Why Quality by Design?

An Executive's Guide to the FDA's Quality by Design

March 2008

Contents

Introduction

Quality by Design is one of the most misunderstood and misused tools available to biopharmaceutical and medical device executives. This is unfortunate because – planned and implemented well – Quality by Design is one of the most powerful strategies in the executive toolkit.

Quality by Design

In mid-2002, the U.S. Food and Drug Administration (FDA) published a concept paper on current Good Manufacturing Practices for the 21st century. This document expressed a desire that companies build quality, safety and efficacy into their new biopharmaceutical products as early as possible. This concept became known as Quality by Design.

> Average time to market for a new drug or biologic is now 10-15 years at a cost of more than $1.2 billion.

Years later, the meaning and impact of Quality by Design is still not clear to many. Is this a new way to develop drugs and biologics? Can this shorten the product development cycle time? Will it provide more business flexibility? Where, when and how should it be applied? For many executives who tried to adopt Quality by Design, confusion gave way to frustration.

And yet, properly conceived and executed, Quality by Design works. Earlier this year, at a workshop in Washington, D.C., I discussed the results of two clients who had adopted Quality by Design. The first company cut more than 3 years off their time to market, reduced costs by 8% and increased their success rate to 85%. The second company saved 1 year, reduced costs by 3%, and achieved a 32% greater success rate.

The following pages present an overview of Quality by Design and the ways in which it can give your company a powerful competitive edge.

Background of Quality by Design

Outside of FDA regulated industries, Quality by Design is not new. In the 1970s, Toyota pioneered many Quality by Design concepts to improve their early automobiles (see the article, "Elucidation: Lessons from the Auto Industry" in the June 2007 issue of *BioProcess International*).

Since that time, other industries – technology, telecommunications and aeronautics – have taken up most of the concepts that make up Quality by Design. The car you drive, the airplane you ride, the computer you use and the phone you answer, are all products of Quality by Design.

In the 1990s, medical devices began to appear that incorporated many Quality by Design aspects. These drove down risk and cost while improving patient safety and product efficacy. FDA officials realized that biologics and drugs could also stand to benefit from Quality by Design.

Internal discussions in the FDA began in the late 1990s, culminating in the 2002 concept paper on 21st Century Good Manufacturing Practices. With the assistance of several biopharmaceutical companies, pilot programs were started to explore Quality by Design application and understanding.

Quality by Design Defined

By 2004, the FDA coalesced its thinking on Quality by Design and its role in product quality and patient safety. The FDA produced a guidance document entitled *Pharmaceutical cGMPs for the 21st Century*. This publication defined Quality by Design as:

1. Developing your product to meet predefined product quality, safety and efficacy; and
2. Designing your manufacturing processes to meet predefined product quality, safety and efficacy.

While this clarified FDA's approach, it left far too many questions unanswered. Companies were left to tackle Quality by Design on their own. Some focused on improving clinical testing. Others looked to improve manufacturing quality. Such a scattershot approach did not achieve the results the industry was expecting.

Varied interpretations of Quality by Design further complicated the scene. Regulatory Affairs professionals and Quality Assurance personnel each saw different things. Consultants pushed risk management. Scientists argued that by eliminating the need for some tests, Quality by Design undermined scientific rigor. The result was – and in many cases, still is – confusion and frustration.

Clearing the Confusion

Over the past two years, I've written extensively on my clients' successful implementations of Quality by Design. Our achievements are based on the definition of Quality by Design we found most useful:

> *Quality by Design is everything you do to directly promote and prove the safety, efficacy and quality of your product, from proof of concept to the point at which customers are buying it on a regular basis.*

Behind that single sentence lies a significant amount of information. My clients have come to realize that when Quality by Design is planned and implemented properly, the benefits are enormous. When Quality by Design is tackled haphazardly, the benefits fizzle.

For the FDA, adoption of Quality by Design provides companies:

- Streamlined product development and premarket reviews
- Easier regulatory compliance and flexibility
- Faster improvements to product maturity and manufacturing

Few executives, shareholders or patients would argue with such objectives. Indeed, so persuasive is the argument in favor of Quality by Design that following publication of the FDA's guidance document,

the International Conference on Harmonization (ICH) published its own guidance documents approved by regulatory agencies in the US, Japan, Canada, New Zealand, Australia, and Europe. Quality by Design has become a world-wide expectation.

Quality by Design Across the Product Lifespan

To achieve Quality by Design, you need to develop your product and processes to ensure predefined product quality, safety and efficacy. This requires you to know how your product makeup and processes influence quality, safety and efficacy. You can then draw upon this information to continuously improve once you are on the market. Seen in this light, Quality by Design stretches from your early pipeline to postmarket controls.

> Quality by Design is a strategic, systematic approach to get your new product pipeline to market faster, easier, and for less.

Development

The riskiest, costliest phase of drug and biologic lifespan occurs during new product development. In my consulting engagements, my clients have seen how a well planned and executed Quality by Design strategy that starts in new product development programs provides the most powerful results – reducing time, effort, risks and costs.

Preclinical

The ability to use prior knowledge – from previous products, from literature surveys, from personal experiences, and so on – is one way that Quality by Design improves product development. Prior

knowledge and patient needs allow you to identify the specific characteristics your new product must meet.

Nonclinical

To meet these predefined specifications, you conduct experiments in both preclinical and nonclinical to assess the ability of your developing product to meet these targets. This includes *in vivo* and *in vitro* tests, and, depending on your product, *in serum* testing drawn from feasibility experiments, toxicology tests or even Phase I clinical.

FDA reviews Quality by Design submissions 63% faster.

Clinical

Under a Quality by Design product development model, clinical studies are confirmatory. You can use a traditional approach to clinical trials or try adaptive trials. By Phase III, you should be focused solely on micro refinements to your product and your manufacturing processes.

Scale-Up

Scale-up experiences are also part of Quality by Design. This allows you to document changes and rationales during the changeover from small-scale pilot to full-scale manufacturing.

For instance, imagine that in the switch from pilot to full-scale manufacturing, you had to increase the nozzle size on a piece of equipment due to the higher spray rate needed on the manufacturing line. As long as the larger nozzle size maintained the same droplet size as in pilot production, then no further testing, validation and verification would be required. This information is then included in your final submission for market approval.

Submissions for Market Approval

Submissions based on Quality by Design have more scientific information on your product, processes, and controls. This allows faster reviews. The FDA's own internal analysis has shown that

Quality by Design-based applications are processed 63% faster than traditional submissions.

Manufacturing

Quality by Design in the manufacturing of biologics and pharmaceutical drugs provides more business flexibility and efficiency. Historically, firms that wanted to make major manufacturing modifications needed regulatory approval prior to implementing changes. Under Quality by Design, this review can be eliminated by relying on the elements of "real-time" quality control, process analytical testing and design space.

Design Space

Product processes that do not impact product quality, safety or efficacy, or that always produce results that do not impact product quality, safety, or efficacy, are known collectively as "design space." Changes within design space do not require regulatory review or approval.

The more information you have on the impact – or lack of impact – of a process on your product's quality, safety or efficacy, the more business flexibility you have under Quality by Design. This information originates with product development. Once your product is on the market, you refine this information – and thus your product and processes – with techniques such as Six Sigma and process analytical technology.

Quality by Design allows you to optimize your manufacturing.

Process Analytical Technology (PAT)

The effects of process change on final biological and pharmaceutical products can be difficult to predict. An essential part of Quality by Design is accepting that even if the complex interplay of process change and impact cannot be fully predicted, it can be monitored and controlled.

Known as process analytical technology (PAT), this allows you to continuously monitor, test, analyze, trend and adjust your manufacturing processes to enhance control and improve efficiency.

"Real-Time" Quality Control

The third aspect of Quality by Design in the manufacturing arena is the ability to shift quality control upstream into production. This reduces waste and the cost of producing a batch or lot that ultimately may fail quality control. By embedding quality control checks throughout manufacturing processes, Quality by Design allows you to optimize your production, improve your product and streamline your processes.

> Quality by Design allows you to ask, "If this test, process or control does not impact our product's quality, safety or efficacy, why are we going through the expense?"

Control Strategies

Embedding "real-time" quality control checks is just one of the control strategies that helps ensure product quality. Remember that Quality by Design means designing and developing your product and processes to meet predefined product quality, safety and efficacy. Linking the product design and development phase directly with process development gives you the degree of control necessary.

Risk-Based Decisions

Central to Quality by Design in product lifespan is relying upon risk management techniques to make decisions. Good risk management decisions rely upon the knowledge you gain throughout the product development phase into full-scale manufacturing.

Continuous Improvement

If we think back on the definition of Quality by Design as "everything you do to directly promote and prove the safety, efficacy and quality of your product," then continuous improvement is part and parcel of promoting and proving safety, efficacy and quality. It allows you to focus on making your production processes efficient without negatively impacting the product.

Continuous improvement is demonstrated through measuring, tracking, trending, controlling and – most importantly – acting upon that information. Failing to act appropriately jeopardizes your compliance, your patients and your bottom line.

Product Performance

Key to successfully implementing Quality by Design is identifying those characteristics of your product that are critical to its safety, efficacy and quality, plus those aspects of your processes that impact those product characteristics. These are called critical process parameters (CPP) and critical quality attributes (CQA).

If you can prove that a drug or biologic characteristic (such as an inactive ingredient like food coloring) has no impact on safety, efficacy or quality, then you can decide not to bother testing, tracking or controlling it any further. Likewise, processes that have no impact on product safety, efficacy or quality can also receive minimal testing, tracking and control. For most companies, this dramatically lowers the costs involved in product development and production.

7-Step Quality by Design Start-Up Plan

The best way to assess how to implement Quality by Design in your organization without making the same mistakes that other companies have made is to utilize a simple seven step process:

1. Hire an independent Quality by Design expert
2. Audit your organization and processes with the expert conducting a gap analysis
3. Hold a basic Quality by Design workshop with all your personnel – the expert should lead this and design it to speak to multiple levels, from the factory floor to the boardroom
4. Review the expert's report and recommendations
5. Draft an implementation plan, timelines and estimated costs
6. Assign the resources (or contract out)
7. Retain the independent expert as your "project assurance" advisor

Quality by Design as a Competitive Tool

Quality by Design is a strategic, systematic approach to get your new product pipeline to market faster, easier, for less. Quality by Design's emphasis on sound science, logical controls and risk management consistently speed time to market, reduce costs and increase success.

The faster your product is on the market, the greater your chance of a positive return on investment. More scientific information and controls help insulate you from liability. And the proprietary processes and product knowledge you develop under Quality by Design give you a long-lasting competitive edge.

Are you ready?

If you would like a complete copy of the industry report and workbook, *Is Quality by Design Right for My Organization…?*, referenced in this guide, send an email to *reports@ceruleanllc.com* or visit the "Resource Library" on the Cerulean website (www.ceruleanllc.com). The workbook is free to readers of this guide. Simply note you read this executive guide in the "other information" section of the booklet request form.

About Us

About Cerulean Associates LLC

Cerulean Associates LLC (www.ceruleanllc.com) specializes in streamlining FDA and ICH compliance and quality programs, preventing intellectual property theft and ensuring new product development success. To get your head-start on faster time to market, easier compliance and a better bottom line, request our free *Executive Quick-Start Pack* on the Cerulean website.

About FDA Expert Briefings

FDA Expert Briefings (www.expertbriefings.com) is a leading provider of expert analysis and interpretation of regulatory activity at FDA and other federal agencies. Our professional teleconferences and webinars enable you to keep your entire staff current on a wide range of topics affecting regulatory affairs, clinical research and operations without leaving your office.