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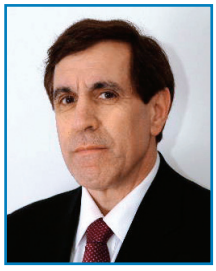
Compliance Notes

Quality by Design: The Case for Change

Executive management leadership is essential in the effective implementation of QbD

Organizations that recognize quality by design (QbD) as a necessary component of an integrated enterprise-wide strategy will have a distinct competitive advantage over those who do not. Moreover, it is important to note that the competitive advantage potential is not confined to arcane statistical issues in product development or manufacturing. It permeates all critical aspects of enterprise performance from research and development (R&D) to commercialization, from speed to market to acceleration, and predictability of regulatory approval to product quality risk and life-cycle cost minimization.

Adoption of QbD tools and tactics by individual functional silos may result in isolated pockets of improved performance, and there is certainly an advantage to be gained by enhancing organizational competence in the fundamental tools of QbD. However, the full strategic potential of QbD may not be realized if there is an absence of coordinated leadership, and ironically, overall organizational performance may be degraded.



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The broad cross-functional implications of effective integration of QbD into the overarching strategy of the enterprise and the downside potential of ineffective integration and functional coordination are the reasons leadership by executive management is essential.

As FDA phases out three-batch validation, organizations that can capitalize on this change will have a significant competitive advantage.

THE EMERGING SHIFT IN COMPLIANCE PARADIGM

For decades, the pharmaceutical and biotech industries have been mired in a flawed and costly regulatory and quality assurance paradigm. Raw-material specifications and process parameters were locked in at the clinical phase by a validation protocol, which documented that three batches of a product, produced under virtually identical conditions, had yielded in-specification results. As a result, quality assurance became almost exclusively dependent on ensuring a pedantic reproduction of validation conditions and on exhaustive raw material and final product release testing.

Ironically, this approach to quality has had collateral effects in other areas that have increased the risk of failure, inflated total lifecycle cost, and impeded improvement. For example, the R&D department has much more incentive to simply get

past validation to produce product for the clinical phase than to optimize processes to minimize total life-cycle cost. Meanwhile, methodologies for designed experiments in product or process development that have been proven in other industries to significantly reduce total lifecycle cost and risk-of-failure have been viewed as incongruent with validation and, therefore, unnecessary.

Now, a new regulatory paradigm is emerging as FDA and international regulatory agencies are placing greater emphasis on fundamental understanding of manufacturing processes as the basis for a knowledge-driven, risk-management approach to quality. Increasingly, FDA's position is that pharmaceutical manufacturing should have reproducible manufacturing processes and, thereby, be able to mitigate the risk of an event that could threaten public safety. Instead of engaging in an adversarial relationship, the industry and FDA would share knowledge. Regulatory processes would be proportional to the level of risk and applied in a consistent and predictable manner. This collaboration represents a clear shift away from a long-standing position of rigid regulation and inspection to achieve quality standards.

These new approaches to regulation, compliance, and quality are embodied in the adopted quality guidelines of the International Conference on Harmonization.

ICH Q8 *Pharmaceutical Development* addresses the key concepts of QbD and design space (DS), and establishes the principle of designing quality into products and processes rather than testing for quality after the fact. ICH Q8 defines *design space* as the "multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality." The guidance goes on to say, "working within the design space is not considered as a change." This statement means that pharmaceutical manufacturers can adjust the process within the design space to make continuous improvements without formal regulatory approval. Companies have the opportunity to continuously reduce the costs and consequences of poor quality without fear of having to refile each time they change a product or process parameter.

ICH Q9 *Quality Risk Management* describes a systematic process for the assessment, control, communication, and review of quality risks. The guideline provides examples of quality risk-management tools. These principles and tools can be applied to all aspects of pharmaceutical quality including development, manufacturing, distribution, and the inspection and submission or review processes throughout the life cycle of drug substances, drug products, and biological and biotechnological products. From a business and operational point of view, the focus is no longer on rushing past validation but on fully understanding and managing risks from the product's inception and throughout its life cycle.

ICH Q10 *Pharmaceutical Quality System* outlines the goals of a quality system that can be applied to all phases of a product's life cycle. Where a company chooses to apply QbD and quality risk management linked to an appropriate pharmaceutical quality system, opportunities arise to enhance science- and risk management-based regulatory approaches.

As the industry continues to globalize, the need for international harmonization embodied in these initiatives will only grow more urgent. In the same manner, as QbD increasingly becomes a prominent component of new drug applications (NDAs), companies that have failed to adopt QbD will be at a distinct disadvantage.

FUNCTIONAL LEADERSHIP'S ROLE IN SHAPING STRATEGY

As FDA continues to phase out three-batch validation in favor of statistical evidence of process understanding, organizations that can capitalize on this change will have a significant competitive advantage. Yet, in the five years since ICH outlined the concept of design space in its Q8 guideline, pharmaceutical and biotech companies—despite depending on innovation for their livelihood—have been slow to adopt QbD. The reasons for resistance are familiar: fear of change, worry about its cost, and perhaps most importantly, lack of full understanding of the competitive business benefits of QbD on the part of executive decision-makers. As the 21st century continues to shape up as a tough time for the pharmaceutical industry—with major patent expirations, thin pipelines, soaring manufacturing costs, and downward pressure on prices—this resistance looks less and less tenable. While QbD may not be the solution to all of the industry's ills, the improved process understanding and more robust processes it promises can produce significant business and competitive benefits that more than justify its cost.

First, however, those who best understand the full potential of QbD because they best understand the science and technical implications must be able to translate that knowledge into the language of financial, operational, marketing, and strategic advantages that is the lingua franca of CFOs and other top leaders. Those with expertise in R&D, process design, and regulatory and compliance issues and who are fluent in CpK and design space must become equally at home with the business case for QbD. That general business case involves development of a strong cost-benefit analysis, as follows:

- Organizational readiness to capitalize on the emerging compliance paradigm
- Clearly defining how QbD reduces risk and cost for your specific enterprise, (i.e., product pipeline versus the organization's historical cost and speed profile).

Beyond the general business case lie the challenges of engaging the larger organization in undertaking and developing the specific business case for the company's particular situation and embarking on a QbD initiative. Those challenges include the following:

- Enrolling management in a more rigorous assessment of costs and benefits
- Developing a phased, integrated path to organizational competence
- Recognizing and achieving new paradigms in cross-functional coordination.

By making the general business case for QbD and mobilizing executive management to undertake its careful consideration, you can not

only help show the way to untapped business value but also greatly increase the scientific rigor and competence of the organization's technical functions.

DESCRIBING HOW QBD REDUCES RISK AND THEREBY INCREASES PROFITABILITY

QbD is not simply about avoiding the cost of lost active pharmaceutical ingredient (API). Millions of dollars of costs that could be avoided in a QbD environment have occurred in the following areas:

- Manufacturing downtime
- Lost sales revenue due to backorder
- Wasted marketing spending as a launch stalls in backorder
- Rejected product and disposal costs
- Deviation investigation and report generation
- Repeated quality control testing and method revalidation
- Engineering costs in calibration and product recovery attempts
- Incremental process characterization
- Supply chain disruptions and expediting
- Manufacturing overtime
- Increased regulatory scrutiny and inspection
- Lost market share due to erosion of patient confidence in quality and efficacy
- Managerial distraction from the core business.

All of these costs degrade profit, and companies go to considerable lengths to avoid them. But as anyone who has been involved with pharmaceutical or biotech development and manufacturing knows, the risk and cost profile of a process may be the result of a complex interaction of factors, including raw-material characteristics, process parameters, and environmental factors.

Traditionally, a process has been a kind of black box. The process at the time of validation is not well understood, but as long as the specs are rigidly locked down and maintained for each variable, it is hoped that the box will continue to churn out acceptable product. But variation is inevitable in processes, and raw materials not only almost always vary from batch to batch but also those variations interact in complex ways with the other variable controllable aspects of the manufacturing process. When deviations occur post-commercialization, the search for causes can be time-consuming and costly. There is no guarantee that remedies will be sustainable, and the barriers to regulatory approval of change may be considerable.

By contrast, QbD is a proven, systematic way to achieve maximum process understanding at minimum expense. Employing sophisticated statistical techniques and design of experiments (DoE) to develop a robust and reliable system, QbD may be applied to any manufacturing or development activity, including formulation and process development. By fully understanding the complex interactions of multiple variables, the "design space" can be mapped (i.e., the possible combinations of the critical process parameters that would keep the resulting product within specifications). The process can then be more easily characterized, validated, and controlled, resulting in products within a defined target product profile.

Given these stark differences between the traditional approach to quality and the QbD approach, decision-makers should ask themselves these questions: which approach has a lower risk and cost profile? Is it more cost-effective to understand the contents of the black box before going into production or to proceed by trial and error, investigation, regulatory scrutiny, and corrective action while trying to meet customer demand? Is an understanding of the relationship between factors and having the flexibility to leverage that knowledge to reduce product variability preferable to being locked into the best guess used to produce the first three batches?

AN EXAMPLE OF COSTS BEYOND API LOSSES

The experience of a major pharmaceutical manufacturer vividly answers these questions. The manufacturer was experiencing problems with a product capsule consisting of three components: immediate release pellets, sustained release pellets, and enteric release pellets. The dissolution performance of both the immediate release pellets and the sustained release pellets was poor. Although recent production batches had met specifications, they were trending out of spec, requiring investigation and justification for release. The shift in performance of the pellets appeared to coincide with a change in the API supplier, which resulted in a change in particle size distribution. The organization took some stopgap measures to mitigate the problem, but making those measures permanent would have resulted in significant and costly yield loss and would have required an amended filing to be submitted to FDA.

Prior to the change in the API supplier, the process capability was such that the probability of failure was less than one batch in 2500. Following the change, failures were occurring at a rate of approximately one batch in 25. To avoid a stock-out situation, it was crucial to determine the root cause of the problem, remediate it, and release the out-of-trend finished product. The problem was already costing approximately $250,000 per month in lost batches and yield. A stock-out of greater than 21 days had the potential to cause losses in excess of $400,000 per day and a serious loss in market share.

To solve the problem, the company turned to QbD tools that enabled them to identify a relationship between process parameters, API particle size distribution, and dissolution profile. They were then able to reduce the probability of failure to less than one batch in 5000. Further, the change in the process parameter was within the spec ranges that had been originally filed and, therefore, did not require a filing change. By significantly reducing the risk of failure, QbD tools had essentially eliminated the stock-out risk and costs of poor quality.

DEFINING THE GENERAL COMPETITIVE ADVANTAGES OF QBD

As the experience of the manufacturer demonstrates, QbD is not just a tactic for reducing costs but a strategy for increasing competitiveness that cuts

across all functions of the enterprise. In considering QbD, it is important to adopt a strategic perspective in order to understand the full value that QbD can generate within and across functions and in the marketplace.

In making the case to leadership for adopting QbD, it's worth dwelling on some of the following key business benefits and advantages.

Greater Speed to Market

Every day that a product makes it later rather than sooner to market means lost or deferred revenue. QbD can greatly reduce time to market and speed up return on investment because it maximizes the probability that a product in development will make it smoothly and effectively through scale-up, technology transfer, and validation. It is, however, exceedingly important that one doesn't just take some arbitrary cost per day by dividing the total R&D budget and multiplying it times an arbitrary number of days which might be saved. This invariably rings hollow and, it should. An analysis of the organization's historical performance, delays in product commercialization and failure modes will not only generate a better estimate, it will enhance credibility.

Lower Cost of Quality

When quality is produced through extensive control, as it is in the traditional approach, the result is high cost. By contrast, QbD's science-based understanding of processes frees manufacturers to focus their control efforts on the factors that are critical to quality. Greater process understanding also enables more accurate and thorough validation than the three-batch standard and more robust processes that can accommodate inevitable variations in raw materials.

Better Allocation of Resources

The best-laid plans in the allocation of resources can be waylaid by unpredictable and costly quality problems. But with QbD, companies can have greater confidence in their ability to maintain in-specification operations, freeing resources for more productive and predictable investment.

Improved Manufacturing Performance

The more processes that QbD permeates, the more the organization will realize bottom-line benefits through improved yield, increased equipment uptime and plant and capacity utilization, capital cost avoidance, and reduced rework and fewer rejected batches.

Reduced Regulatory Burden and Continuous Improvement

Once an organization understands the design space, the manufacturing processes within that design space can be continuously improved without further regulatory review. FDA can use risk assessment and management approaches to reviews and inspections, and continuous improvement of processes can lead to greater cost reduction and reliability of products and processes.

QBD IN THE COMPLEX PHARMACEUTICAL WORLD

In addition to these key business benefits, QbD can be a key enabler for companies that want to get ahead of one of today's biggest challenges in the development of drugs, diagnostics, and therapies: their sheer complexity. The days have long passed when medications were taken briefly to treat relatively straightforward conditions. Whole new classes of drugs have appeared to treat chronic diseases and address extremely complicated therapeutic areas like oncology, AIDS, Alzheimer's, and Parkinson's. QbD is particularly well suited for these complex contexts, because it has the ability to scientifically establish the complicated multi-dimensional interactions of the input variables and process parameters that determine the quality of a product. In the increasingly complex world of the life sciences and therapeutic needs, companies that have adopted QbD are likely to have a strategic advantage. ◆