1
Quality by Design

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1.1
History

The pharmaceutical industry has been a highly regulated industry in the past for many good reasons [1]. While pharmaceuticals have greatly improved the mortality and morbidity rates, there is still some element of risk to the patients. These risks are greatly mitigated with the delivery of medicine at the appropriate purity, potency, delivery rate, and so on. While pharmaceutical regulations have clearly protected the population from much of the needless harm such as that incurred early in the twentieth century, there has been a concern more recently that overregulation may be associated with stifling innovation that can improve pharmaceutical quality even further [2] – innovation that has the potential to greatly improve the quality, cost, and time to market new and improved medicines. The twenty-first century began with the pharmaceutical industry using manufacturing technologies that have been employed since the 1940s and did not make significant changes in manufacturing process unless significant compliance or costs saving advantages could justify the high costs and long cycle time needed to gain approval. This often resulted in inefficient, overly expensive processes that were ultimately not in the best long-term interests of patients. As a result, the FDA (Food and Drug Administration) and other agencies around the world have embraced a new paradigm for regulation [3]. The ''desired state'' was to shift manufacturing from being empirical to being more science, engineering, and risk based. Another regulatory guidance that had major impact was the Process Analytical Technology (PAT) Guidance [9]. The continuous, real-time monitoring of manufacturing processes is a key enabler to achieve greater process control. Finally, the current Good Manufacturing Practices (cGMPs) for the Twenty-First Century Guidance acknowledged the undesired impact of good manufacturing practices (GMPs) on understanding manufacturing science and sought to set the framework for additional guidances that encouraged risk- and science-based understanding in exchange for more freedom to introduce innovations and improvements that will result in enhanced quality, cost, or timing.

Process Understanding: For Scale-Up and Manufacture of Active Ingredients, First Edition. Edited by Ian Houson.

Table 1.1 Comparison of the current state to the future desired QbD state.

Aspect	Current state	Desired QbD state
Pharmaceutical development	Empirical; typically univariate experiments	Systematic; multivariate experiments
Manufacturing process	Locked down; validation on three batches; focus on reproducibility	Adjustable within design space; continuous verification within design space; focus on control strategy
Process control	In-process testing for go/no-go; offline analysis	PAT utilized for feedback and feed forward in real time
Product specification	Primary means of quality control; based on batch data	Part of overall quality control strategy; based on product performance
Control strategy	Mainly by intermediate and end product testing	Risk-based; controls shifted upstream; real-time release
Lifecycle management	Reactive to problems and OOS; postapproval changes needed	Continual improvement enabled within design space

Juran is often credited with introducing the concepts behind Quality by Design (QbD) [4]. Pharmaceutical QbD is a systematic approach to development that begins with pre-defined objectives and emphasizes product and process understanding based on sound science and quality risk management (ICH Q8R2). The holistic and systematic approach of QbD was relatively new to the pharmaceutical industry at the beginning of the twenty-first century. However, elements of QbD were certainly being applied across the industry long before then. QbD was put into practice in a big way with the advent of the FDA CMC pilot program in 2005. Nine companies participated in the program and eventually submitted regulatory filings based on a QbD framework [1, 2, 5–7]. Much was learned from these initial filings that help steer the industry and regulators toward a common vision for QbD. A comparison of the ''current state'' to the future ''desired state'' was succinctly summarized by Nasr in Table 1.1 [8].

A process is well understood when

- all the critical sources of variability are identified and explained;
- variability is managed by the process, and;
- product quality attributes can be accurately and reliably *predicted* over the *design space* established for materials used, process parameters, manufacturing, environmental, and other conditions [9].

Process understanding is the major goal of a QbD program. A complete list of characteristics of a successful QbD program is summarized in Table 1.2.

Table 1.2 The characteristics of a successful QbD program.

Involves product design and process development
Risk-based, science based
Primary focus is patient safety and product efficacy
Business benefits are also drivers
Results in improved process understanding
Results in improved process capability/robustness
Systematic development
Holistic – applies to all aspects of development
Multivariate – interactions are modeled
Provides PAR, design space, or suitable equivalent
Requires a significant reduction in regulatory oversight postapproval

1.2 Defining Product Design Requirements and Critical Quality Attributes

In order to design quality into a product, the requirements for the product design and performance must be well understood in the early design phase. In pharmaceuticals, these product requirements can be found in a Quality Target Product Profile (QTPP). The QTPP is derived from the desired labeling information for a new product. Pharmaceutical companies will use the desired labeling information to construct a target product profile that describes anticipated indications, contraindications, dosage form, dose, frequency, pharmacokinetics, and so on. The target product profile is then used to design the clinical trials, safety and ADME studies, as well as to design the drug product, that is, the QTPP.

In addition to defining the requirements to design the product, the QTPP will help identify critical quality attributes such as potency, purity, bioavailability or pharmacokinetic profile, shelf-life, and sensory properties as shown in Figure 1.1. In some cases, these attributes are directly measurable, for example, potency. In other cases, surrogate measurements are developed indirectly to measure the quality or performance, for example, *in vitro* dissolution for a controlled release product.

There are numerous ways to represent a QTPP. Another example of a QTPP for a lyophilized sterile vial is shown in Table 1.3.

A crucial element of QbD is to ensure that the measurement systems being used are truly assessing the quality of the product or performance. Very often it is the case that attributes that have little to do with quality are measured, for example, dissolution test for an immediate release Biopharmaceutical Classification System (BCS) class I drug (high aqueous solubility and high permeability). Drugs of this type are rapidly and completely absorbed; therefore, a dissolution test provides little value from a quality control perspective. Quality attributes can sometimes be modeled on the basis of first principles or other multivariate analysis. Predictive models are extremely important components of QbD [10]. In the case of bioperformance, predictive statistical, mechanistic, and analytical tools

QTPP to Critical Quality Attributes									
	Quality Target Product Profile	Critical Quality Attributes							
		Assay/Potency	Impurities	Content uniformity	Stability	Dissolution	Average weight	API solid form on bead	Water content
Product Requirements	Paediatric sprinkle dosage form								
	2 mg, 4 mg & 8 mg dose	✔		✔	✔				
	Oral, once-daily dosing					✔	✔		
	Shelf life at least not less than 2 years at 25C/60% RH				✔			✔	
	Blister and bottle packaging				✔			✔	
	Same in vivo performance as adult product					✔	✔		
	No food effect					✔			
	Degradants/impurities below safety threshold or qualified		✔		✔			✔	✔
	Meets Pharmacopoeial requirements for oral solid dosage forms								

Figure 1.1 Product requirements from QTPP help to identify potential critical quality attributes.

are being applied, which can guide Active Pharmaceutical Ingredient (API) particle size selection, dissolution method design, and setting specifications [11].

While a QTPP is basic to QbD, additional product or process design requirements may need to be considered while designing the manufacturing process for a new API or drug product. In API route design, major decisions need to be made regarding which chemistry will yield a synthetic route that delivers high purity at an acceptable cost [12]. Likewise, a drug product formulation and process technology decision needs to be made that also delivers a drug product that conforms to the quality requirements at an acceptable cost. An understanding of the product (formulation) design is critical to product performance. A clear rationale for why excipient types, grades, and amounts are selected is part of the product understanding. An understanding of which material attributes contribute most to the excipient functionality is important to performance. Supplier specifications may be a poor indicator of excipient functionality in a dosage form and hence may not be critical material attributes. In some cases, it may be necessary to introduce additional testing on incoming materials that are more relevant to how the excipient impacts the dosage form performance [13]. Likewise, the solid form of the API needs to be engineered for quality. The selection of the proper

Table 1.3 Quality target product profile for a lyophilized sterile vial.

Quality target product profile for a lyo vial for sterile injectable	Requirement
Indication	Chronic disease (treatment of nervous breakdown)
Dosage form	Lyophilisate for solution for injection
Dosage strength	Nominal dose 20 mg/vial
Administration route	Subcutaneous (0.8 ml)
Reconstitution time	Not more than 2 min
Solution for reconstitution	1 ml 0.9% saline (provided by the pharmacy)
Packaging material drug product	2R glass vial, rubber stopper, meets pharmacopoeial requirement for parenteral dosage form
Shelf life	Two yr 2–8 °C
Drug product quality requirement	Meets pharmacopoeial requirement for parenteral dosage form as well as product specific requirements
Stability during administration	Reconstituted solution is stable for 24 h at temperature ≤30 °C

salt, solid form (amorphous, polymorph), particle size and morphology, and degree of aggregation will impact critical quality attributes such as solubility, dissolution rate, chemical and physical stability as well as manufacturability (bonding index, stickiness, flow, filterability). Advances in crystal engineering enable better control and understanding of how to achieve targeted API particle properties (Chapter 7).

Finally, the role of the packaging systems for the raw material, in-process materials, and final drug product needs to be understood. All packaging systems should be demonstrated to protect the materials and not introduce contamination, for example, leachables or extractables, during transport and handling. The QTPP will set expectations for the final drug product packaging. True product understanding should translate into design spaces for the API properties, formulation, manufacturing process, and the packaging systems.

One of the biggest challenges is to integrate the design and process development at the key interfaces in the supply chain. Interfaces that present significant challenges to process understanding and hence process control are highlighted in Figure 1.2.

While QbD does target designing quality into processes, it can also be equally effective in identifying methodologies directed at reducing the high costs of development and manufacture of pharmaceuticals. Inclusion of attributes that measure costs directly or indirectly is essential to optimize the quality, time, cost, and risk relationships. Figure 1.3 shows the ''cost of quality rework'' relative to the stages of the R&D and manufacturing lifecycle [14]. The greatest opportunity to manage process costs and the product quality of a pharmaceutical is in the early process and product design phase when decisions are made about technologies and materials to be used. Although these are major decisions for pharmaceutical

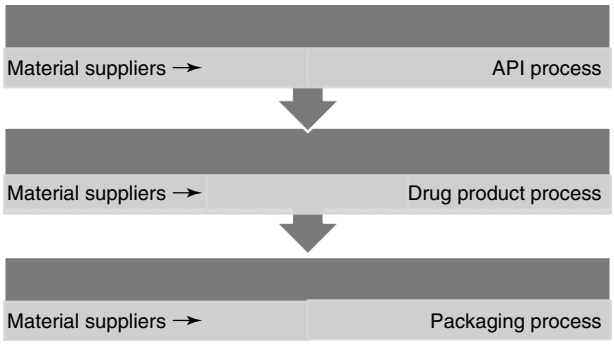

Figure 1.2 Key material-process interfaces in a pharmaceutical product.

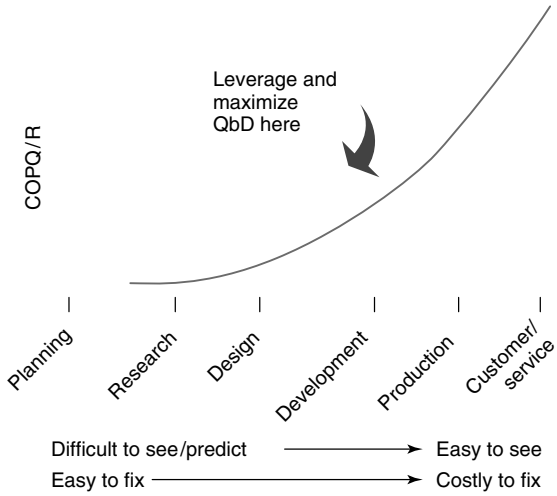

Figure 1.3 Cost of product quality or rework.

companies, they are often made implicitly rather than explicitly. Interestingly, few companies actively manage this phase of design and assume that decisions made in a vacuum were appropriate (Chapter 12).

1.3 The Role of Quality Risk Management in QbD

ICH Q9 discusses the role of risk management in pharmaceutical development as follows:

> To select the optimal product design (e.g., parenteral concentrates vs. pre-mix) and process design (e.g., manufacturing technique, terminal sterilization vs. aseptic process).

To enhance knowledge of product performance over a wide range of material attributes (e.g., particle size distribution, moisture content, flow properties), processing options, and process parameters.

To assess the critical attributes of raw materials, solvents, Active Pharmaceutical Ingredient (API)-starting materials, API's, excipients, or packaging materials.

One role for management in QbD is to ensure that teams utilize risk assessment tools that are capable of providing risk- and science-based reviews at critical milestones in the R&D lifecycle. One such critical milestone is prior to finalization of process technology, synthetic route, or a qualitative formulation. Decisions made at these milestones will generally impact the quality and costs attributes to a much greater extent than decisions made during process development and later in the product lifecycle. As with any rigorous risk assessment, it is important to include appropriate subject matter experts to obtain prior knowledge and apply feedback learnings to these major decisions.

Process understanding is achieved when the relationship between critical quality attributes (CQAs, y) and all the sources of variation (x) in the manufacturing process are understood:

$$y = f(x)$$

The principle sources of quality variations (examples) or inputs to a process include

- material attributes (peroxides, water content, impurities);
- process parameters (temperature, force, speed);
- equipment design (baffles, agitator type, surface type);
- measurement system (sample prep, extraction time);
- environment (relative humidity, temperature, oxygen content);
- person (operator, analyst).

It is important to note that the total process variation as measured by the variance or standard deviation (σ) of the average batch data is a function of all sources:

$$\sigma_{\text{Total}} = f(\sigma_{\text{Material}} + \sigma_{\text{Process}} + \sigma_{\text{Equipment}} + \sigma_{\text{Measurement}} + \sigma_{\text{Environment}} + \sigma_{\text{Person}})$$

The goal of process understanding is to be able to predict how the sources of variation (x) will impact the CQA performance (y) and be able to control these parameters to control quality. One of the initial challenges to design and develop a new API or drug product is to identify all the possible sources of variation for a particular new manufacturing process. The list of possible sources of variation will be very large, too large to study experimentally. The challenge presented to a scientific team is to sort out which inputs are at highest risk for impacting the process. Fortunately, QbD (e.g., ICH Q9) provides tools to systematically risk assess all the possible inputs to a process to identify those relatively few that have the greatest potential to impact the process. Table 1.4 provides an ISO 3100 list of

Table 1.4 Success factors in risk management.

Risk management should
Create value
Be an integral part of organizational processes
Be part of decision making
Explicitly address uncertainty
Be systematic and structured
Be based on the best available information
Be tailored
Take into account human factors
Be transparent and inclusive
Be dynamic, iterative, and responsive to change
Be capable of continual improvement and enhancement

success factors for successful risk management [15]. Any organization embarking on QbD and or a QRM program could use this list as an internal quality check for their QRM program.

Ishikawa (fishbone) diagram is a very effective tool to capture a brainstormed list of potential process inputs impacting variation. Mapping the manufacturing process using a process flow diagram (PFD) is helpful to define the scope of the risk assessment and to identify possible process inputs. API mapping may include unit operation, chemistry pathways, and an impurities cascade. An example of mapping API and drug product processes is shown in Figure 1.4.

FMEA (failure modes and effects analysis) or use of a prioritization matrix (cause and effect matrix, Figure 1.5) is helpful in identifying the process inputs that impact on quality attributes. In some cases, a deeper dive into the driving forces at critical control points in the manufacturing process can yield a more fundamental understanding of sources of variation.

Once the CQAs and process performance attributes (PPAs) are associated with inputs to the process, $Y_i = f(x_1, x_2, \ldots, x_n)$ through a risk assessment process, experiments can be efficiently designed to develop predictive models and confirm causal relationships.

Before embarking on extensive experimentation, a critical next step is to make sure that critical measurements are made using ''fit for purpose'' methodology. A comprehensive risk assessment should identify those measurements that are suspect. A simple frequency plot of the data with specification limits will provide an indication of when variation is a potential problem (Figure 1.6).

The time spent improving a nonrobust analytical method can provide significant return on investment when experimental results yield true process understanding and control [16]. In this author's experience, sampling and sample preparation are typically high-risk areas for product quality measurements, for example, chromatography. Gage R&R studies are useful QbD tools to assess the relative contribution of the measurement system to the total variation of a manufactured product [17]. If the measurement contributes more than 10% of the total variability, additional method development is often warranted. However, some methods must contribute

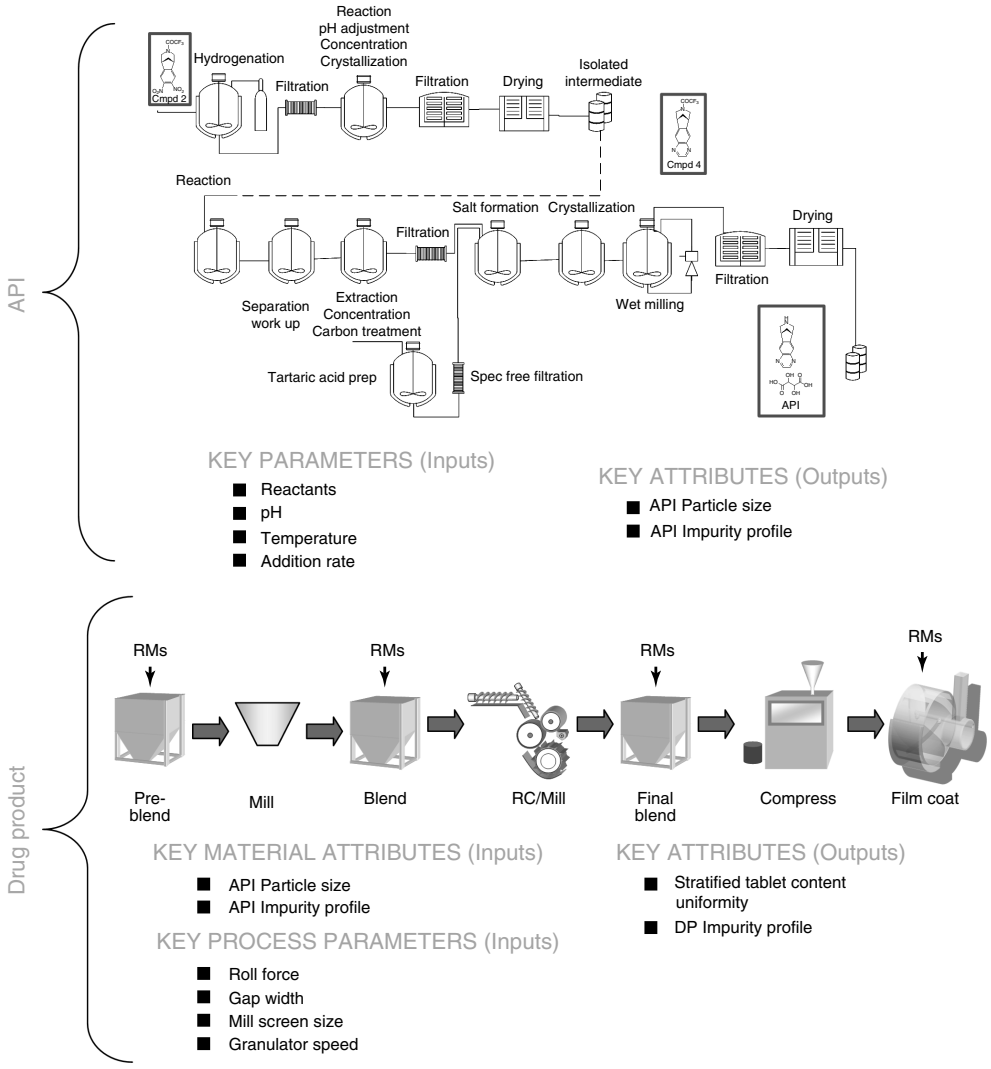

Figure 1.4 Process map of API and drug product manufacturing processes.

a much lower variance to the total. Measurement of trace levels of genotoxic impurities is often a particularly challenging method development exercise since safety limits are approaching the limits of quantitation [18]. The opportunity to improve analytical methods or implement a totally new method may be more rapidly achievable in the future if the concept of an ''analytical target profile'' is adopted. The ATP defines the analytical criteria necessary to achieve equivalent or better analytical performance [19]. Analytical method understanding is crucial to

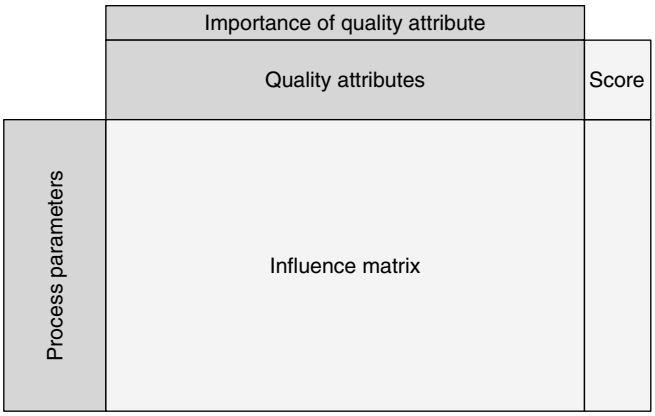

Figure 1.5 Cause and effect matrix related process parameters (inputs) of quality attributes (outputs) of a process.

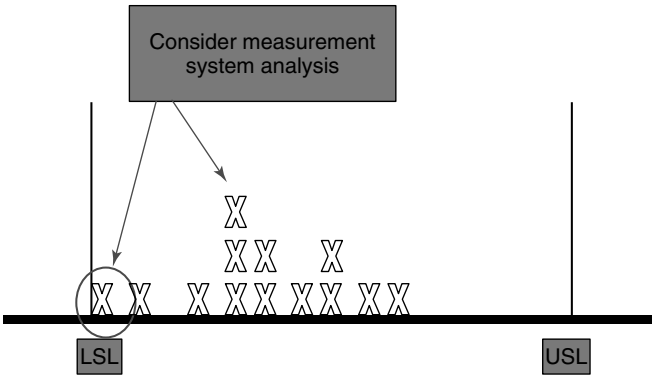

Figure 1.6 Frequency plot of data from tablet potency measurements with specification limits. Note that this distribution of potency data is off-centered and relatively wide compared to the specification range, leading to questions about recovery and reproducibility of the method.

QbD. For example, how the materials are processed can impact the capability of the method to accurately quantitate an analyte. Compaction pressure is known to impact the near-infrared (NIR) spectra and may need to be included as a parameter in an NIR calibration program [20].

Ideally, these relationships are modeled such that interactions among the input parameters are known. Simple or complex models can then be used to create a design space that defines an acceptable operating region for the process.

Combining formal risk ranking and a statistical design of experiments (DoEs) is a powerful duo of tools in QbD, which is used extensively in the industry today (Figure 1.7). One of the reasons for this combination to be so popular is that most companies have access to the expertise required to utilize this combination; it is

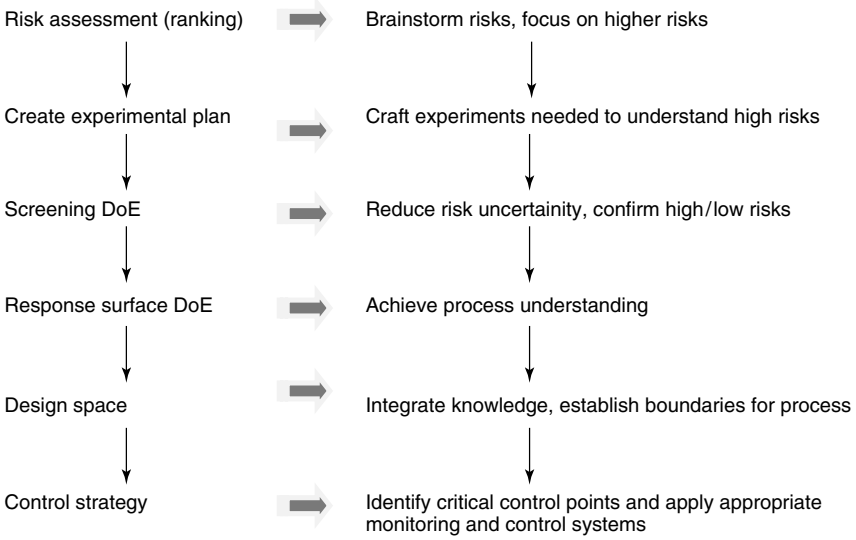

Figure 1.7 Combination of risk assessment and statistical design of experiments (DoE).

also highly effective and efficient. A typical sequence of study is discussed in the example below.

A risk assessment ranked the process parameters likely to impact charge heterogeneity of a monoclonal antibody (MAb) as measured by the ion-exchange chromatography (IEC). The CQA of interest was charge heterogeneity. Multiple screening and response surface DoEs were performed that included testing of charge heterogeneity to confirm which process parameters impacted charge heterogeneity. The DoE analysis eventually enabled identification of process ranges that would control charge heterogeneity to an acceptable value [21].

Additional knowledge can be extracted by applying multivariate analysis [LVM, principal component analysis (PCA)] and data mining to integrated batch, process, stability, and bioperformance datasets. These tools have the benefit of extracting knowledge from a single product database or a portfolio of products with similar processes and technologies.

Another application of risk management tools is deciding which attributes and parameters are ''critical'' from a regulatory perspective. There has been much discussion and debate within the industry on how criticality should be defined and practiced. The ramifications of the critical designation are quite significant in the pharmaceutical industry as it defines the composition of the design space and the focus for the control strategy. The CQAs and critical process parameters (CPPs) are the foundation from which regulatory commitments are made. Changes to the design space or the control strategy would typically require a prior approval from regulators. Process validation protocols typically stipulate what are the CQAs and CPPs and monitor and control their performance.

The ISPE PQLI subcommittee on criticality has attempted to establish guidance on deciding critical parameters and attributes. Criticality is viewed on a continuum from low to high criticality. The realization that a parameter or attribute criticality can vary over a wide range was viewed as a breakthrough. However, the reality is that regulators expect pharmaceutical companies to draw a clear distinction between noncritical and critical to assist with the application of regulations.

FMEA and FMECA (Failure Mode, Effects, and Criticality Analysis) are useful as decision-making tools and also as risk mitigation tools. An example of how FMECA can be employed as a criticality decision-making tool is shown in Table 1.5.

1.4 Design Space and Control Strategy

ICH Q8(R2) defines design space as:

> . . . the multidimensional combination and interaction 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 postapproval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval (ICH Q8(R2).

In some cases, boundaries will be identified that are known to be an *edge of failure*. In these situations, it may be important to set boundaries at acceptable tolerance intervals around the edges of failure to better mitigate the risks near such edges (Figure 1.8). Application of a tolerance interval is generally not necessary when the edges of failure are not in play at design space boundaries.

To make matters more complicated, an understanding of how the CQAs interrelate is important. If multiple CQAs are impacted by one or more of the same process parameters, the acceptable operating region can be greatly limited. A variety of multifactorial and multivariate modeling approaches should be considered. Modeling based on first principles, for example, reaction rate kinetic model, is the preferred approach; however, empirical methods can also be very effective. In order to establish acceptable boundaries, that is, design space for multiple interrelated CQAs, the response surfaces of these CQAs should be overlayed upon one another using the same parameter axes. CQA trade-offs may be required. As an example, the high cationic concentration of pDNA favored the biological activity of a vaccine but was deleterious to the physical stability of the liquid product. Trading some stability for biological activity was necessary to finalize the design space and optimize the formulation [22]. Modeling approaches and examples will be discussed in more detail in other chapters.

Once a sufficient level of process understanding is achieved, a control strategy should be developed that assures that the process will remain in control within the normal variation in material attributes and process operating ranges. The process understanding will identify where the appropriate control points are in

Table 1.5 FMECA used to assess the criticality of a process parameter.

Parameter name	Potential failure mode	Potential failure effect	SEV (1–10)	Potential causes (optional)	OCC (1–10)	Current controls	DET (1–10)	RPN (S*O*D)	Criticality designation	Justification
Reaction temperature	High temperature	Increased levels of impurity "x"	10	• Recipe error • Temperature sensor issue • Pump issue	3	• Automated recipe control • Sensor calibration • Back-up pump available	3	90	CPP	Impurity "x," which is a CQA, formed during API step where purge is minimal. No rework procedure available presently to reduce elevated levels. Deemed a CPP as a result, in spite of good controls described
	Low temperature	Slow reaction rates	5	• Recipe error • Temperature sensor issue • Pump issue	3	• Automated recipe control • Sensor calibration • Back-up pump available	1	15	Non-critical	Reaction completion; IPC in place, which will mitigate against incomplete reactions. Plant controls in place including demo run prior to first batch deemed sufficient to minimize risk

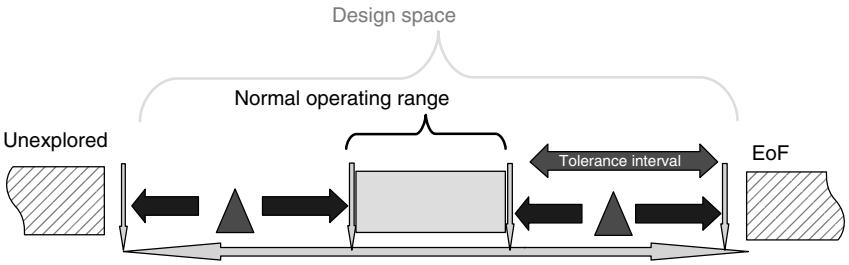

Figure 1.8 Design space with an edge of failure (EoF) and use of tolerance interval to mitigate risk.

the manufacturing process. Typically, these control points would be located where the variation is highest or where a CPP dominates control of the resultant product quality. For example, critical raw material attributes may be critical inputs to a process step. One mechanism to control the process is to control the quality of that material such that it always delivers a consistent product. Impurity fate mapping (IFM) is such an example in which the raw material and process impurity sources are identified and their fate mapped throughout the process. The process capability to remove these impurities at CCPs is an essential element of the control strategy [23].

Another control strategy could be to adjust the process parameters to accommodate the variation in the raw material attributes. This latter strategy would be dependent on having measurements systems in place that could measure critical material attributes, which then adjust other critical process parameters accordingly to maintain process control. For example, the amount of water and granulation mixing endpoint may vary batch to batch based on the granule size and count [24]. Control strategy is a cornerstone of a modern quality system. It can be a combination of parametric and attribute-based controls. Generally, real-time monitoring and control of the process is preferred over relying on end product testing. For example, the logical place to test for a major process impurity would be at the last step at which the impurity is purged from the process. Spiking studies could be performed to demonstrate the robustness of the process to purge high levels of the impurity. Over time, it may also be possible to demonstrate high process capability (Cpk $>$ 2) and reduce or eliminate the test and rely more on parametric control. The control strategy should allow adjustments in testing plans based on commercial batch experience, that is, process capability and process understanding.

1.5 Quality Systems

While QbD is most effective when it is employed at a product/process design level, it should also be accomplished in the manufacturing and quality assurance environments. The authors of ICH Q10 foresaw the need to provide guidance on a modern quality system that would be critical to support QbD and continuous improvement

of pharmaceutical products over their lifecycle. Continuous improvement of a product and process should be employed throughout the lifecycle of a product. Process capability (CpK) is an extremely valuable metric to indicate which CQAs or other PPAs are least robust. CI efforts generally focus on the low CpK attributes.

A modern quality system may necessitate retooling the quality assurance workforce to be capable of interpreting more complex technical reports that rely more on predictive models, multivariate analysis, simulations, and advance process controls. Some of the PAT and design space models may require periodic updating. Interpreting the risks associated with process changes may be more complicated, as the risks change depending on how close the process is to an edge of failure.

As regulators entrust industry to make significant improvements in product and process quality, quality systems become more important to manage the changes that occur in pharmaceutical manufacturing. The FDA utilizes a postapproval management plan (PMP) to clearly articulate under what conditions the FDA will need to be informed or approve of such changes. Hudson has proposed a more detailed structure on how to format a PMP [25].

Finally, as Janet Woodcock, MD, Deputy Commissioner for Operations/Chief Medical Officer at FDA, stated at the 2008 PDA meeting, ''QbD is an evolution and not a revolution'' – an evolution that is in response to the increasing cost pressures on both the regulatory agencies and industry to control the escalation of drug prices [26]. QbD will continue to evolve for years to come as new tools and technologies advance to improve the way we mitigate risks and increase our understanding and control of the manufacturing processes. In addition to increasing quality, the pharmaceutical industry will reduce development and manufacturing cycle times as well as costs in the process.

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