

BioPharm

INTERNATIONAL

November 2009

The Science & Business of Biopharmaceuticals

Compliance Notes



QbD and GMPs: How the Convergence of Science and Compliance Will Change the Way We Work

The focus on the design space will lead to a new workspace and will affect staff in the development, manufacturing, and quality functions

July 2, 2008, marked a significant milestone for the biopharmaceutical industry. That's when the US Food and Drug Administration announced its pilot program for the submission of quality information for biotechnology products consistent with the principles of Quality by Design (QbD).



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The greater product and process understanding provided by QbD can help companies in a variety of ways. Greater process understanding means more accurate and thorough validation and more robust processes, thus improving quality. More robustness also helps lower manufacturing costs by increasing yield, reducing manufacturing downtime, and decreasing the amount of rework and rejected batches. By strengthening the manufacturing process, QbD can speed time to market, thus increasing the return on investment. In addition, QbD holds out the promise of reduced regulatory burden, including fewer postapproval submissions, reduced end-product release testing, and the possibility of introducing process improvements without further agency review.

Achieving those many benefits, however, will require adopting new ways of working and a new outlook

on good manufacturing practices (GMPs). What will QbD mean in that regard? The answer lies in the convergence of science and compliance at the heart of QbD: (1) robust processes designed to provide statistically defined performance characteristics that ultimately result in products with a defined target product profile, and (2) good biopharmaceutical quality, defined as an acceptably low risk of failing to achieve the target profile. In other words, QbD combines increased scientific understanding of products and processes with the risk-based compliance that such understanding makes possible.

This convergence of science and compliance will profoundly affect all areas of GMPs, including the nearly 20 such areas covered in the International Conference on Harmonization (ICH) Q7 guideline.¹ Each GMP could, of course, be the subject of extended discussion in light of QbD, but more generally, the convergence of science and compliance will mean:

- more integrated, coordinated activities across departments that have traditionally worked in separate silos
- fundamental changes in focus for many personnel in development, manufacturing, and quality
- changes in training to establish these new ways of working.

QbD requires creating a continuous feedback loop between development and manufacturing.

Under QbD, GMPs will be reconceived as a framework, rather than as the driver, for the performance of risk-based, flexible processes. In other words, if biopharmaceutical companies are to maximize the benefits of QbD, the technical and compliance revolution it embodies will need to be accompanied by a cultural and organizational revolution.

COORDINATION ACROSS DEPARTMENTS

Most companies have spent years carefully establishing and elaborating the steps involved in the manufacturing of biopharmaceutical products—from the initial cell culture vial through scale-up, bio-reactor production, downstream processing, formulation, filling, and packaging. Not surprisingly, this approach has encouraged the development of functional silos, each narrowly focused on its area of expertise, inhibiting the diffusion and integration of knowledge throughout the organization.

This model of drug production, with little crossfunctional involvement after each hand-off to another function, and with quality ensured through analytical testing near the end of the process, has served biopharmaceutical companies reasonably well for decades. But with tighter regulation and cost pressures that now reach into development and manufacturing, companies are seeking more efficiency in manufacturing processes by improving process understanding and control.

QbD, with its aim of achieving a scientific understanding of manufacturing processes as early in the development process as possible, and of enabling continuous improvement in manufacturing, requires a

much more integrated and holistic approach by staff in all functional areas. For example, in elucidating and, in particular, documenting the process design space (defined in ICH Q8)², development groups may need to operate with an increased attention to GMP guidelines because the data they develop by using design of experiments (DOE) to define the design space will be used to support manufacturing decisions to the FDA. Analytical and bioanalytical support functions will share in the responsibilities for this key element of process design and control.

In essence, succeeding with QbD requires creating a continuous feedback loop between development and manufacturing, with upstream, downstream, and analytical personnel increasingly looking as far down the production process as possible, and manufacturing personnel reaching back into earlier stages of development, all tied tightly together by improved communication and documentation facilitated through IT groups.

CHANGES IN JOB FOCUS

This holistic way of operating will mean some fundamental changes in focus by staff in key functions. For example, consider the age-old disjunction between development and manufacturing. It's often been said that development personnel "threw their creations over the wall" to manufacturing who would say, in effect, "thanks, we'll take it from here." GMPs meant simply following the rules established during validation and then performing quality assurance (QA) to make sure each batch of product met product specifications.

But validation under a QbD regime aims to establish the design

space within which changes may be made to process or product inputs while keeping the product within specifications. As a result, development and manufacturing will have to look together over the entire lifecycle of the process. Development personnel will therefore widen their scope to include issues of manufacturability. Conversely, manufacturing personnel will be looking at development data. Further, risk-based compliance means that manufacturing personnel, who have traditionally focused on issues of efficiency, will have to become decision-makers and risk managers, deciding which parameters to change when necessary or desirable and understanding the associated compliance risk.

QA personnel also will need to be involved in defining the design space during validation, working closely with development staff. QA will change its focus from procedures and investigations to ensuring that the design space isn't breached and that risks are appropriately identified, assessed, managed, or mitigated. QA will likely ensure that the appropriate personnel have weighed in on a situation and that there is documented justification for decisions and actions taken. Often, justifications will come from technical reports, which in most organizations are not as regulated as GMP documents. This may require a new flexibility on the part of QA, because non-GMP documents may take on a new level of credence in the approval process and beyond.

From one point of view, it's possible that flexibility for QA could come in the form of fewer deviations and investigations, because the design space will provide clear boundaries to define these. Under QbD, there could be fewer release data to be scrutinized, and acceptance criteria for release specifications would be more scientifically justified. Upstream process data could become more essential to the product quality equation,

rather than only quality control (QC) end product testing. Batch records themselves might be less directive and more prescriptive. QA will need to ensure the appropriate data and justifications are documented during processing, rather than simply recording actions taken. All of this may require more process knowledge on the part of QA, but more likely requires only a different outlook on data credibility. For example, during vendor audits, the job will be to assess the risk that materials and services rendered pose to the valid design space. This will require an approach that is more scientifically based than a GMP-checklist style audit, which is currently common in the industry.

From another point of view, it's possible that the FDA's evaluation of GMPs will not accommodate a completely flexible approach to document requirements. Because data produced by development staff must help define the space in which the manufacturing group is free to operate and make changes, quality oversight may in fact increase under QbD. How these issues are resolved between the industry and the agency will be important for conferring the freedom to operate within a design space. The prospect of having such freedom is a major appeal of QbD to the industry in the first place.

Changes in the nature of the QC group's work will be driven by the trend toward real-time quality control embodied in initiatives like process analytical technology (PAT).³ This carries two implications for QC. First, insofar as such control becomes increasingly automated, some QC staff will be freed up to focus on attributes deemed critical to product quality. Second, smart companies will not simply throw new technology at process controls. Instead, armed with greater process understanding, they will be able to determine precisely where the

In vendor audits, QA will have to assess the risk that materials pose to the design space, rather than conducting a GMP-checklist style audit.

greatest risks and opportunities lie in their operations and to address them strategically. Personnel supporting the manufacturing process therefore will need to become adept at creating, maintaining, and refining PAT and control strategies in line with the goal of continuous improvement embodied in QbD.

TRAINING FOR NEW WAYS OF WORKING

These changes in the ways various functions do their part in ensuring GMPs will require additional training, which under ICH Q7 is itself a GMP.¹ Different functions will, of course, require different kinds of training. For example:

- QC staff will need training in PAT technology and strategy and in complex upstream analytics.
- QA and manufacturing personnel will need training in risk-based assessment and compliance, and in appropriate process and analytical understanding
- Development staff will need help with DOE, and effective, or even compliant, documentation, and manufacturing constraints such as cost-of-goods efficiencies, GMPs, and risk analyses.

But the convergence of science and compliance in QbD lends a common theme to all such training: the understanding of the design space. For some personnel, that will mean understanding the design space conceptually and, in specific instances, knowing the relevant parameters for purposes of control and the like. For others, particularly those who actually determine the design space, it means familiar-

ity with the advanced statistical methods that are used to map the complex relationships among product quality attributes, the manufacturing process, and clinical safety and efficacy, and to determine the various permutations of critical input variables that will keep the product within specifications.

SUMMARY

It is precisely because biological processes involve many raw materials, numerous upstream and downstream processing steps, numerous types of equipment and operating conditions, and high levels of variation that the analytical and statistical rigor of QbD are required for designing highly robust and reliable systems. Many biopharmaceutical companies already use many of these statistical tools but not necessarily in a full-fledged QbD program. However, these tools are rarely subject to compliance oversight, and they are not easily amenable to the current procedural GMPs practiced in most biotech companies.

Achieving GMPs in a QbD environment will also require that personnel from diverse functions learn how to work in crossfunctional teams. Such teamwork will be required to ensure product quality and that each function achieves some degree of crossfunctional understanding. For example, development, IT, and statistics personnel will need an appreciation of GMPs, while the quality and manufacturing groups ensure that the spirit of GMPs is captured as part of the project and lot histories. If effective

and accountable team leaders are deployed, then cross-functional teams can function smoothly as long as they have management support.

In essence, the focus on the design space leads to what we might call a new workspace. Crossfunctional teamwork, the changing focus of work in specific functions, and a more holistic approach to quality are all part of this new workspace. Just as science and compliance converge in QbD, teams, functions and organizational processes will converge in this new workspace to realize the

vision of more efficient development and production of biopharmaceuticals. ♦

REFERENCES

1. International Conference on Harmonization. Q7. Good manufacturing practice guide for active pharmaceutical ingredients. Geneva, Switzerland; Nov 2000, p. 6
2. International Conference on Harmonization. Q8(R2). Pharmaceutical development. Geneva, Switzerland; Nov 2005, p. 11.
3. US Food and Drug Administration. Guidance for Industry. PAT—A framework for innovative pharmaceutical development, manufacturing, and quality assurance. Rockville, MD; 2004.

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