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Quality by Design: Manufacturing Has It Right

By John R. Wilson, Jr.

Pharmaceutical manufacturing established a risk-based approach to quality more than a decade ago, yet its adoption in clinical trials has been slow. As the pressure for fundamental change in clinical research quality continues to grow, we can learn much from our colleagues in pharmaceutical manufacturing.

While similarities between clinical research and manufacturing operations may not be obvious at first glance, there are a number of conceptually similar components in the two processes. Table 1 lists four such areas. There are many more.

Table 1. Pharmaceutical Manufacturing vs. Clinical Research

Process	Manufacturing	Clinical Research
Product realization	Batch and continuous processing operations	Continuous processes with some batch elements
Concurrent adjustments	In-process controls	CTMS, adaptive clinical trial design, allowing for in-process modifications to statistical analyses and study procedures
Outsourcing as risk-mitigation strategy	Third-party manufacturing	Use of CROs*
Continuous improvement	Failure Modes and Effects Analysis (FMEA), other root cause and corrective analysis tools	Corrective and Preventive Action (CAPA), which is aligned with quality-by-design via the model of continuous improvement

* While outsourcing is usually viewed as a cost reduction or resource management strategy, shifting from entirely fixed to variable resources is also a vehicle for risk mitigation via the infusion of fresh ideas and minimizing the "not invented here" syndrome.

Change is Here

At a 2010 CTTI meeting, Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, noted that, "given the ever-growing and ever-changing clinical trial landscape, stakeholders in the research enterprise have shared concerns regarding whether the current trial oversight model is sustainable and effective."[1]

In August 2011, FDA released the draft "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring," in which the agency described changes in the clinical trial landscape that it believes have altered the way the industry should approach quality:

> In the past two decades, the number and complexity of clinical trials have grown dramatically. These changes create new challenges in clinical trial oversight, such as

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> increased variability in investigator experience, ethical oversight, site infrastructure, treatment choices, standards of health care, and geographic dispersion. In light of these developments, FDA wishes to encourage more effective monitoring of clinic investigations, to ensure adequate protection of human subjects and the quality and integrity of clinical trial data.[2]

More recently, a December 2011, Oliver Wyman report on pharmaceutical R&D cited a 70% fall in productivity. The authors implored, "Whether your company is among the successful depends on how much you are willing to move the R&D organization away from historical mindsets."[3]

Clearly, the FDA draft Guidance and the Oliver Wyman report call for a shift from historical methods of assuring quality via inspection, to a more proactive approach of Quality by Design (QbD).

Quality by Design is the Right Kind of Change

FDA's August guidance stated that, "Quality is a systems property that must be built into an enterprise and cannot be achieved by oversight or monitoring alone."[2] While hardly a controversial statement, to understand its fullest expression one needs to step back and look at first principles, which are nowhere as important as in clinical research. After all, clinical research is an exercise in experimenting with human subjects.

It is hardly necessary to define quality for the readers of this article, whether one adheres to "fit for use," "meeting customer requirements," or any of the other useful definitions of quality. However, while QbD is a common expression, in practice it is clear that industry does not have an equally common definition or one that can guide optimal practices.

Quality by Design, while calling for major shifts in thinking and practice, is not a complicated theory. In essence, QbD is the practice of building quality into a clinical trial rather than trying to inspect it in or test it in. QbD is entirely consistent with ICH Guideline Q8 (Pharmaceutical Development). Equally important is that QbD is a dramatic improvement over the traditional practice of retrospective auditing against standard operating procedures.

QbD in the manufacturing arena can include Lean and Six-Sigma processes for supply chain management. While these processes are generally lacking in the clinical realm, advanced EDC and CTMS methods can provide similar benefits.

ICH Q8, using the term "design space," defines a quality system 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."[4] Quality is thus built in, and not a product of work activity that is tossed over the wall from one department to another.

The Oliver Wyman report further echoed the need to integrate quality: "Companies that move forward need to be suspicious of familiar processes (have they changed enough?) and familiar metrics (do they provide enough guidance for a changed era?). The new mindset must give rise to new behaviors, and those behaviors must become an integral part of process, culture and reward systems."[3]

Woodcock suggested applying manufacturing quality principles to the clinical research process. Based on the successful application of QbD principles in the drug manufacturing arena, she noted there is good reason to believe that the QbD model could be adapted to the requirements of clinical trial conduct.[1]

QbD is comprised of four basic principles:

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- A systematic approach to development
- Predefined objectives
- An emphasis on product and process understanding and control
- A foundation in sound science and quality risk management

The primary difference in a QbD approach is that it is risk-based, and therefore "majors in the major," i.e., focuses on the truly important components of a clinical trial. Across the entire drug development lifecycle, activities that are deemed to pose the greatest risk to data quality or to human safety become the focus of quality processes.

Traditional approaches to quality have focused on risk aversion. Woodcock contends that this "perceived obligation to mitigate every potential risk, especially for those activities that minimally affect data quality and patient safety" is a barrier to change. She argues that a QbD approach allows sponsors to "conduct their trials in compliance with applicable statutes while producing the key data needed to facilitate regulatory decision-making."[1]

Further, evidence suggests that quality is not diminished with a risk-based approach. Lawrence X. Yu, deputy director for science and chemistry at the FDA's Office of Generic Drugs, found in a 2007 study that "Using QbD, pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables. Product testing confirms the product quality."[5]

What's Wrong with the Old Way?

The problem with not employing QbD prior to commercial production is that it is extremely difficult to later insert or force quality into a suboptimal process. Doing so leads to awkward and inefficient practices, duplicative efforts and "Band-Aid" approaches to quality. Building a quality pharmaceutical product begins with building quality into the research and development phase.

A poorly designed Phase I pharmacokinetics study can lead to incorrect dosing choices in a Phase II dose-ranging study, which can lead to ambiguous results in a Phase III pivotal study, which can lead to suboptimal doses in a marketed product, which can lead to lack of clinical effectiveness or high rates of adverse effects.

One may argue that QbD is already built into the process through the audit function of clinical quality assurance (CQA). While clinical auditing is certainly an important part of clinical research, it does not build quality into the process. Because it is traditionally conducted as point-in-time assessments, it does not provide a continuous assessment over the course of the trial and therefore cannot be considered part of a "process."

The same criticism can be levied against traditional on-site monitoring practices.[2] With monitoring, one also gets snapshots of progress of the clinical trial, albeit with more data points than with auditing. The principle remains, though, that these snapshots do not provide a continuous flow of real-time study metrics.

The Oliver Wyman report states that "Investors remain wary of R&D spending, rewarding companies that cut and penalizing those that don't — a sign of limited confidence in the industry's use of its capital."[3] Mitigating the risks that actually matter could be a better use of limited resources that quells investors' fears without exhausting their pocketbooks.

Conclusion

As industry moves toward changing its approach to clinical research quality, it should look to the success that manufacturing has experienced in implementing the four basic principles of QbD.

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