Establishing, Assessing, and Comparing Quality Attributes from a Small Sample of Development Batches through Full-scale Production

Kimberly Vukovinsky
Senior Director, Statistics

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Pfizer

International Society of Pharmaceutical Engineering (ISPE) Comment

- The three areas of application discussed in the reflection paper are entirely different situations for patients and for manufacturers.
  - e.g. The goal of a biosimilar comparison is different than a small molecule site transfer.
- The analysis approach might be very different in each of these situations and the issues raised in the paper may be more or less important in each case.
- ISPE recommends that the reflection paper be split into several documents. The scope of the current reflection paper is quite large and difficult to thoroughly cover.

Outline

- Focus on Comparability during Pre-/Post-Manufacturing Change
- Will describe a practical approach discussed within several member companies to establish, compare, and control quality attributes
- Using Content Uniformity as an Example

Manufacturing Pre-/Post- Change Comparability Topics

- **Comparison Objectives**: (Section 4.1) Goal is to show two processes “highly similar” safety and efficacy
  - *Target Product Profile (TPP)*
  - *Quality TPP (QTPP)*
- **Translation to Statistical Objectives**: (Section 5.1.2) Non-inferior quality; (Section 7) deciding upon one- or two-sided comparison
- **Predefine Acceptance Region**: (Section 5.6) arbitrariness of acceptance ranges might be unavoidable (Section 4.1) past … statistical intervals … the context rarely clear in relation to conclusions drawn

Establish, Compare, and Control Quality Attributes
ICH Unit Dose Uniformity (UDU) Test

Table 1. ICH UDU Content Uniformity Test

All measurements of dosage units and criteria values are in percentage label claim (%LC).
At each stage calculate the sample average $\bar{X}$ and the sample standard deviation *s*.

Stage	Number tested	Pass stage if:
S_1	10	$\lvert M - \bar{X}\rvert + 2.4s \leq 15.0$, where M is defined below.
S_2	20	i) $\lvert M - \bar{X}\rvert + 2.0s \leq 15.0$ using all 30 results ($S_1 + S_2$) ii) No dosage unit is outside the maximum allowed range of 0.75*M to 1.25*M.

M is defined as follows:

If T is less than or equal to 101.5%LC, and

(i) If $\bar{X}$ is less than 98.5%LC, then M = 98.5%LC.

(ii) If $\bar{X}$ is between 98.5 and 101.5%LC, then M = $\bar{X}$.

(iii) If $\bar{X}$ is greater than 101.5%LC, then M = 101.5%LC.

If T is greater than 101.5%LC, and

(i) If $\bar{X}$ is less than 98.5%LC, then M = 98.5%LC.

(ii) If $\bar{X}$ is between 98.5 and T, then M = $\bar{X}$.

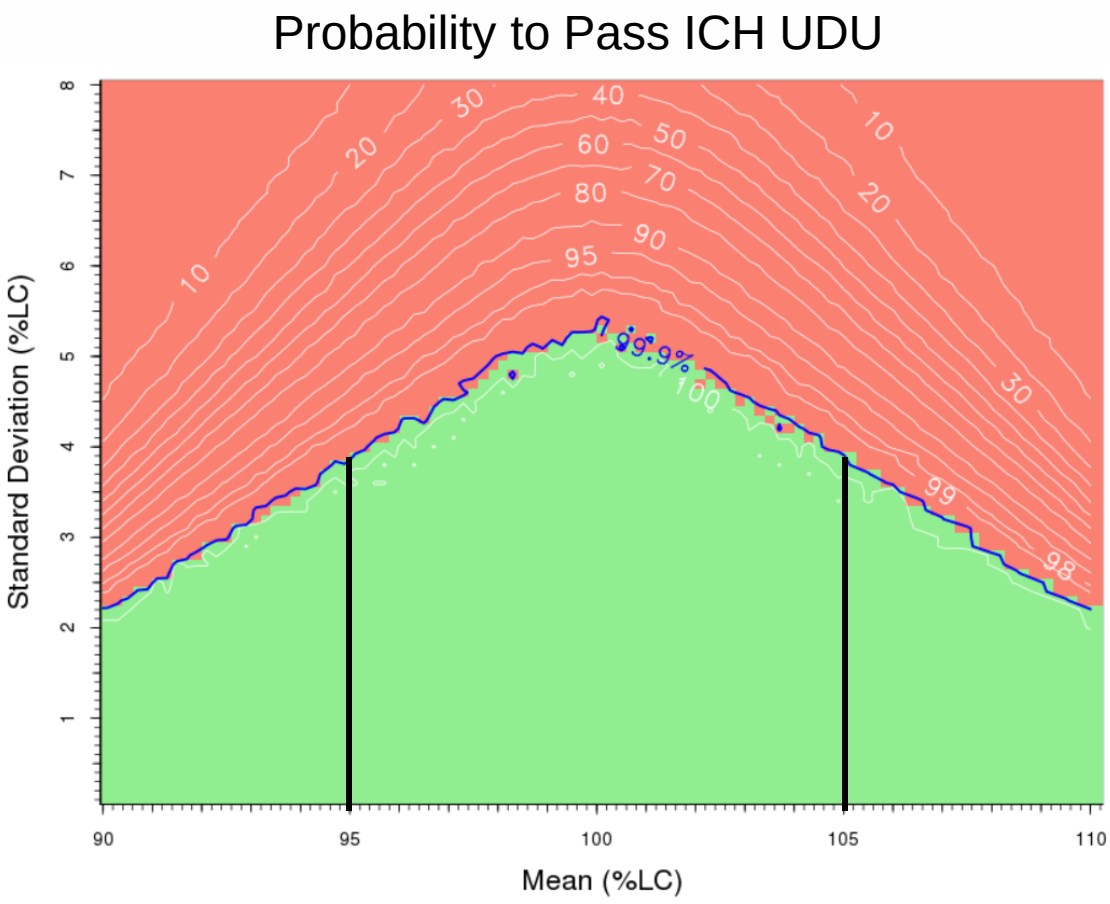
(iii) If $\bar{X}$ is greater than T, then M = T.

T is the Target content per dosage unit at the time of manufacture, expressed as percentage label claim. Unless otherwise specified in the individual monograph, T is 100.0%LC.

Setting Acceptance Range – What is Manufacturing Goal?

Start with the end in mind:

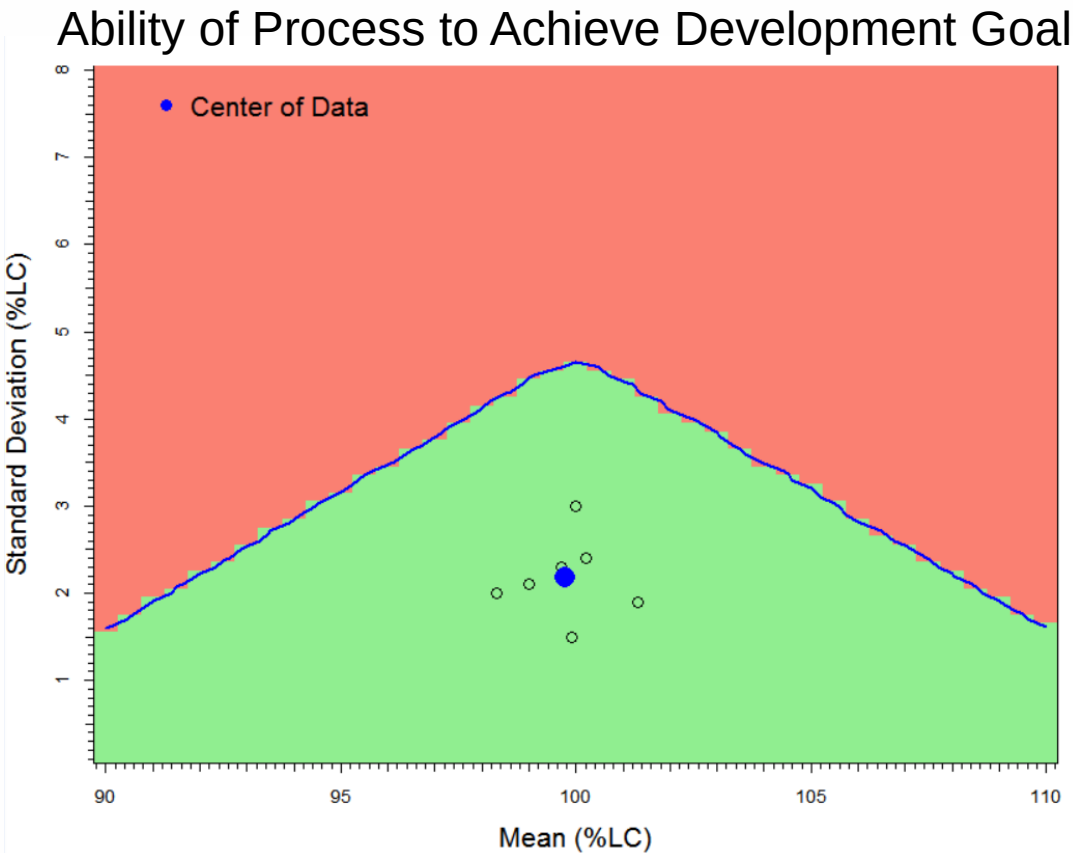
- The probability to pass ICH UDU can be calculated from the test rules.
  - Goal based on Process Capability; appears arbitrary
  - Very well inside safety and efficacy considerations
- A region of indifference (sufficient similarity) can be selected where operation anywhere in the space is acceptable.



Pre-change Assessment – What is Development Goal?

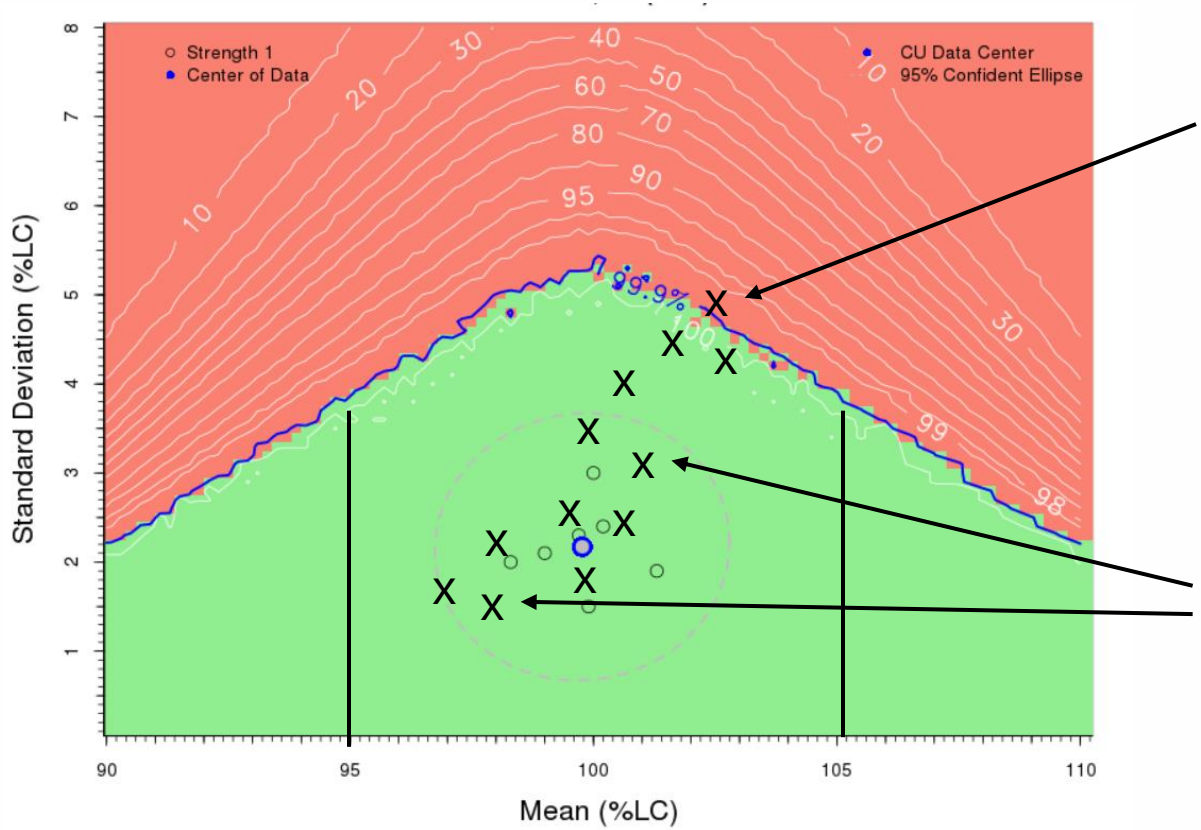
Quality by Design; Develop a process (average performance)

- Stratified Sampling of Content Uniformity data preferred (Section 5.3)
- Transfer from development to manufacturing usually includes a small number of lots pre- and post- change (Section 4.1)



Post-Change Comparison: What is Transfer Goal?

- Visual Comparison Using Pre-defined Limit
- Is Product Performance at Scale Comparable to Development?
- Is Post-Change highly similar with respect to safety and efficacy?



- Investigate
- Work to Understand Variability

- Difference is Acceptably Close and Within Comparison Criteria
- Sufficiently Similar

Elements in Manufacturing Comparability

- Meaningful specification numerical limits
  - Types: Compendial (e.g. potency, content uniformity), Safety-based (e.g. tox study), Data-driven
  - Would like to realize a highly capable process, e.g. Ppk of 1.33 (4 sigma) or Ppk of 1.67 (5 sigma)
  - At times, data-driven based on a small set of data, e.g. min/max (~2 sigma) or 3 sigma (Ppk of 1.0) even in light of relevant knowledge
- Sample Size
  - Tends to be small, even when much knowledge available
  - Reliable estimation of Standard Deviation
- Distributional Considerations (Normality) / Science and engineering of the product and the control strategy
- Risk prioritized
- Criteria can vary attribute to attribute and product to product

Conclusion

- Comparability is Integral to Design, Develop, and Transfer a Reliable, Consistent, Capable Process, and Manufacture a Safe, Efficacious, High Quality Product
- Required:
  - Properly Engineered Formulation and Dosage Form
  - Meaningful specifications
  - Well Designed and Controlled Processes and Methods
- For Manufacturing Transfer Recommend:
  - Understanding of data in context of science and engineering
  - Risk based prioritization to attribute selection
  - Statistical methods/criteria vary attribute to attribute
  - Statistical approach can include comparison against a goal
  - Always plot data; visual comparison