Considerations for Analytical Method Validation Lifecycle Controls

ICH is set to implement new regulatory guidance dedicated to analytical method development

The news that the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) intends to implement a new Quality Guideline, ICH Q14, "Analytical Procedure Development," along with revising the ICH Q2(R1) Guideline on "Validation of Analytical Procedures: Text and Methodology," is welcomed as, currently, there is no regulatory guidance dedicated to the topic of analytical method development.

When providing documented evidence for the suitability of an analytical procedure, a company would commonly reach for the method validation report. However, as with a manufacturing process, the validation is just one component of the lifecycle for that process and a key element is the process development. With ICH Q14, it is expected that an analytical method development report will be an expected regulatory document that will accompany the validation report as part of the agency submission.

A consideration at the initiation of the development phase for the analytical procedure is defining the goal/requirements for the test procedure. It is common for companies to validate a test procedure and report the results from the method validation in terms of accuracy, precision, and linearity, but rarely is there consideration as to whether the results of the method validation meet the requirements of the method's intended use. Furthermore, a company's analytical method validation standard operating procedure will commonly define the criteria for accuracy, linearity, precision, etc., with an assumption that such criteria are consistent for all quantitative test procedures.

Currently, there is no regulatory guidance on establishing the criteria. The upcoming ICH Q14 guideline may recommend that the analytical method validation criteria consider the material specification range for the attribute the test procedure is to measure—a similar approach when defining an analytical test method system suitability requirement. For quantitative test procedures, it should be recognized that the reported result only approximates the actual value for the material attribute that is being measured, and that there is an "uncertainty" associated with the reported result.

The USP analytical product lifecycle stimuli article by Martin, G.P., et al.,"Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification," Pharmacopeial Forum 39(5), September–October 2013, refers to an "Analytical Target Profile" (ATP) where it is defined as the required quality of the reportable value from a test procedure in terms of Target Measurement Uncertainty (TMU) In turn, TMU is the maximum measurement of uncertainty that the reportable result can have where the method can still be considered fit for use. Both the test procedure's precision and bias contribute to the TMU. The acceptability of the TMU considers the specification range for the attribute that is being reported and assesses the risk of an investigation being required due to the uncertainty of the value that is generated by the test procedure.

The Eurachem/CITAC 2015 guide "Setting and Using Target Uncertainty in Chemical Measurement" references that the Target Uncertainty (Utg) should be eight times smaller than the compliance range Utg = Qmax – Qmin/8. Essentially, any method where the measurement uncertainty consumes the material specification range is not a suitable method. It should also be understood that the various sources of the method uncertainty are cumulative. For example, Little, T.,"Establishing Acceptance Criteria for Analytical Methods," Biopharm International 29 (10) 2016, recommended that the repeatability is evaluated as follows: Repeatability % Tolerance = (StDev Repeatability * 5.15)/(USL – LSL) where the criteria is less than 25% and that for bias the criteria is as follows: Bias % of tolerance = bias/(USL – LSL) * 100 where the criteria is less than 10%. [Note: USL = Upper Specification Limit and LSL = Lower Specification Limit.]

As the effects of bias and repeatability are cumulative and the reduction of one would allow a larger value for the other, there is a benefit of assessing the impact of bias and repeatability in combination. USP Chapter <1210>, Statistical Tools for Procedure Validation, provides guidance as such where tolerance intervals can be calculated from a series of experiments utilizing a Control Sample (CS). A CS is invaluable in demonstrating the continued suitability of the method when used

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as part of the method lifecycle control. The CS will be extensively characterized, commonly by duplicate analysts, by the subject test procedure, but also by an orthogonal procedure and there will also be a theoretical understanding for the level of the analyte from the synthesis. The goal from the characterization is to define an accurate level of analyte within the CS, and thus, provide an accurate bias value for the method. The testing of the CS will be defined within the test procedure and will be part of the method's system suitability.

Tolerance intervals for the CS can be calculated as follows: *Xbar ± KS*

Where S is the standard deviation for the multiple measurements of the CS, Xbar is the afforded mean, and K is the percentage of the population at a certain level of confidence. For example, the value of K required to enclose 95% of the population with 95% confidence for fifty samples is 2.382. The repeated measurements of the CS will provide an assessment of the method's bias and repeatability.

As part of the initial method validation, and through periodic assessment of method performance, the demonstrated method capability tolerance intervals should be compared to a criterion. This method validation criterion would be based upon the defined analyte concentration of the CS and an acceptable interval, based upon the TMU. Such an approach aligns with the USP stimuli article by Martin, G.P., et al., "Proposed New USP General Chapter – The Analytical Procedure Lifecycle <1220>," Pharmacopeial Forum 43 (1), January 2017, where there is reference to Example 2 for the ATP, which states that the reportable value for the analyte must be within a TMU of ± C% where the TMU is a fraction of the specification range and considers the acceptable difference between a measured value and target value.

Through method development, there should be an understanding what analytical method attributes impact the analytical target profile. The FDA's July 2015 Guidance for Industry: "Analytical Procedures and Method Validation for Drugs and Biologics," recommended that method development includes an assessment of method robustness through design of experiments systematic testing where it is understood which method attributes will impact the instrument output, the reported result, and, thus, the measurement uncertainty.

Ultimately, through a robust method development, there would be fewer investigations, such as OOS, where the root cause is the method measurement uncertainty not aligning with the material specification range, rather than the quality of the material that is being tested. It is recommended that robustness is evaluated during the method development phase, when the necessary method controls are defined and confirmed for suitability via method validation.

A question that may be raised by industry professionals is, "How does the upcoming ICH Q14 guideline impact the methods that I currently use?" The FDA's July 2015 Guidance for Industry: "Analytical Procedures and Method Validation for Drugs and Biologics" references analytical method development, the use of statistical tools during method validation, and lifecycle management of analytical procedures. It is recommended that for in-use methods there is a program for periodic assessment of the method performance/capability where continued method suitability is confirmed. This can be assessed via an evaluation of investigations, which involves data that is generated by the method, and determining through trend analysis whether method capability was a potential cause.

There should also be a continual assessment of the method system suitability test regime and criteria when there is verification that the method's system suitability is sufficiently discriminative and meets the method's needs. Further, there should be consideration of incorporating a CS to ensure that the measured method's uncertainty continues to align with the TMU. The periodic method assessment should also verify that there is an understanding, through method robustness studies, of the critical method attributes and their impact on the method's measured uncertainty value.

One of the significant benefits of a comprehensive and structured analytical method development program is understanding the potential impact of any "change" to the method. For lifecycle management of the test procedure, it is recommended that risk assessment, per ICH Q9, "Quality Risk Management," is utilized to determine the potential impact of any change—be it to the method itself or the manufacturing process it is supporting—to the method uncertainty value and then assessing the need for method redevelopment or revalidation.

Historically, analytical method validation was the exercise to demonstrate that a method was "fit for purpose." The goal is to determine what the requirements for the method are in terms of the material/process that is being tested, define the ATP (which for quantitative methods considers the TMU), and then, through a structured method development program, demonstrate that the developed method meets the requirements of the ATP—and that it is known which method critical attributes impact the ability to meet the ATP. Therefore, the method development report is critical when evaluating the potential impact of any proposed change to the method.

It is recognized that ICH Q2(R1) does not provide specific guidance for the development and validation of non-chromatographic methods. However, the FDA's March 2015 Draft Guidance for Industry: "Development and Submission of Near Infrared Analytical Procedures" provides direction for the development and validation of a spectroscopic PAT analytical method. This document also provides expectations on what should be submitted within the regulatory filing relating to the development of the PAT method along with the method validation. In addition, there is also guidance relating to the lifecycle management of such a method and considerations for when further method development/revalidation is required. It is recognized that this guidance is geared towards the development and validation of a NIR PAT method, and, as such, a significant focus of the guidance is towards the development and validation of the calibration model using chemometric software to define the relationship between NIR spectral output to the analyte of interest. However, it is expected that the upcoming ICH Q14 guideline and revised ICH Q2(R1) guideline will have similar focus on method development for both chromatographic and non-chromatographic methods. **CP**