

The pharmaceutical industry has faced an increasingly difficult economic climate and the number of new molecular entities approved each year has declined. Patent expiration and pressure on healthcare costs, together with compliance and supply chain issues, have resulted in greater attention to the way pharmaceuticals are developed and manufactured.

QUALITY BY DESIGN

Benson and McCabe benchmarked the manufacturing performance of a typical pharmaceutical plant compared with a world-class factory and showed that there was considerable room for improvement in all the metrics (Table 1). It has been estimated that many pharmaceutical processes operate at 2.5 to 4.5 sigma quality levels, but resource-intensive pharmaceutical company quality systems achieve 5 sigma quality levels by, for example, sorting and reworking to prevent defective product leaving the factory.

Arguably, quality organisations within pharma had become overly focused on compliance and ‘quality by inspection’, and the perception – real or otherwise – is that regulatory systems inhibited change, which has resulted in a very conservative industry, reluctant to introduce innovation and continual improvement into manufacturing.

The efficiency gains needed to achieve world-class manufacturing performance cannot be realised by continuing

Table 1: Benchmark data from Benson & McCabe

Measure	Pharmaceutical industry	A winning pharmaceutical factory	A world-class factory
Stock turn	3-5	14	50
On time in full delivery	60-80%	97.4%	99.6%
Right first time	85-95%	96.0%	99.4%
Process capability CpK	1 to 2	3.5	3.2
Overall equipment effectiveness	30.0%	74.0%	92.0%
Cycle time (hours)	720	48	8
Safety/100,000 hours	0.100	0.050	0.001

Contributor profiles



Graham D Cook, senior director, Process Knowledge/Quality by Design, Wyeth Pharmaceuticals, is responsible for leading Wyeth’s QbD efforts in Europe, Asia-Pacific and Latin America. He holds the Wyeth vote in the ASTM International E55 committee, which is developing consensus standards for QbD/PAT in pharmaceutical manufacturing.



Thirunellai G Venkateshwaran is senior director, New Products Quality, Wyeth Pharmaceuticals. He is responsible for the quality planning of new products (small molecules) and for developing approaches for the consistent implementation of quality risk management and quality by design.



Stephen P Simmons is head of New Product Quality & Quality by Design at Wyeth Pharmaceuticals. Prior to joining Wyeth, he held positions of increasing responsibility in the quality organisation at sanofi-aventis and its predecessor companies.

Efficiency gains to achieve world-class manufacturing performance can no longer be realised through the quality-by-inspection method. Graham D Cook, Thirunellai G Venkateshwaran, and Stephen P Simmons, Wyeth Pharmaceuticals, discuss their company’s approach to increasing its understanding of development and manufacturing, which has resulted in high-quality pharmaceuticals.

this approach to quality. Instead, companies need to invest in understanding their products and processes to reduce variability and waste: building quality into the product and process, and seeking continual improvement throughout the product lifecycle – ‘quality by design’ (QbD).

QbD adoption

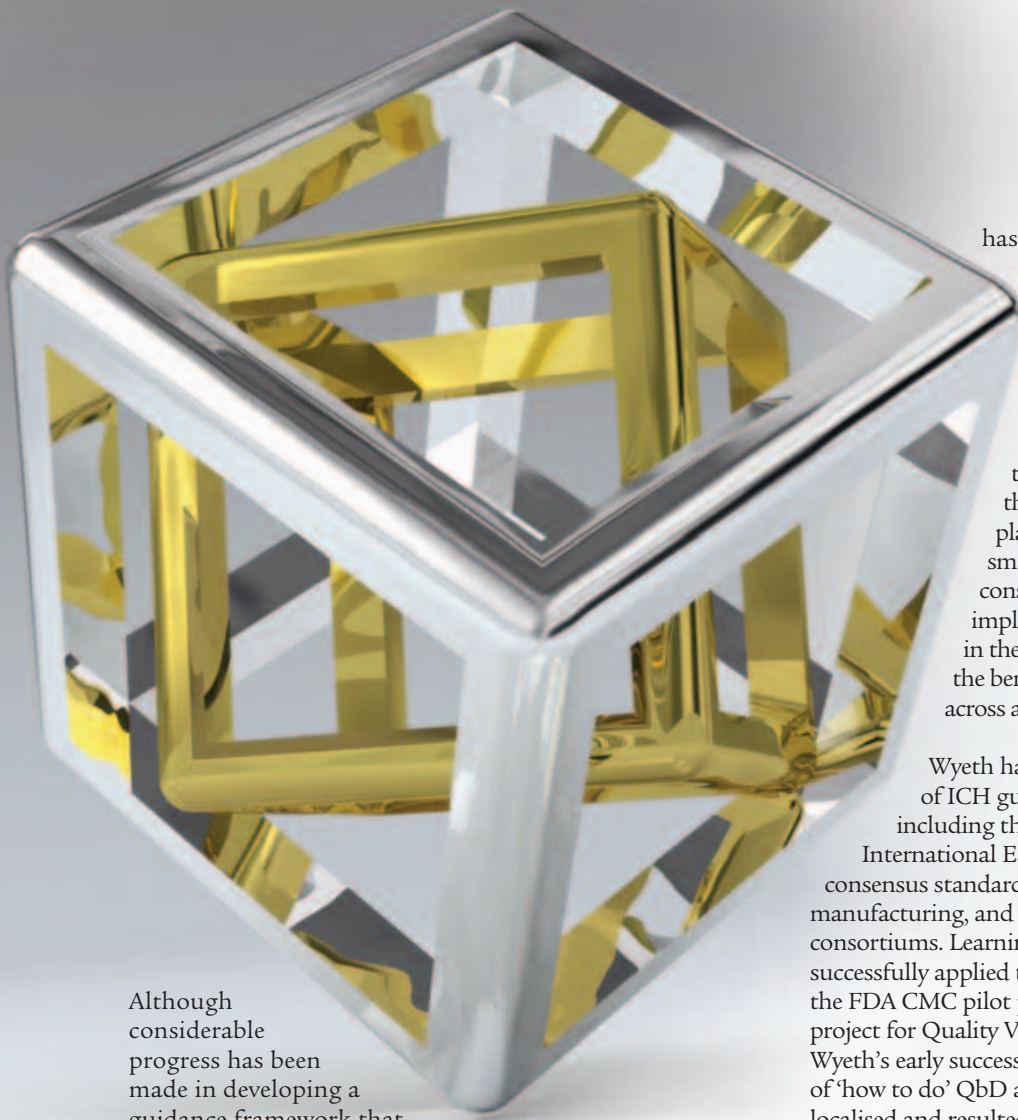
To facilitate industry adoption of quality by design, key guidance documents have been developed (Figure 1). The FDA championed process analytical technology (PAT) as part of the *cGMPs for the 21st Century Initiative* aimed at creating ‘a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight’.

Experts from the three regional groups (US, EU and Japan), working on the Quality Topics within International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), created a vision for the future pharmaceutical quality system and the ICH Q8, Q9 and Q10 guidance documents. In the EU, the EMEA PAT Team published a reflection paper aimed at assisting industry with regulatory submissions.

The ICH vision recognises that industry and regulatory agencies will benefit from QbD by enabling them to prioritise and allocate resources more efficiently, while patients will benefit from improved access to medicines and an enhanced assurance of quality.

Figure 1: Regulatory guidance documents facilitating QbD.

- ICH Q8 (R1) – Pharmaceutical Development. Step 4, November 2008.
- ICH Q9 – Quality Risk Management. Step 4, November 2005.
- ICH Q10 – Pharmaceutical Quality System. Step 4, June 2008.
- PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. FDA. September. 2004.
- Reflection Paper: Chemical, pharmaceutical and biological information to be included in dossiers when Process Analytical Technology (PAT) is employed. EMEA/INS/277260/200.



Although considerable progress has been made in developing a guidance framework that offers the pharmaceutical industry opportunities to adopt modern manufacturing practices, the pace of change in the industry appears slower than might be expected. There may be a number of reasons for this, for example:

- A company is committed to implementing QbD, but development times for new products mean that it may take several years from the application of QbD principles until a marketing authorisation application is submitted for approval by a regulatory agency.
- A company is open to QbD, but is unsure how to proceed. It adopts a wait-and-see strategy because the QbD principles described in the guidance documents are optional, and it wants to determine how and where to implement QbD when regulatory agency expectations are clearer.
- A company continues with the current quality paradigm because the QbD principles described in the guidance documents are not mandatory. It judges that the ROI for QbD is inadequate for its products or business, or perhaps it doubts that the reduced regulatory burden and other benefits can be realised in all markets around the globe because of differences in regulations.

Implementation of a new paradigm like QbD is likely to represent a significant challenge for many, if not all, pharmaceutical companies. Wyeth Pharmaceuticals

has been actively contributing to the development of QbD and PAT and applying the principles to both new and existing products.

QbD: the Wyeth approach

Wyeth is a diversified biopharmaceutical company, with sales growth generated by the biopharma business, represented by the therapeutic proteins and vaccines technology platforms allied to more conventional small molecule ethical pharmaceuticals and consumer healthcare divisions. Although PAT implementation had been pioneered by teams in the small molecule areas, interest in gaining the benefits from the new QbD paradigm exists across all technology platforms.

Wyeth has been involved in the development of ICH guidances and other external activities including the ISPE PQLI initiative, the ASTM International E55 committee developing global consensus standards for PAT and QbD in pharmaceutical manufacturing, and initiatives by trade associations and consortiums. Learning gained through these activities has been successfully applied to QbD/PAT regulatory submissions in the FDA CMC pilot project and the EMEA worksharing pilot project for Quality Variations. Project teams involved with Wyeth's early successes gained valuable practical experience of 'how to do' QbD and PAT, but this experience was localised and resulted in inconsistencies in interpretation and differences in approach. These experts needed to be brought together to enable them to share knowledge, develop agreed approaches to topics such as criticality, and replicate best practices. This knowledge needed to be transferred to a much wider group of personnel who wanted to understand and apply QbD principles to develop and manufacture new products.

This effectively represents a cultural transformation of the business, and it is likely to take several years to fully embed QbD in a large, global organisation. Two tools or approaches were developed to address these issues and foster the implementation of QbD in Wyeth: the QbD Community of Practice; and the QbD Manual intranet guide.

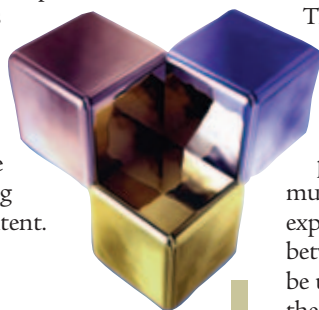
QbD practice and training

Communities of Practice are recognised as an effective means to enable experts and others interested in a topic area to collaborate and share knowledge. A design team of experts in QbD and PAT from different functions and divisions developed the vision, mission, organisation and initial objectives for the QbD Community of Practice. A video explaining the benefits of QbD implementation for the business and membership of the Community of Practice to the individual employee, was produced and screened at sites around the world in the lead-up to the launch in 2008. The launch involved over 20 sites and resulted in a community membership exceeding 400 employees across all divisions and functions.

QbD and PAT have introduced new terminology and thinking to the pharmaceutical industry. Although QbD/PAT concepts and tools may be similar to Lean-Six Sigma, their application still represents a paradigm shift in approach for much of the pharmaceutical industry. That is why it is important that QbD/PAT practitioners and would-be practitioners can easily access information relevant to their role and responsibilities.

To address this need, Wyeth developed a QbD manual, an extensive intranet guide, consisting of around 150-200 web pages of information related to QbD and PAT. The website also provides a portal into the QbD Community of Practice. Parts of the QbD Manual website content were developed with the help of consultants and then refined to reflect Wyeth practice and thinking. Website users can download documents that provide practical illustrations from Wyeth examples of the concepts described on the website.

User testing was conducted on an early website prototype to help ensure that navigation was intuitive and information was grouped into sections that met user expectations. In addition, a 'beta' version of the site was operated in the website development environment before making it available to all Wyeth employees on the main 'Inside Wyeth' intranet site. A 'Common Interest Group' within the QbD Community of Practice is working to enhance and update the website content.



The principles of QbD can be applied to any business, but how they are best exploited will vary.

Effective training is another important element that underpins successful implementation. Training packages are being developed and delivered to facilitate the transformation in ways of working. These include awareness training and in-depth training, which may be incorporated into an individual's training curriculum. Computer-based training is also being developed as part of the mix to ensure a cost-effective and sustainable programme.

Senior management support

Tools and approaches can be developed to meet the needs of different groups, but successful implementation of QbD will be unlikely unless senior management support the initiative. In Wyeth, visible support was created through capital investment in facilities and equipment to support the application of QbD principles and PAT tools, such as its Pharmaceutical Development Centers. Senior leaders in the operations and quality organisations were interviewed for the Community of Practice launch video, QbD and PAT news features have been broadcast via email to all employees and, in a recent global simulcast, Wyeth's CEO acknowledged the importance of QbD to the future of the company.

A visible and effective means of ensuring QbD and PAT use is through the inclusion of specific goals in the cascade of divisional, site, departmental and personal objectives. Linked to this are changes to business processes, such as, incorporating QbD/PAT deliverables that must be achieved before a project can progress to the next stage of development. Enhancement of the company's Quality System to fully realise the goals described in ICHQ10 is also in progress.

Pharmaceutical development centres

Like many companies, Wyeth is increasingly using process analysers, such as spectrometers, attached to process equipment to gain information about the materials being processed. This data can be fed in the process control system to assure quality and enhance manufacturing efficiencies. Wyeth is constructing Pharmaceutical Development Centres, late-stage development and scale-up pilot plant laboratories, at several manufacturing sites to gain product and process understanding through the use of PAT tools, such as Design of Experiments (DoE) and process analysers.

The impact of process parameters and attributes of the raw materials on the critical quality attributes of the finished product must be understood so that a robust manufacturing process and effective control strategy can be developed. Quality Risk Management can be used to prioritise the variables to study, and DoE offers an efficient, multivariate approach to gain maximum information from experiments and investigate whether there are any interactions between the input variables. Data gained from this work may be used to develop process models and/or a design space, and these outputs can be incorporated into the control strategy for product manufacturing.

Finding the right approach

QbD and PAT principles must be consistently applied within a company, but the approach to QbD/PAT implementation and deliverables can differ across technology platforms. In Wyeth, each division must determine how to apply QbD principles and PAT tools in a way that meets the needs of its business model. The timing, resource allocation and prioritisation may be different in the Small Molecules Pharmaceuticals division, which may be different from the Consumer Healthcare division, and also from the Biopharma and Vaccines divisions.

This diversity in approach to QbD and PAT implementation will probably be reflected across the industry. The principles for QbD can be applied to any business, but how they are best exploited will vary depending on whether the pharmaceutical company is a generics business, innovator, contract research/manufacturing organisation or drug substance manufacturer. Similarly, raw material suppliers, equipment vendors and other service providers may all find aspects of QbD principles that can be implemented to provide business benefits.

Although adoption of QbD may seem slow, it is clear that the industry is changing. More companies are engaging in the initiative and the industry, regulatory agencies and, importantly, patients are starting to gain the benefits. **WPF**