Introduction
Quality by Design (QbD) is increasingly becoming an important and widely used term in the pharmaceutical industry’s lexicon. QbD can be considered to be a holistic, systems-based approach to the design, development, and delivery of any product or service to a consumer.

QbD starts by considering the customer’s wants and needs and has the goal of delivering a product that meets at least those needs. Recognizing that customer expectations evolve and develop with time, QbD also considers what is necessary to enable a product to be continually improved throughout its lifetime, until it is eventually withdrawn or superseded. Putting this philosophy into practice is one of the most important priorities for both the pharmaceutical industry and regulators globally.

QbD is closely aligned with many of the high level concepts found in the ICH Guidelines Q8, Q9, and Q10. These concepts coincide with a burgeoning industry movement toward building quality into pharmaceuticals from development through manufacturing; bridging gaps between pharmaceutical development and manufacturing; and using sound science to demonstrate and assure the product’s safety, quality, and efficacy throughout its entire lifecycle.

The purpose of this Knowledge Brief is to provide the basic elements of Quality by Design. The information contained within is drawn from the Product Quality Lifecycle Implementation (PQLI) initiative, an industry-driven effort lead by ISPE to find pragmatic approaches for those wanting to implement the high level concepts found in ICH Q8, Q9, and Q10 and QbD. For further information on QbD and PQLI visit the ISPE web site.

QbD vs. Traditional Approach
QbD generally starts when a promising drug candidate is identified. Development scientists (chemists, pharmacists, analysts) will work in close conjunction with non-clinical and clinical colleagues to identify the optimum delivery route and form, the ideal characteristics of the drug product, and the essential characteristics of the active ingredient that will be incorporated into that drug product formulation. If this
process is truly successful, the outcome of these deliberations would be the product specification(s).

In a traditional approach to pharmaceutical development, the product formulators often had to design their formulations to overcome shortfalls in the properties of the active pharmaceutical ingredient (API). For example, the API might have had poor flow properties, low melting point, and/or inadequate solubility. Specifications would then be set after batches had been manufactured and would reflect the product attributes that could be produced by the manufacturing process. These may not have been entirely in line with what the customer really wants!

**Identifying Critical Quality Attributes**

In a QbD systems approach, the formulator identifies the critical attributes required of both the formulation and the API. The formulator asks that the API attributes be ‘designed in.’ For example, the chemist might examine different presentations (salt forms, polymorphs, etc.) of the API to tailor the molecule to the formulator’s needs, and ultimately the needs of the patient.

QbD then goes a step deeper into the process of producing the API by examining each step of the synthesis or production process (e.g., for a biotech API) to identify the critical-to-quality attributes (CQA) required at each stage. CQAs can be identified by examining their potential impact on ultimate product quality should there be a variation in the process. To date, there is no agreed process to establish key or critical quality attributes, nor their related key/critical process parameters. Quality Risk Management tools, such as illustrated in the ICH Q9 guideline, are often employed. Quality Risk Management is a dynamic process and will often be revisited throughout a product’s lifecycle as process improvements occur, or as patient needs evolve.

Once CQAs have been identified, the next step is to gain a comprehensive understanding of the way variation impacts the quality of output at each stage of the API process. One way of gaining this understanding is through Design of Experiments (DoE). QbD demands that the product manufacturer has an enhanced understanding of their product and its manufacturing process. An enhanced understanding can come only when a true multi-variate ‘model’ of the product and process has been developed.

Again, traditional development approaches are often limited by experiments that test one-at-a-time variability. Comprehensive Design of Experiments will build on Quality Risk Management through use of multi-disciplinary teams to design and execute soundly based statistical designs to gain a full understanding of the product and its manufacturing process. The output of DoE confirms CQAs and Critical Process (CPPs) that need to be controlled in the manufacturing process.

It should be apparent that QbD embraces both API and drug product design and development. So an entirely analogous process will be undertaken by the product formulator.

**Design Space**

The ICH guideline Q8 (Pharmaceutical Development) describes the essential components for the drug product. Q8 introduces the concept of Design Space to the pharmaceutical industry. Design Space is defined as “the multidimensional combination of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.”

There is still much to be done in clarifying how to develop, submit, review and approve design Space. Some of this will be addressed in the forthcoming addendum to ICH Q8.

Clearly one cannot establish a Design Space before the CQAs and their limits have been established (i.e., for the finished product, the specification) and so it becomes evident that in a QbD world the product is being developed to
meet a specification rather than the specification having been developed to reflect the manufacturing process capability. Once again, QbD is reversing many of the traditional thoughts, and the original ICH guidelines on specification setting (Q6A/B) may well need to be revised to reflect the new QbD paradigm.

**Technology Transfer**

However a product is developed, at some stage there must be a transfer from the R&D environment to production. For a QbD product, the critical sensitivities of the product will be known and technology transfer can be expected to be faster and less problematic. For example, it may have been shown that, where appropriate process monitoring and controls are implemented, manufacturing scale is unimportant. The inter-relationship between process analytical technologies (PAT) and QbD is still being developed but there are both overlaps and synergies. Indeed, it is still hard to see how full QbD can be implemented without a comprehensive application of PAT.

As emphasized earlier, QbD is a systems approach and technology transfer, which is a process of knowledge transfer, should also be approached systematically. ICH is in the process of developing a guideline on Quality Systems (Q10) and a company will be encouraged to have in place as part of their quality systems appropriate procedures for capturing and transferring knowledge.

**Enhanced Regulatory Flexibility**

Before the product can be marketed, regulatory approval is obviously required. As well as the obvious benefits that accrue from manufacturing a well understood product, a significant incentive to those embracing QbD is the enhanced flexibility that regulators in the three ICH regions have agreed to (see ICH Q8). These include the possibilities of 'real-time release,' and reduced post-approval submissions.

**Continuous QbD**

QbD does not end as a product is commercialized. Manufacturing experience should build upon the existing knowledge of product and process understanding and enhance it. One of the fundamental tenets of a Design Space is that movement within it does not constitute a change that would require regulatory approval. Thus the manufacturing process can be optimized within the Design Space (continual improvement).

There may be occasions where production experience shows that the initial model had some limitations and the Design Space needs to be modified, or expanded; this should be seen not as a failure of the approach but the successful acquisition of further knowledge. And this knowledge accumulation and utilization should be part of the standard processes of continual improvement handled by a company’s quality systems (also see ICH Q10).

**Conclusion**

The goal of QbD is to bring medicines to patients in a better-understood, more reliable way. All stakeholders benefit. Manufacturers will see production improvements with significantly reduced batch failures, stock-outs, etc. Regulators will have greater confidence in the robust quality of products they are being asked to approve and will be able to reduce the intensity of their regulatory oversight, again assisting the industry to innovate and continually improve. The patient will benefit from a greater consistency in the medicines they take, and a reduced likelihood of unexpected product unavailability or withdrawal.

**About the Author**

John Berridge, PhD, is ISPE’s European Regulatory Affairs Advisor. He retired from Pfizer Global Research and Development at Sandwich at the end of January 2006 as vice president of pharmaceutical sciences. He spent more than 31 years at Pfizer, starting as an analytical chemist, and more recently responsible for all aspects of chemistry, pharmacy, analytical, and regulatory CMC in Europe. His research interests have been directed toward high-performance liquid chromatography, with special emphasis on the use of chemometrics to aid method development. More than 40 papers and a book have been published and this research has been recognized by the award of the Chromatographic Society’s Jubilee medal in 1989. Berridge has been involved in the ICH processes from their inception, representing EFPIA in the quality topics discussions. He has contributed to guidelines on impurities in drug substances and their dosage forms, specifications, was the industry rapporteur for the Common Technical Document (Quality) and is currently the industry rapporteur for the pharmaceutical development guideline (Q8). At FIP’s 55th World Congress in Stockholm in 1995 he was presented with an IPS award for his outstanding contribution to industrial pharmacy, and in September 1997 he was awarded the Royal Pharmaceutical Society Chiroscience award for his services to the pharmaceutical industry and for his work within ICH. Berridge now works as a consultant, representing Pfizer at EFPIA, and thus will continue to support the ICH activities.

For more detailed information on Quality by Design and ISPE’s Product Quality Lifecycle Implementation initiative, you can search ISPE articles and publications on this subject on the ISPE Web site.