PEER REVIEWED

Bridging the Gaps in the Analytical Procedure with Bayesian Statistics

The ICH-Q2 has stated that the objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose, yet it – as well as the ICH-Q14 – fails to clearly define the actual aim of analytical procedure, leading to misunderstanding and confusion. Bruno Boulanger, Ph.D., Global Head Statistics and Data Science at PharmaLex, discusses how Bayesian statistics and interpretation bridge the gaps in the guidelines.

In early 2022, ICH released two important guidelines for comments: ICH-Q2 "Validation of Analytical Procedures" and ICH-Q14 "Analytical procedure development", both of which are closely interconnected through the concept of the Analytical Target Profile (ATP), which is used to assess the quality of results generated by analytical methods. The ATP and ICH-Q14 are intentionally more aligned with the Quality-by-Design (QbD) ICH-Q8 document on process development, qualification and control. This introduces the concept of QbD applied to analytical procedures (AQbD).

But, as opposed to ICH-Q8 that starts with the target product profile (TPP) or the properties that a product and its related process should achieve, both ICH-Q2 and Q14 miss the central point that applies to all analytical procedures: defining what is a good fit-for-purpose measurement or reportable value. The fact that the actual aim of analytical procedure is not clearly defined causes misunderstanding and confusion about various concepts such as accuracy, linearity and range.

Bayesian statistics and interpretation address these misunderstandings, helping to bridge the gaps that exist in these two guidelines.

Uncertainty of Measurement

The ICH-Q2 (R1) describes the linearity of an analytical procedure as "its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample".[1] The idea is that by increasing the quantity or the potency, the result will be proportional to the increase. Trust in the result during routine use of a validated method is the concept of uncertainty of a measurement – a concept routed in Bayesian statistical theory. Applying Bayesian statistics allows the user to take results obtained during the validation of the analytical procedure and predict the uncertainty around any future result.

In pharmaceutical manufacturing, it is this concept of uncertainty, or Target Measurement Uncertainty, that allows the user to determine with a high probability (for example 95%) that the true value of the batch or sample is within a pre-specified quality range. So, if an analytical procedure is used to release a batch of a drug product and the specification limits are that it must fall within +-2mg, then the uncertainty associated with a result should be much smaller than the +-2mg in order to keep the risk acceptable. (See figure 1). In keeping with Six Sigma thinking, the rule of thumb is that TMU should not be greater than one sixth of the specifications of the product to reduce the risk of making a wrong decision.

Going back to the concept of AQbD, elements of which are employed in the Q14, the point is to be sure that for any future test the product will be within specifications. However, what is missing from the Q14 and the Q2 guidelines is they don't define what the specifications on the uncertainty should be in relation to the quality of the product, which means that the fit-for-purpose concept is not explicitly defined.

The importance of this has been underscored by the International Organization for Standardization, which states in its standard

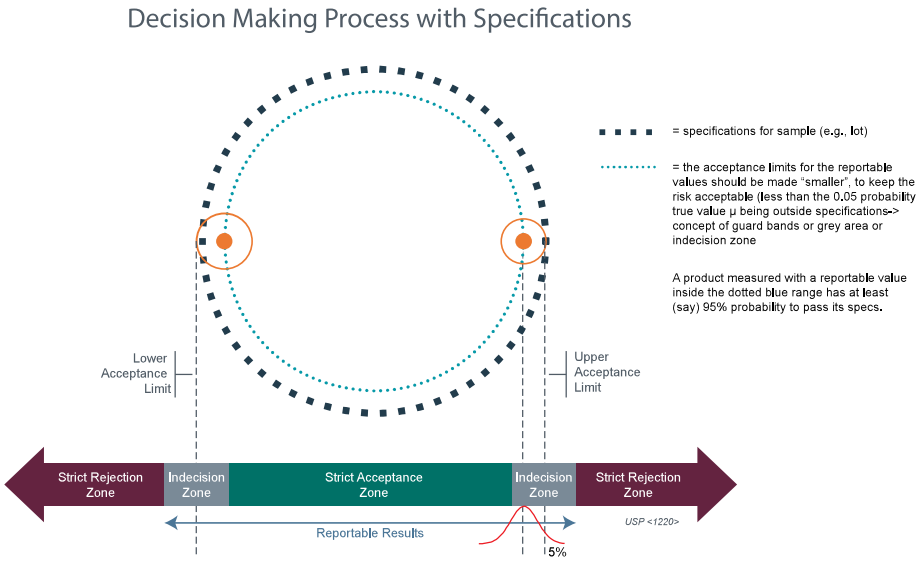

Figure 1

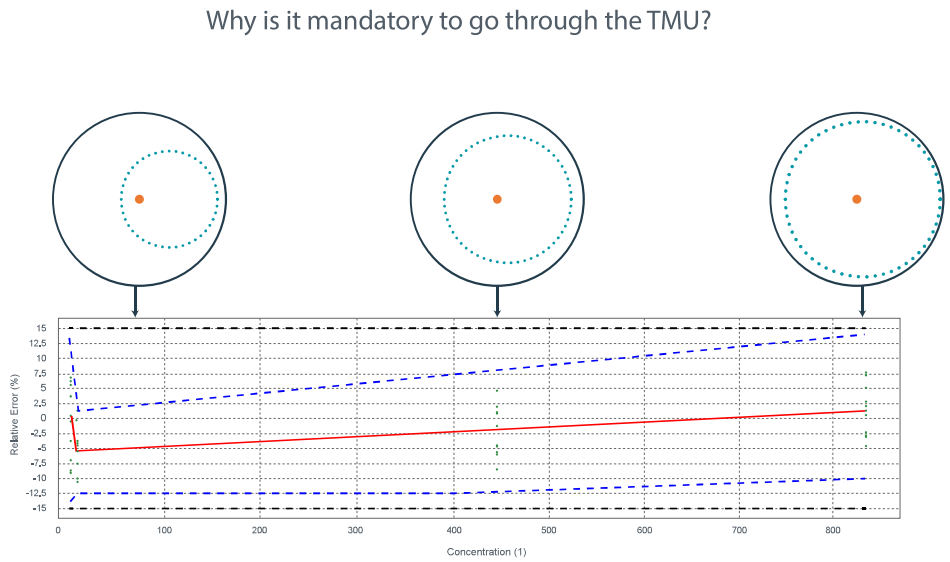

Figure 2

ISO 21748: "Without quantitative assessments of uncertainty, it is impossible to decide whether observed differences between results reflect more than experimental variability, whether test items comply with specifications, or whether laws based on limits have been broken. Without information on uncertainty, there is a risk of misinterpretation of results."[2]

The objective of an analytical procedure is to be able to provide any reportable value close enough to any future unknown quantity (within a predefined range), with a high probability. Since ICH-Q2 is about validation of analytical procedures, it's important to work with a known sample to try to determine the accuracy of a result (a combination of bias and precision). By applying Bayesian theory, the reviewer uses predictive distribution – the distribution of possible future values given the results observed in validation – to evaluate future uncertainty. As long as the uncertainty of future measurement is small in validation, assuming there is a definition of "small" in the TPP of the analytical target performance, the analytical procedure can be accepted. But this is missing in the ICH-Q2.

The issue is different when moving to the routine, where use of a validated analytical procedure requires trust in the measurement – unless there is some evidence showing a problem occurred during the analytical procedure when generating that reportable value. Therefore, the only way to trust a result during the routine phase on an unknown sample is by referring to the analytical procedure and its performance, as assessed during the validation.

Diagnostics and Drug Products in Validation and Routine

Perhaps the clearest example of measurement during the validation versus routine phases is with diagnostic products. Specifically, diagnostic tests deal with sensitivity and specificity and are important indicators of test accuracy. On one hand, sensitivity is the proportion of true positives versus false negatives in tests of patients with a given condition, while on the other, specificity is the percentage of true negatives versus false positives of all subjects who do not have the condition.

The question for diagnostic tests is, how to determine the probability of an outcome (for example, does the patient have cancer

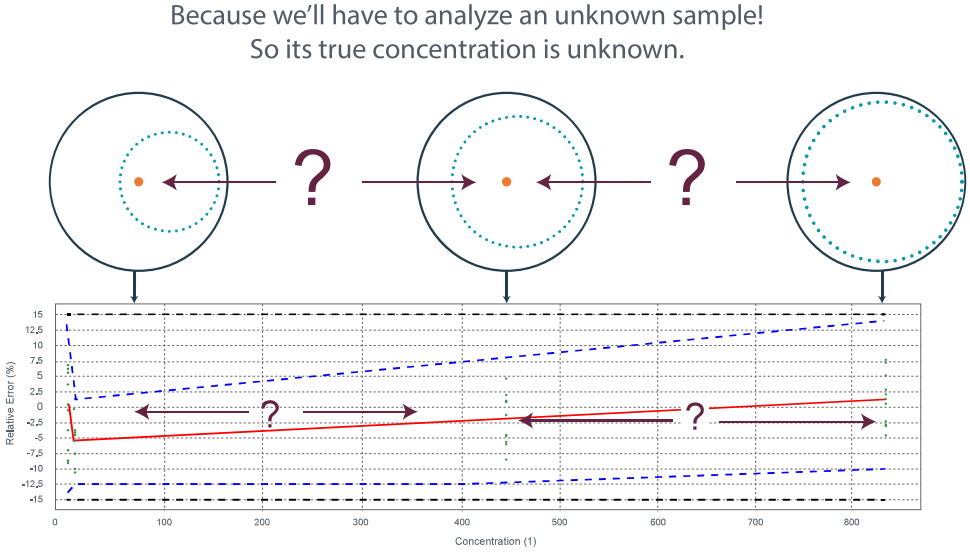

Figure 3

or not) given the result is positive. During the validation phase, the result is based on the known sample, while in the routine it is inverted to ask what is the probability of the sample being truly positive given the positive result? This inversion is built on Bayesian theory. During validation, therefore, the sensitivity and specificity of the device is tested to demonstrate its performance, while during routine, the manufacturer needs to prove what is called the predictive positive value (PPV) and negative predictive value (NPV).

The yes/no measurement scenario, which is standard in diagnostics, gives the reviewer all the reportable values (Xi) given the sample is positive. In routine, the reviewer needs to determine where, with high probability, the true unknown content of the sample will be, given there is one measurement. A decision needs to be made for each reportable value. Through the Bayesian theory of uncertainty in measurement, reviewers can determine the distribution of the unknown true value with 95% reliability.

Returning to pharmaceutical manufacturing, an analytical procedure could be used for the release of a batch of drug product based on its potency or concentration, to assess the stability of batches, to evaluate the dissolution of tablets, and so on – all with the purpose of supporting low-risk decision-making about the batch. The specifications applied to any reportable value will be directly derived from the specifications of the product or the test as defined in the TPP. First, though, it is important to define the target measurement uncertainty or greatest uncertainty allowed over an intended range of true values to be covered in the future.

During the validation, it's necessary to characterise the uncertainty based on different levels of concentration. However, given unknown samples will be used during routine, the bias, precision and uncertainty will also be unknown.Figures 2 and 3 shows a range between 40 and 800. The reviewer may have a sample at a concentration of 600, but if they have never carried out validation at 600 they don't know what the uncertainty is. What they do know is that between specified concentrations measured during validation – in this example between 40 and 800 – there is a high probability that the sample is within the target measurement uncertainty (the two black horizontal lines in figures 2 and 3). It is only the TMU that allows the reviewer to know the risk made during a decision in the routine. So, using Bayesian statistics, the reviewer can say given the result during validation using the known sample, it is possible to predict over a range the probability that a future unknown sample will be within the TMU.

The ICH-Q2 asks manufacturers to prove that different concentration levels work, but does not show how that is feasible with unknown future samples. Using Bayesian theory and given the result from the validation of the known sample it is possible to say, with a probability of more than 95%, that it will be within the TMU. The target measurement uncertainty should be the objective of Q14 and by defining the TMU, or the quality of the measurement in future, it is possible to connect the objectives of the ICH-Q2 and Q14, which ultimately should be to support decision-making about capability of an analytical procedure to provide reliable results. Unfortunately, ICH-Q14 uses the wording Total Analytical Error instead of Uncertainty because errors during validation with known samples are still confused with future uncertainty of a measurement about an unknown sample. Using Bayesian statistics helps to make this link.

Bayesian theory helps to bridge the gaps and address the questions posed by many regulations and guidelines, including the ICH-Q2 and Q14. Among the problems it helps to solve are ensuring reportable values can be routinely trusted given the validation results and helping to define the TMU and be confident it can be achieved in future results. Certainly, in the case of validation of analytical procedures and ICH-Q14 analytical procedure development Bayesian is the best way to address the gaps in understanding and reduce risk in decision making.

REFERENCES

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