FDA’s quality-by-design initiative is gradually reshaping the paradigm for pharmaceutical manufacturing and the opportunities and challenges in outsourcing.

The US Food and Drug Administration’s quality-by-design (QbD) initiative, a science- and risk-based approach to manufacturing, adds another layer to the relationship between sponsor companies and contract manufacturers. Enhanced process understanding is at the core of QbD, which is deepening the nature of outsourcing.

A regulatory framework
At one level, QbD simply extends the collaborative nature inherent in an outsourced relationship. "Contract manufacturers can apply the same mindset to process development and manufacturing as the sponsoring company. We encourage the use of quality risk management for both design of the process-control strategy as well as for life-cycle management," says Christine M.V. Moore, acting deputy office director of the Office of New Drug Quality Assessment in the Center for Drug Evaluation and Research at the US Food and Drug Administration. "A large part of a QbD approach is enhanced understanding of the product and process. This understanding should be openly communicated between the contract manufacturing organization and the sponsor such that good science and risk-based decisions can be made."

A sponsor-company perspective
As drug companies adopt QbD in their own development and manufacturing, their expectations of contract-service providers are changing. "There are several possible scenarios in which a QbD approach to development can impact the relationship between a sponsor and a contractor," says Mary Oates, vice-president of global quality operations at Pfizer Global Manufacturing (New York). The first scenario is when the sponsor is fully responsible for development and transfers the final process to the vendor. A second scenario would be when the sponsor and firm collaborate on the development effort.

Under the first case, sponsors historically have interacted with contract-service providers to address quality, supply, and technical needs and may also engage in continuous improvement activities. "These items will continue to be important, but QbD will require far greater collaboration, beginning with the technical transfer and continuing as long as the contract-service providers manufacture for the sponsor," says Oates.

She offers an example of that greater collaboration and the continual need to garner process understanding under QbD. "For example, the contract-service providers must have full access to development data in order to understand the allowable design space, and if and when changes can be made within this design space, to ensure the product remains consistent," she says. "Once routine manufacturing begins, every lot that is manufactured becomes part of the overall body of knowledge, and the data collected must be assessed to verify that the product and process are performing as expected. This involves much more analysis than simply comparing results to a list of specifications. The contract-service providers must be capable of performing and interpreting this analysis in a routine manufacturing environment, alerting the sponsor to any changes observed and ensuring that required adjustments to the product or the process are implemented."

For the second case of when a sponsor company and the contract-service provider partner on the development effort, Oates offers an example of a recent QbD project between Pfizer and a contract-service provider. "The contract-service provider determined the critical attributes of a functional excipient in the drug-product formulation and their impact on product performance," she says. This information was used to determine the specification for the material. The contract-
service provider also used computational fluid dynamics to model the spray-drying process and engineering models to take it to commercial scale. Designs of experiment for several unit operations were also completed by the contract-service provider. "Most importantly, scientists from the contract-service provider were vital members of the development team and routinely participated in key meetings," she adds. For example, they were also given author access to the documentation system, so they could directly write their sections of the regulatory submission. "This extent of collaboration, where the contractor is a true partner in the development process, is unique in our experience," says Oates. "However, it is likely to become more common as the adoption of QbD accelerates, and outsourcing of development efforts due to technology or cost-drivers increases."

**Vendor selection.** QbD comes into play not only in the execution of an outsourced project but also in vendor selection. "Material characterization and identification of significant quality attributes of raw materials (both drug substance and excipients) is an important aspect of process understanding," says Oates. "In some cases, vendors are willing to work with the sponsor to provide extensive material-characterization data. This is often the case if the vendor is supplying a new or unique material, but may not be the case for commodity items. Once the necessary quality attributes are identified, vendors who can routinely supply acceptable material must be qualified for use. If API manufacturing is outsourced, the sponsor must understand and include known critical quality attributes into the purchasing and quality agreements. Finally, if a drug product developed using QbD, perhaps including a novel technology and control strategy, will be outsourced, the vendor must have the technical sophistication and quality systems to effectively manufacture and test the product."

**Supplier performance.** QbD also has the potential to change supplier metrics. "Although typical measurements will still be used to evaluate supplier performance, additional ones will be added," says Oates. "These may include the ability of the supplier to control the product and process by effectively using the design space; the supplier's commitment to continuous quality verification by evaluating and communicating to the sponsor the process data that is generated by all lots; and the supplier's willingness to facilitate regulatory changes to modify or enlarge the design space as allowed by the data."

**Contract manufacturers' views**

Contract manufacturers also recognize the changing expectations of sponsor companies. "Applying the principles of QbD requires an holistic approach to drug development and manufacturing, both for contractors and pharmaceutical companies," says Ian Elvins, executive vice-president of global quality at Lonza (Basel, Switzerland), a contract manufacturer of small-molecules and biologic-based APIs. "Therefore the principles of QbD can be and should be applied throughout the life of a drug from familiarization and development through qualification, validation, and production. The QbD approach will be used to streamline development, to identify potential risks, and to develop ability in products and processes. The risk assessment allows us to tailor the process development work to the goals needed at a specific point of a product's and process's life cycle. As an API runs through the phases of its life cycle, the process knowledge grows together with the increasing needs for information."

Lonza is adopting the principles of QbD for both chemical and biologic APIs. It recently made two bolt-on acquisitions to enhance its technology positions and QbD capabilities for biopharmaceuticals. In November 2009, it acquired Algonomics (Gent, Belgium), a contract research organization providing immunogenicity screening platforms. In 2007, it acquired AggreSolve, which provides an in-silico protein analysis platform to solve problems associated with protein aggregation. "The Algonomics and AggreSolve technologies enable us to identify drug safety or manufacturing challenges early on, which provides the opportunity to address them and create safer and more cost-effective products," says Elvins.
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By Patricia Van Arnum

Other contract manufacturers further point to the deepening of the outsourced relationship. "QbD helps inform API selection, drug formulation, and manufacturing processes upfront, potentially resulting in better, more optimized drug design," says Jan-Olav Henck, senior director of scientific operations at Aptuit (Greenwich, CT), a contract manufacturer of APIs and finished drug products and a provider of formulation-development services. "Rather than changing the relationship between sponsor companies and their outsourcing partner, QbD aligns well with outsourcing relationships based on scientific expertise that generates high-quality data that can then be strategically applied to the drug-development process."

As an example, Aptuit recently developed a solid-state chemistry production screen. "The production screen applies the practical application of advanced theoretical developments to increase our understanding of APIs and drug formulations," says Henck. "We're able to characterize the proclivity to change a compound when introducing mechanical pressures, and we apply that information to contribute to the development of safe and effective drugs by enabling reproducible and predictable performance at critical interfaces in the drug-development process."

Ash Stevens (Detroit, MI), a contract manufacturer of APIs, also points to how its approach is aligned with QbD. "After the basic process is identified, we can perform parametric studies to identify or confirm the critical process parameters," says Gary A. Baker, vice-president of quality assurance and regulatory affairs for Ash Stevens. "We can use the information obtained to perform process optimization. We can then perform one final set of experiments to challenge the process to demonstrate that purity and quality will be maintained at the extremes of the critical parametric ranges. When the process transfers to manufacturing, we continue to build a lot history to keep the process under control. We can insert 'alert-limits' and 'action-limits,' tighter than those limits in the regulatory filing, to make us aware of undesirable trends."

Others point to the value of QbD. "QbD encourages use of in-process controls to reduce risk," says Carl I. Oberg, president of Pharma Tech Industries (PTI, Royston, GA), a contract provider of manufacturing and packaging services for prescription and over-the-counter drugs. As a contract manufacturer, PTI already uses in-process testing as a control mechanism to ensure quality products prior to quality-assurance release testing and to reduce the risk of further stage processing of materials that may be compromised. However, we are seeing more customers willing to entertain the idea of in-process testing and statistical process control to ensure the lot being produced is of the optimal quality throughout the lot."

Risk mitigation is one benefit of in-process testing and provides a business case for QbD. "Incorporating more in-process control mechanisms that give real-time feedback should reduce risks," says Oberg. "In-process controls not only ensure a quality product, but also reduce financial risk associated with high-cost excipients and active pharmaceutical ingredients. We do see the pharmaceutical industry evolving into this approach and feel that contract manufacturers will need to participate in order to assess the best approach for process monitoring and correct sample sizes. This approach is not only good for the quality of the product; it is also good business sense."
On the horizon...

Batch manufacturing prevails for active pharmaceutical ingredients, but in the future how viable is continuous processing? Continuous processing lends itself to in-process monitoring and is compatible with the US Food and Drug Administration’s process analytical technology (PAT) initiative and move to a science- and risk-based approach under quality by design (QbD). Here are some perspectives.

Jan-Olav Hend, senior director of scientific operations at Aptuit (Greenwich, CT): “Parallel synthesis and continuous manufacturing, as related to APIs, absolutely has a future in the industry. It is just a matter of determining how to effectively use data to inform new processes and process conditions to maintain control of identifying information and regulatory requirements. Other industries’ abilities to move from batch-manufacturing processes to continuous manufacturing are much more straightforward than it is for the pharmaceutical industry, but I am confident that as an industry we can adapt to enable the increased productivity we all strive for. Regulations surrounding drug development and the ways in which we are required and accustomed to documenting regulatory submissions are centered on a batch-manufacturing approach, particularly as it is related to identifying specific batches that are called into question. PAT will be absolutely critical for releasing material and maintaining and enabling the necessary data for identification purposes.”

Dominique Robarge, head of business development of microreactors at Lonza (Basel, Switzerland): “Lonza is one of the leaders in continuous flow and microreactor technology, and we believe these technologies will be a significant part of our industry’s future. In addition, we developed a complete microreactor toolbox that totally avoids the concept of parallel synthesis and is applicable from Phase I to Phase III clinical products. Highly consistent and robust processes were recently demonstrated on a large-scale, 2-ton campaign. Where microreactors have an advantage over batch manufacturing, it will be applied. To develop the products and processes using microreactor technology, the QbD concepts and PAT tools will be used where needed.”

Gary A. Baker, vice-president of quality assurance/regulatory affairs for Ash Stevens (Detroit, MI): “We see the potential to yield high-quality product at a significantly reduced cost over batch processing at scale. In addition, processes that may be extremely hazardous at scale have the potential to be conducted much more safely.”
In keeping with a quality-by-design (QbD) model, the International Conference on Harmonization (ICH) Q10 Pharmaceutical Quality System guideline specifies the modern quality systems needed to establish and maintain a state of control that can ensure the realization of quality drug product and facilitate continual improvement over the product’s lifecycle. The guidelines of ICH Q10 also extend to the control of any outsourced activities and the quality of purchased materials, including incorporating quality risk-management.

“A pharmaceutical firm must have a strong quality system in the area of outsourcing to protect the patient. This is true regardless of whether a traditional or a QbD approach is used for development and manufacturing,” says Mary Gates, vice-president of global quality operations at Pfizer Global Manufacturing (New York). As a result of Q10 and recent public events related to drug supply chains (i.e., heparin, melamine), firms are obliged to review the controls they have in place and ensure they are as strong as possible. This may result in the need for strengthened agreements between the firm and the contractor; more and longer on-site visits to monitor contractor performance; and enhanced due diligence to ensure that the contractor is an acceptable partner.”

Consequently, increased collaboration is needed between the parties across the supply chain. For example, a firm may wish to audit a drug product contract manufacturer’s active pharmaceutical ingredient supplier. This has traditionally been handled by assessing the contractor’s controls over their suppliers. The pharmaceutical firm must be satisfied that it has sufficient knowledge of the supply chain to ensure patient safety.

To help pharmaceutical companies as well as contract manufacturers better understand these guidelines, FDA expects to hold ICH-sponsored training on Q10 (Pharmaceutical Development, Q9 Quality Risk Management, and Q10 guidelines) some time in mid-2010. These forums and workshops are general for all of the pharmaceutical industry, including small and large pharmaceutical companies, generic-drug companies, and contract manufacturers.

For a web exclusive on FDA’s perspective on ICH 10 and contract manufacturing, see www.PharmTech.com.