



# Quality by Design—Bridging the Gap between Concept and Implementation

As Europe strives to firmly incorporate quality-by-design principles, there are several key issues that still need to be addressed.

**T**he drive to embed quality-by-design (QbD) principles into the pharmaceutical regulatory framework of the European Union has reached a key point 10 years after the European Medicines Agency (EMA) first backed QbD concepts. A relatively small number of marketing approval applications made in Europe have supporting QbD data, with EMA conceding that application dossiers with QbD information are far from becoming a standard approach. Nonetheless, the pharmaceutical industry has been internally adopting the QbD concepts laid down in the guidelines of the International Conference on Harmonization (ICH) covering pharmaceutical development (Q8), quality risk management (Q9), pharmaceutical quality systems (Q10), and the development and manufacture of drug substances (Q11) (1–4).

The international pharmaceutical companies in particular have benefited from applying QbD principles to their manufacturing operations. These companies have seen increased production efficiencies and yields as a result, with fewer off-specification outputs and a decrease in production recalls. Some of the leading pharmaceutical companies have been pace setters in including QbD data in authorization dossiers for approval of new medicines. Most pharmaceutical manufactures, however, have been reluctant to tie their marketing-authorization applications to this higher standard of quality management.

### THE NEED OF GLOBAL REGULATORY ALIGNMENT

QbD is now at a “critical step” between regulatory support for its concepts and a much deeper implantation of its principles, Georges France, external relations head of quality at Novartis, noted at a joint quality-by-design workshop of EMA and Parenteral Drug Association (PDA) in London in late

January 2014. According to France, the next step involves a streamlined system of regulatory review of QbD applications that needs to be extended to a “global regulatory alignment.”

The workshop, which included participants from FDA and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), revealed that there are, however, a number of big hurdles to widespread adoption of QbD despite considerable progress in its acceptance by the industry in recent years. One of the speakers at the meeting, Christine Moore, acting director of FDA’s Office of New Drug Quality Assessment (ONDQA), summarized the main concerns as being the classifying of criticality, levels of details required in process descriptions and in risk assessments, design-space verification, and changes to non-critical process parameters (non-CPPs).

Other major issues emerging at the conference, which focused on six case studies of QbD submissions evaluated by EMA, included real-time release testing (RTRT), application of QbD to continuous manufacture and biopharmaceutical production, dealing with post-approval changes to QbD processes, and the need for international harmonization of assessment methods. Regulators at the meeting complained that one big difficulty comes from the differences in terminology as well as the definitions used by pharmaceutical companies in their submissions, or during consultations on QbD matters.

“We have dealt with doubts about the terminology of terms by asking companies to verify what they mean before we review submissions,” commented one regulator speaking from the floor. “But the use of different definitions by companies for the same terms is something that should be sorted out between regulators.”

Some differences in terminology appear to have stemmed from companies adopting QbD concepts internally to gain greater operational efficiencies but in the absence of making QbD submissions with marketing-authorization appli-



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cations, some of these companies have lost touch with the terminology in the ICH QbD guidelines.

### LESSONS FROM A QbD DOSSIER

In a QbD dossier drawn up by GlaxoSmithKline (GSK), which was the subject of a case study presented at the meeting, the company used terms created before the ICH guidelines were finalized. As a result, “ICH terminology was not always followed, which in some situations, made it difficult to follow the information in the dossier in relation to guideline requirements,” said Gorm Herlev Joergensen, head of pharmabiotech, Danish Health and Medicines Authority, and Theodora Kourti, senior technical director, GSK, who jointly presented the case study (5). With some aspects of QbD, the ICH guidelines do not provide definitions. Non-CPPs, for example, are not defined in the guidelines.

Regulators at the meeting also stressed the need for QbD submissions to provide sufficient data for the sake of clarity and also to enable companies to justify properly the adoption of certain approaches to quality issues. The GSK dossier was praised by its regulatory assessors for the thoroughness of the data provided. The assessors, however, warned about the inclusion of complex statistical calculations in QbD submissions for this case study.

According to the case study, evaluation of statistical calculations, such as multivariate analysis, and the choice of experimental models on which QbD approaches are based, are challenging and require advanced statistical knowledge. Common quality assessors and GMP inspectors, however, usually do not have such knowledge, the study noted.

### DESIGN SPACE VERIFICATION

Both regulators and industry executives at the meeting conceded that

QbD requires more resources to gather extra data and to answer the questions triggered by the data. This is particularly the case when drawing up design spaces that set the combination of variables and process parameters needed to ensure quality but have to be based on a scientific understanding of how these factors interact.

As a result, “industry experience to date suggests that design spaces for more complex products (e.g., biopharmaceuticals) may be harder to get approved,” said Tone Agasoester of the Norwegian Medicines Agency and Graham Cook, senior director, process knowledge/quality by design at Pfizer, in a joint presentation on design space verification (6).

A key issue with design spaces is that they are often developed at a small scale at the laboratory or pilot level. Despite that, design spaces have to show that they match the quality requirements needed at commercial scale. The incentive behind the resources devoted to design space development is the greater operating flexibility they allow in the post-approval phase so that process variations do not have to be authorized.

### INNOVATION IS KEY

Process innovation with a greater assurance of quality is a driving force behind QbD but it has to have the support of a simplified procedure for the approval of variations. “We need to be more innovative if we are to be successful in delivering consistent and reliable quality for all products,” said David Tainsh, chief product quality officer at GSK, and Keith Pugh, expert pharmaceutical assessor at the UK Medicines and Healthcare products Regulatory Agency (MHRA), in a joint presentation on innovation (7). The barriers to innovation include limited availability of new skillsets, an unwillingness to deploy new technology,

perceptions of high regulatory hurdles, and the absence of a procedure to manage complex lifecycle management changes, said the speakers. Above all, they added that there is “a lack of an overall vision on how to modernize pharmaceutical manufacture.”

Among the novel products to which QbD principles are having to be applied are advanced therapeutics, oligonucleotides, and microneedles, while innovative methods of manufacture and control include continuous processing, synthetic biochemistry, discrete manufacture, and analytics. Tainsh and Pugh cited, as an example of innovation, liquid dispensing with process analytical technologies (PAT), such as near infrared (NIR) inspection, ultraviolet (UV) solution analysis, droplet weight checks, and pad inspections. The future “desired state” would be an enabling regulatory strategy and a procedure that keeps pace with innovation with increased scientific dialogue between regulators and industry. It would even include regulators being trained in new skillsets. There would also have to be “enhanced scientific and risk-based approaches to QbD to match new technologies with a simplified and streamlined variations process,” said Tainsh and Pugh.

There have been signs of an acceleration in the numbers of QbD submissions. Yoshihiro Matsuda, of the PMDA’s office of standards and guidelines development, told the meeting that after averaging approximately three QbD applications annually for a few years, the number jumped to 11 submissions per year in 2011–2012 and to six submissions up to mid-2013. EMA has reported that after averaging approximately five submissions per year since 2008, QbD applications went up to eight submissions last

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## IN THE PIPELINE

### Dartmouth Researchers Develop New Approach to Chronic Lymphocytic Leukemia Treatment

Dartmouth researchers have developed a new approach for treating chronic lymphocytic leukemia (CLL), a blood cancer. The researchers modeled the lymph node micro-environment where CLL cells are found in the laboratory. They were able to disrupt the activity of a pathway (NF-kappaB) that ensures the survival and resistance of the CLL cells in such microenvironments. The study findings were published in the March 15, 2014 issue of *Clinical Cancer Research*.

"In this *in vitro* microenvironment, we used MLN4924 to disrupt the activity of the NF-kappaB pathway by targeting Nedd8, which controls activation of NF-kappaB," said Alexey V. Danilov, MD, PhD, assistant professor at the Geisel School of Medicine at Dartmouth and Hematologist-Oncologist at the Norris Cotton Cancer Center, in a press release. "This decreased the survival of CLL cells and re-sensitized them to conventional chemotherapy as well as novel agents. Because the CLL cells used were obtained from patients with this disorder, these findings are immediately relevant to the clinic."

Danilov says this new approach is unique because it does not directly target proteins within the B-cell receptor pathway.

### Medimmune and University of Cambridge Announce Oncology Research Collaboration

MedImmune and the University of Cambridge have entered into a three-year oncology research collaboration. This partnership aims to advance cancer research by using imaging technologies to measure key biologic changes within growing tumours. MedImmune will contribute both funding and a post-doctoral scientist to work in the area of tumour targeted therapies.

The University of Cambridge is using magnetic resonance-based molecular imaging to detect the earliest signs of a tumour's response to treatment, including cell death. These technologies may help identify effective therapies earlier in the development process.

The University brings expertise in advances in molecular imaging that produce sensitive pictures of cells within patients' tumours, particularly through the use of <sup>13</sup>C hyperpolarised molecules. According to the company, these advances will help MedImmune identify biomarkers to support future clinical trial design, such as improving dosing schedules and identifying appropriate patient populations in clinical trials.

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year. The rise in QbD applications from a low base could be evidence of more pharmaceutical innovations stimulating a higher uptake of QbD principles. There is, however, still a long way to go in Europe before QbD principles are firmly incorporated into regulatory procedures.

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