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SCIENTIFIC OPPORTUNITIES THROUGH QUALITY BY DESIGN

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Quality by design (QbD) is about understanding the relationships between the patient's needs and the desired product attributes by ensuring that all process attributes and parameters that are functionally related to safety and efficacy are consistently met. The value of prospectively developing enhanced product knowledge and process understanding can significantly minimize patient risk. The application of QbD principles also strengthens the balance between continued product improvements, technical innovation, business needs, and regulatory oversight. A QbD approach can serve as the foundation that links research and development, manufacturing, and regulatory conformance through a fundamental common language that is based on a science and risk-based principles.

For decades, much of the activity in quality and quality management focused on compliance rather than utilizing a fundamental understanding of the science behind process understanding. Business practices adapted to procedures and focused on minimizing regulatory risk. The implementation of new technology was not typically part of a strategy because oversight for novel technology was not precedented. Extremely risky and high attrition rates of research programs, unlike other industries, coupled with the lack of global regulatory harmonization fostered a minimalist paradigm and, significantly challenged investments in new technologies and using modern methodologies for development. In the 1990s the use of PAT started to gain interest in pharmaceutical manufacturing; however, it was primarily used for business purposes and not seriously considered for regulatory purposes. Describing to regulatory authorities a comprehensive view of process understanding was generally avoided for fear of being held accountable to increased scrutiny and higher standards.

In August 2002, the FDA launched their GMPs for the twenty-first century initiative in partial response to academics and consultants who criticized the pharmaceutical industry for not manufacturing to the highest standards. Companies were encouraged to use risk-based assessments, in particular when identifying product quality attributes, and adopt integrated quality systems that operated throughout the lifecycle of a product. This movement toward science-based regulations has not been limited to the United States as seen by the guidance provided by The International Conference on Harmonization (ICH). Thus, quality by design for the pharmaceutical industry evolved from a conceptual approach that envisioned an efficient, agile, flexible sector that reliably produces high-quality drug products without extensive oversight [1]. Guidance for QbD was crafted through the ICH process to what is now considered the "QbD trio"; ICH Q8, Q9, and Q10 (ICH Q11 for drug substance in progress). This movement away from prescriptive development programs has become an exciting and empowering platform for chemists, scientists, formulators, and engineers. While many elements associated with QbD, such as risk assessments, design of experiments (DoE), operational control strategies, etc., have been employed well before the adoption of the ICH guidelines, application was frequently not systematic, concerted or prospective, but rather retrospective in response to issues or problems encountered during development or after commercial launch. Consequently, companies were reluctant to pursue a QbD approach or introduce supplemental studies

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on process capability for fear of unnecessarily increasing regulatory "requirements" and potentially delaying regulatory approvals.

QbD begins with a prospective vision that accepts and builds upon a science and risk-based platform with a commitment to maintain focus on the patient. It starts with the establishment of a quality target product profile (QTPP) that provides an inventory of expectations or "product attributes" required to ensure patient safety and efficacy and product quality. Using the QTPP, relationships between product attributes and the sources for meeting those attributes can be derived from drug product and drug substance platforms to establish a holistic understanding of how attributes are linked to patients needs, and how these attributes are functionally related through the entire manufacturing process. Ensuring patient safety and efficacy is not about "what measures we apply" to maintain the QTPP, it is about "how we develop" process understanding to establish the appropriate design and control elements of a process. The approach is predicated on executing a rigorous risk management exercise to determine "what we need and what we have" to demonstrate that quality is consistently met. It is about identifying the relationship between each attribute and its functional relationship to manufacturing variables and consistently controlling these relationships.

It is generally recognized that the three fundamental concepts of QbD are design space, control strategy, and criticality; where design space and control strategy are the deliverable outcomes from a systematic application of risk and science-based assessments, analyses, experiments, technical innovation, and control. The development of design spaces and control strategies is a *symbiotic relationship* that encompasses all of the concepts contained within the chapters of this book. In adopting a QbD approach and applying the science and risk-based principles to assess quality attributes and process parameters, design space can be created to describe the boundaries within which unit operations of a manufacturing process may operate. In essence, design space can demonstrate control of variables that may impact a critical quality attribute, and a control strategy can be established parametrically to as the resulting design modate design space. For example, a combination of well-space boundaries and real-time release testing can effectively demonstrate and confirm control and serve as the basis for release of the product without the need for specific end-product testing. Therefore, where the risk is understood and the severity and probability of impact are controllable, the demonstration of process control through the creation of design space could conceivably reduce the need to perform in-process testing as well. Continuous formal verification to demonstrate process capability in accordance with well-grounded design space criteria could serve as the basis for product release to a specification derived largely from critical quality attributes (Figure 5.1).

Scientists who embrace an enhance approach to development should consider these types of questions:

- How is prior knowledge substantiated, how can internal and external knowledge be used to leverage more accurate risk assessments?
- What level of detail is required to justify risk assessments?
- How should design space be presented and conveyed to demonstrate quality assurance?
- How can modeling be used to justify commercial manufacturing process changes?
- How should the control strategy connect drug product and drug substance quality attributes to process parameters and material attributes?
- Is there an attenuation of regulatory latitude for post-approval optimization and continual improvement?

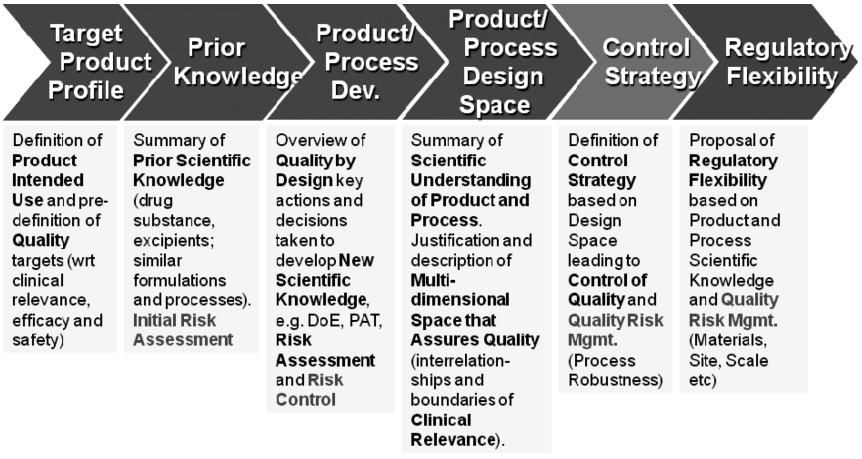

FIGURE 5.1 General outline of approach to application of quality by design. *Source:* EfPIA QbD WG.

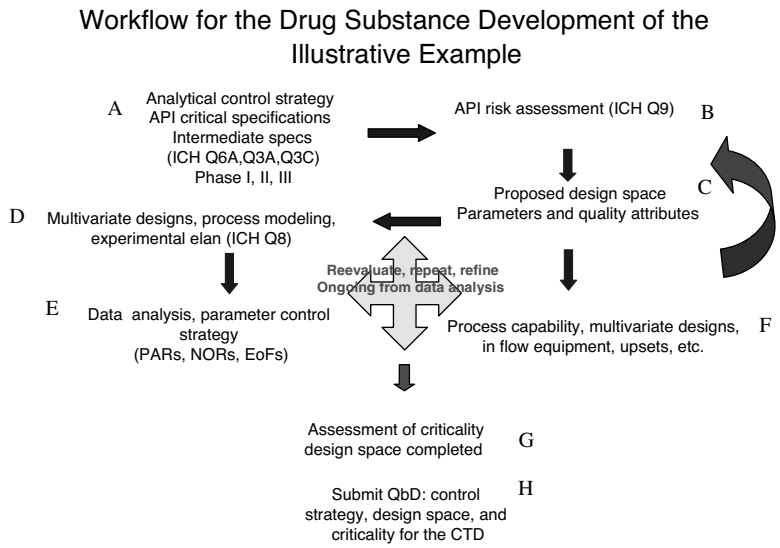

FIGURE 5.2 Small example of drug substance workflow for QbD.

In addition, there are many general processes that can be adapted to sketch out a general procedure for any team of subject matter experts to adapt a science and risk-based approach. One example is given are Figure 5.2. A Common thread that runs through all varieties of QbD applications is repeated risk assessment of process parameters and material attributes and their connectivity to the QTTP; adoption of an an iterative approach to risk and experimental data evaluation; creative experimental design to understand parameter interaction in a multivariate process; establishment of a well grounded design space and control strategy that ensures safety and quality. Finally, transparency in the interpretation and presentation of data and its justification for process design must meet the standards for peer review and "pass the red face test" for regulatory authorities. There are many options for implementing QbD. However the fundamental conceptual elements of the risk and science-based approach have emerged as relatively consistent within the industry. With appropriate scientific justification and consistent application most options are acceptable. Far from suppressing progress, the refinement of the meaning, application and implementation of QbD has stimulated regulatory authorities and industry to pursue clarification. As a result, subsequent progress has improved the consistent application and value of these concepts.

The intrinsic advantages of investing in enhanced process understanding increases confidence and assurance of product quality. Tangible benefits, for example, reductions in manufacturing costs associated with improved efficiencies and innovations, reduction in manufacturing recalls, and failures or extraneous investigations attributed to uncertainty, are largely realized over the lifecycle of a product.

The fundamental scientific premise derived from the application and implementation of Quality by Design principles that attracts scientific support from every discipline across this industry is driven by a common passion to develop improve process understanding and product knowledge. The movement away from prescriptive and in many cases retrospective development approaches has become an exciting and empowering platform for chemists, scientists, formulators, and engineers. QbD has also played an instrumental role in establishing the value and importance of cross-functional, scientific relationships in pharmaceutical development through proactively developing and understanding processes and formulations. Perhaps, most importantly, the application of a QbD approach and investment in robust Pharmaceutical Quality Systems are expected to reduce unexpected variability in manufacturing processes and unanticipated failures in product quality, thereby improving quality assurance of products.

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