REVIEW

Development of Quality-By-Design Analytical Methods

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ABSTRACT: Quality-by-design (QbD) is a systematic approach to drug development, which begins with predefined objectives, and uses science and risk management approaches to gain product and process understanding and ultimately process control. The concept of QbD can be extended to analytical methods. QbD mandates the definition of a goal for the method, and emphasizes thorough evaluation and scouting of alternative methods in a systematic way to obtain optimal method performance. Candidate methods are then carefully assessed in a structured manner for risks, and are challenged to determine if robustness and ruggedness criteria are satisfied. As a result of these studies, the method performance can be understood and improved if necessary, and a control strategy can be defined to manage risk and ensure the method performs as desired when validated and deployed. In this review, the current state of analytical QbD in the industry is detailed with examples of the application of analytical QbD principles to a range of analytical methods, including high-performance liquid chromatography, Karl Fischer titration for moisture content, vibrational spectroscopy for chemical identification, quantitative color measurement, and trace analysis for genotoxic impurities. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:797–812, 2011

Keywords: quality-by-design (QbD); analytical methods; high-performance liquid chromatography; Karl Fischer titration; genotoxic impurity analysis; method development strategy; analytical chemistry; chromatography; mass spectrometry; spectroscopy

INTRODUCTION

Quality-by-design (QbD) has become an important paradigm in the pharmaceutical industry since its introduction by the US Food and Drug Administration.[1–4] The overarching goal of QbD is to embed quality into pharmaceutical products to ultimately protect patient safety. Many other regulatory agencies around the world have also adopted similar approaches. The International Conference on Harmonization (ICH) defines QbD as a systematic approach to drug development, which begins with predefined objectives, and uses science and risk management approaches to gain product and process understanding and ultimately process control.[5,6] ICH Q10 describes a holistic and integrated quality management system applicable to the QbD environment.[7] The QbD concept can be extended to analytical methods.[8–19]

This paper summarizes the current state of QbD as applied to the development of analytical methods for pharmaceutical manufacturing and quality control (QC). A brief overview of QbD in pharmaceutical development to illustrate the larger themes and overall status in the industry, prior to focusing the discussion upon analytical aspects of QbD, is given in the second section. Then, the various approaches to analytical QbD that have appeared to date in the literature are discussed within a structured method development strategy (MDS) framework that highlights the application of QbD principles during method development. Applications of analytical QbD to various techniques are given using the MDS approach, including high-performance liquid chromatography (HPLC), genotoxic impurity analysis, spectroscopic determinations of identity and color, water content determinations, and tablet dissolution testing. Also, general trends observed to date and future applications are reviewed prior to concluding the paper.

PHARMACEUTICAL QUALITY-BY-DESIGN

The QbD initiative has been developed in a variety of guises within the pharmaceutical industry. These include applications of QbD principles to

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small-molecule pharmaceutical process development, including synthesis of the active pharmaceutical ingredient (API) and formulation, and biopharmaceutical process development. In this section, we introduce the principles of QbD and briefly review the overall status of QbD in the pharmaceutical industry to illustrate the position that analytical QbD occupies in this paradigm.

QbD Principles

Drug development using the principles of QbD emphasizes a systematic approach, starting with predefined objectives, and applying scientific understanding and risk management approaches. This emphasis underlies the QbD principles and approaches to analytical method development discussed in the present work.[2] Two key concepts can be introduced that further aid in implementation and understanding of QbD. The first concept is "design space."[2–5] ICH Q8 defines design space as an "established multidimensional combination and interaction of material attributes and/or process parameters demonstrated to provide assurance of quality."[5] Understanding the design space for a pharmaceutical process generally involves the identification of critical attributes for the input materials, the process, and the final product.[2] A modified definition of design space has been proposed for analytical methods, wherein the design space includes any combination of the input variables to a method that have been demonstrated to provide assurance of the quality of the data produced by the method.[5,16] Under this definition, changes within the design space of the method are not considered to be a change to the method. Another important QbD concept is that of the "control strategy."[5] The purpose of the control strategy is to ensure the final quality of the product. The control strategy is obtained from the process understanding gained from modeling the design space. For example, QbD control strategies have presented for control of the levels of chemical impurities from a synthetic process.[20,21] An analytical adaptation of control strategy has been proposed, where it is defined as the controls on input factors to a method that ensure the method meets both traditional system suitability criteria and wider performance-related goals.[16]

Applications of Traditional Analytical Methods in QbD Process Development

Most QbD applications to date have not focused on the analytical methods but instead have been implemented in the context of the overall pharmaceutical manufacturing process, with emphasis placed on the process understanding gained by application of QbD principles, and in some cases the development of a design space and control strategy for a process. Examples of applications using traditional analytical methods in overall QbD process development are given in Table 1.[20–26] On-line process analytical technologies (PAT) appear frequently as analytical methods in the guise of QbD process development. When enough information is collected, PAT can ultimately lead to real-time release testing (RTRT) approaches wherein end-product analytical testing is no longer necessary to ensure product quality, as the real-time information gathered already provides a guarantee that the product is acceptable.[5,26–28] The RTRT approach extends the more established approach of parametric release,

Table 1. Examples of Published Applications of Traditional, non-QbD Analytical Methods to Pharmaceutical QbD Process Development

Application	Reference
IFM in the development of a chemical process, involving a theoretical and experimental search for potential process impurities, many of which are then synthetically prepared and spiked into the process at the relevant stage, after which their levels are tracked by analytical methods.	20
Genotoxic impurity fate mapping, using spiking and purging studies that again rely on specially-developed analytical methods, to obtain extensive knowledge of the fate of genotoxic impurities and the purging capability of the chemical process, allowing for analytical testing to be moved upstream so that conventional HPLC methods could be used to ensure genotoxins would not appear at unacceptable levels in the API instead of costly HPLC-MS testing of final API.	21
At-line NIR spectroscopy study of powder blending, including critical factors of blender size, powder cohesion, and blender rotation rate	22
Off-line study of API crystallization processes using X-ray diffraction methods, to build phase diagrams and gain a complete knowledge of the stability and interrelationships between solid-state forms	23
On-line real-time NIR monitoring of turbidity and crystal size combined with multivariate analysis of a dispersion-forming coprecipiation process involving naproxen and a polymer, enabling direct observation of key events, such as incubation, nucleation, and crystal growth and contributing to improved process understanding.	24
On-line real-time NIR monitoring of powder blending process kinetics and determination of powder blending end-points	25
NIR RTRT of tablets manufactured using a high-shear wet granulation process, based on a correlation established between the NIR model and actual tablet disintegration testing.	26

QbD, quality-by-design; API, active pharmaceutical ingredient; HPLC, high-performance liquid chromatography; RTRT real-time release testing.

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which uses real-time process data to support release in cases where a particular analytical measurable is difficult to obtain from end-product analysis, such as the use of a surrogate measure for a terminal sterilization procedure on a packaged product to obviate the need for microbial end-product testing.[28] At-line and off-line analytical methods have also been employed in QbD impurity fate mapping (IFM) studies of genotoxic and nongenotoxic chemical impurities, a process by which the ability of a process to purge chemical impurities is fully understood through spiking studies.[19–21] Beyond individual analytical methods and results, combinations of methods also play a critical role in providing input for more detailed multivariate modeling of complex pharmaceutical processes, where multiple analytical measurements are combined to build process understanding and achieve control.[29] Analytical measurements that range from raw material chemical and physical properties to intermediate granule density measurements to imaging analysis of final products can be combined using multivariate approaches to model the design space for a pharmaceutical process. Although the model is generated for the process, the quality of the analytical methods and their results underpins the entire QbD control strategy.[29]

Methodological Aspects of Analytical QbD

Beyond the use of traditional analytical methods in QbD applications, it is possible to apply QbD principles to the development of the analytical method itself. This topic, the focus of the present paper, can potentially apply to a wide range of analytical methods and techniques. This approach can lead to better analytical methods, and can positively impact the broader QbD aspects of drug development since the data from these methods underpin much of the QbD strategy for a process. In light of the variety of analytical methods that can potentially benefit from QbD approaches, a structured approach to analytical method development that transcends the technique used is necessary, such as the MDS approach.[8–12] The structured steps utilized in the MDS approach are shown in Figure 1 and begin with the definition of a goal for the method and collection of background information, systematic scouting and evaluation of alternative methods, selection of a promising method that meets the goal, assessment of the method for risks using structured tools, and finally development of a control strategy to ensure method performance. The MDS approach emphasizes the use of scientific understanding and QbD principles during each step in method development, rather that testing quality into an already-developed method. The method goal terminology used the MDS approach has also been described as "design intent" in the literature.[14] A key component of the MDS process is the use of structured risk assessment tools, such as the design of experiments (DoE) and measurement systems analysis (MSA) methodologies, for the evaluation of robustness and ruggedness. Because of their importance, these tools are discussed in detail in a later section as part of the QbD method development process. These tools can also be used in a stand-alone fashion to probe existing methods developed with a traditional approach (e.g. from older products) and help mitigate risk in the use of these methods, by gaining knowledge about the existing method and allowing for more effective control strategies for critical parameters. Although shown in Figure 1 for clarity, method validation is considered to be a separate step that occurs after the MDS process. Method validation is performed to fulfill ICH requirements, but because the MDS process verifies method performance during development, for practical purposes validation serves a confirmatory role in a QbD analytical approach. The MDS approach has been applied to a range of analytical techniques as discussed in later sections.

A closely related analytical QbD approach has also been proposed for HPLC.[14] This approach also starts with assessment of method performance requirements, then proceeds to method development, risk assessment and design space definition, and then to a method control strategy.[14] The method development stage is not specified in this approach, and analytical QbD is defined as a subset of the overall control strategy for the synthetic or formulation process, providing a useful link between the analytical activities and the overall product development QbD activities. Similar generalized approaches to QbD analytical method development have been proposed and described.[13,16]

Statistical Tools for Support of Analytical QbD

In addition to the well-established statistical analysis tools used during method development, such as DoE and MSA, other statistical approaches have been implemented to assist in the development of QbD analytical methods. For example, it has been proposed that changes with the potential to take a method outside of its known design space could be evaluated and subjected to a validation exercise to ensure method performance criteria are still acceptable.[16] In order to assist with such changes, a more advanced statistical approach based on two one-sided tests (TOST) was found to have advantages over intermediate precision studies for demonstration of method equivalence, and for reliable inter-method comparisons to established specifications.[30] In addition, the setting of acceptance criteria, which represent an acceptable bias between the original and changed method, was linked with the both the design and sample size of an equivalency study.[31]

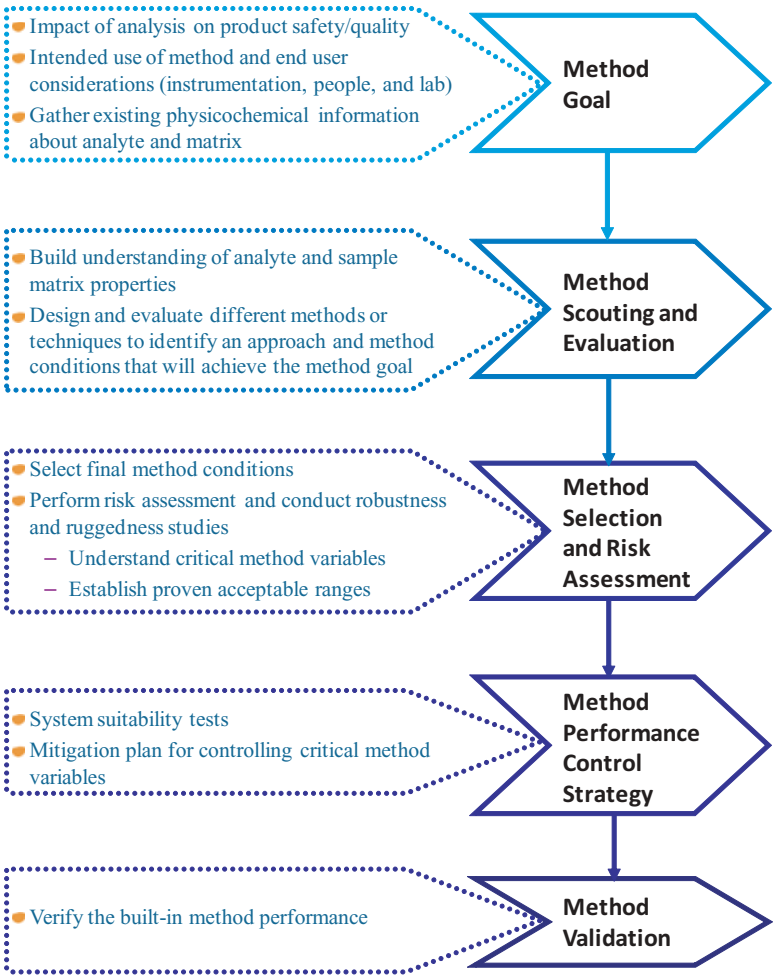


Figure 1. Generalized method development strategy (MDS) approach for QbD analytical methods. Although shown in this diagram for clarity, method validation is considered to be a separate step that occurs after the MDS process.

Analytical Target Profiles

Another approach to analytical QbD involves the definition of an analytical target profile (ATP), a set of criteria that define what will be measured and the performance criteria of the method, but without specifying the method itself.[14] Using material, process, and product attributes as input, the ATP thus defines the analytical variable to be measured (e.g. the level of a specified impurity), as well as the performance characteristics to be obtained by this measurement (e.g. accuracy, precision, and range). The ATP provides a link between the eventual analytical method and the chemical or formulation processes.[14] As a chemical process is defined, for example, the need for a particular analytical method to measure impurities at a certain level can be defined in an ATP. Different methods can then be developed to meet the ATP throughout the development lifecycle; for example, a generic method can be used early in development to meet the ATP, while a more efficient method that meets the original ATP can be developed near to product launch. The principal motivating factor behind the ATP approach is the desire to gain flexibility in the method used to perform testing, and avoid costly post-approval changes to the registered analytical methods that require proactive discussions with regulatory agencies.[14] Instead, under this scenario, each method that meets the ATP would be appropriately validated and documented but would not require changes to the registered method, as only the ATP would be registered.

QBD ANALYTICAL METHOD DEVELOPMENT STRATEGIES

The application of QbD principles to analytical method development is focused on the concept of building quality into the method during development, as opposed to testing methods after development for quality. Because of this, the actual method development process for an analytical QbD method should follow a structured approach, as illustrated

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by many examples reviewed in this section. Traditional analytical method development can incorporate some structured aspects, but often is applied in a reactionary manner to address issues encountered with the method.[8,14,15] The discussion in this section is structured around the generalized MDS-based approach to QbD method development provided in Figure 1.

Method Goal

The goals and intent of the method to be developed must be clearly defined at the outset, if the method is to comply with QbD principle of predefined objectives. Starting with a method goal also helps to emphasize the need for product and process understanding. A number of factors, such as patient safety, product efficacy, and quality requirements, as well as prior knowledge of similar drug compounds on the market, must be taken into consideration for the development of a method goal.[8–12] The operational intent of the method and end user requirements must also be considered, including instrumentation capabilities at future testing laboratories, geographical location and climate of the laboratories, and potential constraints on access to chemical reagents.[8–12]

The method goal concept can be illustrated using HPLC as an example.[8,13] The goal of an HPLC method for API is generally to separate and quantify the main compound and the critical quality attribute (CQA) impurities that may impact the quality of the drug product. This must be achieved while meeting method performance criteria based on regulatory requirements, such as specificity, linearity, accuracy, precision, sensitivity, robustness, and ruggedness. Since determination of CQA impurities is a key objective of the HPLC separation, analytical chemists generally work closely with other functions to assess the manufacturing process, starting materials, API, and drug product to identify process related impurities and degradation products.[8] Authentic markers for these impurities are generally needed. Background information is collected prior to starting experimental method development activities, including physicochemical characteristics such as pK_a, ultraviolet (UV) chromophore, solubility, and chemical stability. Some properties, such as pK_a, can be predicted using commercial software for molecules not yet available in sufficient quantities.

Obtaining goals for method performance can be assisted using stringent desirable method attributes to guide the method development effort.[8] The method attributes are constructed from knowledge and scientific understanding of the underlying discipline (e.g. chromatography), as well as business and regulatory requirements and generally accepted expectations of method performance. Method attributes can be classified into two major categories: "must have" and "intend to have", as illustrated by reported method attributes for an HPLC impurity method.[8] For example, the chromatographic resolution for a pair of adjacent peaks must not be less than 1.5, and is intended to not be less than 1.8.[8] Also, there must not be artifacts within two peak widths of a critical impurity, and it is intended that there should be no artifacts within four peak widths of a critical impurity. Meeting predefined desirable method attributes during method development helps avoid the need to address problems during validation or use in the manufacturing environment.

In addition to these criteria, other operational factors are also often included in method goals. These operational factors, also referred to as the operational intent of the method, take into account the actual laboratory environments in which the method will be used, including factors such as the typical temperature and humidity in the laboratory, reagent availability, and requests from QC laboratory staff.[8,9,16] Operational factors, such as the need for short analysis times and "user-friendly" behavior, are also considered.[13]

Method Scouting and Evaluation

With the method goal in hand, method scouting can commence, typically with the use of detailed flowcharts and decision trees to aid the analyst in deciding among the options.[8–12] Although it is not possible to capture all knowledge about a technique in such a format, it is possible to capture many important points frequently encountered during method development for many of the techniques of interest, such as HPLC.[8] The development of an MDS involves the preparation of these flowcharts and decision trees, and also seeks to continuously update them as new methods and technologies appear and older technologies are retired. The flowcharts and decision trees seek to combine traditional knowledge of best practices in an analytical discipline with current state-of-the-art approaches to method development. Using these tools, the scouting and evaluation of methods then follows a systematic experimental approach. This approach can be augmented by automation. For example, an efficient and comprehensive experimental design based on systematic, automated scouting of all three key components of a reversed phase (RP) HPLC method (column, pH, and organic modifier) has been presented.[8] The scouting experiments are followed by optimization of chromatographic performance using simulation software, wherein experimental data from scouting experiments are entered into the software, which then simulates and predicts separations for a very large number of chromatographic conditions based on the limited data set obtained in the scouting experiments.[8] The experimental data and predicted separations provide a comprehensive database that assists with method

understanding, optimization, and selection, and can be used to evaluate and implement future changes to the method, for example if the column used is no longer commercially available, or if a particular impurity is no longer relevant to the process.

Beyond scouting for HPLC methods, which generally involve selection of method conditions within the technique of HPLC, other examples of method scouting and evaluation can involve choosing between different techniques that require different instrumentation while also evaluating method conditions. For example, method scouting and evaluation for water content determination by Karl Fischer titration (KFT) primarily involves evaluation of method conditions on two different types of instrumentation, direct-addition KFT (direct KFT) and oven-assisted KFT (oven KFT).[9] A similar situation is encountered in the development of methods for genotoxic impurity analysis, where different techniques and detectors are scouted and evaluated in addition to a wide range of sample preparation, pretreatment, and derivatization steps.[10] Different techniques are also evaluated during method scouting for vibrational spectroscopic chemical identity methods.[12] Initial scouting and evaluation experiments can be performed, for example, to determine whether sample fluorescence or burning precludes the use of Raman spectroscopy (which is an otherwise desirable approach to identity testing because of sampling advantages) instead of infrared (IR) spectroscopy.[12] MDS approaches for quantitative color measurement by visible spectroscopy also make use of scouting protocols with multiple analytical techniques.[11] Approaches to the scouting of methods for these techniques are reviewed in more detail in a later section.

Method Selection and Risk Assessment

After systematic method scouting and evaluation, methods that best meet the method goal can be selected for risk assessment. The risk assessment involves the identification and prioritization of risks in a structured fashion, followed by ruggedness and robustness testing. In some cases, the primary method identified by scouting and evaluation will undergo the risk assessment process without identification of any significant risks.[9] Nevertheless, it is desirable to select at least one backup method in case the risk assessment of the primary method indicates potential problems. If the primary method fails the risk assessment, the backup methods can then be risk-assessed until a suitable method is identified. Occasionally, with especially challenging methods, two or more competing methods may each offer significant advantages, but the disadvantages may be unclear. In these cases, the risk assessment and subsequent ruggedness and robustness testing can be performed on multiple methods to provide additional selection criteria for choosing the best method.

As previously noted, ICH Q8 and Q9 require a risk-based approach as a key component of QbD.[5,6] To implement this guidance for analytical methods, structured methodologies for risk assessment can be used. These include tools such as Fishbone diagrams, failure mode and effects analysis (FMEA), and the prioritization matrix.[32,33] These tools help identify and prioritize potential risks to the method caused by a variety of situations, such as small unintentional changes to method parameters, and changes that might occur between laboratories, analysts, instruments, reagents, and the period of time in which the method is performed. The other factors identified as risks during the risk assessment are categorized as either noise, to be tested by ruggedness studies, or parameters, to be tested by robustness studies. A robust method has a performance that is insensitive to small variations in parameters (generally instrument settings), whereas a rugged method is one that is tolerant to any noise likely to be encountered during use. The risk assessment approach stands in contrast to the older non-QbD approach, in which the method is developed independently by the transferring laboratory, several batches are selected, and the transferring and receiving laboratories run the method on these batches prior to completing method transfer.[34,35] In the QbD approach, the risk assessment includes the receiving laboratory, so that any risks can be located prior to the transfer.

Prior to performing a risk assessment, it is beneficial for the analysts who have developed the method to work directly with analysts who will initially be using the method in a quality control laboratory. For more complex methods, a complete method walkthrough is often utilized. Each of the steps within the method is performed and observed, such as sample preparation (including dissolution and extraction when necessary), experimental procedures, and data analysis. This helps to identify nuances in the way that a method is performed and also helps to identify particular parameters or factors that would may consideration during the risk assessment. Using this information as input, a risk assessment can begin. One of the most common ways to perform a structured risk assessment is to use a Fishbone diagram, also known as an Ishikawa or cause-and-effect diagram, to identify potential factors that may influence the method performance.[36] Fishbone diagrams segregate risks into different categories, such as those associated with instrumentation, materials, methods, measurements, laboratory climate, and human factors. For example, a generic Fishbone diagram for water content determination by KFT was presented as a starting point for more detailed method-specific risk assessments.[9] A generic Fishbone diagram for HPLC

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tablet assay methods has been developed to facilitate method-specific risk assessments.[16]

After risks have been assessed, they are typically grouped into three categories: high-risk factors that should be tightly controlled, potential noise factors, and factors that can be probed experimentally to determine acceptable ranges. Typical high-risk factors that can be fixed at the time of method development include data analysis methods and sample preparation methods. These factors can be included with other potential noise factors in a prioritization scheme using the FMEA approach.[32] The factors with the most severe impact on the analytical results, likelihood of happening, and difficulty of detection are then challenged using tools such as MSA.[37] MSA is used in the design and analysis of studies to determine the reproducibility of a method. The goal of an MSA study is to identify which noise factors will need control, and which noise factors do not impact method performance under normal operating conditions. MSA studies often use standard designs; for example, a staggered crossed-nested design was conducted for an HPLC impurity profile method, whereas a simplified MSA design was used for a KFT method.[8,9] During MSA studies, the same set of samples is generally used across all experiments to avoid confounding sample issues with the method ruggedness analysis. A typical MSA study for a late phase HPLC method is executed against the noise factors determined in the risk assessment, such as different analysts, HPLC systems, column batches, laboratories, sample batches, and dates of analysis.[8] The results are then statistically analyzed, with the ultimate outcome being the interpretation of visualized data presented in variability plots. These plots allow for a complete assessment of the variation between the factors studied as well as identification of any cases of variability due to assignable causes. For example, for an HPLC impurity profile method, the results from statistical analysis indicated the variance for the determination of API content and impurities content was not significant, demonstrating good ruggedness.[8]

The third category of risks identified from the Fishbone analysis contains instrumental parameters that can be prioritized and probed using the Design of Experiments approach (DoE).[38] For example, based on the output of the risk assessment for a KFT method, a total of seven method parameters were recommended for a DoE study in order to understand their impact on method robustness.[9] A 2^4 fractional factorial DoE design plus 4 center-points was selected, which resulted in a total of 20 titration runs.[9] The results suggested that the method was robust, because the parameter ranges for each of the seven method factors were well within the range needed to meet the registered specification of not more than 1.0% (w/w).[9]

Finally, it should be noted that if the final method is selected against well-chosen desirable method attributes, it is likely that the selected method will be reliable. This consideration also factors into the risk assessment for a method, because it can limit the amount of work necessary to demonstrate ruggedness and robustness and the number of controls that must be fixed.

Method Control Strategy

The control strategy is an important QbD feature of an analytical method, because it assures that the method is performing as intended on a routine basis. Several factors can be identified as a result of risk assessment activities and considered when implementing a method control strategy. If the risk assessment activities indicate that the overall understanding of method performance can be improved, and the risk to obtaining reliable data is high and difficult to manage, a more appropriate method may be needed. If the risks are low and well managed, then the method control strategy can be defined, which generally consists of appropriate system suitability criteria to manage risk and ensure the method delivers the desirable method attributes. An appropriate system suitability test may be the only control element needed to ensure performance of the selected method. This is true for the example KFT method described previously, in which the PARs for all seven method parameters explored in the DoE studies were wider than their corresponding performance ranges verified during routine maintenance.[9] The risk assessment can also help identify a specific control strategy. For example, during robustness studies for an atomoxetine hydrochloride HPLC impurity profile method, it was found that resolution of the impurities of interest followed the same trend when method parameters such as *n*-propanol and temperature were varied.[13] As a result, an early eluting impurity pair was chosen for system suitability and became a convenient method control strategy because the two compounds involved were easily obtained. In certain cases, the system suitability test may need to be augmented with additional controls to properly manage risk. For example, if a KFT method is developed for a hygroscopic product, humidity controls in the laboratory or within a glove box may be necessary to ensure the sample water content is not altered by the sample handling procedure. Thus, laboratory controls such as humidity probes might be necessary.

Validation and Postmethod Development Considerations

Method validation is a key activity that traditionally occurs after method development. The validation exercise is typically a separate activity, removed from development, which occurs only once. Once a

QbD analytical method is developed and assessed for risk, resulting in appropriate definition and control of method parameters, formal method validation can commence. Although validation still follows ICH Q2 guidance, a proper method development and risk assessment process for the method makes validation a formality. Because the method has been thoroughly developed and evaluated, issues with the method are unlikely to be discovered during validation.

Because of the large amount of knowledge accumulated during analytical QbD method development, there is a general need for repositories that can maintain this knowledge for future use.[14] Throughout the lifecycle of the method, this repository can be maintained and updated by the R&D and QC organizations. The repository allows for potential changes to the method to be considered in light of method scouting and evaluation knowledge, and the previous risk assessment.

Specification setting using methods developed with analytical QbD approaches can also be improved beyond traditional specification setting practices. Because the method performance is well understood, the testing of a large number of batches is again a formality. Specifications can be set with a greater level of comfort whether method performance is not an issue in causing out-of-specification results, and thus requests from regulatory agencies to tighten specifications can be accommodated if necessary.

APPLICATIONS OF THE MDS APPROACH

A number of applications of analytical QbD have appeared that can be aligned with the previously described MDS approach. In this section, these applications are categorized by analytical technique and specific application, and are then reviewed in detail to highlight the key aspects of analytical QbD in each type of method. Not all of the examples described in the following sections implement each step of the MDS process shown in Figure 1, but all implement some aspects of QbD in their approach.

HPLC for Assay and Impurity Profile

A comprehensive RP-HPLC MDS approach using QbD principles has been described.[8] After definition of method goals, experimental scouting of key RP-HPLC method components, including column, pH, and organic modifier is performed as depicted in Figure 2. With the assistance of computer simulation software, the interrelationships between components can be studied without the need for extensive laboratory experiments, and preliminary optimized conditions can be obtained for each combination of column, pH, and organic modifier. After the selection of a method, a risk assessment is applied followed by initial ruggedness and robustness studies. The comprehensive MDS approach was applied to the development of RP-HPLC impurity profile methods for pazopanib hydrochloride API, intermediates, and starting materials.[8] MSA and DoE studies of methods developed using the MDS failed to identify any critical factor that would need to be tightly controlled beyond good laboratory practices (equipment qualification/calibration, proper column maintenance, and general system suitability requirements).[8] Finally, during the application of the MDS for the pazopanib hydrochloride RP-HPLC methods, a database of method conditions was built up.[8] It is possible to begin constructing this database from the early phases of development.[39] By the time a project reaches the later stages of development, this extensive database of acceptable method conditions helps ensure that the scientific aspects of the method are well understood, and potentially allows for flexibility whether any future changes are needed to the method in QC laboratories.

An example of a gradient RP-HPLC method developed using the MDS approach is shown in Figure 3a. The method meets its goal and readily separates impurities A–E from *N*-(2-chloropyrimidin-4-yl)-2,3-dimethyl-2*H*-indazol-6-amine (**I**), the stage 1 intermediate in the chemical synthesis of pazopanib hydrochloride. The HPLC method used a Waters XBridge C18 column, with mobile phase A as 10 mM ammonium acetate buffer (pH = 6.8), mobile phase B as acetonitrile, a gradient increasing from 16% B to 47% B over 20 min, and a detection wavelength of 242 nm. A critical aspect of the RP-HPLC MDS approach occurs during the scouting and evaluation phase in Figure 2, when the change in the retention factor (k') with pH is assessed as shown in Figure 3b. It is critical to select a pH range where k' is not changing rapidly, to ensure that the method will not be susceptible to performance issues arising from minor changes in buffer. Here, a pH of 6.8 was selected to achieve this goal. Furthermore, the UV spectra of each impurity were carefully evaluated to select the detection wavelength of 242 nm, as this wavelength was not on the slope of any of the UV spectra, thus avoiding potential peak area variations caused by detector wavelength variation. This approach to pH and wavelength selection is an example of the use of careful scouting experiments to minimize the potential issues that might be encountered in a later risk assessment.[8]

A complete MDS approach was also applied in the development of an RP-HPLC impurity profile method for atomoxetine hydrochloride API.[13] First, the method goal was established by a review of the synthetic route and tabulation of potential process impuritiesas well as intermediates and starting materials that might carry through to the final API.[13] One of these was a highly polar compound, whereas several others were highly nonpolar compounds, requiring special consideration during method

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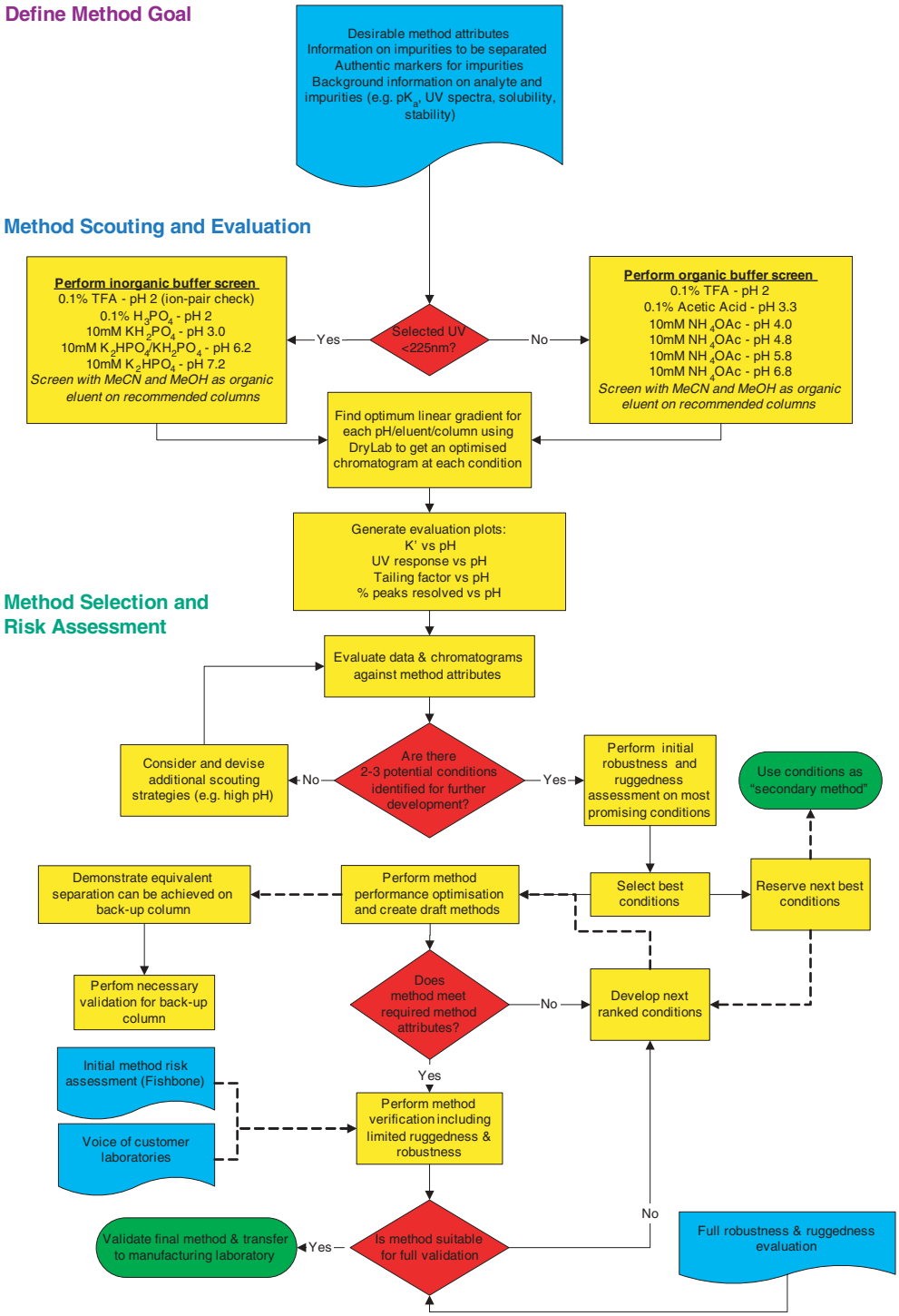


Figure 2. Flowchart for RP-HPLC MDS steps showing detailed method scouting, evaluation, selection, and risk assessment activities. Inputs are shown as shapes with a wavy bottom, experiments/guidance are given as boxes, decision points are shown as diamonds, and endpoints are shown as rounded rectangles.

development. Scouting then began after the observation that a gradient RP-HPLC method would be needed to separate the known and predicted impurities based on their polarity.[13] However, scouting experiments with a RP-HPLC gradient method under low pH conditions yielded problematic peak shapes on several different columns.[13] The scouting effort then turned to screening of solvents for an isocratic ion-pairing approach, which proved promising and was optimized via a systematic screening of columns.

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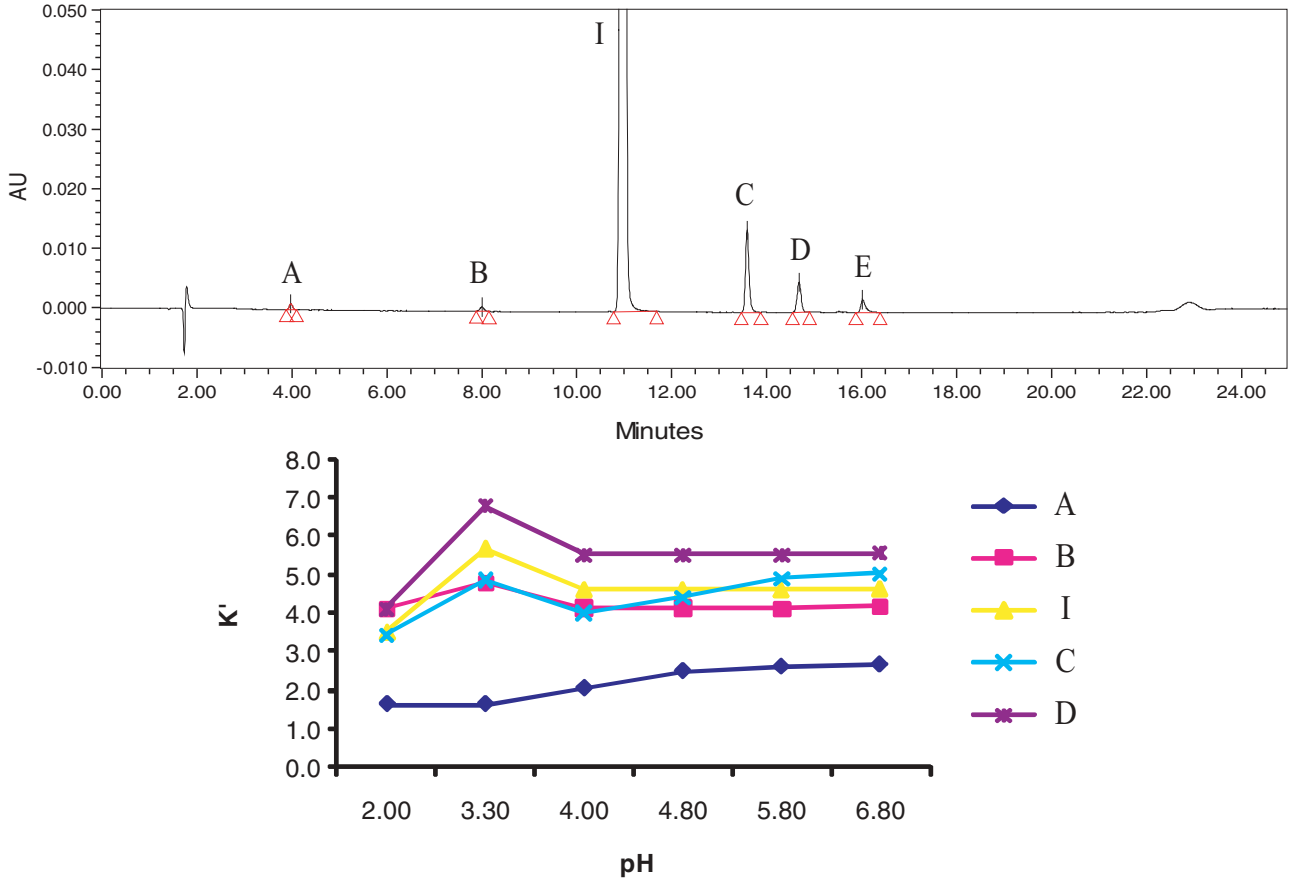


Figure 3. (Top) Chromatogram showing typical results from an HPLC method developed using an MDS approach, involving the separation of *N*-(2-chloropyrimidin-4-yl)-2,3-dimethyl-2*H*-indazol-6-amine (**I**), the stage 1 intermediate in the chemical synthesis of pazopanib hydrochloride, and four critical impurities (A–D). Impurity E was discovered after the method was developed, but because of the MDS approach and its structural similarity to impurity D, the method performed well for its analysis. (Bottom) Plot showing the change in retention time for the intermediate and impurities A–D, illustrating the MDS approach to selecting a pH for the method in which retention time will not be affected by potential minor variations in pH in user laboratories.

The final method used a C8 column with a mixed aqueous/organic mobile phase consisting of phosphoric acid (pH 2.5), octanesulfonic acid, and *n*-propanol. An example of the performance of the final method for a complex mixture of potential impurities (many more than observed with the process) is shown in Figure 4. Understanding of the separation mechanism was gained throughout this process, in that selectivity of the ion-pairing method was linked to mobile phase composition, thus suggesting that changes in column performance should not strongly affect the overall method performance.[13]

A risk assessment was then performed for the ion-pairing RP-HPLC method for atomoxetine hydrochloride. The DoE approach was used to evaluate factors such as column temperature, mobile phase composition, and pH.[13] The method was found to be particularly sensitive to the percentage of organic modifier in the mobile phase and the column temperature, indicating a need for tight control of these factors as part of the method control strategy. The extensive knowledge gained about the method also led to a control strategy that also helped reduce the need for impurity reference standards. The separation of two early eluting impurities, phenyl methylaminopropanol [PMAP (±)3-methylamino-1-phenylpropanol] and mandelic acid, was found to correlate with the separation of other impurities that eluted near the main sample component. As a result, the resolution of this peak pair was used as a system suitability test without the need for impurity reference standards, and formed a key part of the method control strategy. An MSA study was not conducted; instead intermediate precision was assessed during method validation.

The use of HPLC to analyze drug products, including assay methods and methods designed to detect degradation, also requires sample preparation steps when working with most common formulations such

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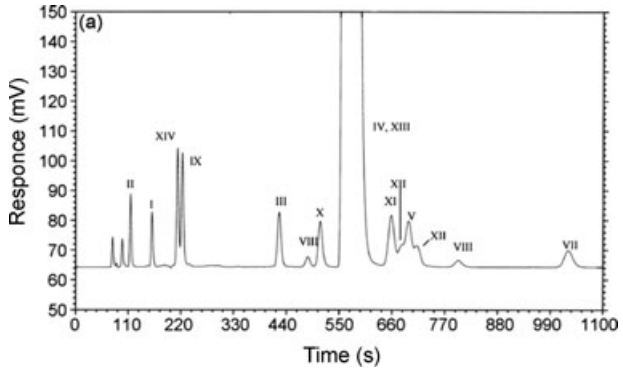


Figure 4. Chromatogram showing the performance of an isocratic RP-HPLC method developed using a QbD approach. Roman numerals refer to a variety of potential process impurities that potentially could be observed in the process; however, only the peaks labeled III, IV, V, and VIII are observed in actual batches and were part of the control strategy for the process. Reproduced with permission from Ref. 13.

as oral tablets. These sample preparation procedures are an essential part of the method and are critical to the results obtained, and can also benefit from analytical QbD approaches, although no report detailing such an application has yet appeared in the literature.

Other approaches to HPLC method development that employ QbD principles have largely focused on applying risk assessment, robustness, and ruggedness tools to existing HPLC methods.[15,17–19] The goal of these efforts is thus focused on the identification of issues with a method after method development. Another recent example of this approach utilized the JMP (SAS Institute, Inc., Cary, NC, USA) statistical analysis software package to assist in DoE studies of HPLC methods, to help identify critical method parameters and predict method performance over the range of parameters explored.[19] The role of the DoE design (including Plackett-Burman and fractional factorial designs) was illustrated for finding interactions between parameters.[19]

Genotoxic Impurity Analysis

The MDS approach can also be applied to the development of methods for analysis of genotoxic impurities.[10,40] Currently, potential genotoxic impurities are controlled at a generic threshold of toxicological concern of 1.5 μg per day in drug products, corresponding to low ppm% (w/w) levels in API.[10,40] These levels are typically several hundred times lower than impurities controlled with the HPLC methods described in the previous section. Methods must be precise, accurate, and robust to achieve this goal. Because many genotoxic impurities are also chemically reactive, the need for low detection limits and methods that do not destroy the analyte of interest present significant analytical challenges. Both limit tests and full quantitative methods are needed in different scenarios, depending on the method goal.[10,40]

Several different analytical techniques can potentially be used for genotoxic impurity analysis, many of which are not well established as routine tests within the pharmaceutical industry. To guide the developer through the scouting phase, detailed flowcharts and decision trees such as that shown in Figure 5 are used for method development, principally using HPLC as a separation method but with gas chromatography (GC) methods recommended in certain key situations, and also including a series of potential sample preparation, pretreatment, and matrix-deactivation options.[10] Because of the complexity of these methods, the proposed MDS for genotoxic impurity analysis addresses sample preparation, separation, and detection in detail, based on a detailed understanding of the properties of the analyte and matrix.[10] Sample preparation can involve extraction and preconcentration, chemical derivatization, ion coordination, or matrix deactivation and is often necessary to stabilize an analyte or enhance its sensitivity for detection.[10,40] Extraction methods are often required when the method is intended for use with formulated drug products. Because of the trace level detection performed, matrix effects are frequently magnified in genotoxic impurity analysis, leading to loss of sensitivity and abnormal recovery. The MDS approach emphasizes careful development of the sample preparation step to avoid these problems.[10,40] If derivatization is employed, the sample preparation step can be linked with the selection of both the separation and detection steps.

The separation method for a genotoxic impurity method is typically driven by the volatility of the analyte toward either HPLC or GC. For nonvolatile analytes, reversed-phase HPLC is a common choice.[10,40] Headspace sampling is a common approach when GC is used and the analyte is thermally stable and has sufficient volatility.[10,40] However, genotoxic impurity methods can require more sophisticated separation methods, such as hydrophilic interaction liquid chromatography for HPLC-based separation of very polar analytes, and 2D GC methods to minimize instrument contamination.[10,40,41] The MDS provides guidance on the choice of separation based on analytical properties.[10]

The detectors used in genotoxic impurity analysis are relatively complex comparedto many other approaches reviewed here. Mass spectrometry (MS) detection or another sensitive detector (such as electron capture detection in GC) is often the core of the method, because of its sensitivity and selectivity for low-level analytes in complex matrices. High-sensitivity mass analyzers such as triple-quadrupole designs might be necessary to achieve sensitivity. Common detection methods, such as UV detection,

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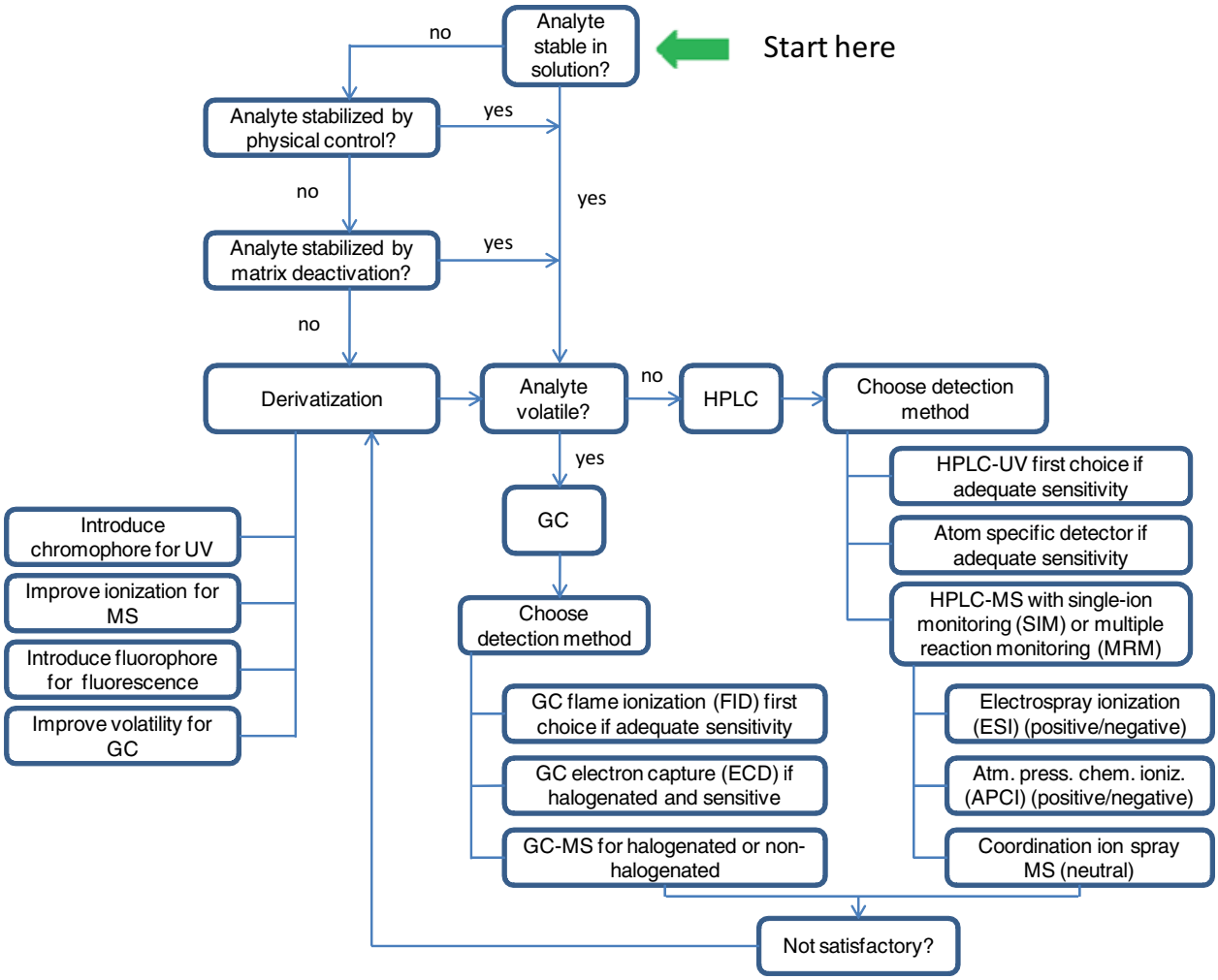


Figure 5. Decision tree for an MDS approach to genotoxic impurity analysis, highlighting the high-level criteria used for choosing between analytical techniques, including sample preparation, separation, and detection methods (see Ref. 10 for details).

are generally not applicable for genotoxic impurity analysis unless the impurities are controlled at an earlier stage in the process where they are present at higher levels.[10,21,40]

Because of the underlying complexity of the method, the instrumentation, and the sample preparation steps, methods for genotoxic impurity analysis often contain more variables than many of the other analytical methods to which an MDS approach has been applied. The risk management stage of an MDS approach can therefore be more complex, in that more factors must be evaluated and extensive robustness and ruggedness may be needed.[10] Simplicity must be emphasized during method development to avoid failed risk assessments, particularly if the method is to be used in manufacturing quality control laboratories where sophisticated instrumentation and highly trained analytical specialists may not be readily available. To avoid problems, the structured flowcharts and decision trees used during the scouting phase help guide the method developer toward a simplified method.[10]

Karl Fischer Titration for Water Content

KFT is widely used for the determination of water content in APIs and drug products, and is also a limiting factor to the accuracy of drug content calculated on anhydrous and solvent free basis. The variability of the KFT results, therefore, has a direct impact on water and drug content specifications. Because of its importance, and the complexities that can arise during method development, a comprehensive MDS for KFT has been introduced.[9] The MDS begins with a method goal, which includes desirable method attributes. For example, a typical oven KFT method attribute would require the method to accurately and precisely measure water content, at levels of 10 µg per sample. The goal is informed by knowledge that the results of the KFT method are commonly used to assess and prolong chemical stability, to report accurate assay values on

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an anhydrous and solvent-free basis, and to help set limits to control microbial growth.

After gathering information about the analyte and sample matrix, flowcharts and decision trees are presented to help choose which KFT approach to pursue and useful scouting experiments.[9] For example, oven KFT is frequently preferred when the sample is thermally stable, side reactions could potentially occur if the sample was directly added to the titration media (as in direct KFT, and if automation is beneficial. When direct KFT is chosen, different reagents can be evaluated in a systematic way, with knowledge of the molecule and impurities in hand, to avoid side reactions that alter the water content result. Experiments using HPLC-MS analysis of the titration media can be performed during the scouting phase to ensure that a direct KFT method does not lead to side reactions such as electrochemical oxidation of the analyte, which can lead to subtle but erroneous water content results. Finally, the application of risk assessments to KFT methods can make use of a generic Fishbone diagram as a starting point as there are many common factors between methods (e.g. laboratory humidity, sample weighing, and titrator end point parameters).[9]

Quantitative Color Measurement

The color of APIs, starting materials, and synthetic intermediates can be a critical factor in the quality of the final API, because color variation can be indicative of contaminants, impurities, or degradation products. As such, the color of the pharmaceutical materials is typically specified and determined using visual appearance testing. To avoid the inherent subjectivity of visual appearance testing, to understand the linkage of material color to the process parameters, and to facilitate quality agreements between the customer and vendor, quantitative color measurements are increasingly performed using visible spectroscopic methods. An MDS has been proposed for the development of quantitative color measurement methods using analytical QbD principles.[11] A number of flowcharts and case studies are used to illustrate the method scouting process for quantitative color methods, to help the analyst choose between a solid or solution-phase method, which consequently leads to the selection of either a diffuse reflectance sampling method for solid powders or solution-phase transmission sampling. The selection of a solid-state approach, which may be needed for certain applications (such as situations where color changes upon dissolution), can lead to additional complexity in sample preparation and challenges in achieving ruggedness, and the need for careful controls. The choice of color space, which are derived from the spectrum and report the final quantitative color values, can also affect the precision of the method. Quantitative color methods developed using the MDS approach help inform the specification setting process and limit potential batch failures, which are a major risk with a color specification.[11]

Chemical Identification by Vibrational Spectroscopy

Identification testing of pharmaceutical starting materials, solvents, intermediates, APIs, excipients, and packaging materials is commonly performed using vibrational spectroscopy, which includes the three major techniques of mid-IR, Raman and near-IR (NIR) spectroscopy. A systematic MDS has been developed for the development of robust and rugged chemical identification methods that seeks to minimize misidentification and failed identification errors.[12] Potential issues in identification method development are illustrated with a variety of examples, and guidance is given to help the user select the most appropriate technique and sampling method, including the selection of solution-state or solid-state methods. One issue with applying a QbD approach to an identification method is the need to obtain a numerical measure of the agreement between a reference spectrum and a sample spectrum so that methods can be evaluated and assessed for risk; several approaches to obtaining such a numerical measure are described.[12]

Dissolution Methods

A dissolution method for extended release tablets has been evaluated using a QbD approach involving a risk assessment followed by structured application of DoE and MSA tools.[42] This allowed for identification of method factors requiring tight control in order to ensure that tablets would pass specification. The method variables examined included preparation of the dissolution medium (pH and surfactant concentration), source of reagents, weighing techniques, paddle rotation speed, and UV detector settings.

DISCUSSION

The QbD analytical approaches reviewed here illustrate some of the general themes appearing as the pharmaceutical industry begins to grapple with the implementation of this evolving concept. In this section, these themes are reviewed with attention to the probable next steps in the development of QbD analytical methods.

Future Applications of Analytical QbD Approaches

Extensions of analytical QbD approaches, such as the MDS approach, can be envisioned for other commonly used analytical methods. For example, inductively coupled plasma optical emission spectroscopy (ICP-OES) and related methods are used to detect metals at low levels in API and drug product. Although the goal is generally to avoid use of metals testing in a manufacturing environment, situations occur where ICP-OES or a similar method is required. Matrix

effects can be a significant issue in these methods, in addition to complex instrumentation requirements and sample preparation approaches, all of which could be systematically developed and later challenged during the risk assessment stage. Methods for solid form analysis, such as X-ray powder diffraction (XRPD), are needed for API and drug product testing in some cases; XRPD methods can also have substantial inherent complexity and can benefit from QbD approaches. Particle size analysis (PSA) is another area where analytical QbD could lead to improved methods, as these methods play a critical role in particle engineering strategies, while particle size distribution is often included in the API specification for oral and inhaled products.[43] Applying a structured approach to PSA method development would help the user select between dynamic light scattering and laser diffraction methods, for example, and then help assess the risk of the chosen method with the structured DoE and MSA tools. Structured approaches to PSA method development including decision trees have already been proposed to help guide the method developer,[44] although no example has appeared to show the application of risk assessment tools to the evaluation of a PSA method. Other methods that characterize API may also benefit from analytical QbD approaches, including residual solvent testing by GC with headspace sampling and salt counter-ion quantification by titration or ion chromatography (IC) methods; because these are often simple methods, a generalized QbD approach could be applied to the method for use with many different APIs.

Methods that characterize excipients may also benefit from analytical QbD approaches.[45] Excipients play a critical role in the performance of the drug product, and are highly complex materials, but are often only tested for identity and other simple criteria by analytical methods that are frequently outdated. There is a growing need to develop methods that probe excipient composition and properties, such as impurity profile and particle size, to ensure that functional excipients perform as expected.[45]

Finally, the analysis of biopharmaceutical products is an area where analytical QbD approaches would be beneficial. Biopharmaceutical processes development, including lyophilization and formulation development, has already seen initial applications of QbD principles.[46–49] Biopharmaceutical products and processes require a range of analytical methods to ensure product quality at release and during stability testing, including potency assays, concentration measurements such as absorbance at 280 nm (A280), impurity analysis using immunoassays, RP-HPLC, enzyme-linked immunosorbent assay (ELISA), quantitative real-time polymerase chain reaction (qPCR), identity testing using binding assays and capillary isoelectric focusing, and contaminant tests such as bioburden, bacterial endotoxin, adventitious viruses, and mycoplasma. An analytical QbD approach would help to ensure performance of many of these methods, particularly complex methods such as potency assays.

Outcome of QbD Analytical Approaches

Although the field is in its infancy, the outcome of science- and risk-based approaches will ensure optimal performance and reliability of methods and the data generated. The most important outcome of a successful QbD analytical method development is thus a robust, rugged method that will likely be useful for many years with few problems. For example, a recent successful regulatory filing for pazopanib hydrochloride in the US and Europe included six HPLC methods developed using the MDS approach. The methods were highly rugged and robust, were accepted by regulators without questions, and were successfully adopted in the manufacturing analytical laboratory with strong positive feedback.

There is also the possibility of gaining additional flexibility for analytical methods because of the QbD approach used in their development. For example, because the key parameters of the method are well understood, and robustness studies are often done over an extended range, the registration of ranges for the parameters of a method can form the basis of a regulatory filing. A parameter that can be varied over a wide range without significant impact to the performance of the method can be specified loosely, so that the manufacturing site can operate within this range as needed. The previously discussed concept of the ATP is also an effort to gain additional flexibility, where the development of methods that meet an ATP using QbD methodologies might ultimately lead to the ability to substitute analytical methods without the need for regulatory notification.[14]

CONCLUSIONS

The field of analytical QbD is likely to continue to develop within the pharmaceutical industry, as favorable results have already been realized from its application. The most common benefits include methods that are more robust and rugged, and thus survive the challenges of long-term usage by quality control and manufacturing laboratories with a decreased likelihood of failure. The approaches published to date emphasize the structured development of a method through sound decision-making obtained from scouting and evaluation of methods. The knowledge built up during the development of complex methods (such as HPLC methods for impurity profile) is used to select methods that meet pre-defined, stringent performance criteria and goals. These methods are then thoroughly assessed for risk, amended and optimized as appropriate, and challenged with

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performance-stretching tests before being released for use in other laboratories. The development of analytical QbD hinges on continued investment by industry members, and the avoidance of generic methods except in cases where such methods and associated risks are already well-understood.

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