Informatics Engine Drives Pharma Development toward Quality by Design

Learning from other industries

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The pharmaceutical industry is looking more at holistic approaches to improve the process of bringing new products to market. Adopting these approaches can accelerate product development while lowering operational costs. Quality by Design (QbD) has come relatively late to the pharmaceutical industry. For years, other industries, including the automobile, aviation and food & beverage industries, have adopted, very successfully, the Six Sigma QbD philosophy. The International Conference on Harmonisation (ICH) rolled out its first framework for a QbD concept for Pharmaceutical Development in 2003. Some years later, the U.S. Food and Drug Administration (FDA) introduced its first concept for risk-based current Good Manufacturing Processes (cGMPs). Over the years the industry has been warming up to the benefits of QbD.

Analysis of QbD has identified many potential benefits. In terms of quantifiable benefits, value comes from four main areas: a reduction of Cost of Goods Sold (COGS) and capital expense, increased technical development productivity, improved quality (and lower risk) and increased sales. These four combined could potentially provide $20-$30 billion more in profit.[1] While the pace has been slow, new International Society for Pharmaceutical Engineering (ISPE) Product Quality Lifecycle Implementation (PQLI)[2] guidelines seem to accelerate adoption and are embraced by the FDA and the European Medicines Agency (EMA). Managing knowledge across pharmaceutical development studies, technology transfer activities, process validation studies, manufacturing experience, continual improvement and change management activities are complex subjects. This article explores the informatics journey and its role in driving QbD adoption within Pharma Development and gives some explanation of the concepts behind QbD.

QbD focuses on a better understanding of the processes and the product attributes that affect final drug quality. In doing so, regulatory and business opportunities are provided that can improve product quality and performance through the use of more effective, efficient and robust meth-

ods that bridge the entire product development cycle, from research through development to manufacturing.

Two factors that commonly work against QbD are the fear that it is very expensive and will drive up costs and the fear that it will require a lot more time for analysis. Research has showed that the cost to implement QbD is in fact minimal, and the increase in time spent, if present at all, is negligible.[3] In the development phase, QbD will create more robust and efficient processes and provide a significantly higher understanding of the causes of product variation, all at a lower cost. For manufacturing QbD could lead to faster release of batches, with substantially higher quality and high cost savings. The industry has reported reductions in the time of batch releases from days to hours. Process Analytical Techniques (PAT) is replacing traditional time-consuming off-line laboratory testing methods with direct on-line measurement.

SIMPLE IS BEAUTIFUL

Quality by Design is a simple concept. It asserts that inspection does not create quality products, processes do. Thus, design, development and manufacturing processes result in a predefined quality drug. To achieve this QbD requires a full understanding of how formulation and manufacturing process variables influence product quality. Done well, QbD confers competitive advantage. "Quality" becomes something that organizations define for themselves and strive to achieve during every phase of product creation — from research and development to manufacturing and marketing. Witness the near-constant retooling and reinvention of manufacturing processes in the automotive, semiconductor and electronics industries that started with Six Sigma now extending to and fully embracing QbD. The evolution to QbD is a logical next step since QbD is built on top of Six Sigma[4, 5] and extends into the design space. Quality that is embedded in the design phase of development is a mindset that supports continual improvement. This mindset must be reinforced throughout the company from senior management to the manufacturing shop floor.

CONTINUAL IMPROVEMENT DRIVES QUALITY

The approach toward defects should be one of avoidance, prevention and resolution. The aim should be to do things right the first time — anyplace, anywhere, anytime — in the product quality lifecycle implementation. Successful QbD strategies include cross-functional development of people across departments, supporting communication and increasing the ability to think in terms of quality. When this attitude is applied throughout the process, defects will be reduced dramatically, and the output of any process will be improved. The farther downstream defects or design errors are detected, the more costly they will become to correct. In all cases, defects should be corrected during the design or manufacturing phase; there should never be a risk of product recalls or harm to the customer. The cost of resolving errors, referred to as the "Cost of Quality," grows exponentially when detected later in the process — it clearly puts the focus on the design. With this in mind, well planned products with Quality involvement in design, as well as in production, will cost less to manufacture and to maintain. In addition, it will cost less to own or buy the product or service and will improve customer satisfaction.

$$Y = f(x_1, x_2, x_3, ...)$$

Output measure or dependent variable (Y) is the lagging indicator while the X is the leading indicator, which means that any X will determine the Y, therefore, we only have control of the Y through the X. When we look at a process, it consists of

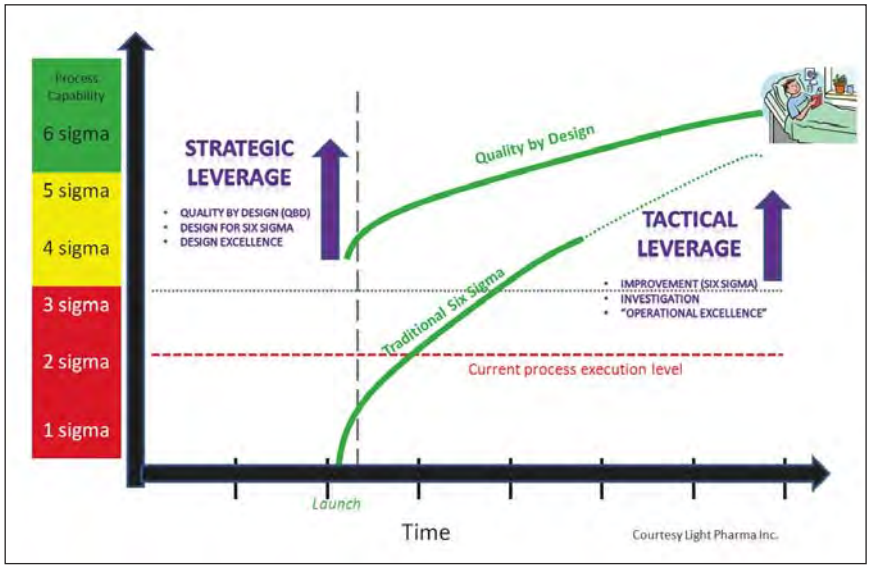

Figure 1: Knowledge Management Enables Continuous Process Improvement

Table 1		
Phase	Activity	Tools
Identify the opportunity	Prioritize Customer's needs and translate those needs into design requirements	• Definition of the business case • Project charter • Benchmarking
Define the requirements	Customer's needs and wants are translated into verifiable requirements.	• Requirements and gap analysis[7] • Critical to Quality (CTQ) • House of Quality (HOQ)[8]
Develop the concept	Develop a concept which will meet the customer requirements.	• Project management techniques[9] • Six Sigma tools
Optimize the design	Optimize the design in such a way that the maximum output is obtained from the developed concept	• Failure mode and effects analysis (FMEA)[10] • The theory of inventive problem solving (TRIZ)[11] • Design of Experiments (DoE)[12]
Verify Conformance	Validate against established process controls, exercise a complete cost-benefit analysis	• Cost calculation • Product Testing • Validation tools

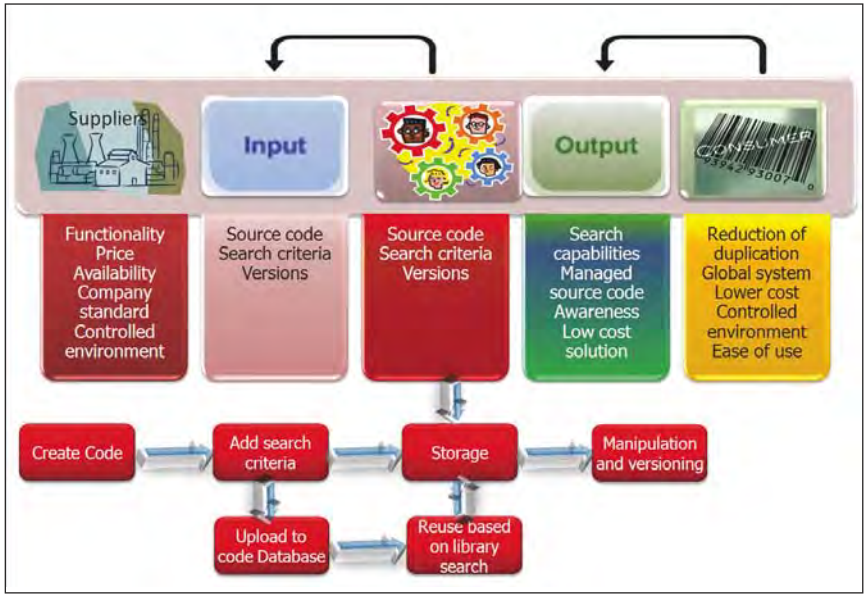

Figure 2: SIPOC process map helps to visualize the scope of a process

many steps. The total variation in the output depends on the number of variables and their respective contribution to the total variation. In other words, to fight back the variation in a process, we have to know the different steps (the x's) and the contribution of the variation of each of them to control the output. The total variation of the output is the sum of the variations of x.

Six Sigma principles and tools define and quantify quality enhancements. The goal is to reduce defects, enhance customer satisfaction and contribute to positive financial results. The key to Six Sigma is a quantitative approach. To get results; a variety of statistical tools are used. The process is completely data driven. Computerized systems supporting the storage and analyses of the measurements are critical, both for speed and compliance. A production facility running at a Six Sigma level is close to perfection, meaning that only 3.4 defects per million opportunities or units will be recorded. Many processes act on lower sigma levels; e.g., a 5 sigma level would result in approx 230 defects per million opportunities. Many processes may not even reach this level of variation despite the efforts; three or four level sigma may be the best that can be achieved. When this sigma wall is hit, no further process improvements can be made. In these cases there could be a fundamental problem in the design of the product or service, preventing further improvements. Redesign of the product is the only possibility to further improve the quality level. Design or redesign of products should be a customer-focused activity. It is important to find the balance between the "Voice of the customer" and the "Voice of the process," defining the products that you create and resulting in maximum customer satisfaction. Rosenau[6] suggests that the former relay process of passing the product from one department to another is obsolete. Multifunctional team activities involving many departments are needed for effectiveness and speed-to-market. This consists of two main parts: an idea-generating, brainstorming front end and a later product development phase.

Project management tools are critical for verifying correct execution of the

Table 2: Mapping of the traditional Six Sigma DMAIC	
Design	Track process steps, designs, attributes and values to understand what variables affect critical quality attributes
Measure	Implement statistical methodologies such as design of experiments (DOE) and statistical process control to mathematically sample and model the design space
Analyze	Automate high-throughput, parallelized experimentation to further explore process and product variability affecting critical quality attributes Store, mine and share information necessary to understand the design space in a lab operating environment that supports consistency and comparability
Implement	Utilize predictive and simulated modeling techniques to demonstrate a full understanding of the design space
Control	Leverage accumulated information effectively across all areas of the enterprise — research, development, scale-up, clinical and manufacturing

project and controlling cost and scope. A tool that has proven is worth is SIPOC. It provides a graphical way of describing a process with a clear link between the customer requirements (the What) and the process capabilities (the How). Having clear process boundaries will prevent too large a scope. Unavoidably, requirement analyses are crucial for quality by design. If we manufacture products that the customer doesn't need, however well designed they may be, then, we will fail.

Excellence = Quality * Acceptance. This simple equation illustrates the essence of successful manufacturing. Reaching the top in pharma manufacturing mandates a full understanding of all acceptance criteria, at all levels within the product value chain.

EXPLORING THE DESIGN SPACE WITH INFORMATICS

The most obvious shift in thinking proposed by the regulatory bodies during the past decade has been the articulation, exploration and understanding of the therapeutic "design space." The ICH guideline defines this space as "the multidimensional combination of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality"[13] and stipulates that working within the approved design space is not considered a change, while movement out of the space can initiate a regulatory change. As its definition implies, development of the design space involves fully understanding the statistical relationships between input variables (e.g., raw material and active pharmaceutical ingredient (API) attributes), manufacturing process parameters and critical quality attributes (CQAs) of the finished drug product.

THE INFORMATICS JOURNEY TO IMPROVED QUALITY BY DESIGN

The journey begins with the transition from paper to digital, which includes both the transfer of paper-based processes to "glass" and the identification and adoption of information and process standards to harmonize data exchange. The completion of this step propels organizations down a path towards clean, tractable data, drives out human variability and improves data integrity. Automated laboratory systems speed execution by eliminating the need for scientists to document

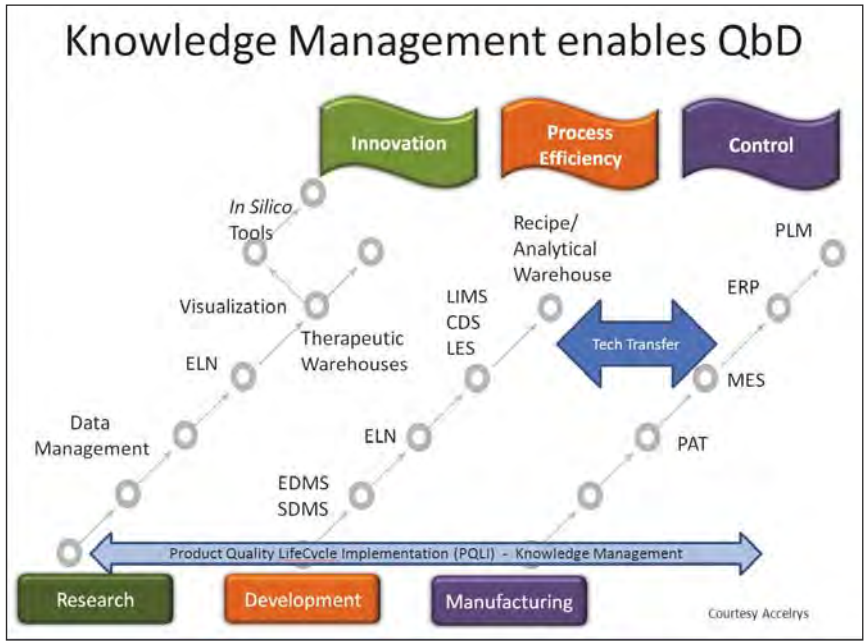

Figure 3: Creating knowledge from data at Accelrys

what they are executing. And vast, rich data sets can be mined and modeled to enable data-driven, predictive control. This helps organizations better understand and describe the variables affecting the critical quality attributes of a product and, ultimately, optimize processes to achieve product and organizational goals more quickly and efficiently — the essence of QbD.

With an informatics system supporting QbD in place, scientists can resolve critical regulatory and QA/QC bottlenecks through the use of existing informatics tools. For example, the informatics system can capture electronically all information describing both the process and the product, including automated audit trails and version control.

STREAMLINING STANDARDS-BASED TECHNOLOGY TRANSFER

The Electronic Laboratory Notebook (ELN) is evolving to adopt compliance with international industry standards such as ANSI/ISA-88 (covering batch process control) and ANSI/ISA-95 (covering automated interfaces between enterprise and control systems), both of which are commonly used in manufacturing. By incorporating these standards and structuring data in a fully searchable format, the ELN enables scientists to mine information from development and manufacturing for improved process and product design. In addition, information is more readily transferable between systems. For example, a recipe delivered in early development can be rapidly transferred to a Lab Execution System for API manufacture and then to a Method Execution System for mainstream manufacturing.[14]

ADDRESSING CRITICAL QUALITY ISSUES – AN EXAMPLE FROM BIOLOGICS

The goal of a successful QbD informatics strategy is efficient, consistent, accurate data capture and re-use that enables an organization to transform data into information, knowledge and, eventually, product and process wisdom. For informatics to support QbD, especially in the process and product development space, organizations need to move away from the paradigm of "How" a product behaves to answering "Why" a product behaves the way it does. This not only moves organizations to understand more deeply what type of variation affects quality; it also provides important clues as to what is the optimal product from a cost, quality and product efficacy standpoint.

ADOPT A NEW MINDSET FOR QUALITY

Good leadership, outstanding processes and quality-driven culture are the ingredients for making companies successful. Technology just enables the achievement of that goal. Develop people cross-functionally to spread quality across departments, investigate root-causes and learn from quality events. The common element that will catalyze the greatest benefits throughout the development lifecycle is knowledge management. ICH Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of the product lifecycle.[15] The integration of meaningful quality metrics such as the Cost of Poor Quality (CoPQ) can substantiate the ROI of adopting the QbD mindset and culture. SC

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