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## Introduction to Quality by Design (QbD)

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### 1.1 Introduction

The aim of this chapter is to introduce the principles of Quality by Design (QbD) to those who want to understand pharmaceutical QbD, and that may include readers from industry, academia, regulators or indeed anyone interested in finding out more about this important subject.

The content is applicable to development scientists, manufacturing specialists and those in supporting roles, such as quality, analytical, engineering, validation and more. It is intended to be helpful, practical and wide-ranging and for use by novices, experienced practitioners or those who want to expand their current knowledge.

Each of the subsequent chapters is written by experts in their field and provide relevant, up-to-date and tailored information. Each part will stand alone, but it is the sum of these individual parts that makes QbD whole and provides the compelling story that will ultimately benefit patients and give clarity of understanding in what is important when designing, manufacturing and supplying products to our customers.

So, who are these customers? Some may be our family or friends or colleagues, but most will be individuals we do not know and will never meet. A customer may choose a generic medicine from a shelf in the pharmacy, their choice perhaps being influenced by the descriptions on the packaging or by marketing and advertising, or, alternatively, they may

have their medicine prescribed and administered by healthcare professionals. Some may be supporting others, for example, a parent helping their child, or an adult helping an elderly relative or colleague.

But no matter what the circumstances are in which someone takes a medicine, there is one overriding principle: that every patient, healthcare professional, parent or caregiver has to trust the pharmaceutical industry to provide what is intended and that the medicine will be safe, efficacious and of the required quality.

So it is important that we value this trust we have been given. History says that most of the time the pharmaceutical industries have delivered on this trust, but there have been occasions when the industries have not, and such mistakes, albeit small in number compared with all the medicines that are taken, have sadly damaged the trust that customers put in the industry.

So how does this impact the development, manufacturing and distribution of pharmaceuticals? First, we should recognise that we in industry have the detailed technical knowledge, and the customers usually do not. Second, we should ensure strong linkages across the product lifecycle, from development to manufacturing to supply. Third, we not only have to understand the underlying science, what risks there might be and mitigate these risks proactively before products reach the patient, but we have to communicate these risks effectively. So, for example, if there are a million tablets in a batch, we have to be sure, to the best of our ability, that these tablets have been produced of the appropriate quality, as each one may go to a different customer.

And this is where the term QbD comes in – sometimes referred to as ‘a science and risk-based approach’, and this set of words gives a little more insight into what QbD is about.

The definition of QbD [1] is:

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

The term ‘Quality by Design’ was first used by Juran in 1985 when the first draft of his book [2], published in 1992, was available for consultation by 50 senior representatives of industry. The Juran Trilogy stated: ‘Managing for quality is done by use of the same three managerial processes: planning, control and improvement’ [3].

This book will provide detail to expand this same idea into a practical reality, but for this introduction, we can consider QbD as helping the pharmaceutical industry to continue to take a science- and risk-based approach to enable safe and efficacious medicines to be developed and produced over the product lifecycle, that lifecycle being from the time the product is being conceived to the time it is finally withdrawn from the market, including managing the impact of any changes that may occur during this period.

## **1.2 Background**

Historically, an ultra-compliant approach had dominated the way the pharmaceutical industry operated, perhaps even threatening, wrongly, to potentially swamp the underlying science, rather than compliance being seen as a partnership with science. Fear of seeking

change for already approved regulatory documents, even when new enhanced science or technology developments came to light, has meant that industry continued to operate within compliance-driven, historically established boundaries. One example might be where manufacturing limits had been approved in a regulatory submission. Yet, over time, as more product and process knowledge accumulated to support widening – or maybe tightening – the original limits, industry had a fear of discussing this new knowledge with regulators. Sadly, this fear still partly exists today, though it is not as prevalent.

So why did compliance come to have such an overbearing role? Maybe it was a perceived fear of regulators? Or business pressure to have approvals in place to meet rapid launch of products ahead of competitors? Or was it to assess matters as either ‘right’ or ‘wrong’, rather than recognising there is a continuum of risk in regard to pharmaceuticals – or indeed in any product that is designed, manufactured and supplied to customers? It could be none, any or all of these reasons; one will never know.

This compliance-focussed mindset did not mean that quality problems were not occurring. Indeed, one could sense, looking back, some frustration within industry and also for regulators, particularly when things did go wrong, as they occasionally did. Regulators started to impose increasingly large fines, but this did not seem to resolve recurrence of quality issues.

This point was captured in a *Wall Street Journal* article of 3 September 2003 [4]:

Dr. Woodcock had been among the architects of an FDA crackdown under which the agency fined drug makers as much as \$500 million for manufacturing failures in recent years. Yet ‘we still weren’t seeing acceptable levels of quality’, she says, because ‘production techniques were outmoded. Just refining procedures and documentation wasn’t going to change that’.

This article was significant as it gave a reflection of what was happening at that time both within the industry and for regulators, but it also recognised that the public were beginning to take a keener interest in the pharmaceutical industry and expecting regulators to continue to play their part in ensuring quality.

One other important factor was that the pharmaceutical market was becoming increasingly international, yet regulators, who were normally based in one country, were, understandably, focussed on ensuring their own particular local interest was protected, both for imports and for products made within their national boundaries.

Gradually it became apparent that a less local perspective would be beneficial, and in 1990 the International Conference on Harmonisation (ICH) was created [5].

ICH is an interesting concept as it brings together regulators, industry associations and observers from different parts of the world to meet and jointly write guidance documents. The members include US, EU and Japanese regulators and industry bodies, as well as observers from the World Health Organisation (WHO) and others.

As is stated on the ICH web site [5]:

The ICH Parties comprise representatives from the following regulatory parties:

- European Union, the Regulatory Party is represented by the European Commission (EC) and the European Medicines Agency (EMA).
- Japan, the Regulatory Party is the Ministry of Health, Labour and Welfare (MHLW).
- USA, the Regulatory Party is the Food and Drug Administration (FDA).
- Canada, the Regulatory Party is the Health Products and Food Branch (HPFB).
- Switzerland, the Regulatory Party is the Swissmedic.

As well as from the following industry parties:

- Europe, the European Federation of Pharmaceutical Industries and Associations (EFPIA).
- Japan, the Japan Pharmaceutical Manufacturers Association (JPMA).
- The United States, the Pharmaceutical Research and Manufacturers of America (PhRMA).

ICH produces guidelines under headings of Safety, Quality and Efficacy. It has eminent and broad-ranging groups of experts involved in producing these guidelines, so these guidances are as near to global as one can obtain, even though they are neither global nor mandatory, unless – as happens in some cases – regulatory agencies include them in their national Good Manufacturing Practices (GMPs). Most can be considered, to all intents and purposes, as internationally applicable.

It was ICH that first brought the term QbD to the pharmaceutical industry when in 2009 it published ICH Q8 (R2) [1], ‘Pharmaceutical Development’.

This was a watershed moment for the industry, as, after this, the importance of taking a science- and risk-based approach moved to front stage, and even terms like ‘manufacturing science’ began to be heard.

### **1.3 Science- and Risk-Based Approaches**

Science, of course, has always been a fundamental element of the development of pharmaceuticals and, historically, innovative application of science has been core to producing the many life-saving and life-enhancing drugs that the industry has produced over time.

So why all this supposedly new approach? What has changed?

Well, the fundamentals driving the need to understand pharmaceutical science remain the same, but perhaps the following are factors that influenced a change in perspective:

- The application of science is becoming more complex; for example, biotechnology-based drugs are more complicated to understand, make and analyse compared to small molecules; specialised therapies such as advanced therapeutic medicinal products, gene therapies, etc. are beginning to emerge.
- The use and application of more sophisticated tools, for example, process analytical technology (PAT), [6] has become more commonplace – although this tool is relatively new for the pharmaceutical industry, it has been in use by other industries for many years.
- More powerful data processing is now available to enable such tools to be used. An example is design of experiments (DoE) (see Chapter 7) and multivariate analysis (MVA) (see Chapter 8) can now be used for more sophisticated analysis than was possible previously.
- The industry has become more global, often with many differing countries involved in the supply chain, which has made it necessary to maintain quality across various international boundaries and cultures.
- The supply chain has become more fragmented and diverse, with many more parties involved, including contract research organisations (CROs), contract manufacturing organisations (CMOs) and external suppliers. ‘Virtual’ companies are now emerging, a role that did not exist a few years ago.
- Internal organisations are being re-structured. An ‘over the wall’ attitude for technology transfer, development and manufacturing is being heavily discouraged. Business benefits are being seen in having closer working internal partnerships.

- Knowledge management is becoming increasingly important, from development to manufacturing to supply. Knowledge is not just about knowing the pure science but is also about embracing the application of that science through technology, manufacture, engineering, materials science and many other disciplines.
- Regulatory pressures are continuing. The recent US Food and Drug Administration Safety and Innovation Act (FDASIA) law [7] and the current discussions about quality metrics is an example, as is the stronger emphasis on data integrity, lifecycle, process validation and many other topics.
- Public pressure continues to grow. The pharmaceutical industry is expected to not only do things right but to also reduce costs.
- Location of manufacture is moving east. India, China and other countries have more dominant and extensive pharmaceutical industries.

All these factors have reinforced the need to not only understand pharmaceutical science, but to also understand where any potential risks lie, to mitigate and control these risks, and to ensure clear communication over the lifecycle of the drug to deliver safe and efficacious products to patients.

So industry has always recognised the importance of science and that risks should be quantified.

But there is probably one major factor that has been a significant gap, and that is the rationale has not been as clearly articulated as it could have been.

So QbD is not just about doing the science- and risk-based work; it is also about explaining the story clearly, both verbally and in written form. Everyone who is a part of a product's lifecycle has to be made aware of their role in ensuring product quality is in place at all stages – be they a development scientist, an operator on the manufacturing plant, a business leader, a regulatory department, a third party supplier, an equipment vendor or anyone else involved in this, at times, complicated supply chain.

## 1.4 ICH Q8–Q12

The following published ICH Guidelines set forth the principles about how a science- and risk-based approach should be delivered.

The key ICH documents that make up the QbD ‘family’ are:

- ICH Q8 (R2) – ‘Pharmaceutical Development’ [1].
- ICH Q9 – ‘Quality Risk Management’ [8].
- ICH Q10 – ‘Pharmaceutical Quality System’ [9].
- ICH Q11 – ‘Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities’ [10].
- ICH Q12 – Concept paper (at the time of writing this) – ‘Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management’ [11].

Taking each of these in turn, in brief:

ICH Q8 (R2) lays out the principles of using science for development of a drug product. It was the first ICH document to use the term ‘enhanced, Quality by Design’ approach. It includes two Parts and two Appendices. Part 1 is Pharmaceutical Development; Part 2

gives the Elements of Pharmaceutical Development, also introducing the terms laid out in the next section of this chapter, and details for Submissions; Appendix 1 is about differing approaches and gives examples of ‘minimal’ and ‘enhanced, Quality by Design’ approaches; Appendix 2 is Illustrative Examples. The development and manufacture of drug product with the application of ICH Q8 (R2) is discussed in detail in Chapter 6 of this book by Mark Gibson.

ICH Q9 lays out a framework on approaches for quality risk management, including risk initiation, assessment, control, review, communication and the tools to use. This framework is explained in more detail later in this book in Chapter 2 (Noel Baker). ICH Q9 has two Annexes: the first is on methods and tools to use, and the second is about applications. Importantly, ICH Q9 uses clear terms and definitions, and this author recommends being consistent and rigorous in using these terms, as they enable clearer communication both within a company and externally, be this to third parties or regulators.

ICH Q10, ‘Pharmaceutical Quality Systems’, lays out the fundamentals of what a quality system should cover, including management responsibility, and continual improvement of process performance and product quality and also of the quality system itself. Quality systems and knowledge management are discussed further in Chapter 3 of this book by Siegfried Schmitt.

ICH Q11, ‘Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)’, is a partner to Q8, and is based on similar principles, with extensive use of the term ‘enhanced’. Significantly, it covers API (active pharmaceutical ingredient) for both large and small molecules. It covers selection of starting materials, control strategy, process validation, submission and lifecycle and gives some examples. See Chapter 4 of this book by Gerry Steele for more details on the development and manufacture of small molecule drug substances.

ICH Q12, at the time of writing this book, is being drafted. The concept paper indicates it will cover the regulatory dossier, the quality system and lifecycle change management. Further reference to this and other regulatory guidance is given in Chapter 12 of this book.

All these guidelines form the basis of taking a science- and risk-based approach to cover the product and process lifecycle.

## 1.5 QbD Terminology

The ICH Q8–Q11 documents have helped bring great clarity to terms and definitions. The pharmaceutical industry is complex and does not help itself when companies or individuals use different language to describe in essence the same thing. Indeed, there are examples where the regulators have been concerned when there has been a lack of clarity.

The following are some of the key terms on which QbD is founded:

- Quality target product profile (QTPP).
- Critical quality attribute (CQA).
- Critical process parameter (CPP).
- Critical materials attribute (CMA).

- Design space (DS).
- Control strategy (CS).
- Lifecycle.

The following chapters in this book will expand, bring alive and give context to these terms.

Use of ICH terminology enables industry and regulators to use a common language both in-house as well as, say, during regulatory applications. No longer it is acceptable to sloppily mix terms such as *parameter* and *attribute*. They mean completely different things and using terms precisely enables clarity of communication within development and on to manufacturing and, indeed, over the full product lifecycle. So, it is strongly recommended that ICH terminology is used wherever possible.

## 1.6 QbD Framework

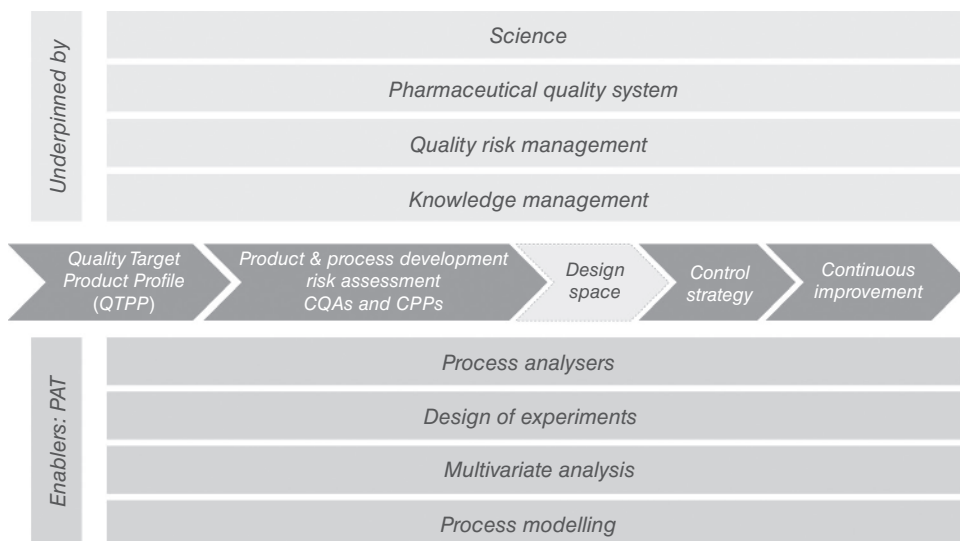
The following ‘QbD framework’ given in Figure 1.1 will be used for this book.

The following chapters will expand on and explain the elements of this diagram.

## 1.7 QbD Application and Benefits

QbD fundamentally links patient requirements to drug product and then drug substance. It is used to understand product specific requirements, which can then be supported by GMP [12].

QbD normally starts in development and progresses through to manufacturing, with the intent of producing a control strategy for commercial-scale production. Sometimes, say,



**Figure 1.1** A framework for QbD.

with a legacy product, QbD may start with an existing manufacturing process, for example, where a rich history of product and process knowledge is available.

QbD can be applied to small and large molecules, to drug substance and drug product, to vaccines, to combination products, to all or parts of a process, to novel drugs or to generics. It can be used by leading companies, by contract research or contract manufacturing companies or 'virtual' companies. It is up to the particular organisation to decide an appropriate level and application of QbD. QbD can be applied nationally or internationally.

Understanding the science underpinning a product and its associated risks helps prioritise what is important for manufacturing and so normally leads to efficiency gains and cost benefits. On the basis of a survey of several companies, Reference [13] concludes that companies found strong business benefits in using QbD. Part of the Concluding Remarks stated the following:

QbD seems strongly embedded in the companies interviewed. The benefits realized have met the expectations set by companies when they embraced QbD.... improved product and process understanding; a more systematic approach across the development portfolio; to continue to improve patient safety and efficiency; to improve manufacturing efficiency; and to improve development efficiency.

## **1.8 Regulatory Aspects**

QbD is not mandatory, but product and process understanding is an expectation of regulators. So how does one obtain such understanding without considering QbD principles? With difficulty, is the answer!

As indicated earlier, legacy products with an established history can provide a wealth of qualitative data to confirm, for example, that ranges and acceptance criteria set during manufacturing have produced products of the appropriate quality. Such knowledge is extremely valuable, as regulators are not insisting that companies should go back and start doing experiments afresh to provide quantitative evidence (unless, of course, there is demonstrably a lack of product and process understanding), but they do expect an assessment has been made that products of the required quality can be produced.

It is significant that ICH documents are increasingly being referenced by regulators, in areas where compliance is expected. For example, validation is a regulatory requirement, and it is interesting that ICH Q8, Q9 and Q10 are referenced in guidelines for the United States, EU and elsewhere.

One other matter of importance relative to this area is the US FDA internal guideline Manual of Policies and Procedures, MAPP 5016.1, Applying ICH Q8(R2), Q9, and Q10 Principles to CMC Review [14]. As it says: 'This MAPP outlines and clarifies how the chemistry, manufacturing, and controls (CMC) reviewers in the Office of Pharmaceutical Science (OPS) should apply the recommendations in the ICH Q8 (R2), Q9, and Q10 guidances to industry'. It also interestingly says: 'OPQ product quality reviewers will consider ICH Q8(R2), Q9, and Q10 recommendations when reviewing applications that may or may not include QbD approaches'.

## 1.9 Summary

This book includes chapters on quality risk management, quality systems, knowledge management, development and manufacture of drug product and drug substance, the role of excipients, DoE, multivariate analysis, process analytical technology, manufacturing and process controls, analytical QbD and regulatory guidance. Within each of these chapters is a wealth of information written by practitioners who have been and are actively involved in this important subject.

So, in summary, QbD is about gaining product and process understanding, communicating it and delivering it, such that patients can continue to benefit from the medicines they may take.

Hopefully this book will help provide some tools to enable this to be put into practice.

## 1.10 References

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