

WORKSHOP

21st OCTOBER, 2016

**Modern analytical techniques in Pharmaceutical Industry
Moderne tecniche analitiche nell'Industria Farmaceutica**

A tool to support pharmaceutical quality and to ease regulatory process
Aula Magna - Collegio A. VOLTA
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**Regulatory aspects of GC/MS HPLC/MS techniques as tools during
the R&D study in an API development**

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Introduction

The goal of manufacturing process development for the drug substance is to establish a commercial manufacturing process capable to consistently produce drug substance of the intended quality.

The Drug substance manufacturing process development requires adherence with six quality principles :

- Drug-substance quality linked to drug product
- **Process-development tools**
 - Approaches to development
 - Drug-substance CQAs
 - Linking material attributes and process parameters to drug substance CQAs
 - Design space

Introduction

The analytical instrumentation and methods play an important role as tool in the API process development .

Recent progress in methods development has been largely a result of improvements in analytical instrumentation based on that GC/MS HPLC/MS techniques are very important also in the phase of the drug substance development.



Development process

In general within the process of developing an active substance a key part is represented by QbD defined as a systematic approach, which begins with predefined objectives, and uses science and risk management approaches to gain product and process understanding and ultimately process control.

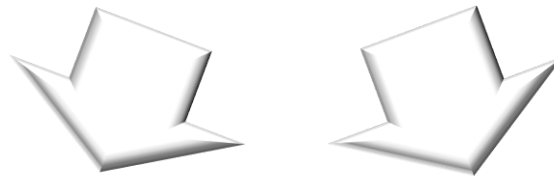


The QbD concept can be extended to the analytical methods development

Key concepts



In general adopting the principles of QbD two key concepts can be introduced that further aid in implementation and understanding of QbD.

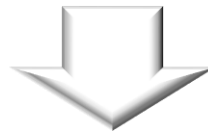


Design space

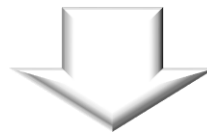
Control Strategy

Principles

The first concept is "**design space**". 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." 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.



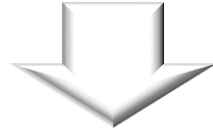
A modified definition of design space has been proposed for analytical methods, wherein the design space includes any combination of the input variables to a method that have been demonstrated to provide assurance of the quality of the data produced by the method.



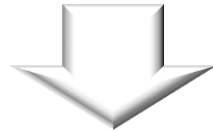
Under this definition, changes within the design space of the method are not considered to be a change to the method.

Principles

Another important QbD concept is that of the “**control strategy**”



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 been presented to control of the levels of chemical impurities from a synthetic process.

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 presentation, can potentially apply to a wide range of analytical methods and techniques.

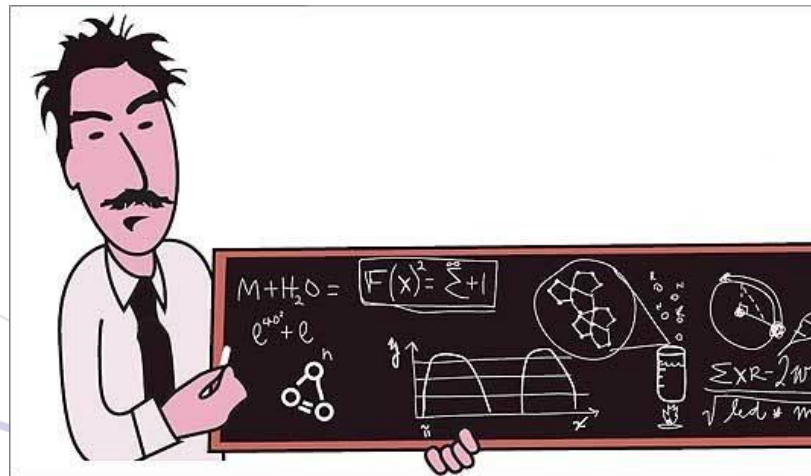
This approach can lead to better analytical methods, and can positively impact the broader QbD aspects of drug development since the data from these methods underpin much of the QbD strategy for a process. In light of the variety of analytical methods that can potentially benefit from QbD approaches, a structured approach to analytical method development that transcends the technique used is necessary, such as the MDS approach.



Methodological Aspects of Analytical QbD

The structured steps utilized in the MDS (Method Development System) approach are shown in the **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 than testing quality into an already-developed method.



Methodological Aspects of Analytical QbD

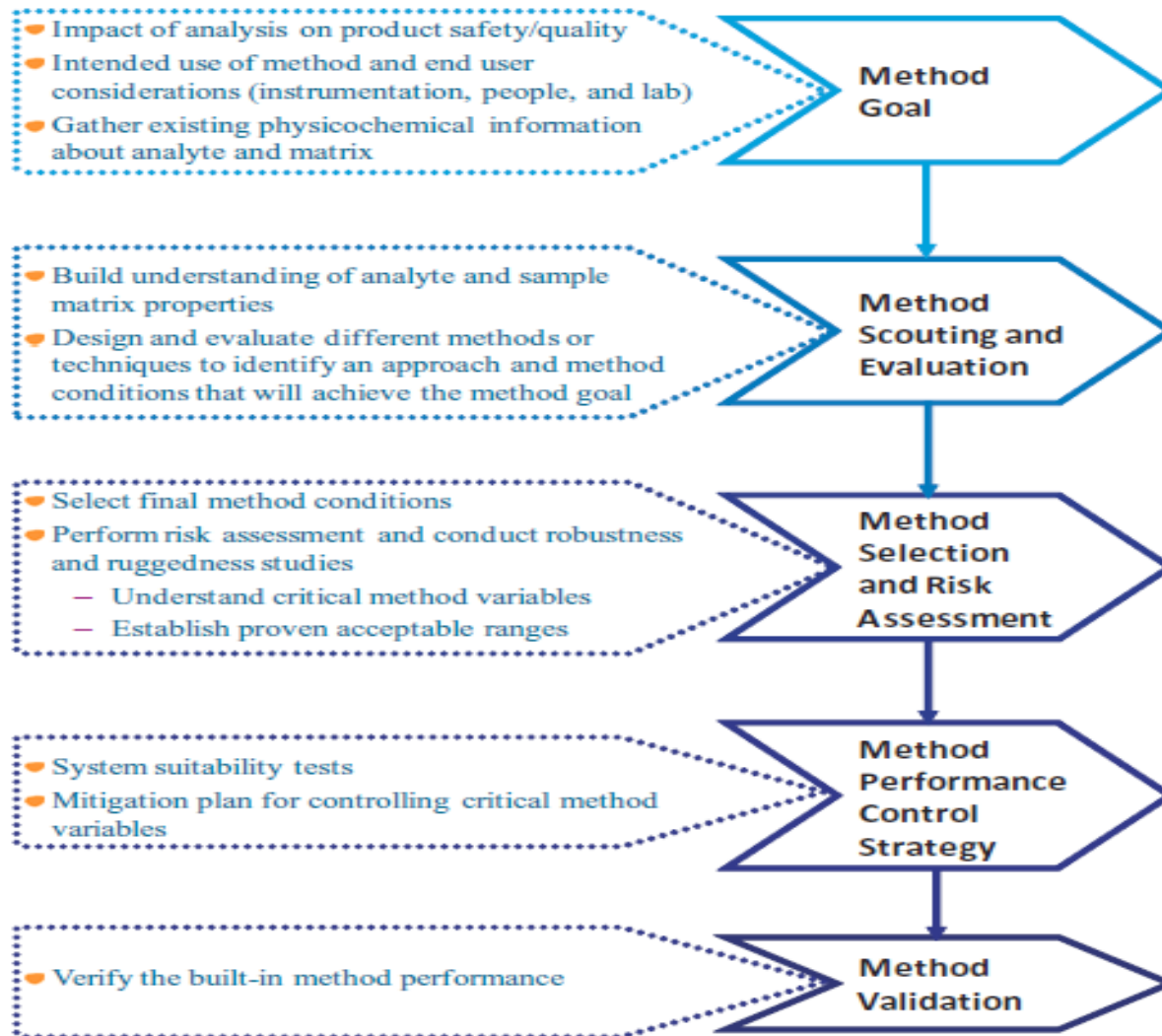


Figure 1

QbD analyticals 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

Because of this, the actual method development process for an analytical QbD method should follow a structured approach

Traditional analytical method development can incorporate some structured aspects, but often is applied in a reactionary manner to address issues encountered with the method.

Method Goal



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.

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**.

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.

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.



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 not 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.



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.

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.



Application 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.



Application of the MDS approach

Mass spectrometry (MS) is an analytical technique that ionizes chemical species and sorts the ions based on their mass to charge ratio. In simpler terms, a mass spectrum measures the masses within a sample. Mass spectrometry is used in many different fields and is applied to pure samples as well as complex mixtures.

An important enhancement to the mass resolving and mass determining capabilities of mass spectrometry is using MS in tandem with chromatographic and other separation techniques.

A common combination is gas chromatography-mass spectrometry (GC/MS or GC-MS). In this technique, a gas chromatograph is used to separate different compounds.

Similar to gas chromatography MS (GC/MS), liquid chromatography-mass spectrometry (LC/MS or LC-MS) separates compounds chromatographically before they are introduced to the ion source and mass spectrometer. It differs from GC/MS in that the mobile phase is liquid, usually a mixture of water and organic solvents, instead of gas.

HPLC for Assay and Impurity Profile

Here a comprehensive RP-HPLC , MDS approach using QbD principles has been described.

After definition of method goals, experimental scouting of key RP HPLC method components, including column, pH, and organic modifier is performed.

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.

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.

The goal of these efforts is thus focused on the identification of issues with a method after method development.

Genotoxic Impurity Analysis

The MDS approach can also be applied to the development of methods for analysis of Genotoxic impurities. Currently, potential genotoxic impurities are controlled at a generic threshold of toxicological concern of 1.5 ug per day in drug products, corresponding to low ppm% (w/w) levels in API.

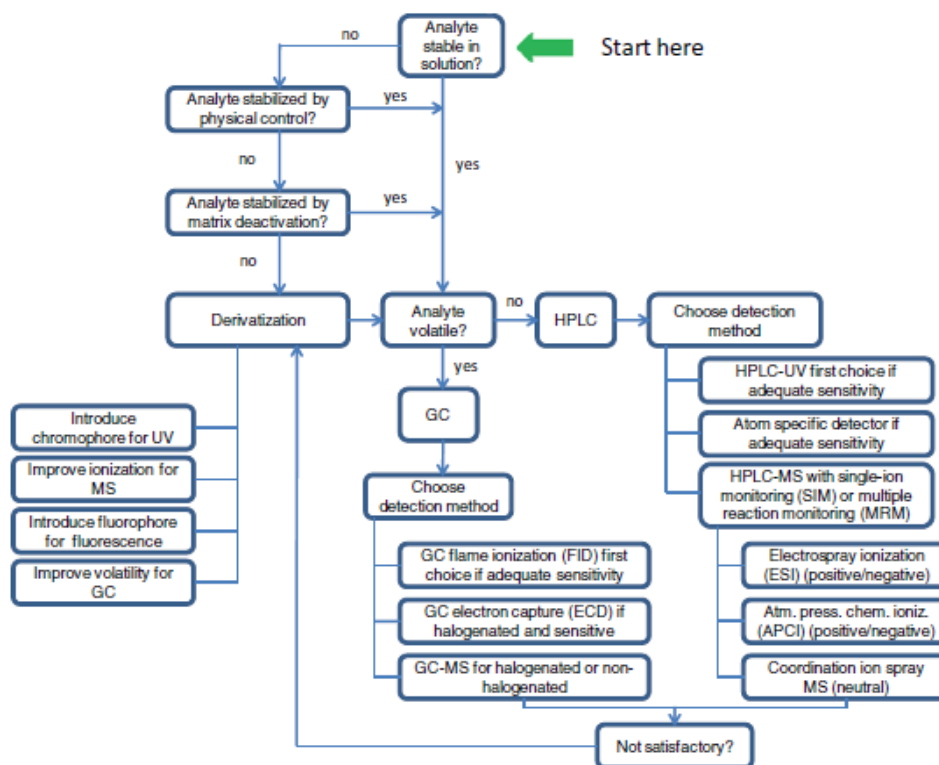
These levels are typically several hundred times lower than impurities controlled with the HPLC methods described in the previous section. Methods must be precise, accurate, and robust to achieve this goal. Because many genotoxic impurities are also chemically reactive, the need for low detection limits 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.

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.

Genotoxic Impurity Analysis

To guide the developer through the scouting phase, detailed flowcharts and decision trees such as that shown in the figure 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.



Genotoxic Impurity Analysis

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.

The detectors used in genotoxic impurity analysis are relatively complex compared to 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, 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.

Genotoxic Impurity Analysis

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.

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.



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.



Further 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 (ICPOES) 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.

Further Applications of Analytical QbD Approaches

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.



Conclusion

- 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 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.



THANKS FOR YOUR THE ATTENTION!!!