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How to Make the Business Case for Quality by Design

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ABSTRACT

Even though the US Food and Drug Administration (FDA) and biopharmaceutical industry leaders have touted the merits and business benefits of Quality by Design (QbD) for quite a while, adoption in the industry has been slow. This article examines barriers in the industry and how to overcome them. Only when this happens can QbD reach the manufacturing floor in a way that benefits the public and the long-term viability of biopharmaceutical companies. This article also shares insight into making the business case for QbD based on the typical criteria that decision makers use to evaluate new initiatives and related technology.

Quality by Design (QbD) has become a buzzword in the biopharmaceutical industry, but the concept is not new. For decades, quality pundits have presented QbD as a way to improve manufacturing process outcomes. The biopharmaceutical industry, however, has not been quick to adopt the concept. This is because QbD often falls low on the long list of immediate priorities to be tackled. Making a successful business case for QbD can be done by making the business benefits clear, and planning the initiative in a way that takes near- and long-term returns into account.

QUALITY BY DESIGN'S DEEP ROOTS ACROSS INDUSTRIES

In his 1992 book, *Juran on QbD, The New Steps for Planning Quality into Goods and Services*, manufacturing quality expert Joseph M. Juran explored the reasons a book on quality planning was needed at that time, noting "the gathering awareness by companies that they have been enduring excessive costs due to chronic quality-related wastes." Much of this waste, he adds, consists of "redoing work already 'done'."¹

Applying this idea to biopharmaceutical manufacturing today, we can certainly relate to the concept that such waste costs money, maintains needless

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risks of consumer harm in the system, and hurts companies' and the nation's ability to compete. By failing to find and correct the root cause of problems early in the design phase of the process and product development cycle, companies risk quality and yield problems in their processes.

Other industries have been quicker to adopt QbD because they felt the financial crunch of competition sooner than pharmaceutical manufacturers who were able to leverage blockbuster drugs and patents into large profits in past decades. Today, as many manufacturers struggle with shrinking new drug pipelines and competition from generics caused by expiring patents, QbD should be viewed as an opportunity that brings with it business benefits for the entire organization.

QBD LEVERAGES LESSONS FROM EXPERIENCE

Previous experience is valuable to the accumulation of institutionalized knowledge. When designing processes that can cope with variability, we need to look at historical production data to learn from mistakes and successes. The FDA's Janet Woodcock has frequently stated that QbD is derived from a combination of prior knowledge, experimental assessment, and a cause-and-effect model that links critical process parameters and critical quality attributes.

Achieving the goal of manufacturing process excellence through QbD requires us to begin the work in process development. It's natural to think of the flow of data and information in the forward direction from process development into manufacturing, but data and information also needs to flow backward from manufacturing into process development.

By using data and information from current commercial processes to assist with future process development for new products, we leverage investments that we have already made and experience we have already gained. To do this, on-demand data access and investigational analysis are required for successful collaboration between the process development and manufacturing teams. This allows us to design and build additional risk reduction and ruggedness into the next process so that it can better handle variability.

The FDA's Process Analytical Technology (PAT) guideline shows the value of continu-

ous learning that comes from analyzing process data when coupled with systems that support the acquisition of knowledge from those data, saying:

"Continuous learning through data collection and analysis over the lifecycle of a product is important. These data can contribute to justifying proposals for post-approval changes. Approaches and information technology systems that support knowledge acquisition from such databases are valuable for the manufacturers and can also facilitate scientific communication with the Agency."

QBD REDUCES RISK

By increasing process understanding, QbD reduces process risk and variability, and can move us toward real time quality assurance.

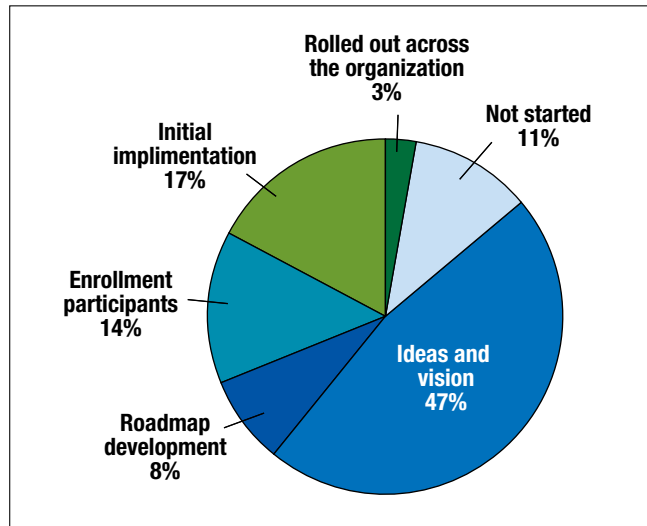
Most organizations are still thinking about QbD rather than implementing it. The top reason? "Too many other things to do."

Thus, building QbD into future manufacturing processes is one of the most important benefits of the effort undertaken by collaborative product development and manufacturing teams conducting retrospective data analysis.

The FDA knows that accurate and reliable predictions are a reflection of process understanding, which is inversely proportional to risk. A well understood process reduces the need for final product testing, because the process is under control while it is running, i.e., in real time, or relevant time. Parametric release, or real time release, is based on this idea that the more companies understand about their processes, the more assured the quality outcome, and the lower the risks to consumers.

Four years ago, the FDA also started a risk-based inspection program that offers fewer and less intensive inspections when a manufacturer can demonstrate process understanding that leads to better control of the

Figure 1. At what stage is the Quality by Design initiative at your company?



To get buy-in, break down the initiative into workable goals and ensure you don't overreach the scope.

variability in process outcomes through QbD. A site risk potential (SRP) score, developed as a way for the FDA to prioritize plants for inspection, is made up of facilities risk (e.g., establishment type and defect history), product risk (e.g., prescription, injectable, or over-the-counter drugs), and process risk (e.g., process controllability and contamination potential)—with the date of the last inspection factored in. Thus, making better choices when designing future manufacturing processes also can reduce the process risk portion of the SRP score and improve future inspection records. Of course, fewer inspections translate to large savings in time and money.

Therefore, the question at hand is clear: With these manufacturing and business benefits within reach, why aren't more companies embracing QbD as an essential part of their businesses?

WHY QBD IS STALLING

As an industry, we need to move QbD initiatives forward by helping internal teams see potential benefits, so they will give QbD a higher priority. In September 2007, Aegis

Analytical Corporation conducted a survey in collaboration with AMR Research to examine the industry's use of QbD.⁴

As Figure 1 shows, 58% responded that their QbD initiatives were only in the "ideas and vision" stage or "not started," while a mere 3% had rolled out the initiative across their organizations. So most organizations are "still thinking about QbD" as part of their corporate strategy rather than engaging in implementation.

When asked about the biggest obstacle to progress on a QbD initiative, the largest factor was "too many other things to do" cited by 45% of respondents (Figure 2). This is a huge disappointment. How could this be? Presumably, we are all putting out fires and no one has enough time to look to the future. That reason was followed by "most people don't know what it is" and "management commitment" (both cited at 19%).

What this survey data may mean is that, so far, the business case for Quality by Design has not been successfully made in many companies. When there is a compelling business case for something, it's interesting how quickly it becomes a top priority. Surely, this can happen with QbD as well.

MAKING THE BUSINESS CASE

Those who are on board with QbD as a way to achieve reduced process variability may need help getting management to buy into this idea in their companies by putting together a convincing business case. New initiatives and related technology at pharmaceutical companies usually are evaluated by decision makers and their influencers, based on how well they do the following:

- apply to existing priorities
- leverage existing investments
- have a clear project definition and scope
- offer near-term return to the bottom-line
- make a significant impact on corporate goals.⁵

Relating a QbD initiative to these criteria can help highlight the business benefits and gain management buy-in. As we have seen, significant business and quality compliance benefits can be achieved through QbD when process development and manufacturing teams collaborate. But to achieve these benefits, the right enabling technologies are also required.

1. Application to existing priorities

It is advantageous to align QbD with existing corporate priorities. Initiatives can be tied to two overarching themes that are likely to be high up on companies' priority lists because they are essential for staying in business, given the regulatory and competitive pressures that exist today: 1) operating in the public's best interest through regulatory compliance and 2) remaining competitive for the long-term in the marketplace.

If there is not a clear common thread between QbD and existing corporate priorities, perhaps it is more prudent to first make a case for adjusting corporate priorities to take the current regulatory environment and the company's long-term competitiveness more fully into account.

2. Leveraging existing investments

Particularly in terms of information technology (IT) investments, it is important to demonstrate how process development and manufacturing teams can easily access and get added value out of data in existing systems, such as laboratory information management systems (LIMS), paper records, enterprise resource planning (ERP), manufacturing execution systems (MES), and in some cases, electronic batch record (EBR) systems. This is an important factor to IT decision makers, as well as CFOs, who may be evaluating the merits of QbD initiatives.

A strong argument to use is reversing the Pareto Principal, also known as the 80/20 rule. This rule was popularized by the late Juran, who observed that 80% of effects come from 20% of causes. Juran named this principle after Italian economist Vilfredo Pareto, who observed that 80% of income in Italy went to 20% of the population. In the pharmaceutical industry, if 80% of time is typically spent trying to access the necessary data and only 20% of time is spent analyzing data to understand and control the cause of process variability, there is a clear business reason for reversing those percentages. Easy, on-demand access to all types of data provided in appropriate context for users' needs is the best way to reverse the 80/20 rule.

3. Clear project definition and scope

To get buy-in, it is critical to clearly convey the parameters of QbD initiatives by breaking

QbD implementation teams need to take a long-term view rather than promote unrealistic expectations about near-term returns.

down the big picture into workable goals and objectives—ensuring you do not overreach in terms of the scope. Implementing QbD in stages can help get the green light turned on. An implementation plan that starts with a quick and clear return on the project cost can be beneficial to demonstrating return on investment (ROI) and getting approval for longer-term implementation projects.

It's also important to demonstrate the value and benefits of having teams collaborate on QbD initiatives. Process development, manufacturing, and quality assurance all need to work together. There was good news in the Aegis/AMR survey regarding which groups were involved at those companies that were planning or already implementing QbD initiatives (Figure 3).⁴ Having these groups work together requires the right technology that enables access to data in the right context for various users.

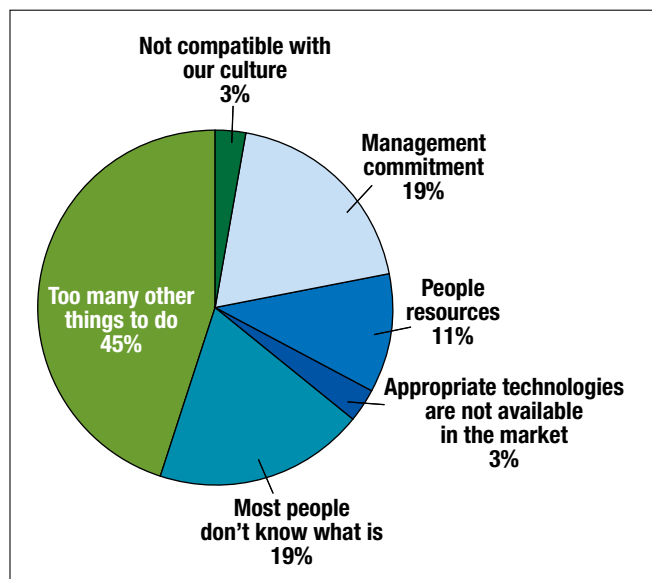
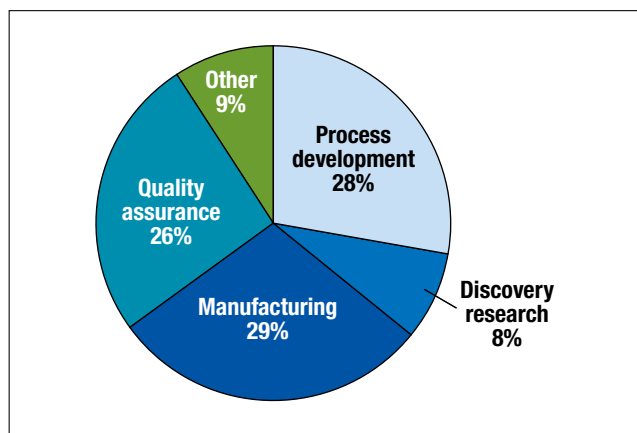


Figure 2. What is the biggest obstacle to progress on a Quality by Design initiative at your company?

Figure 3. Which of the following organizations are involved, or will be involved, in your QbD initiative?



Companies who adopt QbD can expect significantly reduced risks of costly deviation investigations and rejects.

4. Near-term return to the bottom-line

The fact that most US companies typically make decisions based on near-term results presents a challenge. In the case of return to the bottom-line, QbD implementation teams really need to take a mid- to long-term view rather than promote unrealistic expectations about near-term returns.

As mentioned above, structuring an implementation program to show an early return based on a limited scope can build confidence in the potential for larger, longer-term benefits. For example, choose a new process with a high degree of process variability for a pilot implementation to show time saved by removing variability from the process. Showing how a reduction of as little as three weeks of process development time saves \$20 million of out-of-pocket and opportunity costs is, for example, a very compelling ROI.

Looking specifically at opportunity cost, the numbers grow large very quickly. The total revenue for the biotech industry in 2002 was \$42.6 billion, derived from sales of the 130 biotherapeutic drugs on the market at that time.⁶ The estimated revenue potential of an average biotech drug can thus be calculated as \$328 million per year. This converts to an opportunity cost of roughly \$1.3 mil-

lion per day for each day of the working week that a new biotherapeutic is in process development rather than on the market. Taking the midpoint of the range of process development project resource hours (406,000 hours) and the midpoint of the time such projects take (42.5 months), and using a fully burdened technical personnel cost of \$225 per hour, we can calculate the burn rate of a biotherapeutic development project at roughly \$107,000 per day for each day of the working week. So, the full cost to a biopharmaceutical company for each working day that a new therapeutic is in process development rather than on the market is on the order of \$1.4 million per day.

5. Significant impact on corporate goals

As mentioned previously, corporate goals need to be appropriately aligned with the objectives of QbD in terms of 1) operating costs, 2) the public good, and 3) remaining competitive. If company goals follow these themes, QbD initiatives can definitely help achieve those goals over the long-term.

Some of the specific, potential longer-term business benefits that can be related to the bottom line and corporate goals include:

- reduced batch failures, final product testing, and batch release costs
- lower operating costs from fewer failures and deviation investigations
- increased predictability of manufacturing output and quality
- reduced inventory costs from raw material, work-in-progress, and finished product
- faster technology transfer between development and manufacturing
- faster regulatory approval of new product applications and process changes
- fewer, shorter, and less costly regulatory inspections.

The last benefit should be driven home when the FDA completes its aforementioned study assessing the value of QbD information in applications.

TECHNOLOGY REQUIREMENTS FOR QBD

When outlining business benefits, identifying and explaining the technology requirements needed for understanding the sources of process variability is critical to persuading corporate decision makers to give higher priority to a QbD initiative. There is an expect-

tation that companies who adopt QbD, together with a quality system as described in the ICH Q10 guideline, *Pharmaceutical Quality System* will achieve a “desired state” of pharmaceutical manufacturing.⁵ These companies can expect a significant payback in reduced risks to customers and therefore to the business itself, as well as in significantly reduced risks of costly deviation investigations or rejects and consequent enforcement actions as a result of the FDA’s commitment to science-based regulation and risk-based enforcement.

The technology platform needed for QbD and its associated process improvement initiatives must allow immediate user access to all the process development and manufacturing data sources and data types, so that their value can be leveraged together with data from newer (PAT) instruments. The data must be available on-demand in the same working environment with the analytics, visualization, and reporting capabilities that allow exploration of cause-and-effect relationships by collaborative multidisciplinary teams of process

development, manufacturing, and quality users that work across geographic locations.

Different types of data must be easily accessible in a way that automatically accounts for their different formats, naming conventions, and their intra- and inter-batch genealogies. The data access method must let users move directly into identifying and understanding cause-and-effect relationships between critical process parameters and critical quality attributes without spending excessive amounts of time on manual programming tasks and manually collecting and reconciling data. This is the modern replacement for what is so often the spreadsheet madness that occurs today when things go wrong and the process needs to get back on track under crisis conditions.

SUMMARY

Quality by Design can rise on the priority list only when organizations understand the business benefits it enables and have a full picture of what is required in terms of time, monetary, and resource

investments. Detailed research and presentation of the regulatory and cost benefits enabled by process understanding that leads to reductions in process risks and variability will help more companies get on board to prioritize QbD ahead of other initiatives and demonstrate ROI. ♦

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