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Quality-by-Design for Analytical Procedures: Introduction

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Peer Reviewed: Method Validation

A new approach to analytical procedures has arrived. For production processes, quality-by-design (QbD) is being used successfully; the same QbD approach can be applied to analytical procedures. In addition, there is now a technique to definitively link the data to its intended use. These are exciting times for testing laboratories and the users of the data they produce. This series of articles will introduce, describe, and explain this QbD approach so you can start to use it with the analytical procedures in your laboratory.

With this new approach comes a number of buzzwords: QbD, analytical procedure lifecycle, analytical target profile, decision rules, measurement uncertainty, and target measurement uncertainty. Before discussing these terms, take a look at the reasons this approach is needed and is being developed and adopted.

A major deficiency with today's approach to analytical procedures is an inability to definitively demonstrate and ensure the data is fit for its intended use. Have you ever wondered if a method is fit for use and you can't get a clear answer? Have you ever wondered why the transfer of a method that is fully validated to today's standards fails a method transfer? Have you been in a situation wherein you needed to know how much variability comes from the manufacturing process and how much comes from the analytical procedure but had difficulty determining these variability components?

There are multiple causes to these problems. We do not have a defined process to quantify the risk and probability of failure and the purpose of the data. The method to completely and adequately characterize variability is not broadly known or used. There is no commonly accepted, statistically-based technique to adequately translate the use of the method into key performance criteria for method validation. This can be summed up by there being no guidance on how to demonstrate if a method is fit for its intended use. The *United States Pharmacopeia (USP)* General Chapter <1225> on method validation and ICH) Q2 *Validation of Analytical Procedures* provide guidance on the parameters that need to be included in the validation of an analytical procedure, but they do not give guidance as to the acceptance criteria for these parameters, nor how to link the validation to the intended use of the data.

Without these processes, techniques, and guidances, the acceptance criteria for validations of analytical procedures are often vague and are not numerical. Examples of such requirements are:

- The test result must be sufficiently accurate
- Any bias must not be such that an incorrect decision will be made
- The variability of the test result must be small enough so that the decision made is fit for its intended use and not based on random variability
- The result is based on the data and is not based on random variability
- The test method must be sufficiently sensitive so that the decision that an analyte is present or absent is correct and not solely based on the method's capability.

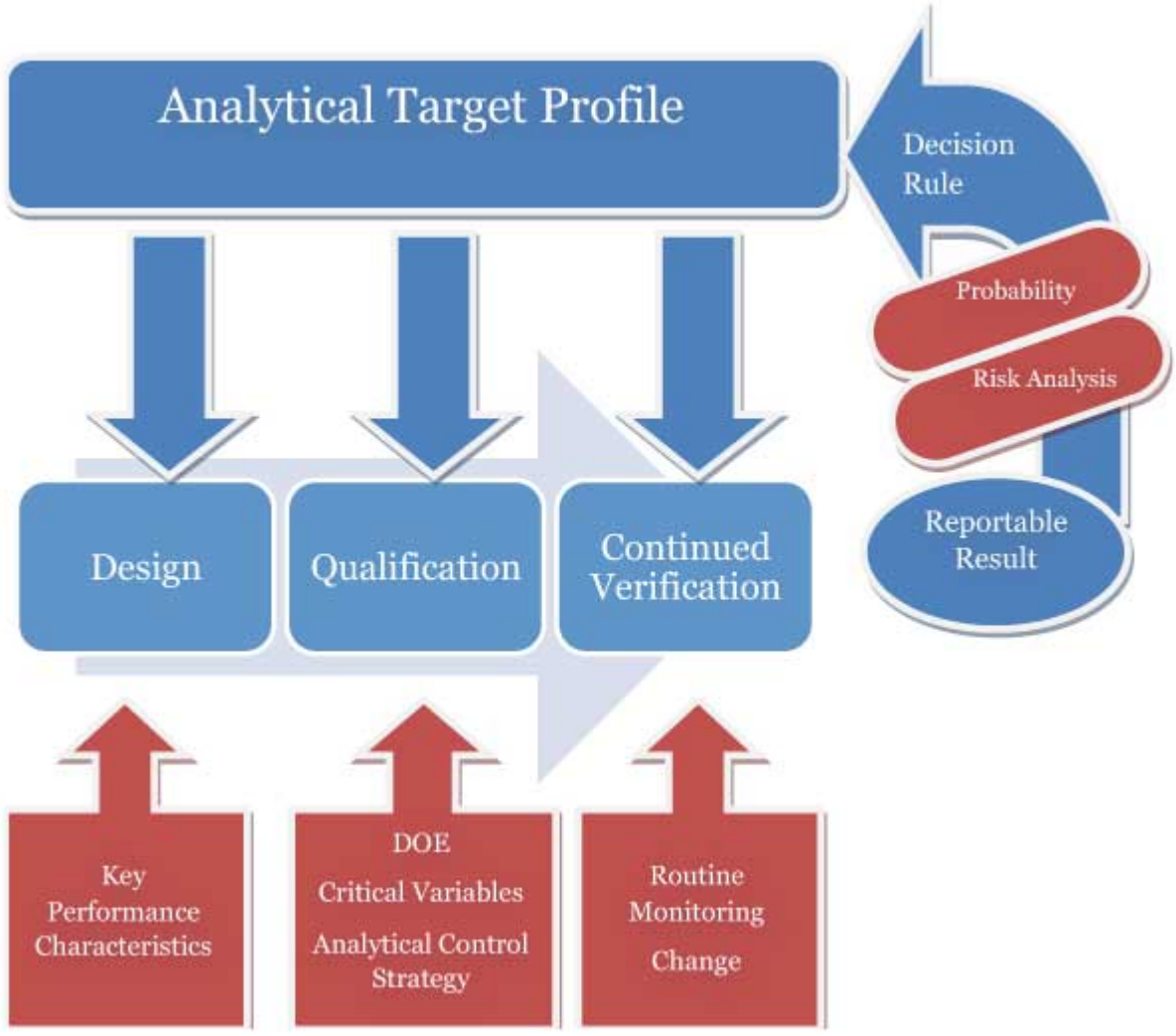
These are laudable goals of a validation, but are not numerical and not practicable because it is difficult to judge if they have

been met. Often the decision that the method validation passed contains an element of subjectivity.

The good news is that the new QbD approach uses risk analysis and probability to clearly define the purpose of a procedure using a decision rule. From this, the analytical target profile is created that is “the combination of all performance criteria required for the intended analytical application that direct the method development process.” (1)**.** The analytical target profile then guides the analytical procedure through its entire lifecycle, ensuring the method produces data that is fit-for-its-intended-use.

The QbD approach as applied throughout the lifecycle of an analytical procedure is illustrated in the Figure. The analytical procedure has three stages in its life. Method design includes the research and development of a method to meet the key performance indicators. Method qualification demonstrates the critical variables, those that affect the uncertainty, are in control, and a major outcome of method qualification is the control strategy for those critical variables. Qualification includes the activities now associated with method validation. Continued verification includes those activities, such as control charts, used to confirm the method performs adequately during routine use and in response to change, including method transfer between laboratories. The overall driving control for these activities is the analytical target profile that is derived from the decision rule that defines the purpose of the reportable result.

Figure: The QbD Approach as Applied throughout the Life of a Method from Method Design, Qualification, and Continued Verification.



In the next paper, the analytical procedure lifecycle and QbD approach will be presented in greater detail.

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