

## PHARMACEUTICAL ENGINEERING Interviews

# Roger Nosal, Vice President, Global Chemistry, Manufacturing and Controls (GCMC), Pfizer

**R**oger Nosal is currently Vice President of Global Chemistry, Manufacturing and Controls (GCMC) at Pfizer. GCMC is responsible for the development, preparation, prosecution and defense of chemistry, manufacturing and control commitments and data for investigational, commercial and post approval regulatory submissions globally. Nosal currently leads the PhRMA LDKITT on Implementation of Quality by Design and has been instrumental in developing and establishing Pfizer's regulatory approach and position for application of QbD, including the introduction of Real Time Release testing (RTRt), Continuous Quality Verification (CQV), Continuous Processing and extension of QbD for development of analytical methods and stability protocols. He has 32 years of experience in the pharmaceutical industry at G.D. Searle, Monsanto, Pharmacia and Pfizer. During the last 19 years, Nosal has been responsible for developing and executing regulatory CMC strategies and approvals of global commercial applications for 49 new chemical, biological and device products and scores of investigational and post approval regulatory submissions. Prior to his tenure in regulatory, he served as a medicinal chemist dur-

ing which he authored 24 patents for a diverse range of medicinal candidates (PAF antagonists, 5-HT<sub>3</sub> antagonists and 5-HT<sub>4</sub> agonists, COX-2 inhibitors, leukotriene agonists and antagonists, serotonin inhibitors) and as a process chemist, where among other projects, he focused on synthetic development and analytical control of derivatives of aspartame and manufacturing optimization of high order cuprate couplings for synthesis of prostaglandins.

### What do you use for your elevator pitch/lay-persons definition of QbD?

QbD is fundamentally about developing process understanding and product knowledge to improve assurance of product quality. Conceptually, it describes a scientifically grounded approach for prospectively assessing risks, prioritizing experiments and developing a robust and holistic control strategy.

### After several years leading industry toward adoption of QbD, what is the status of implementation of QbD at Pfizer?

The implementation of QbD is pervasive within Pfizer particularly during product development. Risk-based approaches are routinely used to assess manufacturing processes, prioritize experiments and determine criticality of product attributes and process variables.



Pfizer's "Right First Time" paradigm is largely based on principles of QbD.

### Has participation in the pilot programs (FDA Pilot Program and the recent FDA/EMA Parallel Pilot Program) been successful for Pfizer and industry?

Participation in the FDA Pilot Program was successful for Pfizer and industry. Prior to the pilot program, QbD was primarily conceptual. Companies had adopted elements of QbD to assess the technical merits of process and product design, but had been reluctant to share the results from these approaches in regulatory submissions without assurance that regulatory review would not impact approval. The FDA Pilot Program provided a constructive opportunity to engage FDA

on the technical and regulatory merits of the application of QbD. This pilot also began to address the possibility of offering regulatory flexibility where process understanding and product knowledge had been demonstrated to adequately reduce and manage risks.

As for the FDA/EMA Parallel Pilot, it is premature to judge its success as there have been limited examples; however, EMA and FDA regulators have claimed that the Parallel Pilot has been “extremely beneficial for regulators.” Anecdotal comments from FDA, EMA and PMDA (Japan was invited to participate as an observer for the Pfizer candidate enrolled in the Parallel Pilot) suggest the interactions between the regulatory authorities were useful and insightful.

## Have there been any specific hurdles with the implementation of QbD within Pfizer?

The most significant hurdles have been associated with the most recent QbD regulatory submissions where divergent perspectives between industry and regulatory authorities, primarily in the US and EU on definition and verification of design space, change management, level of detail in regulatory commitments, description of control strategy, consistency of submission content and alignment of inspections with regulatory review have become topics that warrant reconciliation.

## What is your assessment of the regulatory receptivity toward QbD in regulatory submissions?

In general, regulators have been receptive to QbD in regulatory submissions. They recognize the value of increased process understanding and its impact on improving confidence in the quality of products. However, regulators have suggested, and industry has acknowledged, that industry needs to improve their stories particularly with respect to describing a comprehensive control strategy.

## Is the adoption, implementation and regulatory acceptance of QbD transparent globally?

Not entirely. In several countries beyond US EU and Japan, i.e., Canada, Australia, New Zealand and China, QbD is transparent as QbD regulatory submissions have been approved in these countries. For many countries where a limited level of detail is not required, QbD is largely invisible, though the benefits of reduced level of regulatory commitments have been realized.

## From Pfizer’s perspective, what elements of QbD have been most successful to date and why?

The most successful elements of QbD for Pfizer have been the paradigm shift to a prospective, risk-based approach to developing process understanding and product knowledge. Pfizer has observed improved process understanding and capability, technical transfers and communication and integration of development and manufacturing operations. Pfizer has also realized reduced uncertainty, recalls, manufacturing anomalies, quality investigations and manufacturing problems with the adoption of QbD.

I also firmly believe that QbD increased the level and depth of communication between regulatory authorities and industry. While this required significant investment and effort, it improved mutual understanding and the opportunity to establish a reasonable risk-based and science based approach to continual improvement and technical innovation.

## From Pfizer’s perspective, what elements of QbD have not been successful to date and why not?

For EU and US regulators, the conspicuous disconnect between regulatory commitments and change management has been a significant surprise. There appear to be a misalignment within regulatory authorities on the connection between a company’s Pharmaceutical Quality System and change management process and

the regulatory commitments described in a regulatory submission. In addition, the apparent lack of comfort with risk associated with the establishment and verification of design space and decreased rather than increased confidence in quality despite the increase in process understanding and product knowledge in a QbD registration. To some extent QbD regulatory submissions have engendered increased numbers of queries and justification than traditional regulatory submissions and the respective regulatory relevance of many of those queries and increased expectations has been questionable.

## What is the primary benefit of QbD to Pfizer? To Patients?

The primary benefit of QbD to Pfizer and patients is improved process understanding and product knowledge that translates to increased assurance of quality and reliability and consistency of supplies.

## How does the PQLI Guide series support the movement toward embracing and utilizing QbD?

The PQLI Guide series translated the conceptual elements of QbD as described in ICH Q8(R), 9 and 10 into a practical demonstration of “how to” adopt, apply and integrate these concepts into a technical and regulatory strategy for designing and developing a product and associated manufacturing processes. The strength of the PQLI Guide series is that it was based on actual examples and experience from industry.

## Is there anything else that you might want to say to our readers? Any last thoughts?

Recent examples of regulatory misalignment on fundamental aspects of QbD offer opportunities to improve consistency in regulatory expectations and establish relevant criteria for product lifecycle management. QbD also offers a scientific and risk based vernacular that can improve global harmonization of regulatory expectations. 