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Quality-by-Design for Analytical Procedures: Decision Rules

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“Any analytical procedure must be shown to be fit for its intended purpose before use.” The United States Pharmacopeia (USP) stimuli article (1) on the lifecycle management of an analytical procedure starts with this statement, emphasizing the importance of producing data that is fit for the decision being made using that data. The stimuli article continues to emphasize decisions in the following quote (2, 3):

> “Results generated using analytical procedures provide the basis for key decisions regarding compliance with regulatory, compendial, and manufacturing limits. The results are applied against Decision Rules that give a prescription for the acceptance or rejection of a product based on the measurement result, its uncertainty, and acceptance criteria, taking into account the acceptable level of the probability of making a wrong decision.”

Decision rules can be used to clearly define the risk probability associated with that decision.

Examples of such decisions are: “Does this drug product meet the specification for potency?”, “Does this in-process batch meet the requirements for further processing, such as filling vials?”, “Is the elemental impurity below the required limit?” The literature on decision rules uses the term product to refer to the material for which a decision is being made. The product can be considered the same as the measurand, defined as “quantity intended to be measured (VIM 2.3)” (4). Information about measurand is available in the *Eurachem Guide Terminology in Analytical Measurement: Introduction to VIM 3* (5).

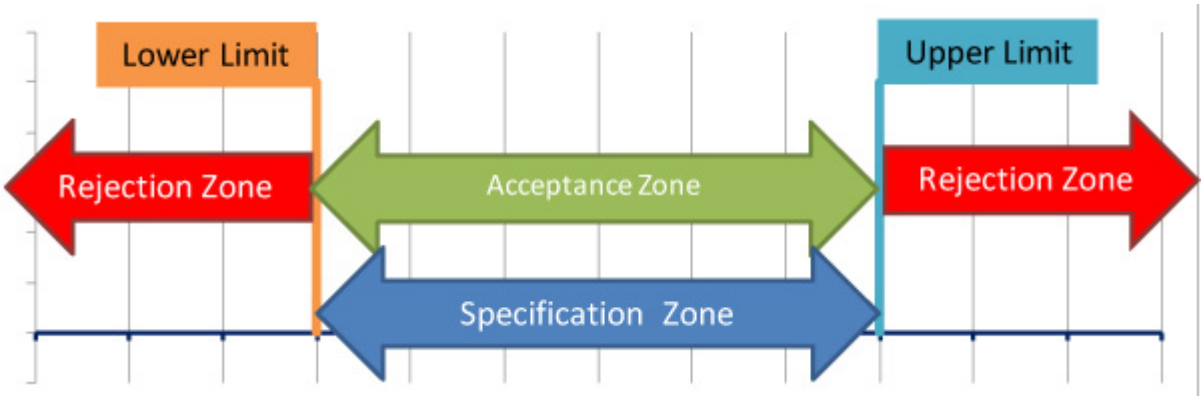
Decision rules have been used for many years, especially in the calibration and physical testing industries. Their use has expanded because they are applicable to any situation in which data is used to make a decision. The terminology for decision rules includes the following zones and types of zones.

Zone	**Definition and Comments**
Specification zone	The values between and including the specification limits.
Acceptance zone	When the measurement result is within this zone, the product is accepted.
Rejection zone	When a measurement result is within this zone, the product is rejected.
Transition Zone	A decision rule could also define a transition zone that is neither acceptance nor rejection. When a result is within this zone, specified actions would be taken, such as additional testing, using a different analytical procedure, or conducting an investigation before proceeding further.
Type of Zone	
Simple	The rejection and acceptance zones line up with the specification zone.
Stringent	The acceptance or rejection zone is reduced from the specification zone by the amount of the guard band.

Relaxed	The acceptance or rejection zone extends beyond the specification zone by the amount of the guard band.
Guard Band	For relaxed or stringent types of zones, the guard band is the magnitude of the offset from the specification limit to the acceptance or rejection zone boundary. The guard band is similar to the “margin for error” of internal release limits used by some companies today. The size of the guard band is a multiple of the measurement uncertainty.

In a simple decision rule, the rejection and acceptance zones line up with the specification zone. The simple decision rule is illustrated in Figure 1. Many compendial monograph specifications may be considered simple decision rules.

Figure 1: A Simple Decision Rule for a Specification with both Upper and Lower Limits. If the measurement result lies in the acceptance/specification zone, product is accepted, otherwise it is rejected.



A stringent acceptance zone reduces the probability of accepting out-of-specification product by increasing the risk of rejecting in-specification product. A guard band zone is established that offsets the specification and acceptance limits to achieve this. The size of the guard band depends on the desired probability of making each type of wrong decision. The stringent acceptance zone can be accompanied by a relaxed rejection zone, which allows the rejection of product even though a measurement result within the specification zone by the guard band amount is obtained. Many companies use such a decision rule and call it “internal release limit.” This decision rule is illustrated in Figure 2 for a specification with both upper and lower limits and in Figure 3 for a specification with an upper limit only.

Figure 2: A Stringent Acceptance Zone and Relaxed Rejection Zones Decision Rule for a Specification with both Upper and Lower Limits. Product is accepted if the measurement result lies within the acceptance zone and rejected otherwise. The guard band is established by the acceptable probability of making a wrong decision and the uncertainty.

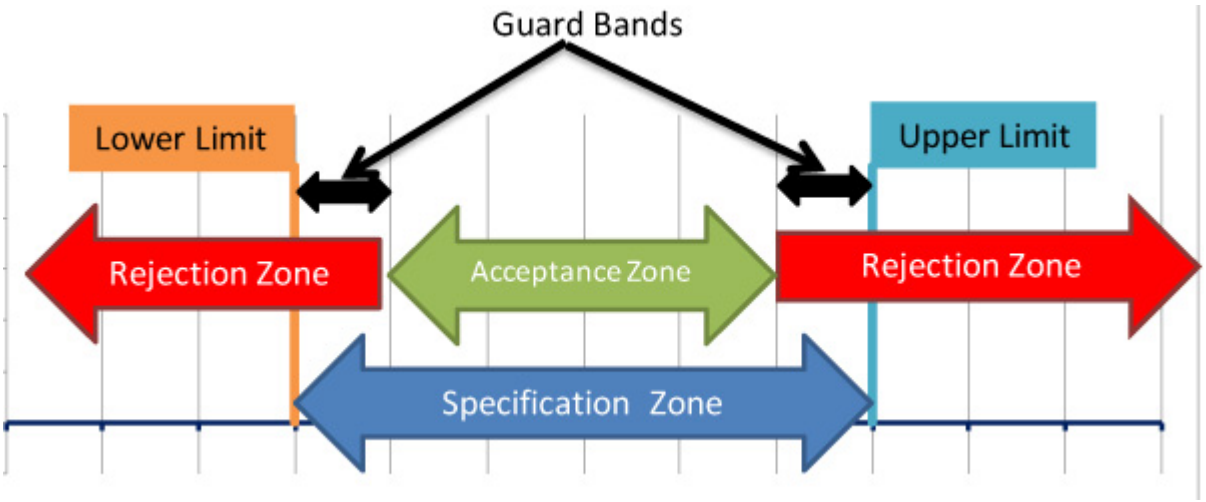
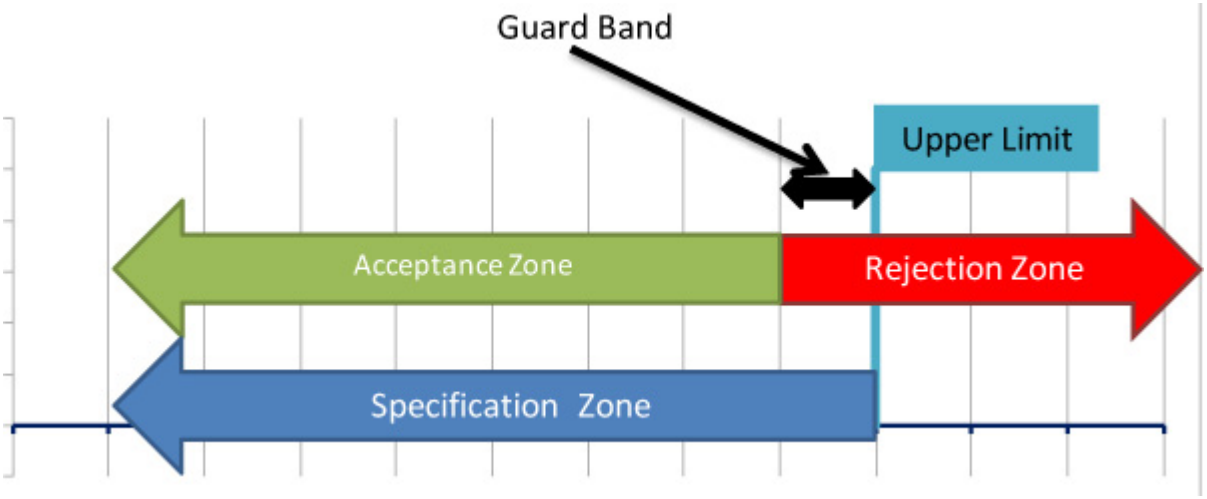
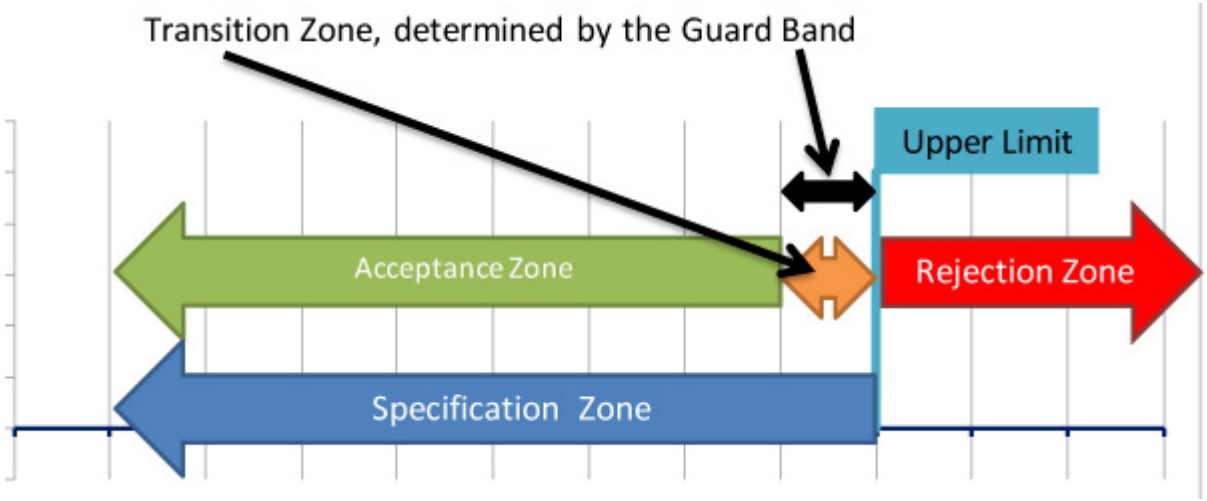


Figure 3: A Stringent Acceptance Zone and Relaxed Rejection Zone Decison Rule for a Specification with an Upper Limit Only.



A transition zone decision rule is illustrated in Figure 4 for a specification with an upper limit only. The transition decision rule should specify the required actions when a measurement result within the transition zone is obtained. The *USP* <905> "Uniformity of Dosage Units" (6) specification is an example of a decision rule that uses a transition zone. If the acceptance value of the first 10 dosage units is less than or equal to L1%, the requirements for dosage uniformity are met. If not, additional testing is performed. The region greater than or equal to L1% can be considered the transition zone.

Figure 4: A Transition Zone Decision Rule for a Specification with an Upper Limit Only.



Decision rule construction requires four components: the measurement result, its measurement uncertainty, the specification limit or limits, and the acceptable level of the probability of making each type of wrong decision. Choice of a decision rule is a business consideration that takes into account the cost of rejecting an in-specification product, the cost of accepting an out-of-specification product, the uncertainty associated with the measurement, the distribution of the measurand's characteristic, and the cost of making the measurement. The analytical quality-by-design (QbD) approach uses risk analysis and probability to determine these four components, hence clearly defining the use of a procedure through a decision rule.

The relationship between these four components allows one to determine if an analytical procedure is fit-for-use and, furthermore, set acceptance criteria for the analytical procedure to meet. Measurement uncertainty and its relationship to decision rules will be explored in future columns.

References

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