistently produce a product that met quality specifications.

The new approach defines each product as having its own unique life-cycle and requires manufacturers to collect data throughout that life-cycle and to evaluate the data constantly and scientifically. This nonstop collection and evaluation—from process design throughout production—provides the scientific evidence that the process can consistently deliver products that meet or surpass the quality standards. For this project, we relied on our understanding of how blend uniformity affects content uniformity (a function of blending speed and blending time). That led us to characterize the process and define the true design space. Here are the basic elements of that work:

- Stage 1: Process design. Gain product and process knowledge and come to understand the sources of variation, which allow us to establish and qualify a true normal operating range.
- Stage 2: Process qualification. Confirm that the process design is capable of reproducible commercial manufacturing.
- Stage 3: Continued process verification. During normal production, analyze the process and product results to ensure the process is in control.

In the example above, API content uniformity was the barometer of success. USP's General Chapter <905> on content uniformity defines an acceptance value (AV) of less than 15 percent as the criterion for releasing the finished product. We have now manufactured more than 100 batches of our client's product, and the AV for the APIs has averaged 4.2 percent and has never exceeded 6.3 percent.

Reducing costs

In contract manufacturing, relevant expertise and product-specific knowledge are major determinants of success and add considerable value to a client's product and overall production efficiency. Consider, for example, our work with a client who wanted to transfer and manufacture its controlled-release product. The client had been manufacturing and marketing the product for quite a while, so its staff had a good deal of experience in formulation, process development, and routine manufacturing.

Now, however, the company sought to perform a routine product transfer that included full-scale process characterization batches (PCBs). These PCBs would confirm the validity of the critical process parameters and re-establish the normal operating conditions for manufacturing.

As our firm addressed process development, our scientists noticed that the product's delivery platform resembled that of other products they had worked on. They were thus able to introduce several process improvements that saved the client from making significant capital investments in unnecessary equipment. We also discovered how the client could reduce raw material costs. But perhaps the biggest savings came from the improved process, which reduced overall product costs by nearly 20 percent. Once these processes were characterized, we manufactured three consecutive commercial-scale batches and placed them on stability. After the successful completion of the stability program, the product and process were validated.

Reducing evaluation and development time

Companies have long recognized the need to supplement their in-house resources with the expertise of specialized, competent partners. Mastering all the techniques available in today's industry is simply no longer an option, especially for small companies. Even large, well-established manufacturers sometimes lack the flexibility to implement and perform critical projects on schedule.

Outsourcing gives companies the flexibility to implement and perform critical projects on schedule.

That's one reason that outsourcing continues to grow: It offers a strategy to advance multiple projects simultaneously. Furthermore, pre-formulation and formulation development are generally labor-intensive, time-consuming pursuits, and screening multiple potential candidates using outside resources adds tremendous value.

Many large companies screen multiple drug candidates, as many as 30 per month, before they conduct early clinical efficacy studies. That kind of volume requires massive internal resources for development and testing. By outsourcing all or some of the work, clients can better manage their development deliverables and meet deadlines.

Identifying value-added services

In the past, how well a CMO performed basic "commodity" services determined who won the business, but today the decision often hinges on which CMO provides the most value-added services. Clients are asking firms what more they can offer in various aspects of the work, and many are seeking turnkey solutions. Among the value-added services of leading CMOs are design, delivery, process development, scale-up, packaging, logistics, and distribution of finished goods.

These services are particularly important to virtual pharmaceutical companies, which lack the infrastructure to undertake even basic operations. In fact, virtual pharmaceutical companies depend on CMOs for almost all of their development, scale-up, and manufacturing needs. Many of these companies prefer to consolidate and man-

age their supply chain through a single CMO and seek to build off the CMO's expertise—from sourcing raw materials and conducting qualifications to providing product packaging and distribution.

One virtual pharmaceutical company with whom we worked was seeking to re-invigorate a branded product it had acquired and asked us to help with the relaunch. That meant providing a turnkey solution: redeveloping and improving the product design and formulation, manufacturing the product, providing packaging design and labeling, and delivering it to retailers.

Formulators can help re-invigorate mature products.

Our manufacturing team started by reformulating the product and reassessing the appearance of the tablets. The original tablets included a black ink logo that was applied using a difficult, slow, and expensive process. Once we redesigned the process, the tablet punch applied an embossed logo, a faster, less expensive approach that presented the logo more clearly. Our addition of a translucent coating gave the tablets better color and a sleeker, more modern appearance.

In addition, our on-site creative services team worked with the client to design and develop the product's label and packaging. Those are important tasks because the label must satisfy the FDA's requirements, and the package must appeal to consumers, increase awareness, and help boost sales. In this case, we packaged the product in our cGMP-compliant facility and sent it directly to retailers.

Conclusion

Contract manufacturing is not only here to stay, it has become essential to many companies' drive to streamline their R&D and manufacturing strategies. That is a big change from the days when companies turned to CMOs for cost efficiencies. Now they are seeking CMOs that offer the experience, equipment, and expertise that allow modern manufacturers to minimize their own capital costs by taking advantage of the manufacturing and packaging expertise of a partner organization. *T&C*

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