

Preface

Occasionally in one's professional career you become aware that the hand of history is resting on your shoulder. So it was in July 2003, in Brussels, when the members of the International Conference on Harmonisation (ICH) Expert Working Groups (EWG) for quality agreed on a new vision and strategy for ICH. Summarized in the statement, "A harmonized pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to quality risk management and science," ICH agreed to progress three paradigm-changing guidelines. These were Q8 (pharmaceutical development), Q9 (quality risk management), and Q10 (pharmaceutical quality system). When I called to order the first Q8 EWG, we all thought that we might be able to take the existing European Note for Guidance on Development Pharmaceuticals and convert it into an appropriate ICH format and that would be it: a simple task. It took us a little while to appreciate the futility of this approach, especially given the growing interest in the application of process analytical technology (PAT) and the growing appreciation that the goal of pharmaceutical development is to design a quality product and its manufacturing process to deliver consistently the intended performance of the product. The only way to achieve that consistency would be by designing a product from the outset that would meet patients' needs, acquiring comprehensive product and process understanding, and establishing a properly controlled manufacturing process. We needed to tell the world that quality cannot be tested into a product; it has to be designed into a product. But, of course, everyone already knew this, so there was nothing new here, but how could we help move the industry from its traditional 3-sigma processes toward 6-sigma? We needed to talk about Deming, Juran, kaizen, risk assessments, experimental designs, even the value of "failed" experiments. We needed to give the industry permission to share the fullness of their scientific knowledge without the fear of creating an ever-increasing list of regulatory questions that added little value but much time to the review and approval processes.

With these things in mind, the EWG drafted the ICH Q8 guideline. Recognizing that traditional development processes would still be needed, we referred to the new thinking as an "enhanced approach," deliberately avoiding the moniker of "quality by design." Even as Q8 went through its final revisions and adoption, it became clear that outside the confines of the EWG, neither the industry nor regulators had a clear understanding of the new paradigm. We were asked to use the addendum to

Q8 to define and exemplify “quality by design,” and we did our best, comparing traditional approaches with an enhanced quality-by-design approach. But even with this effort, and with subsequent Implementation Working Group efforts (which have included question and answer documents, points to consider), there is still mystery and confusion about what QbD really means for the pharmaceutical industry.

Fortunately, our journey has been helped by the foresight and commitment of a number of early adopters. Before the ink was dry on the first part of Q8, a team within the European Federation of Pharmaceutical Industries and Associations developed a mock section P2 (Explain), which demonstrated some of the key elements of QbD including a quality target product profile, risk assessments, design of experiments, and design space. Two more comprehensive case studies, intended for discussion and teaching purposes, quickly followed. The first, ACE tablets, was aspirational in many respects and explored a number of innovative concepts that industry was contemplating. The second, A-Mab, discussed the application of QbD principles to a biotechnology product, stimulating much discussion between industry and regulators at the same time as the FDA was introducing its pilot programs. Other case studies such as the Sakura mock P2 from Japan and A-Vax (QbD for vaccines) and the several mock ANDA submissions have strengthened our understanding and appreciation of both business and regulatory opportunities.

Many would regard QbD for chemical substances as straightforward: our understanding of kinetics and thermodynamics enables rapid building on prior knowledge to provide scalable syntheses. On the other hand, drug product development still remains a complex blend of art and science which may be behind the often experienced challenges of establishing well characterized, robust manufacturing processes that can be described by reliable models. For biologics, it could be argued that the opposite situation pertains. The drug substance is the process: the processes are often exquisitely designed and engineered with feed-forward and feedback control strategies. While the quality is designed from the outset, the many degrees of freedom and the characterization challenges mean that full application of QbD principles is not easy. The list of critical quality attributes is generally extensive, our ability to directly connect them through analytical techniques back to the critical process parameters and forward to the patient is often not straightforward, and the realization of design spaces becomes challenging, especially when you consider the risks associated with movement with a design space. However, application of QbD principles to the final steps, the drug product, is much more straightforward.

Into one insightful volume is collected a wide range of discussions and practical examples of the application of QbD to biological drug products. For those still uncertain about the business benefit, this is the area to start. Biological drug product manufacturing processes lend themselves to the enhanced approach. The risks, science and engineering are all much better understood than those in many other areas of our industry. The degrees of freedom are manageable. QbD principles facilitate developing an effective control strategy, arguably the most critical deliverable of a well planned and executed development program, including real-time release-testing opportunities.

Most of the leading pharma companies now consider QbD to be “business as usual” for the current development portfolio. An increasing number of publications attest to the business benefits that have accrued from QbD programs and filings. Experience is growing with successful regulatory submissions and approvals. For sure, both industry and agencies have been on a steep learning curve with the new paradigm, but in the USA, the small molecule pilot program followed by the biologics pilot program have provided valuable insight and learning. Similar initiatives have occurred elsewhere. The international agencies have mounted joint assessment and inspection programs—our new paradigm is here to stay, and the publication of this book could not be better timed. Now is the time to wholeheartedly grasp the opportunities, to do the great science that surely motivates us all and comprehensively tell the story to the regulators. What are you afraid of? The patient is waiting.

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