PART III

ANALYTICAL METHODS AND APPLIED STATISTICS

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QUALITY BY DESIGN FOR ANALYTICAL METHODS

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29.1 INTRODUCTION

For any analytical measurement used in pharmaceutical development or product quality control, it is essential that the integrity of that measurement is understood. The "rules" that assure measurement integrity were derived during the 1980s through cross-industry consensus and with the regulators via the International Conference on Harmonization [1] These rules were complimentary to the good manufacturing practices (GMPs) enshrined in regulatory law.

The creation of ICH standards followed a period during which instrument-dependant separation techniques (e.g., HPLC/GC) displaced the earlier wet chemistry and manual techniques (e.g., titration/TLC/gravity column chromatography) and during which quality assurance of pharmaceutical product was the concern of governments due to some high profile public health disasters [2]. The pharmaceutical quality context that dominated the creation of these "rules" were as follows:

- Quality assurance of product can best be achieved by following a set of instructions (compliance) that are shown to repeatedly give the same product (product validation) and product quality assurance is supported by analytical testing (quality control).
  - Similarly, assurance of *measurement integrity* can best be achieved by following a set of instructions (compliance) that are shown to repeatedly give the same result (analytical method validation).
- In addition to compliance in following instructions (standard operating procedures, SOPs) and completing validation, it is essential to have an underlying Quality System that enforces training, equipment validation, maintenance, calibration, facilities, and so on.

The benefits of these international agreements have been clarity of regulatory expectations for developing pharmaceutical products and associated test methods worldwide across all regulatory authorities. Although specific variations are required for some countries, in most cases product and methods are expected to receive global market approval. The pharmaceutical company knows what regulators expect to see in a submission for the description of the test method, the control and validation of the method and data sets related to these. The impact on global health should not be underestimated as ease of global registration correlates directly to the rapid access to medicines for the world population. However, this approach of compliance to a strict set of testing instructions has a significant disadvantage. The regulatory control of postapproval changes is a barrier to introducing technology advances during product lifecycle and also drives conservatism in initial product development. The 10–15-year gestation time of a product in R&D followed by the 20–30-year life of marketed product means this barrier has a real effect on the availability of affordable, effective highest quality medicines. The FDA recognized this in 2004 and produced a white paper (FDA PAT Team and Manufacturing Science White Paper—*Innovation and Continuous*

Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing Edited by David J. am Ende

Improvement in Pharmaceutical Manufacturing) [3] calling for an evaluation of development practice to create better products for patients. The white paper led to a dialogue between the industry and the regulators on how product development practices could be improved, and how regulatory submissions and quality management systems could enable innovation while assuring the product integrity for the patient. The use of "Quality by Design" (QbD) as a framework for product development has been widespread in engineering for several years, and was already described in guidance by the FDA for development of Medical Devices [4]. It was recognized that this methodology could also apply to pharmaceutical product development. The subsequent evolution of the Quality by Design concept for development of pharmaceutical formulations and manufacturing processes and practices led to three new ICH papers launched in 2006; Q8, Q9, and Q10 [5–7]. These outline QbD concepts through discussions on pharmaceutical development, quality risk management, and a pharmaceutical quality system. The industry engaged in developing the first products using QbD via pilot programs with close communication with the FDA. These pilots have led to successful approvals and product launches for Pfizer Inc., Astra-Zeneca, GlaxoSmithKline, Merck, Wyeth and others. The QbD approach to product development is now widely adopted throughout the industry.

QbD for product requires a deep understanding of the critical quality attributes (CQAs) that impact final product quality. To gain that understanding, analytical techniques will be applied. This has reinvigorated attention to online analysis and consideration of in-process testing as an alternative to, or complementary to end-product testing in quality assurance. The appropriate use of in-process or PAT techniques is well documented but the development, validation, transfer between laboratories, the control and the life cycle use of methods has remained unchanged, and this is the subject of this chapter on QbD. This chapter describes QbD as a system for analytical method development and lifecycle management. It describes how the concepts of enhanced scientific understanding, the use of quality management systems and structured risk assessments may be applied to analytical methods and how the concept of defining method factors and attributes can be used to define the control strategy for the method to ensure it is robust and rugged.

29.1.1 Criticisms of Current Practices

The FDA PAT Team and Manufacturing Science White Paper—Innovation and Continuous Improvement in Pharmaceutical Manufacturing made the following criticisms of the industry arising from poor lifecycle management of product:

- Pharmaceutical manufacturing operations are inefficient and costly.
- Processes are not robust
  - Out of specification (OOS) observations can occur frequently.
- Measurement systems are not good enough
  - Variability and/or uncertainty in a measurement system can pose significant challenges when OOS results are observed.
  - Measurement system variability can be a significant part of total variability.
- Knowledge Management is poor
  - Information needed for process improvement can be in a different organization and often not available at the right time.
  - Similar and repeating OOS observations for different products across the industry and a less than optimal understanding of variability.
- Continuous improvement is difficult, if not impossible.

These criticisms apply also to analytical measurement for quality control; the methods can be inefficient and costly, the robustness of methods is a frequent cause of OOS results, variability may be poorly understood or is not fit for purpose once product manufacture reaches more exacting efficiency. Knowledge management overly relies on experts and recall. Continuous improvement of methods is stifled by the cost and inconvenience of postapproval changes when conducted on a global scale with multiple regulatory agencies. So the principles that QbD enables for manufacturing products should also give benefit when applied to analytical test methodology.

Beginning in 2007, analytical scientists began to consider how applying QbD principles to the method lifecycle can lead to better methods; methods that work more reliably and give information that not only supports product quality but can support manufacturing process improvements. To do this, the application of QbD principles would need to overcome the barrier that is stifling innovation in analytical technology. The industry bodies, PhRMA and EFPIA each set up subgroups to explore the subject; these groups have collaborated on a concept paper to enable dialogue across the industry and with the regulators.

QbD necessitates a rigorous evaluation of the intended purpose of a measurement, followed by development of a method and routine use built upon a thorough understanding of the science underpinning the analytical methodology selected. There is a need to improve the reliability of the analytical method by understanding, reducing, and controlling all sources of variability. QbD facilitates adopting new technology, particularly where it enhances understanding of the analyte and so enables continuous improvement. QbD also uses knowledge management systems to improve application of the method and understanding of the data.

There are two key concepts in QbD for analytical methods. The first (the analytical target profile, ATP) addresses the

purpose of the measurement and forms the basis for development of the initial method. It is also the basis for substitution of subsequent methods as technology develops. While the product control strategy defines which attributes will be routinely measured to assure the product is of the desired quality, each measurement requirement for each *attribute* is formally defined in the analytical target profile. The ATP is proposed as a new mechanism for describing analytical methods in regulatory submissions that would reduce the burden of postapproval variation. At present, method changes typically involve comparisons of data sets from a common sample pool generated using the original method and the proposed new method. This traditional approach of comparison biases changes to those where the new technology delivers results that are *the same as* the original method, and hence this can stifle continuous improvement by preventing adoption of a technique that *enhances* understanding of the analyte. It is proposed that when an ATP is registered, subsequent method changes would be referenced to the ATP. A significant advantage in the new approach is that it enables introduction of methods with improved reliability and enhanced accuracy providing they meet the ATP descriptors. For example, a method for routine manufacturing use may have been developed to ensure a given attribute lies within specification limits. Modern pharmaceutical production may require knowledge about variability of that attribute within a batch in order to improve batch yield and lower product cost. Introduction of a new technique, or an enhanced method would generate information for both purposes without jeopardizing the quality control application of the method.

The ATP would first be generated at the time a need for a method is identified, in pharmaceutical product development this would relate to the needs generated from the QbD for the product as shown in Figure 29.1. Once the product control strategy is established, the ATP for each CQA of the product or process should be reviewed to ensure it is appropriate and the ATP is then suitable for a filing.

Figure 29.1 compares QbD for analytical methods with QbD for product and illustrates how variations in operating conditions could be managed. QbD for analytical methods starts with a description of the requirements of a measurement, the ATP, which may be derived from a critical quality attribute of a product. In QbD for product, flexibility is gained by the opportunity for varying operating parameters and is based on the design space that has been documented around a CQA of the product or process. In QbD for analytical methods, flexibility is gained by the opportunity for varying *method factors* (defined as *any factor that forms part of the method definition* [8]*, e.g., machines, materials, people, processes, measurements, and environments*) and is based on the design space that has been documented around the ATP. The ATP is in effect a representation of the critical quality attributes of the measurement. In recent years, analytical scientists have sought to minimize detail in regulatory methods in order to allow flexibility in subsequent application of the method. In doing so, pharmaceutical companies focus only on the method factors that they believe are critical to obtaining a true and accurate result. The rationale for why these method factors are critical, and more importantly, the functional relationships between these factors and method performance is typically not included in regulatory filings (nor are they rigorously studied during method development). The discipline imposed by a QbD approach will ensure the essential elements of the method are recognized. Furthermore, as the ATP relates to the product CQA, the benefits of this systematic approach to design and development are realized consistently throughout the quality assurance and quality control of product development, manufacture, and lifecycle management.

The second concept addresses how QbD steps, tools and approaches can be applied to design and development of an analytical method and can be used for implementation and lifecycle management of analytical methods in a manner analogous to those described for pharmaceutical

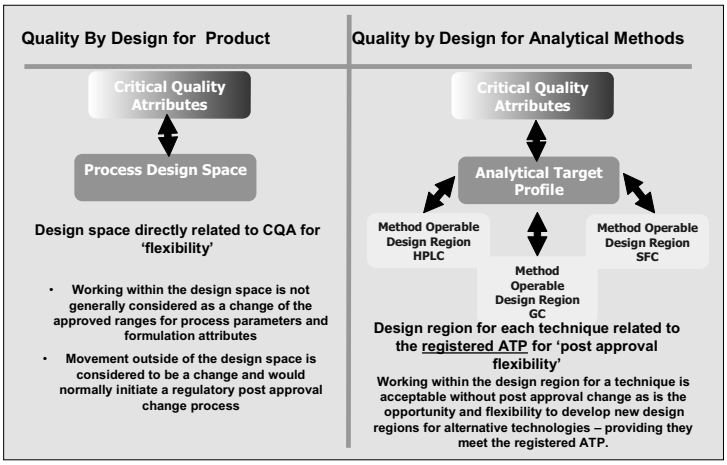

FIGURE 29.1 Comparison of key elements of QbD for product and QbD for analytical methods.

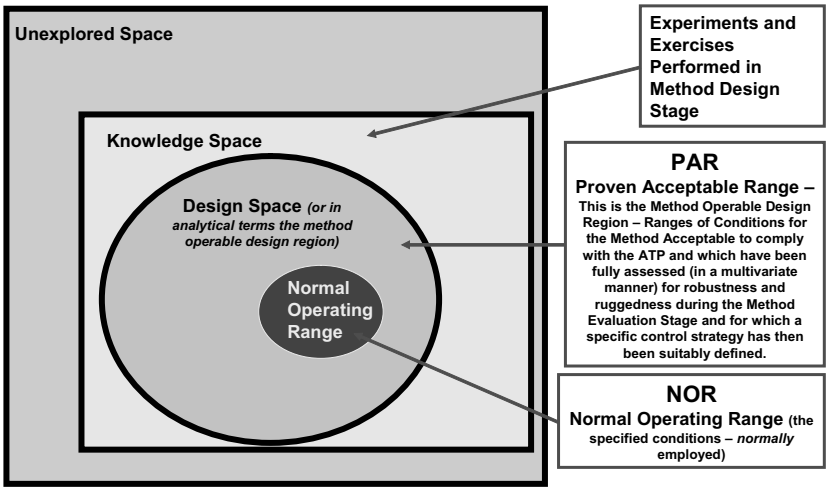

FIGURE 29.2 Description of how the QbD approach to development of an analytical method can be considered in "traditional" QbD terms.

manufacturing in ICH Q8, Q9, Q10. In this concept, the stepwise process of method development, method validation, and method transfer are superseded by a new paradigm with a design phase followed by a comprehensive method development and evaluation. This yields a robust and rugged method that is described in terms of the "method operable design region" where all of the factors that may affect the method have been evaluated or explored through experimentation. The method operable design region is essentially the design space (or proven acceptable range in QbD for product) over which the robustness and ruggedness experimentation has shown the method can meet the requirements of the ATP. For convenience, the method may typically run with more restricted conditions for business operational reasons (i.e., the normal operating range). Of course, in determining the method operable design region some experiments will identify conditions that do not meet the ATP, this is illustrated as the knowledge space beyond the design space. For some techniques there may be conditions that remain unexplored as they are unlikely to yield usable conditions. These terms are illustrated in Figure 29.2.

Figure 29.3 gives an overview of the concepts discussed and illustrates the key components of the process for QbD of analytical methods. The adoption of a well-researched ATP and the implementation of the new approach to change control will result in methods that are exquisitely matched to the requirements for the measurement and that allow changes to facilitate adoption of new technologies that augment continuous improvement. The robustness and ruggedness evaluation will enable changes to method factors to allow flexibility

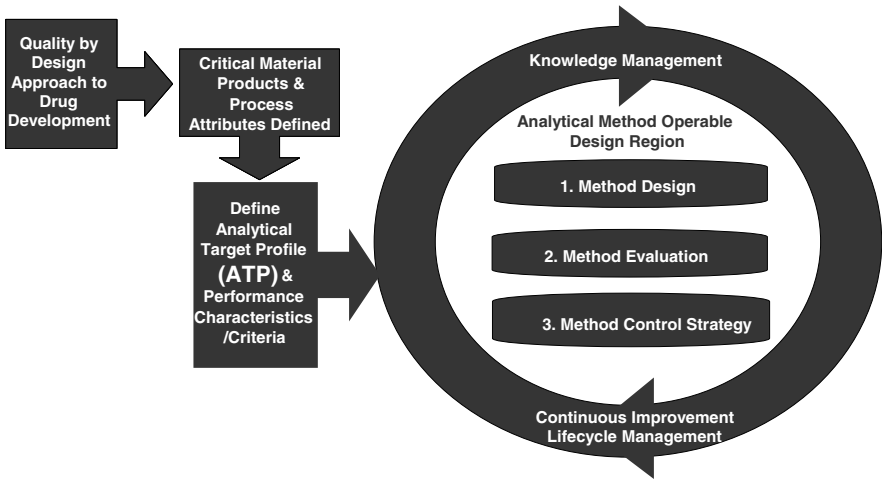

FIGURE 29.3 QbD for analytical process and its relation to both the ATP concept and the QbD approach to drug development.

TABLE 29.1 Example ATP for Measurement of Impurities Present in a Drug Product

Analytical Target Profile: The procedure must be able to quantify specified and unspecified impurities (degradation products) in the presence of API (active pharmaceutical ingredient), excipients and other potential impurities and degradation products over a range of 0.05–0.5% relative to the drug substance. The accuracy and precision of the method must be such that measurements fall within the range of $100\% \pm 15\%$ for levels $\leq 0.15\%$ and $100 \pm 10\%$ for impurity levels $>0.15\%$ with 90% probability

In this example, the impurities are controlled at 0.2% and have a reporting threshold of 0.05%.

during the method lifecycle with an enhanced method control regime. In the sections below the key components as given in Figure 29.3 are described in more detail, giving the general case for application of these components, and illustrated throughout by an example of an HPLC impurity assay for a drug product tablet formulation.

29.2 ANALYTICAL TARGET PROFILE

Creation of an analytical target profile is the initial step for QbD for analytical methods. The ATP is a description of the key measurement system requirements that must be satisfied by the analytical method and will take into account the nature and purpose of the measurement, whether it is being carried out to give process understanding, in-process control or as part of finished API or product release testing. A typical ATP may cite the analytes to be measured, the level at which they are to be measured, the required sensitivity, specificity and/or allowable uncertainty (precision and accuracy) in the measurement. The ATP is not intended to be method or technique dependent in that any analytical method or technique may be deployed if it is demonstrated that the method meets the ATP criteria.

An example ATP for control of impurities in a drug product is given in Table 29.1. At first glance, drafting an ATP may appear to be a simple process. However, creation of a meaningful ATP requires a good understanding of the manufacturing process capability, the effect of the API and/or drug product quality attributes [9] on patient safety and efficacy, and how the generated data will be used, interpreted, and reported. A strong connection between the ATP and the manufacturing processes is important. The ATP should be aligned with critical process parameters and critical quality attributes (definitions provided in Table 29.2) identified during the QbD for product process [10] that are impactful to patient safety and efficacy. A strong connection between the ATP and manufacturing process also enables the design of methods providing the appropriate level of feedback for process development, optimization, and ultimately control. If data will be used to support regulatory filings, appropriate agency and regulatory guidelines should be consulted when developing an ATP. For example, the ICH guidelines for impurity identification and qualification should be consulted when creating an ATP for an impurity method [11,12].

ATP criteria will vary depending on the measurement to be made, the type of sample to be analyzed, and the intended use of the data (whether the measurement/result is required for process understanding, in-process testing or final API or drug product release testing). Several examples are described as follows:

- A limits test for a drug product impurity will have different ATP criteria when compared to a quantitative test for an impurity.
- The requirements for measuring the unwanted enantiomer in an API or drug product could be very different from the requirements for measuring low-level genotoxic impurities where adherence to guidelines and regulatory requirements is critical [13].
- An ATP for water content of drug product tablet blends tested during manufacturing as in-process control testing may be different when compared to water content testing performed for finished goods testing of tablets.

Some considerations when creating an ATP are discussed below:

Identify the Quality Attribute to be Measured: The quality attribute to be measured may be, for example, assay, impurity levels, water content, residual solvents, dissolution, identity, sterility, endotoxins, and particle size. Each quality attribute is likely to result in a unique ATP, although on occasions more that one quality attribute may be combined into a single ATP, such as the quantitation of multiple impurities.

TABLE 29.2 Definitions of Critical Process Parameters and Critical Quality Attributes [14]

Critical Process Parameter: A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality
Critical Quality Attribute: A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality

Identify the Levels and Required Range of Values to be Measured by the Method: When determining the targeted levels to be measured, consider the analyte and the levels that might be expected to be present and consider the levels that may affect safety and efficacy, and also regulatory guidelines. The range of values to be covered by the methodology will direct technique selection, method development and eventually method evaluation. Ranges may be quite wide for some applications, such as methods used to gather data to further understanding of manufacturing processes or more narrow for measurements used to support release testing of finished goods.

Identify the Allowable Overall Uncertainty in the Measurement and Appropriate Probability: An approach that captures the acceptable overall uncertainty allowed in the measurement can be used. The overall uncertainty is the difference between the true value and the measured value and contains contributions from both precision and accuracy. This approach is preferred compared to explicitly stating the individual requirements for both accuracy and precision because it allows for some variability in both the accuracy and precision of the analytical method while still ensuring the value provided by the measurement is within an allowable distance from the true value. In the example provided in Table 29.1, the overall allowable uncertainty varies depending on the levels that are measured, with levels near the reporting limit allowing a larger uncertainty ($\pm 15\%$) compared to levels at or near the specification limit ($\pm 10\%$).

Identify the Required Method Specificity: The required specificity should be stated in the ATP. Method specificity and accuracy are linked in that interferences with the analyte of interest can affect measurement uncertainty depending on the magnitude of interference. Using the example of a drug product impurity, the ATP states that the impurity should be accurately quantitated in the presence of API, excipients, and other degradation products and process-related impurities.

Once an ATP is established, any method that meets the requirements may be implemented provided it is demonstrated to meet the requirements of the ATP and the method is developed following a QbD for analytical methods approach. Having an ATP in place should also facilitate changing from one analytical method to another as shown in Figure 29.1. When changing to a new method, method equivalency is demonstrated by showing the new method satisfies the criteria outlined in the ATP. Business requirements such as efficiency, cost, or improvements to process understanding drive the need to change methodology. Therefore, typically only one method would be in use at any time for a repeat situation such as product release testing. Furthermore, when the requirement for trending is important, for example when trending for stability testing during product development, changing to a new method should be approached with due caution. The requirements for establishing method equivalency are currently being debated by the USP [15] and the pharmaceutical industry.

29.3 METHOD DESIGN

Once an ATP has been created, the criteria contained within it will help guide selection of an appropriate analytical technique. As an example, for the ATP cited in Table 29.1, a chromatographic method could be considered since it has the potential to meet the required selectivity, measurement uncertainty, range, and sensitivity. A spectroscopic method, such as NIR, will likely not have the appropriate sensitivity and selectivity.

The overall objectives of the method design phase are to:

- achieve a set of "starting" method conditions for the selected analytical technique through technique selection and initial experimental screening;
- achieve a list of method factors associated with each unit operation of the method that have been thoroughly assessed with respect to "potential risk" to method "failure";
- achieve a thorough understanding of which method factors will be controlled and how they will be controlled; and
- achieve a list of method factors that require further evaluation to assess robustness and ruggedness and ultimately describe the boundaries of the method operable design region.

The process of method design starts with technique selection. Once the appropriate technique has been selected a series of experiments will be performed to identify a suitable starting set of method conditions that can be further assessed using QbD principles. The separate unit operations of the method are then identified, and an exercise is carried out where all method factors associated with each unit operation are identified. The final step of the process involves a risk assessment exercise where each method factor is categorized and prioritized according to potential "risk." The outcome of this exercise is a list of fixed method factors plus an experimental plan derived to evaluate method robustness and ruggedness using the remaining noise factors and nonfixed method parameters. The following discussion outlines each component of method design in more detail.

29.3.1 Technique Selection

This involves selection of an appropriate analytical technique that will be capable of achieving the desired measurement of the material, product, or process attribute defined in the ATP.

A simple prioritization exercise can be performed to build the rationale for choice of technique. For example, in Table 29.3, rationalization of a suitable technique to meet the ATP requirements is presented. The ATP requirements were listed as the primary technique selection driver and any business drivers were listed as secondary factors that could influence the final choice of technique. It can be seen that more than one technique, if rationalized purely from the ATP performance requirements alone, would be "suitable" from a scientific perspective to comply with the requirements defined in the ATP. However, if the business operational considerations are also accounted for, then it soon becomes clear why uHPLC-UV (DAD) would be a sensible choice in terms of analysis time and costs drivers. HPLC-UV (DAD) would also be sensible, but possibly to a lesser extent due to analysis time. Of course, this selection rationale is highly dependent upon the stage of development of the product for which the ATP is designed. This sort of process is useful to document when designing a method as it captures the rationale behind technique selection clearly—which could well be valuable later in the method lifecycle—or when, for example, a new innovative technology appears on the analytical landscape that could be assessed in the same way against the originally defined criteria.

29.3.2 Initial Experimental Screening to Develop "Initial" Method Conditions

Having identified a suitable technique (HPLC-UV) to meet the ATP and business drivers, the method design process continues with initial experimentation to build a set of starting method conditions for more intensive evaluation. If one were to consider the experimentation process like a funnel that at the top is wide and encompasses a variety of method factors (which are ideally considered in a multivariate way so that interactions and interdependencies are understood) then this stage is the very top of the funnel. All experiments and exercises performed herein contribute to the definition of the knowledge space description for the method (Figure 29.2) and of course ultimately to the definition of conditions that will be extensively interrogated in the method evaluation stage of the process.

The timing of this knowledge gathering within the drug development lifecycle is important to ponder further. Regardless of the development stage in which the QbD for analytical methods process might be initiated—any previous knowledge is certainly valuable to capture in this knowledge space description.

There are of course two possible approaches that companies might wish to adopt here with respect to timing. The first approach might be where a company develops method conditions in a "traditional" one factor at a time (OFAT) manner (these experiments would define the "knowledge space" of the method) and retrospectively applies QbD thinking to that knowledge gathered at a later point during development. At the point of application of the QbD approach, the area around the normal operating range of the method would be interrogated so that method operable design region could be mapped. In defining this method operable design region, the company would be afforded the opportunity to optimize the normal operating range further from the critical "edges" of the method operable design region than it may have originally resided.

The second approach involves application of the QbD process at an earlier stage of development. Here, the systematic application of orthogonal platform screening strategies to thoroughly map the knowledge space and define a suitable set of starting method conditions would be generically applied to all compounds in development regardless of their developmental stage. The next step would then be to perform multivariate experiments to map the likely method operable design region and nominate the normal operating range for ongoing developmental support. The employment of a multivariate approach here would be key to achieving a thorough understanding both of the interdependencies of the method factors and the criticality of each method factor to the method success. As the compound progresses in development (the synthetic route of the API is modified, formulations are developed, degradation mechanisms and structures are understood, etc.), the knowledge space may well be redefined or expanded leading to a slightly different method operable design region. The application of scientifically rationalized orthogonal platform screening approaches in combination with multivariate experimentation allows for a consistent response to building such a description. Once the commercial API route and/or commercial product formulation has been nominated, then a more thorough evaluation of the method in concert with the receiving manufacturing laboratories would be pursued so that the robustness and ruggedness of the method is thoroughly understood and that the optimal normal operating range is selected for routine laboratory use (this is the topic of method evaluation—described later).

29.3.3 Risk Assessment

Whatever the route to defining the "knowledge space," be it though a traditional OFAT approach or through orthogonal platform screening approaches and multivariate experimentation, once a "knowledge space" for a method has been established—an initial set of conditions should have been arrived at for successful operation of the method in order to achieve compliance with the ATP. Now, there is a need to thoroughly interrogate these conditions to ensure that they are indeed robust and rugged for testing laboratories to operate on a routine basis. Historically, little was done at this stage to test the performance of the method in a receiving laboratory. Development laboratories would validate conditions according to ICH Q2(R1) [16] and then eventually

TABLE 29.3 Method Performance and Operational Requirements Influencing Analytical Measurement Technique Selection of an Impurity Method for a Tablet Formulation

	1. Method Performance Requirements			2. Business Drivers				
Technique	Specificity	Sensitivity	Capability to Meet Accuracy and Precision Requirements	Capability for At-line or Online Measurement	Technology Available to Customer Lab?	Analysis Time (H, M, L)	Analysis Cost (H, M, L)	Need for Sample Preparation
uHPLC-UV-MS	×	×	×	×		L-M	M	Yes
uHPLC-UV (DAD)	×	×	×	×	×	L	L-M	Yes
HPLC-UV (DAD)	×	×	×	×	×	M	L-M	Yes
HPLC-UV-MS	×	×	×	×		M-H	M	Yes
TLC	×	×			×	M	L	Yes
CE-UV (DAD)	×	×	×			L	L	Yes
UV			×	×	×	L	L	Yes
GC-MS or GC-FID	×		×		×	L-M	L	Yes
NIR				×		L	L	No

complete a formal exercise to transfer the methodology to a receiving laboratory for release or stability testing laboratory within a company's manufacturing unit using comparative testing. Only if issues occurred during the transfer testing would there be indication of future robustness problems. Ownership of the method transferred to the testing laboratory with little knowledge of how the method was developed or understanding of the operating or design space. In QbD for analytical methods this becomes significantly more of a partnership, with receiving analytical laboratories actively contributing to the method design and method operable design region creation.

A structured risk assessment is conducted to identify all potential sources of variation in the practice of the intended method. The goal is to consider potential functional relationships between each method factor and the performance characteristics/criteria defined in the ATP or those that would be specific to the employed technique, and assign a risk ranking to these method factors through a scoring system. Essentially, all of the method factors that could impact method success are discussed and their relative significance is considered. Before a risk assessment exercise is conducted, several preparatory activities should take place. The receiving/testing laboratory should review the normal operating range conditions for the method and ideally run the method to provide initial feedback, but this could extended to completing testing on materials identified as appropriate for purposes such as formulation development or clinical supply release. Although most experienced analysts should have the capability of participating in a risk assessment exercise by reviewing the method, hands-on experience in preparing samples and operating the instrumentation will likely provide additional perspective. The risk assessment should therefore proceed with representation from both the developing analysts and receiving analysts with the requisite method familiarity. The exercise itself is extremely valuable for understanding different strategies adopted by each site—as even the simplest and seemingly most innocuous method factor can be one that could contribute to method failure. These conversations therefore often highlight and circumvent the common "assumptions" made in method transfers between one laboratory and another that contribute to unsuccessful operation of the method in a receiving laboratory. The three components of a risk assessment are defined below.

The risk assessment process proceeds by first defining the unit operations of the method. For an HPLC method to profile impurities in a drug product formulation, the unit operations may look something like the depiction in Figure 29.4, which also breaks out the subunit operations associated with the tablet sample preparation step.

Once the unit operations have been defined, all method factors that can influence the performance of the method can be mapped to each unit operation appropriately. Method factors can fall into multiple categories including those associated with machines, materials, people, processes, measurements, and environmental conditions. Examples of method factors at the bulk sampling stage could include the batch homogeneity, the integrity/identity of the batch, the sample size being taken, the sampling strategy (e.g., size, % of batch, thief), and the "human" contribution to variability (training/skill/experience); examples for a sonication step in standard preparation could be sonication time, bath temperature, and bath fill volume; and for a sample preparation mixing and extraction step, factors could include shaker type, shaker time, vessel orientation, and shaker speed. Examples demonstrating method factors associated with unit operations are presented in Figures 29.5 and 29.6 for sample preparation of a drug product tablet for an impurity assay and the subsequent HPLC impurity assay.

Now that each factor has been mapped to its appropriate unit operation, the risk assessment exercise may continue either through application of appropriate risk assessment tools or using experience (prior knowledge) or a combination of both. There are several approaches that could be employed to carry out this assessment and the most commonly used are failure mode effects analysis (FMEA) [17,18] and cause-and-effects matrix (C&E) [19]. In an FMEA, potential failure modes of the method (e.g., analytical balance out of

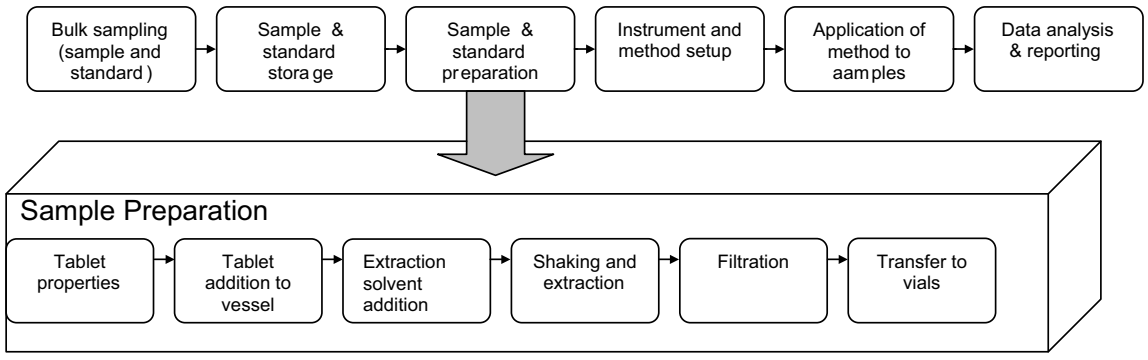

FIGURE 29.4 Unit operations of a tablet sample preparation unit operation within an HPLC impurity method.

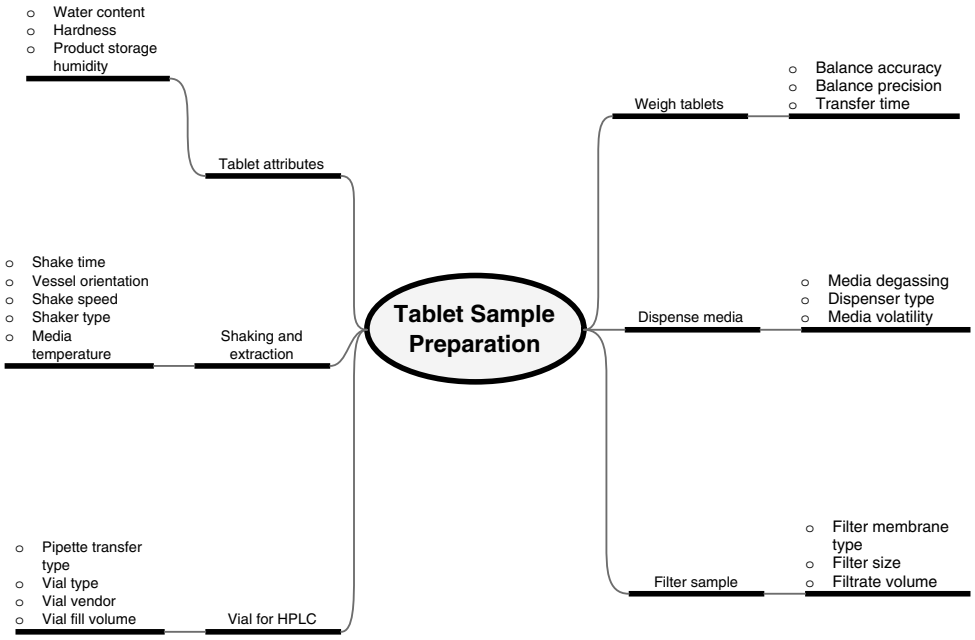

FIGURE 29.5 Mapping example of method factors to the sample preparation unit operation of an HPLC impurity method for a drug product tablet formulation.

calibration) are brainstormed by the group and each of those modes is scored for impact against the performance characteristics/criteria defined in the ATP or those that would be specific to the employed technique. High ranking failure modes are then addressed through experimentation plans or other means (e.g., fixing/controlling factors to specified levels/criteria) that attempt to lessen the risk. In a C&E matrix, the method process is mapped out into individual activities and the factors of each activity; then during the scoring exercise each method factor is evaluated with respect to any attribute that could be considered significant in affecting the performance criteria as defined in the ATP. Note that these attributes may not be specifically listed in the ATP, but do indeed strongly influence the capability of the

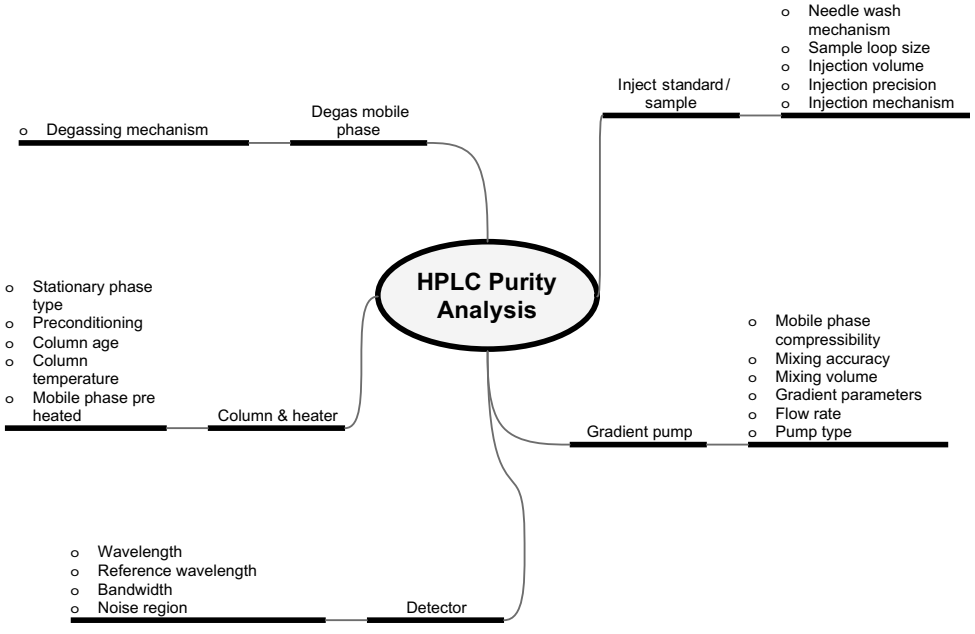

FIGURE 29.6 Mapping example of method factors to the HPLC unit operation of an HPLC impurity method for a drug product tablet formulation.

TABLE 29.4 Definitions of C, N, and X Assignments for Method Factors in Risk Assessment Exercise

C	Analytical Method Factors that form part of the method definition and can be specified at **C**ontrollable unique levels
	These variables do not require experimentation to "optimize"—they are variables that are fixed and should be clearly stated. During the group work between developing and receiving laboratory analysts—these variables are often the important ones to define carefully as clearly communicating how these variables are fixed often circumvents unsuccessful operation of the methodology in the receiving laboratory
N	Analytical Method **N**oise Factors (factors that cannot be controlled or are allowed to vary randomly from a specified population) and if identified as potentially critical may require ruggedness testing.
	Examples of these variables in an HPLC method could include the column batch or the instrument make in a FTIR method for identification
X	Analytical Method Factors that form part of the method definition and can be varied continuously and if potentially *critical* may require e**X**perimentation to optimize the method operable design region
	These variables are important as they will define the starting point for multivariate DoE's in the robustness assessment of the method. Examples of these variables for an HPLC method would include the temperature of the separation or the pH of the mobile phase

method to meet the criteria of the ATP, for example, sample solution stability of an HPLC impurity method. Thereby, a risk factor is assigned to each parameter. As the C&E matrix provides a more thorough understanding of an analytical method, all further references to a risk assessment will reference the application of a C&E matrix.

When a method factor is believed to have a strong relationship to an attribute, it should be scored higher. These exercises tend to bring forth a lot of additional information as any prior experience with similar methodologies or differing laboratory practices can be taken into account to determine whether a method factor should be ranked higher or lower. After each method factor is scored, the influence (score) of a method factor against each attribute is summed. This value represents the risk of a single method factor on impacting the performance of a method where the higher the value, the higher the risk. The team performing the risk assessment has to make a decision on what level of risk is deemed appropriate for designating as "potentially critical" to the success of the method meeting the ATP criteria.

Also during this exercise, as each method factor is being scored, an assignment of method factor "type" is decided. Method factors are designated C, N, or X according to the definitions in Table 29.4

Examples from the outcome of prioritized C&E matrices where the potential critical factors are highlighted and classified as C, N, or X are shown in Figures 29.7 and 29.8.

Factor Parent	Factor Name	Sample Solution Stability	Sample Accuracy	Sample Precision	Final Score	C, N, X	Experimental Strategy
		10	5	5			
Shaking and extraction	Media temperature	9	9	9	180	N	DOE 1
Shaking and extraction	Vessel orientation	9	9	9	180	C	Method controlled
Shaking and extraction	Shake time	5	10	10	150	X	DOE 1
Filter	Filter membrane type	5	10	10	150	X	OFAT 1
Tablet testing	Product storage humidity	9	1	5	120	N	Ruggedness 1
Shaking and extraction	Shake speed	1	10	10	110	X	DOE 1
Vial for HPLC	Vial type	5	5	5	100	N	Ruggedness 1
Filter	Filter size	1	9	9	100	X	OFAT 1
Vial for HPLC	Vial vendor	5	5	5	100	N	Ruggedness 1
Dispense media	Dispenser type	5	5	5	100	N	Ruggedness 1
Filter	Filtrate volume	1	9	9	100	X	OFAT 1
Shaking and extraction	Shaker type	1	5	5	60	C	Method controlled
Tablet testing	Water content	1	5	5	60	N	Ruggedness 1
Vial for HPLC	Vial fill volume	1	5	5	60	N	Ruggedness 1
Tablet Testing	Hardness	1	5	5	60	N	Ruggedness 1
Weigh tablets	Transfer time	1	1	1	20		
Weigh tablets	Balance accuracy	1	1	1	20		
Weigh tablets	Balance precision	1	1	1	20		
Vial for HPLC	Pipette transfer type	1	1	1	20		
Dispense media	Media volatility	1	1	1	20		
Dispense media	Media degassing	1	1	1	20		

FIGURE 29.7 Example from the outcome of a prioritized C&E matrix for the sample preparation unit operation of an HPLC impurity method for a drug product tablet formulation.

Factor Parent	Factor Name	Individual & Total Impurity (area %)	Peak Retention Time	Peak Resolution	Signal/ Noise LOQ	Baseline Quality	Linearity	Peak Area	Peak Plates	System Precision	Peak Tailing	Final Score	C, N, X	Experiment Strategy
		10	10	10	10	10	10	5	5	5	5			
Column & heater	Preconditioning	10	10	10	10	10	5	10	10	5	10	725	N	Ruggedness-1
Column & heater	Column Age - # of injections	10	10	10	10	10	5	10	10	5	10	725	N	Ruggedness-2
Pump (gradient)	Gradient parameters	10	10	10	10	5	5	9	10	5	9	665	X	DOE-1
Column & heater	Stationary phase type	10	10	10	5	10	5	10	10	1	10	655	X	DOE-1
Column & heater	Column temperature	5	10	10	9	5	5	5	10	5	1	545	X	DOE-1
Column & heater	Mobile phase preheated	5	9	9	5	5	5	5	9	5	5	500	N	OFAT-1
Detector	Detector wavelength	10	1	5	10	5	5	10	5	5	1	465	X	DOE-1
Pump (gradient)	Mixing accuracy	5	10	10	5	5	1	1	1	5	1	400	X	DOE-1
Detector	Reference wavelength	9	1	1	9	5	5	9	1	1	5	380	N	OFAT-2
Auto-sampler	HPLC injection precision	5	1	1	10	1	1	10	1	10	5	320	N	DOE-1
Auto-sampler	Injection volume	5	1	1	10	1	1	10	1	1	10	300	X	DOE-1
Auto-Sampler	Injection mechanism (fixed/partial)	5	1	5	5	1	1	5	9	1	5	280	N	OFAT-3
Pump (gradient)	MP compressibility	5	5	5	1	5	1	1	5	1	1	260	N	None
Detector	Detector bandwidth	5	1	1	5	5	1	9	1	1	5	260	N	None
Pump (gradient)	Pump type	5	5	5	1	1	1	1	5	1	1	220	N	None
Detector	Noise region for S/N	1	1	1	10	1	1	1	1	1	1	170	N	None
Pump (gradient)	Mixing volume	1	5	1	1	1	1	1	1	1	1	120	N	None
Auto-sampler	Needle wash mechanism	1	1	1	1	1	1	1	1	1	1	80	N	None
Auto-sampler	Sample loop size	1	1	1	1	1	1	1	1	1	1	80	N	None
Degas	Degasing mechanism	1	1	1	1	1	1	1	1	1	1	80	N	None

FIGURE 29.8 Example from the outcome of a prioritized C&E matrix for the HPLC unit operation of an impurity method for a drug product tablet formulation.

29.4 METHOD EVALUATION

Having established a prioritized ranking of potential influences on method performance, an experimental plan is developed to understand the impact of high-risk method factors that are labeled N or X. A method factor labeled as C might also be at higher risk, but is controlled through execution of the method (possibly understood through previous method development experiments) or by establishing agreed/fixed practices that indicate that the method factor is not allowed to influence the method's performance.

Robustness studies can be designed from method factors labeled X. Often these studies can be completed through a DoE (design of experiments) and input from statistical expertise is particularly helpful at this point. For an HPLC method, an example would be to further refine the method operable design region around resolution of a critical pair of impurities by evaluating chromatographic factors such as temperature, % mobile phase modifier, buffer concentration, gradient conditions, and flow rate. Chromatographic factors in a DoE have been frequently discussed in the literature [20–23], but this approach should be applied to other focus areas of an impurity profile method (factors such as shake time, speed, extraction solvent composition for tablet preparation) or other types of methodology such as dissolution, water content, and spectroscopy. Experimental plans can use an OFAT approach to evaluate a single factor through a univariate study or alternatively explore the interdependence of a number of factors in a multivariate design. Results from these robustness studies could either lead to the control of certain method factors within the methodology or to an understanding of how each can be varied while still meeting the analytical target profile. This is explored a little more in the discussion on method control below.

An example DoE is presented below for a gradient HPLC impurity assay with an inflection point in the gradient profile nearly halfway through the program. The design of this study is consistent with the rankings from the C&E matrix presented in Figure 29.7. Table 29.5 shows the method factors that were investigated, along with their ranges. The study was a fractionated factorial design (2^{6-2}). The advantage of using a fractionated design is that it reduces the number of analyses needed while still incorporating interactions into the results. Additionally, two center points were run.

TABLE 29.5 Method Factors Analyzed in a DoE to Determine Method Operable Design Region for an HPLC Impurity Method of a Drug Product Tablet Formulation

Factor	Center	Low	High
Temperature	30°C	25°C	35°C
Flow rate	1.0 mL/min	0.9 mL/min	1.1 mL/min
Buffer concentration	0.05%	0.025%	0.075%
Gradient time 1	1 min	0 min	3 min
Gradient time 2	18 min	15 min	21 min
Gradient time 3	40 min	37 min	43 min

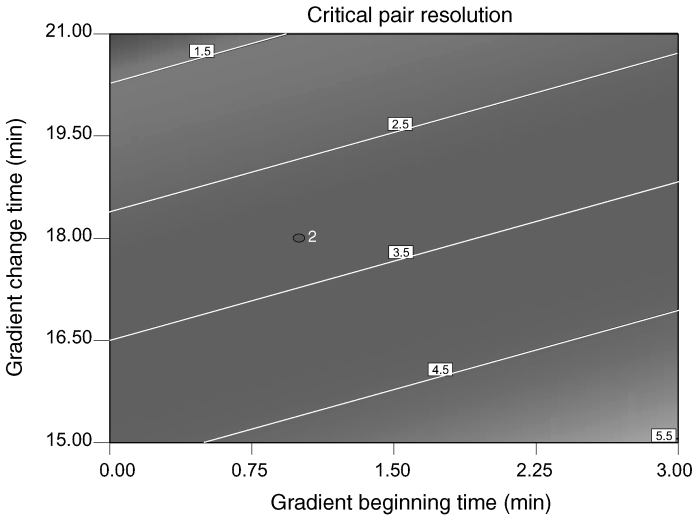

FIGURE 29.9 Influence of gradient parameters on resolution between closest eluting impurities in an HPLC impurity method. All other parameters are held at the center point.

For the above design, attributes evaluated were resolution of critical impurities, limit of quantification, efficiency (theoretical plates), peak symmetry (tailing), main band retention time, and last peak retention time. Based on the results, the attribute that was monitored closest was resolution of two closely eluted peaks. Additionally, main band retention time was looked at in detail because of its relationship to resolution between the main band and several key impurities. Figures 29.9 and 29.10 demonstrate the influence of this design region on the attribute of critical pair resolution. As shown by the area in the statistical contour plot in which the resolution was greater than 1.5, a rather large method operable design region was determined through this study. Although not demonstrated in this design, another factor that should be evaluated to determine the most robust conditions is column type. Finding multiple columns that can offer adequate method performance can afford greater method flexibility as an analytical laboratory may find one vendor preferable over the other for the reasons such as cost, availability, or future changes/discontinuation of the column.

Method robustness for an HPLC impurity assay has been typically described in the literature by understanding the effects of the chromatographic factors. However, understanding of the standard and sample preparation factors can be every bit as critical in the development of the assay. Preparation conditions that either do not extract the API and/or impurities from the sample matrix or do not reproducibly do so can lead to poor analytical results. In

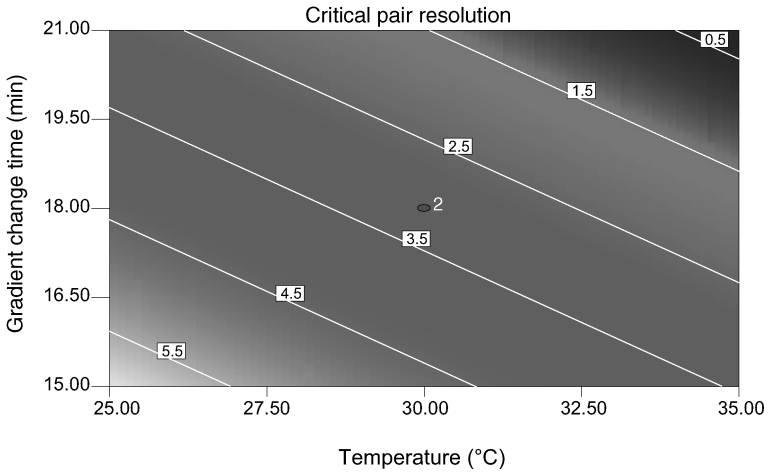

FIGURE 29.10 Influence of gradient parameters and temperature on resolution between closest eluting impurities in an HPLC impurity method. Note that gradient time 1 and all other parameters are held at the center point.

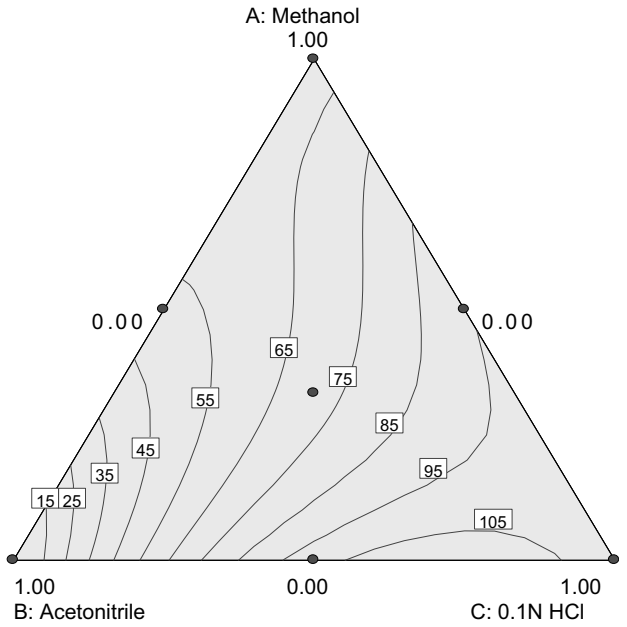

FIGURE 29.11 Contour plot from sample preparation DOE on solvent composition. Design evaluated influence of various solvents on API recovery after 15 min of shaking on a reciprocal shaker. Contours correspond to percent of API recovered from the tablet.

Figure 29.11, a statistical contour plot is provided to demonstrate the most robust solvent composition for sample preparation. For this study, a DoE was run to understand the impact of methanol, acetonitrile, and several aqueous solutions on the extraction of API from an immediate release tablet formulation. Similar studies could also be designed to understand the optimal device for sample extraction (e.g., reciprocating shaker, homogenizer, stir plate), extraction time, and filter type.

Noise factors should be evaluated to understand the ruggedness of the method. These factors can be introduced into the method through environmental conditions (e.g., laboratory temperature, humidity), inputs from the materials described in the method (e.g., filter material variability or reagent source), inputs from the process (e.g., particle size of API on NIR assay for API, tablet hardness on sample tablet preparation), or even human factors like the training/experience of the analyst.

The ruggedness design detailed in Figure 29.12 evaluates noise factors such as the analyst (training/experience) and HPLC column variability. This is done by running an analytical sample with a known value or samples from a well-characterized manufactured lot. This design is very similar to that outlined in ICH Q2 (R1) for an intermediate precision study that is recommended by Japanese regulators. While it is nearly impossible to gain a large understanding of noise factors from such a small study and that this type of study does not afford regulatory flexibility, a variability assessment from the results of this design can point to areas of significant risk. Compiling larger databases to evaluate the impact of noise factors through the lifetime of the method is discussed further in Section 29.5.

Again, statistically designed studies can be completed to understand the impact of the noise factors. To monitor the impact of process parameters on method ruggedness a DOE can be constructed. As part of a NIR tablet assay development and validation, evaluation of process parameters such as tablet hardness and API particle size can be intentionally varied along with percent assay of the API. This type of study demonstrates the variability of assay results when there is noise in process parameters.

As with the experimental factors, OFAT designs can be completed to evaluate noise factors. An example would be a HPLC column lifetime study where multiple injections are made to understand how long a column will last.

The goal at the end of this phase is to have a full understanding of how the method factors influence the method's ability to comply with the ATP. This will include a description of the method operable design region and normal operating range along with a plan for which factors

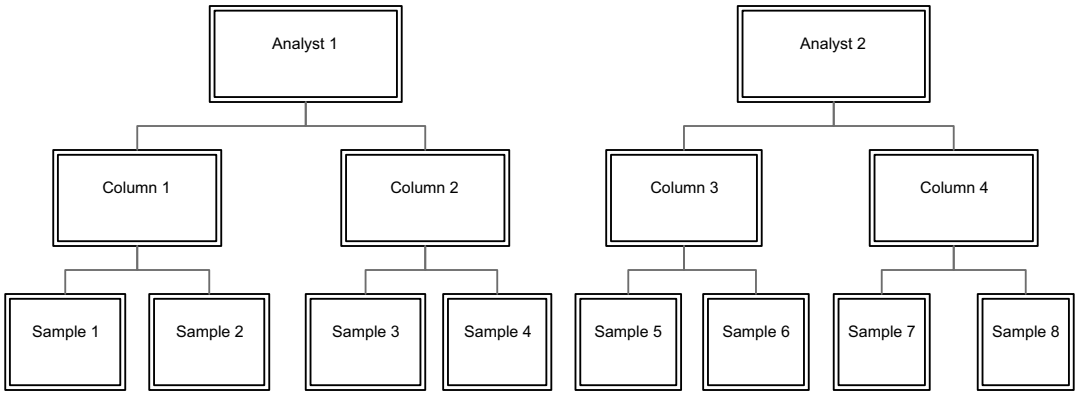

FIGURE 29.12 Ruggedness design to study noise factors in an HPLC impurity method for a drug product tablet formulation.

will be fixed/controlled. Developing sufficient understanding within the design region of the method serves to avoid conventional validation testing as a stand-alone activity. Increased communication, properly designed studies, and critical evaluation of the data set the stage for a relevant and efficient control strategy and continuous improvement.

29.5 METHOD CONTROL AND LIFECYCLE MANAGEMENT

The discussion so far has described how method conditions can be identified such that a good understanding has been developed of the factors that have a significant influence on the performance of the method—this knowledge is the method operable design region of the method. The method operable design region consists of method factors that must be known by the operating analyst in order to obtain accurate results. These factors may be fixed to a single point or two (e.g., light protective glassware used in sample preparation for a photosensitive product) when tightly controlling a factor is critical to meet method performance criteria outlined in the ATP. Alternatively, factors may be described by a range (e.g., column temperature 25–35°C) when it has been demonstrated that the criteria of the ATP are met throughout the range. Sample preparation factors such as extraction time or apparatus can be expressed broadly when demonstrated that multiple techniques can be used to sufficiently recover API from a tablet. An example of a design region for an HPLC impurity method for a drug product tablet formulation is described in Table 29.6. The current expectation for the routine practice of methodologies developed through the QbD for analytical concept is that a target set of conditions will be established within the design region and these will constitute the method that all laboratories utilize for a particular measurement. These target conditions should be seen as equivalent to the normal operating range as defined from QbD for product in Figure 29.1 but are not expected in reality to be practiced as a range. Also, it is not intended that a variety of methodologies or conditions based on individual laboratories or analysts' preferences would be employed for making a given measurement, even if they were all within the design region.

When practicing analytical QbD principles, the current vehicles for demonstrating control of an analytical method and understanding of the influences on its performance—namely method validation and system suitability, may be rendered redundant given the extra information generated in creating the design region. As much of the method operable design region is constructed in a multivariate way, it should be possible to develop significantly more knowledge than is gained from conventional validation experiments for characteristics (or attributes) such as linearity, accuracy, and precision for the entire design region. Additionally, rather than adhering to rigid expectations for these attributes, method performance would be judged directly against the ATP. Other attributes that are currently associated with method validation such as specificity—determined in the chromatographic arena through indicators like resolution, should be less important as the work done in creating the design region will have ultimately determined how varying the chromatographic conditions affect the final result. Specificity should therefore be seen as a way of defining how the chromatography should look when the knowledge of its impact on the final result is not known or well understood. The requirements for these attributes are often set high on the

TABLE 29.6 Example Method Operable Design Region for an HPLC Impurity Method of a Tablet Formulation

Method Factor	Design Region			
HPLC column	Brand X, Y, or Z C18 4.6 × 150 mm, 3 µm particle size			
Mobile phase concentration	Mobile phase A: methanol (15–30%): buffer (70–85%) Mobile phase B: methanol (40–50%): buffer (50–60%) Mobile phase C: methanol (55–65%): buffer (35–45%)			
Gradient parameters	Time (min)	%A	%B	%C
	0	100	0	0
	0–3	100	0	0
	16–20	0	100	0
	37–43	0	0	100
Buffer concentration	0.025–0.075%			
Column temperature	25–35°C			
Flow rate	0.9–1.1 mL/min			
Detector wavelength	250–258 nm			
Sample preparation	Tablets should be prepared at a concentration of 0.1 mg/mL in mobile phase A in light-protective glassware. API should be sufficiently extracted from tablet matrix using a proven process			

assumption that in so doing, the method will be operating well away from any edge of failure without establishing the edges of failure or understanding the impact on the result of allowing a lower requirement. Dictating a high number of theoretical plates, a low tailing factor or a minimum peak width are other chromatographic examples. Current method validation requirements around intermediate precision, ruggedness and robustness again represent relatively crude attempts to assess method performance. Intermediate precision testing represents a very narrow review of the impact of different analysts, equipment and possibly laboratory/site performing the methodology and focuses on establishing that these factors do not impact the results obtained for a particular measurement. This testing is carried out in a very short period, with relatively few measurements being made and compared and is therefore not that relevant to the long-term use of the method. Likewise, robustness testing, as described in current validation guidelines, focuses on establishing that minor deliberate perturbations to the target conditions do not have any effect on the validation rather than understanding the impact on the true result of the measurement.

It is recognized that extracting this information from the DoE/method evaluation exercises and presenting it in a way that would give regulators the same level of confidence that they get from conventional validation reports is work that still needs to be progressed before full adoption of QbD for analytical would be acceptable in all areas. One approach, and that used within the practice of QbD for product, would be to validate the target conditions to be run routinely in the conventional manner (e.g., ICH Q2(R)) and provide analysis results from method evaluation studies that clearly demonstrate the influence of method factor ranges on performance. Any desired change to the target conditions is then subsequently assessed for the potential impact on the validation "status" of the method. Proposed changes might be rationalized as to having little or no impact on the validation status given the knowledge associated with the design region, alternatively some revalidation may be considered appropriate. Changes outside the design region would require more work to justify.

In addition to the current practice of carrying out validation to establish limited knowledge of method performance, it is expected that system suitability requirements are established prior to running a method. System suitability is a further blunt tool that, in the absence of knowledge, seeks to ensure that a method is performing within tight constraints. These tests often focus entirely on the instrumental elements of a method and are in many cases derived from an era when the engineering and instrumentation employed in making analytical measurements were highly variable, with a large potential impact on the result. As instrumentation is much more precisely engineered today, the checking of system suitability attributes such as injection precision for a method employed for impurities (especially with wide requirements for measurement uncertainty) often yields no useful information while there are many parameters associated with determining an accurate result that go unchecked—the extraction procedure being the most obvious. Depending on the design region achieved for a method it may be that some system suitability should be included—particularly if the design region is small and the method conditions are close to the edge—a chiral separation may be an example where in many instances the separation of an enantiomeric pair is achieved only with a specific column chemistry and mobile phase composition with relatively little toleration for variation or the need for injection precision for an assay method with narrow requirements for measurement uncertainty.

Lifecycle management can be thought of in two terms; first is the lifecycle management of the method operable design region for a specific technique. The more progressive definition is lifecycle management of the ATP such that changes from one analytical technique to another may be applied. The following discussion addresses the former term for lifecycle management. Understanding the uncertainty in measurement systems throughout the lifetime of a method is critical for determining the variability of the manufacturing process from batch to batch, and to know when a change is needed to the measurement system. During the lifetime of the methodology, numerous issues could influence the desire or need to make a change within the method operable design region. These issues may be attributed to manufacturing changes or to changes within the analytical method factors. Performance of the methodology could be reviewed through collection and monitoring of a variety of performance indicators such as some of the critical method factors required for system suitability. Data acquisition systems could be set to do this automatically and flag either significant change or a trend away from the initial value. The change could then be assessed against the knowledge within the design region to determine what, if anything should be done. Another approach to monitor long-term performance is that each time the method is run, a reference sample for which the true result is known is run alongside the samples being analyzed by the methodology and the results for the reference material are compared to the true value for that sample. This could be useful in cases where the method operable design region is narrow or sensitive to method factors. Alternatively, a less proactive process could be that the method performance is reviewed only when failures are encountered. The reasons for failure, either out of specification measurements or failure to meet some other requirement that would drive a laboratory investigation would be reviewed in the context of design space. Corrective action could be taken to alter the method conditions within the design region or create more knowledge to expand the design region. Catastrophic failure of the method brought about by changes to components like the column or reagents (change in characteristics or cessation of supply) would also be dealt with in this way. Further, when

the need to change a method is identified, all experiences associated with running the method would be collated and considered to determine a new set of target conditions to be adopted by all analysts making that measurement. The flexibility to make changes would also allow improvements to the overall efficiency of making the measurement or improve the actual quality of the measurement. For example, a simpler impurity profile (impurities no longer observed and therefore do not need to be tracked) brought about by changes to the process or with routine manufacturing experience would provide rationale to make modifications to the method (e.g., shorter run times, fewer criteria needed before running the method, etc.). The presence of these impurities will have had an influence on the design of the original method conditions—their absence represents an opportunity to review the method conditions and potentially speed up the run time to achieve the measurement while still meeting the requirements of the ATP. This change would not only improve efficiency but would ultimately lead to reducing the cost of testing, and therefore, the cost of the product. However, in the current environment, the cost of facilitating the change through refiling and approval processes would outweigh the benefits of making the change for all but the highest cost or highest volume products. The following paragraph proposes an option to address this cost-benefit concern.

In the more progressive and optimal definition of lifecycle management, the ATP will be seen as the regulatory commitment for making the measurement and so variations to the conditions within the method operable design region should be allowed without impacting that commitment. Changes that are recognized as being outside the existing design region would be expected to require further experimental work to redefine the design region such that the new conditions were within it. This might be true of major changes to conditions associated with a particular analytical technique, say HPLC—but would certainly be true if there were a desire to switch to a different technique or technology where a whole new method operable design region would need to be created. Changing from one technique to another but one with the same or similar fundamental principles (e.g., chromatography—and a potential change from HPLC to GC, or vice versa) might be seen as a change of lesser magnitude to a proposed change to a technique with fundamentally different principles, such as a change from a chromatographic technique to a spectroscopic technique. It is the long-term vision that this change would still be "allowed" by regulators, provided the requirements of and commitment to the ATP were unchanged. At the current time, the preliminary feedback from regulators who have commented on QbD for analytical methods suggests that it should be relatively straightforward to achieve the desired freedom for changes within the design region and where the full knowledge set has been laid out. However, changes to a technique or method where a new method operable design region was needed, even though the requirements of the ATP were still met, will likely require significantly more dialogue and may be seen as changes requiring prior approval.

29.6 CONCLUSION

Quality by Design for analytical methods is an evolutionary step in pharmaceutical development as analytical scientists are in full partnership with API and drug product process engineers to understand the requirements of a manufacturing process and align them with the requirements of the measurement technique and technologies capable of making those measurements. There are significant benefits to adopting a QbD paradigm for the development of analytical methodology, irrespective of any freedom to change methodology that might be agreed with regulators. The practice will result in more robust methodology as there will be a greater knowledge about the factors that influence its performance and there will be improved clarity of understanding between those developing the methodology and the community of analysts that will ultimately run it routinely. There will be enhanced focus on both generic laboratory practices as well as the specifics of operating a given analytical method. The other, perhaps more significant benefit, which may take longer to realize, is that this concept will ultimately allow companies to make changes to methodology for a variety of reasons without the need for time-consuming and costly refiling activities required to secure prior approval, provided the changes were within the regulatory commitment represented by the ATP.

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