Setting Acceptance Criteria for Validation

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Agenda

- References and Guidance
- Release Specifications
- Stability Specifications
- Process Dependent Specifications
- Confidence Intervals
- Tolerance Intervals
- Process Capability
- Validation Specifications
- Case Study

References

- CGMP Regulations:
  21 CFR parts 210 & 211

- FDA DRAFT GUIDANCE:

  GUIDANCE FOR INDUSTRY: Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production

References

- ICH Q6A "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances"

- ICH Q6B: "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products"

ICH Definitions - Specification

- Q6A: “A specification is defined as a list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use.... Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.” “Specifications... should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product.”

ICH Definitions - Specification

- Q6B: “A specification is defined as a list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use.... Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.” “Specifications... should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.”

Voice of the Customer

- Any specification should start with the customer requirements.
- The “voice of the customer” will help to determine which attributes are important and should have specifications.

Release Specifications

- The concept of different acceptance criteria for release vs. shelf-life specifications applies to drug products only;
  - it pertains to the establishment of more restrictive criteria for the release of a drug product than are applied to the shelf-life.
  - Examples where this may be applicable include assay and impurity (degradation product) levels.
  - It may also be applied to potency or degradation products for biotech products, though not explicitly required.
- A company may choose to have tighter in-house limits at the time of release to provide increased assurance that the product will remain within the regulatory acceptance criterion throughout its shelf-life.
- In the European Union there is a regulatory requirement for distinct specifications for release and for shelf-life where different.

Stability Specifications

- ICH guideline Q1D and Q1E outline the protocols for stability testing.
- The guideline recommends that a statistical test for batch poolability be performed using a level of significance of 0.25.
- An appropriate approach to retest period or shelf life estimation is to analyze a quantitative attribute by determining the earliest time at which the 95% confidence limit for the mean intersects the proposed acceptance criteria (ICH Q1E).
- Extrapolation can be up to twice, but should not be more than 12 months beyond the period covered by the data.

Process Dependent Specifications

- Parametric release.
- Based on indirect evidence of product quality:
  - Diagnostic method works if reagent component has a purity of at least X%.
- Using process capability within intervals supported by clinical trials:
  - Specifications can be set such that the probability of getting an OOS result is low when the process is in control.

Confidence Intervals

- Confidence intervals for the population mean (μ) has the form:

  Sample Average ± margin of error

- Margin of error depends on:
  - **Level of confidence**
  - **Standard error of the sample average** (Standard error of sample average = $\sigma/\sqrt{n}$)
  - **If we know σ, then we can use Normal Dist**
  - **If we do not know σ, then use $s/\sqrt{n}$ for standard error and use the t-distribution with n-1 d.f.**

Confidence Intervals

- Confidence Intervals are Interval Estimates for population parameters.
- Example for Confidence interval for the population mean (μ).
- Confidence intervals are not statements about individual values or the population of individual values
- The resulting confidence interval is an interval "guess" for the value of the population mean

Tolerance Intervals

- Tolerance Intervals apply to the population of individual values
- Tolerance Intervals:
  - Level of confidence
  - Percentage of population coverage
  - Often of the form:
    - Sample average ± margin
    - Margin here based on percent of population coverage, level of confidence, population variability

Tolerance Intervals

- Can use tolerance intervals to show process capability supports specifications
- Before calculating tolerance intervals check to make sure process is in control (no trends apparent)
- If using assay results as product measures then assay results are more precise when reportable result is an average of replicates

Tolerance Intervals

- Tolerance intervals should incorporate all possible sources of variability in the reportable values:
  - Lot to lot variation
  - Assay variability:
    - Analyst to analyst
    - Day to day
    - Reagent lot to reagent lot
- Either by experimental design or by use of historical data

Tolerance Limits

- Procedure to calculate parametric (based on normal distribution) two-sided tolerance limits, continued:
  - Determine the percent of population coverage
  - Use a tolerance interval table, enter with sample size (degrees of freedom = n -1), confidence level and percent coverage to find k [1]
  - Tolerance Interval: $(\overline{X} - k \times S, \overline{X} + k \times S)$

[1] Table A.10a from (1991) Hahn, G.J., Meeker, W.Q. STATISTICAL INTERVALS: A Guide for Practitioners, John Wiley & Sons. This is one possible source.

Tolerance Intervals

- The multiplier k is dependent on:
  - Level of confidence
    - Confidence decreases, then k is smaller
  - Percent of population coverage
    - If percent of population coverage is lower, then k is smaller
  - Sample size, n
    - As sample size increases, then k gets smaller

Process Capability

- Estimate the process standard deviation from the variation within the subgroups from a control chart. $\bar{R}$

- This estimate of within subgroup variation represents the inherent variation of the process due to common cause.

C_p

- The idea is that the range of a normally distributed random variable is roughly 6σ

- If the process is in control and the distribution is well within the specification limits then the difference between the Upper specification (U) and Lower specification (L) should be larger than 6σ

$$C_p = \frac{\text{UpperSpec} - \text{LowerSpec}}{6 \cdot \overline{R} / d_2}$$

C_{pk}

- For lower (or upper) specifications and to assess the current performance of the process:

$$C_{pL} = \frac{\overline{\overline{X}} - \text{LowerSpec}}{3 \cdot \overline{R} / d_2}$$

$$C_{pU} = \frac{\text{UpperSpec} - \overline{\overline{X}}}{3 \cdot \overline{R} / d_2}$$

$$C_{pk} = \min(C_{pL}, C_{pU})$$

C_{pk}

- C_{pk} greater than 1 shows the process is probably centered and usually able to meet specifications
- C_{pk} less than 1 indicates either the mean is not centered between the specifications or there is problem with variability
- C_{pk} is meant to be used with processes that are in control – gives us a measure of whether the in-control process is capable of meeting specifications
- C_{pk} is not an appropriate measure if there are trends, runs, out-of-control observations or if the process is too variable

P_p

- If the process is in control and the distribution is well within the specification limits then the difference between the Upper specification (U) and Lower specification (L) should be larger than 6σ

$$P_p = \frac{\text{UpperSpec} - \text{LowerSpec}}{6 \cdot \bar{S} / c_4}$$

$$P_p = \frac{\text{UpperSpec} - \text{LowerSpec}}{6 \cdot S}$$

P_{pk}

- For lower (or upper) specifications and to assess the current performance of the process:

$$P_{pL} = \frac{\overline{\overline{X}} - \text{LowerSpec}}{3 \cdot \bar{S}/c_4} \qquad P_{pU} = \frac{\text{UpperSpec} - \overline{\overline{X}}}{3 \cdot \bar{S}/c_4}$$

$$P_{pL} = \frac{\overline{\overline{X}} - \text{LowerSpec}}{3 \cdot S} \qquad P_{pU} = \frac{\text{UpperSpec} - \overline{\overline{X}}}{3 \cdot S}$$

$$P_{pk} = \min(P_{pL}, P_{pU})$$

Validation Specifications

- Usually based on analysis of development runs.
- Should include all sources of variations (days, runs, instruments, operators, etc.)
- Failed runs provide information.

Validation Specifications

- Spec limits should tighten over time
  - IQ > OQ > PQ > Stability > Release
- Using either confidence intervals or tolerance intervals, specifications can be set based on the sample size.
  - Normal QC testing will have smaller sample sizes compared with validation testing

Case Study

- The customer identified that moisture content is the most critical factor.
- From development we know that process temperature and process yield correlate with low moisture content.

Development Data

Batch	Temp	Yield	Moisture
1	51	74	4.9
2	53	79	4.5
3	55	78	4.2
4	47	75	4.9
5	48	82	4.3
6	49	84	4.3
7	51	88	4.4
8	42	84	5.0
9	59	91	3.9
10	51	82	4.8
11	63	93	3.8
12	57	85	4.1
13	55	79	5.0
14	54	81	4.8
15	45	72	4.6
16	49	85	4.8
17	50	86	4.7
18	52	94	3.8
19	48	82	4.7
20	51	77	4.4

Summary Statistics

Statistic	Temperature	Yield	Moisture
Mean	52	83	4.5
Std Dev	4.84	6.03	0.39
Lower 95% CI	45	75	
Upper 95% CI	58		5.0
Lower 99% TI with 99% Coverage	30	60	
Upper 99% TI with 99% Coverage	73		5.9

Specifications

- Based on the development runs, we can get a mean and standard deviation.
- If we run 6 runs for validation, the following would be our acceptance criteria.

	Temp	Yield	Moisture
Mean of 6 runs	45-58	>75	<5
No individual value	30-73	>60	<5.9

Conclusions

- Specifications are the combination of customer requirements, historical data and risk tolerance.
- As more information is gathered, specifications should be tightened.
- Sample size can be calculated that gives a high probability of meeting the specification.