Informatics:
The Glue to Build Enterprise Knowledge

Integrating platforms accelerates QbD continual improvement initiatives

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Extreme cost pressure, consumers demanding reliability and loss of market share were key drivers for the electronic and car industry to adopt Juran's[1] successful QbD theory. It is proven that his theory to adopt continuous improvement strategies to decrease variability resulted in significantly better products and financial performance. In the last year, we have generated more data than all of the previous 5000 years combined!

The analogy of industrial and scientific processes that transforms data into something useful (information) can be taken a significant step further by revisiting how we deploy our current CAPA methodologies.

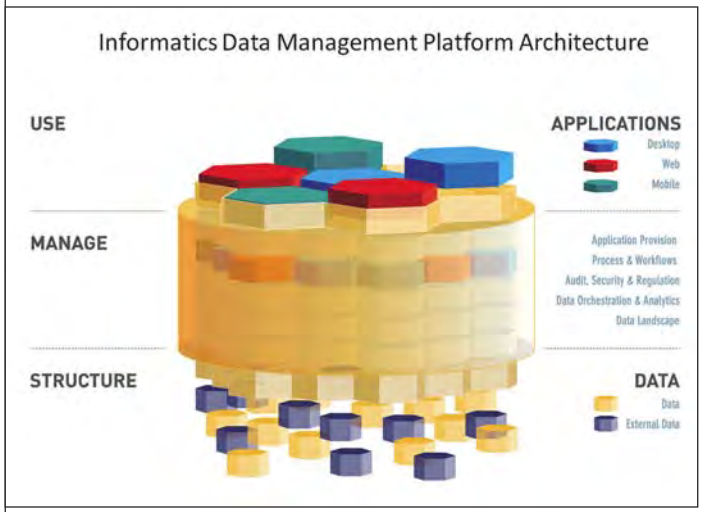
An action to eliminate the cause of a detected nonconformity is referred to in the ICH Q10[2] guidelines as a Corrective Action, while a Preventive Action is referred to as an action to eliminate the cause of a potential nonconformity. A mature CAPA quality system should detect problems before they occur and prevent them. This article explores a different viewpoint about how existing data, stored in different departmental data silos, can create new knowledge to increase our product and process understanding.

HOUSTON, WE HAVE A PROBLEM

Pharmaceutical manufacturing currently operates at a 2-3 sigma level.[3] This means 70 to 95 percent of all manufacturing batches meet specifications, resulting in five to 20 percent failures, while many other industries operate at a 6 sigma level that results only in 3.4 faulty productions in 1,000,000 batches. The *Wall Street Journal* cited Dr. McClellan,[4] former FDA chief who lectured some years ago, while deploying similar manufacturing equipment, that the pharmaceutical manufacturing techniques lag far behind those of potatochip and laundry soap makers.

McKinsey confirmed that many of these shortcomings reflect poor quality practices and represent cost savings opportunities for the Quality by Design paradigm.[5] So, what keeps the industry from changing? And how can informatics contribute to support the QbD mindset effectively? How much more pain is needed for the industry to force a change? Strong patent protection, isolation from economic cycles and conservative regulatory systems made the industry late to respond.

Table 1: Traditional CAPA Workflow Procedure	
Identification	Identify nonconformity, incident or the potential problem
Evaluation	Evaluate the magnitude of the problem and potential business impact
Investigation	Investigate procedure with assignments of responsibility
Analysis	Analyze the root cause of the problem
Implementation	Implement action plan
Verification	Verify assessment of the appropriateness and effectiveness of the actions taken



A managed data landscape is crucial to integrate the necessary decision making data. *Courtesy of IDBS*

ANTICIPATE CHANGE

The A-Mab case study,[6] which is based on a monoclonal, relatively well-defined antibody drug protein, demonstrates the principles of a Quality-by-Design implementation, and illustrates a true practical QbD case from a scientific perspective. Created and contributed jointly by the industry and regulatory bodies, this example demonstrates the willingness to co-operate.

There is a misperception that discovery and early development research are relieved from systematic documenting nonconformances and deviations. Adopting the PQLI (Product Quality Lifecycle Implementation), prior knowledge is an essential source of information. This information is beneficial in a better process understanding in later stages of the process within the lifecycle.

"Not enough life science companies spend enough effort applying predictive analytics and visualization tools to laboratory test results to reduce the risks of product quality issues," says Michael Shanler, analyst at Gartner. Many organizations are still using basic tools like spreadsheets, databases and paper-based systems to track their CAPA issues and efforts. "Often times, the data from laboratory informatics tools is stored in silos," continues Michael. "Rarely is the data easily searchable and leveraged across the enterprise. There are opportunities for improvement."

Agile innovation, the use of process analytical techniques (PAT), widespread access to information and communication technologies, and innovative adaptable systems of workflow now allow scientists across the globe to collaborate on virtual mega-engineering projects that are unprecedented in scale of scope.

THE POWER OF LIFE CYCLE PROCESS IMPROVEMENT

Quality should be built into the design throughout the specification, design and verification process. Performance metrics on nonconformance tracking are mandated and monitored by regulatory authorities. However, metrics on nonconformance are often inaccurate, since an organization is often functioning with too many nonconformance systems, with poor systems that do not do a good job of tracking nonconformances, or with paper-based systems whose metrics cannot be easily managed.

An effective CAPA system has been, in effect, an expectation for many years for companies operating to ISO 9000 Quality Management standards, including medical devices operating to ISO 13485. The pharmaceutical Industry has, over the last decade, put significant effort and resources, in a reactive mode, to managing and investigating deviations, resulting in corrective actions. However, there has been less focus on proactively undertaking preventative actions within the CAPA system.

ICH Q10 describes a comprehensive model for an effective pharmaceutical quality system that is based on International Organization for Standardization (ISO) quality concepts. The standard includes applicable good manufacturing practice (GMP)

Table 2: A-Mab Case Study Objectives

The case does	The study does not
Demonstrate implementation of the principles of Quality by Design	Present a prescriptive approach
Leverage the significant knowledge base of both commercial and investigative monoclonal antibodies	Follow a traditional approach
Show application to both drug substance and drug product	Deal with all possible unit operations
Provide illustrative examples based upon real data	Address all quality attributes or process parameters
Demonstrate a science and risk-based approach	Represent a "mock" regulatory submission
Show there are many ways to implement QbD	Represent a standard

regulations, and complements ICH "Q8 Pharmaceutical Development" and ICH "Q9 Quality Risk Management."[7] ICH Q10 is a model for a Pharmaceutical Quality System (PQS) that can be implemented throughout the different stages of a whole PQLI.[8] ICH Q10 requires an effective CAPA system that identifies areas for improvement as product and process understanding expands, implements improvements, and monitors effectiveness.

Deviations often are seen as singular events, rather than yet another example of a problem that is already identified as a deviation in the system. There is no "look back" to determine if the new event is already covered by a current effort, or the evidence of an ineffective CAPA. Products impacted by the deviation are not evaluated based on scientific data, and the perimeter is not drawn wide enough to include anything beyond the current batch — and certainly not to anything released into the market place.

ADOPTING THE QbD MINDSET

Corrective Action and Preventive Action is one of the four elements to support pro-active continuous improvement process, within this product lifecycle approach. Today's CAPA systems are good, but focusing on a traditional reactive approach. In many cases, these are initiated by an exception in a manufacturing process. The Q10 lifecycle guideline recommends a much more pro-active approach to make biopharmaceutical manufacturing simple, more robust and sustainable. Continuous improvement should start at the source from R&D. Modern informatics platforms will allow organizations to significantly improve the usage of prior knowledge further in the value chain. Scale-up information, clinical research, translational medicines and failed reactions during discovery may well contribute to a better understanding of the drug substance than we have anticipated. These informatics platforms will allow cross-functional data trending and holistic data reviews and significantly influence the way we look to CAPA. It is time to put more emphasis on the preventing facet and re-order the sequence of the CAPA abbreviation into PACA. We now can turn our potential data graveyards into valuable resources to facilitate the QbD promise across the pharmaceutical quality system model.

Table 3:
PACA System Throughout the Product Lifecycle

Pharmaceutical Development	Preventive and corrective actions are incorporated into the iterative design and development process. Informatics platforms are the glue to enable the cross functional collaboration.
Technology Transfer	Effective system for feed-forward and feedback and continual improvement. Informatics platforms facilitate transforming tacit knowledge into shareable information content.
Commercial Manufacturing	Effective process performance for nonconformances, recalls, deviations, audits, regulatory inspections and findings.
Product Discontinuation	PACA should continue after the product is discontinued. The impact on product remaining on the market should be considered, as well as other products that might be affected.

BUILDING BRIDGES

The future of PACA will be more based upon non-exception data types, including data trending and holistic data reviews, increased industry and regulatory surveillance and costs of quality models. Overall, an effective PACA system will provide services to address harmonization, integration and consolidation of business processes in life science research, development and manufacturing. It will answer the "what's in it for me" question and enable cross-functional collaboration between research, development, quality assurance and manufacturing corporations to achieve Quality by Design (QbD) initiatives. SC

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