



Embracing Quality by Design

Applying QbD concepts can help CMOs create value

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THE PHARMACEUTICAL INDUSTRY is buzzing about Quality by Design (QbD). To date, most contract manufacturers have stayed out of the discussion, assuming that the phrase has little to do with their role. In reality, applying the principles underlying Quality by Design can differentiate contractors from competitors, strengthen the contractor/client relationship and make it possible to establish a business plan for products, processes and facilities. What's more, the contractor can realize these benefits regardless of whether the client files a risk-based or a conventional New Drug Application (NDA).

An Option for the Industry

In essence, QbD is a systematic approach to attaining desirable quality through careful evaluation of all attributes that charac-

terize product quality from early development through the entire product lifecycle. Its goal is to assure the product's identity, purity, quality and potency as they relate to efficacy for the sake of the patient. During all pharmaceutical development, studies are conducted to establish the appropriate dosage form, formulation, process and quality attributes. QbD dictates that

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the information compiled during those studies should be used to determine the formulation- and process-critical parameters as well as supportive elements — including facility operation and design.

Currently, QbD is an optional approach for filing NDAs. The Food and Drug Administration (FDA) has opened the door to QbD filings in hopes of moving toward what Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research (CDER), describes as, "a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight."

Moheb Nasr, director of FDA's Office of New Drug Quality Assessment, has said, "The desired state will be realized upon the implementation of Quality by Design to product and process design and development and establishing robust quality systems." Recent guidance supporting the current trend toward QbD includes Current Good Manufacturing Practices (CGMP) for the 21st Century and the International Conference on Harmonization (ICH) New Vision and Quality Strategy. The guidance, however, is not very specific in terms of implementation. What framework there is for QbD can be found in ICH's Q8 and Q9. Similarly, Q10 provides the underpinnings for pharmaceutical quality systems. Q8 addresses collection of necessary knowledge, and Q9 addresses applying the collected knowledge to manage risk. Q10 addresses the need for systems to maintain the process, the facility and, ultimately, product quality throughout the product lifecycle. Implementation of these three concepts supports an efficient, cost-effective QbD-based facility as much as they support a QbD NDA.

Business Benefits

When implemented well, these components of QbD — knowledge capture, risk management and quality systems — can deliver a number of business benefits to the sponsor and the contractor, and ultimately benefit the patient.

- More accurate planning allows greater supply chain reliability and predictability, which drive down the cost of goods. This can result in better product pricing and increased availability.
- Effective knowledge management makes it possible to work smarter — and faster — to make new therapies available sooner.
- The ability to use innovative new technologies accelerates change and enables a proactive product lifecycle marketing plan.
- Better-defined processes lead to better facilities, which can improve product reliability and reproducibility.

For the contractor specifically, a QbD orientation can provide a formal framework that makes it easier to leverage existing knowledge capital when approaching potential new projects. In other words, QbD can help the contractor turn its inventory of knowledge surrounding a class of compounds, for example, into a marketable asset. Drawing on knowledge

gained from experience, the contractor can move more quickly on the client's behalf.

Despite the many potential benefits, the industry has not been quick to embrace QbD. It is not yet clear how much flexibility regulators will offer, particularly since they have not outlined a clear path for filing beyond the high-level discussion in Q8, Q9 and Q10. In addition, a QbD filing requires a significant level of data sharing. (Although, in reality, the data must be made available for review if requested, even for a traditional filing.) Finally, planning for a QbD filing requires significant investment of time and effort to coordinate information early in development, before it is clear whether the investigative product will ever make it to market launch. With such questionable payback, sponsors may not drive demand for QbD from contractors.

Still, contractors can benefit from staying ahead of the curve and using QbD concepts to take a proactive approach to meeting customer needs. The contractor has numerous opportunities to add value by helping the client organize information. QbD requires a solid base of knowledge of the drug substance specifications, including physicochemical properties, excipient interactions, raw material characteristics and variability — and how all those elements support or detract from the ability to reach the target product profile, or "desired state." A contractor who can design a program that will achieve the desired state cost effectively is a valuable partner. In return, the contractor who has a clear picture of the anticipated product lifecycle — the marketing plan as well as the clinical / marketed dosage form design — will have solid information upon which to determine and manage project scope, including facility design and capacity needs.

Whether the sponsor plans to file a conventional or QbD NDA, the components are fundamentally the same, but with a slightly different emphasis on the type of knowledge gathered. QbD requires an understanding of the mechanistic properties of the product and process rather than on empirical knowledge. This knowledge is captured, recorded systematically and used to define the product, the process and the facility. Finally, the facility is designed to accommodate the product's lifecycle. Using this approach, known as design space, can help reduce costs and shorten time to market.

These concepts have been successfully applied in a range of applications, from biotech to medical devices, at different phases of development. For example, one small biotech firm conducted a knowledge inventory and framed a design space before submitting a novel vaccine delivery system. A start-up molecular design/discovery firm did the same in order to develop an early-stage Chemistry, Manufacturing and Controls (CMC) package with the required "curb appeal" for potential partners. By making critical product and process information gained early in the product lifecycle visible and easily portable, the start-up made it easy for a partner to pick up the compound and proceed with commercialization. Similarly, putting that information in a format that is usable for submission may give a contractor an opportunity to add value, or to earn incremental revenue by selling the service. In another case, a large-scale device manufacturer embraced QbD as a means of achieving

seamless reviews and cost reductions as they entered the combination product marketplace.

The Facility's Focus

From a facility and operational view, contractors have an opportunity to add value by applying QbD principles to both the formulation and materials. When considering the formulation, it's important to develop a process that remains within the boundaries of the desired design space. This generates better results, not only in terms of the product's "processability," but also toward eliminating potentially problematic unknowns when the time comes to scale up production. In terms of materials, a comprehensive knowledge inventory supports better planning around equipment, environmental requirements, technology transfer, assessment of primary packaging, and bulk holding times. One aspect that is often overlooked is the specific facility's impact on the process and the product.

For example, suppose a company needs Phase I clinical supplies for a sterile product. In order to keep the product within the design space, the contract manufacturer needs to understand the formulation, the control parameters and how those parameters were established. Data from solubility studies, pH profiles, stability of sterile products, inverted data and upright data can be used to help avoid potential process problems. The knowledge inventory and subsequent asset is particularly useful when working with certain classes of compounds that tend to create problematic manufacturing processes (e.g. hormones). Contractors who develop a store of knowledge based on successful experiences in dealing with such challenges are that much ahead of the game when faced with an opportunity to work with the same compounds again.

The concepts proposed here aren't radical. The normal course of development — from in vitro lab work through clinical trials — generates a body of data. A QbD approach suggests that such knowledge be formally catalogued, so it can be easily retrieved and used to inform other aspects of development and commercialization: the product, the process and the facility. With this approach, a focus on the product lifecycle becomes the key business driver.

With every activity and every new project, a contractor's knowledge grows. Too often, though, this incremental knowledge is lost because it is not inventoried. That's because much of the knowledge is tacit; it's "sticky" knowledge, or "a feel for the process." It is difficult, if not impossible, to inventory this type of knowledge systematically. On the other hand, explicit knowledge of fundamental mechanistic properties — for example, an acceptable temperature range for an active pharmaceutical ingredient (API) — can be set down in procedures and easily codified. As a result, that knowledge can easily be transferred: from the lab to manufacturing, from formulation to facility design, from prototype to production scale. Despite the additional effort and expense required to inventory the information, the knowledge ultimately becomes cost effective, because it can be leveraged across the product lifecycle. It also provides a great value to the sponsor, because the sponsor can more readily incorporate well-organized information into the filing. Systematic data updates support key CMC aspects of the submission.

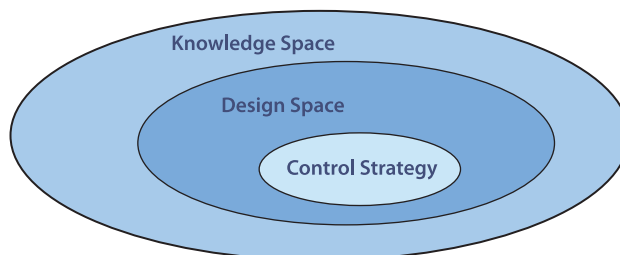
Planning a Knowledge Inventory

The first step in developing a systematic knowledge inventory is determining what information will be most useful to catalog. Generally, the information components necessary to determine facility requirements are the same ones needed to address a review dialog. These broad topic areas may provide a starting point:

- What is needed in a submission?
- What flexibility will the facility provide?
- What is needed to release a product?
- What is needed to manufacture a product?
- What capacity will be required over the product lifecycle?
- What is needed to control a product?
- What will be needed to manage post-approval submissions?

Next, determine what knowledge is already available to shape these areas. This includes scientific elements to be considered and explored for potential product attributes and process parameters. Look at what prior knowledge might be available across other disciplines and therapeutic areas that might have an impact on product attributes or process parameters. The information is available, but must be configured to support the product, the facility and the process. Implementing systems to capture and catalog this knowledge can be challenging, and often requires both internal resources and external expertise. The survey and resulting knowledge space are necessary to understand what is critical to the product, and it provides the foundation for understanding the facility requirements. (See Figure 1.)

Figure 1: QbD Interdependencies



Then, by applying risk assessment and experimental design, it is possible to develop a design space within which it is possible to make the product successfully. This applies both to the process environment and the facility. It encompasses combinations of product formulation, manufacturing operating parameters and raw material quality.

Finally, the knowledge gathered and refined is used to design a control strategy for the product and process that delivers consistent results through its application to engineering,

equipment, process controls and facility requirements. It will address process operating parameters and raw material quality measurements and determine what engineering controls and monitoring systems are necessary to maintain the facility and the process within the design space.

Defining the Design Space

The two most widely accepted definitions of “design space” are from the American Society of Testing and Materials (ASTM) and ICH Q8. ASTM defines design space as the “multi-dimensional region which encompasses the various combinations of product design, manufacturing process design, manufacturing process operating parameters and raw material quality which product material of suitable (defined) quality.” ICH Q8 provides a similar definition, which includes a regulatory dimension. It states, “working within the design space is not generally considered a change of the approved ranges for process parameters and formulation attributes. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process.” In practice, the regulatory aspect may be best addressed in discussions with individual health authorities on a project-by-project basis. One approach that has been successful is to overlay the business needs on the design space and then use risk management for the product to determine a strategy that will best permit a reasonable degree of flexibility within the defined area.

A design review will confirm that the fundamental requirements are incorporated into the overall facility plan. This brings into play a proactive understanding of facility operation and its impact on the product lifecycle. Under QbD, design is an essential compliance process element that brings to bear on functional requirements, critical systems, critical challenges and engineering change management.

Determining exactly what is critical is a function of risk. ICH Q7A defines critical as “a process step, process condition, test requirement, or other relevant parameter or item that must be controlled with predetermined criteria to ensure that the resulting API [or drug product] meets its quality specifications.” Anything — from a drug or device attribute to a process parameter — is critical if it has a direct or indirect impact on patient safety, therapeutic efficacy, in vivo pharmacokinetic or pharmacodynamic performance, or product manufacturing. It is necessary to define critical quality attributes (CQAs), which are quantifiable properties of the intermediate or final product that are critical for establishing the product’s intended purity, efficacy and safety. Measurements for these qualities must fall within a predetermined range to ensure final product quality. Similarly, it is necessary to define critical process parameters — process inputs that have a direct and significant influence on the CQA and so must be maintained within a limited range. Updating this information as one obtains incremental knowledge about the process can go a long way toward preventing later problems at scale-out. It also provides the sponsor with valuable, usable information for the submission.

To support compliance, the facility design should be reviewed with an eye on its intersection with critical quality attributes and critical process parameters. Control zones must

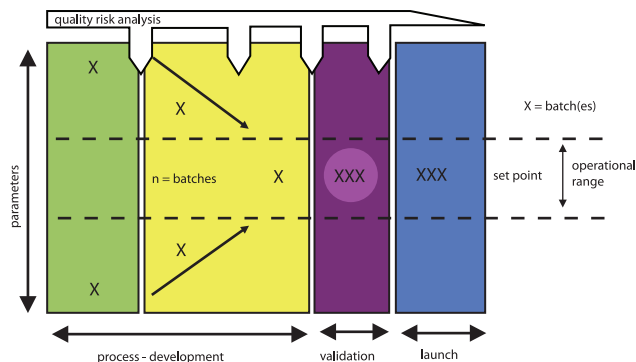
provide levels of protection appropriate for the product components. Critical flows of people, materials and utensils — as well as heating/ventilation and air conditioning (HVAC) systems — should be engineered to prevent cross contamination. Again, the degree to which this is necessary will be determined by the nature of the product components. Critical process elements, including unit operations, process parameters, and components and controls, all must be maintained within the predefined specifications of the design space. In addition to HVAC, other utility systems should be reviewed to determine the degree of impact they might have on critical quality attributes or critical process parameters.

Risk Management and Control Strategies

ICH Q9 guideline addresses quality risk management throughout the product lifecycle. Although it suggests tools and methodology, it does not dictate a specific approach and, in fact, it acknowledges that in many cases, residual risk will exist even after controls have been applied. Experience to date indicates that a sponsor must work toward a system that is based on risk knowledge and addresses contingencies: the “what if” scenarios.

Risk assessment is fundamental to determining critical process dimensions and development of the design space. Risks should be assessed based on cause and effect and relative to probability or likelihood of a consequence, as well as the severity or magnitude of the impact of a consequence. It is also necessary to look at detectability, or the level at which a consequence can be measured, as well as sensitivity, or attenuation of interactions between various dimensions. There are often trade-offs here; the costs of achieving the ability to detect “zero” may not make good business sense. It is only necessary to control process risks to the degree that they might exceed the design space. (See Figure 2.) The contractor who can leverage product and process knowledge to support the sponsor with explicit risk assessment and risk control information brings significant value to the table — and is better positioned to allocate risk and plan for facility needs and required capacity.

Figure 2: Potential nodes for quality risk analysis



Keep in mind that new technologies may make it possible to place all or part of the facility requirements within the

process itself. Such technologies allow the lab experience to be transferred directly into manufacture, thereby eliminating the scale-up issue and permitting a lower risk-based scale-out scenario. In some cases, entire trains of unit operations may be replaced by one highly advanced system. For example, semi-continuous processes such as the Glatt Multicell® process mitigate the risk associated with scale-up by making multiple pilot-scale batches. "Scale up" becomes a function of running the machine longer.

Similarly, Aprecia's 3DP™ computer-aided design and manufacturing (CAD/CAM) process draws on the principles of ink-jet printing technology to build tablets layer by layer. The system provides the flexibility to move from rapid prototyping to commercialization with few scale-up issues, because it manufactures the same unit repeatedly. The trade-off is that systems such as these require significant investment. The investment is certainly worthwhile if it makes the contractor more attractive to the right clients. In investigating all the options, contractors must weigh the balances between the cost of the equipment, the development time, potential multi-use options and flexibility. The bottom line is, establishing the infrastructure early in development makes it possible to move more quickly from development to pilot to commercialization—again, a strong selling point to potential clients.

A Different Kind of Relationship

Becoming a better business partner and being able to make better-informed decisions regarding risk sharing requires that contractors dig deeper for information up front than they may have in the past. To start with, the smart contractor will insist on obtaining fundamental information on which properties of the drug substance have an impact on product performance, what the formulation is intended to do, and any special requirements of the drug substance and drug product. This information can be leveraged to define critical process steps, determine the process parameters for each step and how they must be controlled, and how to design the facility to meet the product's critical quality attributes. The manner in which those questions are answered and risk is allocated greatly affects the business plan and the cost of the process or facility. An understanding of the entire product lifecycle from the outset makes it possible to plan proactively, rather than developing reactive post-approval strategies with regard to the facility and process.

It's also important to know what information is not available, so nothing in the process or facility is based on an assumption. Knowledge gaps are to be expected—and can represent an opportunity for the contractor to demonstrate its value by filling in the missing information or by asking the questions necessary to guide the sponsor toward finding it. Throughout the process, providing explicit knowledge in a clear, concise, systematically catalogued format that supports either a QbD or conventional filing can only serve to make the contractor a valued partner in the sponsor's success. For that reason, QbD provides an opportunity for contractors to add a new dimension of customer service and to differentiate themselves in a competitive marketplace. ■

Resources

- Gasmann, O. and M. Zedtwitz, *R&D Management*, 3, 147 (1998)
- Werther, W.B. and E. Berman, *Organizational Dynamics*, 3, 20 (1994)
- Kieffer, R. and L. Torbeck, *Pharmaceutical Technology*, 6, 66 (1998)
- Butler, J., *The Pharmaceutical Journal*, 1, 31 (1999)
- *Guide to Inspection of Solid Dosage Forms Pre/Post Approval Issues for Development and Validation*. Issued January 1994
- Somma, R., "Using Technology Transfer to Maximize Business Efficiency" *Pharm. Eng.* 27,5 (2007)
- Von Dochren, P.J.; R. St. John Forbes and C. D. Shively, *Pharm Tech*, 6, 139 (1982)
- Somma, R., "The Research-Production Interface", AAPS Annual Meeting, 1999
- Levin, M., *Pharmaceutical Process Scale-Up*. Marcel Dekker, Inc., 2002, New York
- Nash, R.A. and A.H. Wachter, *Pharmaceutical Process Validation*. Marcel Dekker, Inc., 2003, New York
- Somma, R., "Development Knowledge Can Increase Manufacturing Capability and Facilitate Quality by Design," *J.Pharm. Innov.* 2, 87-92 (2007)
- ICH Q8, *Pharmaceutical Development*, Draft 1, No.3, Oct. 25, 2005
- QbD Principles to be implemented in Future FDA Guidance, *DIA Dispatch*, Oct. 28, 2005.
- Somma, R., "PQLI Conference Summation," ISPE PQLI Conference, Arlington, Va., June 7, 2007
- Potter, C., "QbD Now," ISPE PQLI Conference, Arlington, Va., June 7, 2007
- Kibbe, A.H., *Process and Analytical Validation Working Group*, June 2002
- Hussain, A.S., The Subcommittee on Process Analytical Technologies (PAT): Opening Remarks, June 2002
- ISPE Good Practice Guide, *Technology Transfer*. ISPE, Tampa, Fla., 2003
- Spavins, J., "Design Space Summation," ISPE PQLI Conference, Arlington, Va., June 7, 2007
- Shultz, T., "Critical vs. Non-Critical Summation," ISPE PQLI Conference, Arlington, Va., June 7, 2007
- Davis, B., "Control Strategy Summation," ISPE PQLI Conference, Arlington, Va., June 7, 2007
- Migliaccio, G., *Manufacturing Science*, June 2002
- Jacobs, T. and A. Signore, *Good Design Practices for GMP Pharmaceutical Facilities*. Taylor and Francis Group, 2005, New York
- Yu, L.Y., "Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control," *Pharmaceutical Research*, December 2007.



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