Analytical Development Using Quality by Design

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Outline

– Quality by design for analytical methods
– AQbD fundamentals
– Lifecycle stages
– The analytical target profile
– Uses of methods
– Summary
Industry and regulators have begun to recognize that analytical methods generate a product – *measurements*

Like pharmaceutical products, measurements should have adequate quality to meet their intended use – *making a decision*

The fundamental goals of product development are:
- Safety and efficacy (hitting the clinical target)
- Variance reduction

The fundamental goals of analytical development are:
- Accuracy (hitting the analytical target)
- Variance reduction
AQbD (cont.)

  - Modeled after FDA Validation Guideline

- Moving analytical methods into the world of QbD

- Follow-on workshop
  - 8-9 Dec, Rockville, MD
“Validation” is a demonstration of fitness-for-use
“Validation” is a continuous process
“Demonstration” should include consideration of risks
  - Risk of making decisions from an “invalid” procedure
  - Risk of invalidating a procedure which is in control
Risk is directly related to “uncertainty”
Movement towards metrology and ISO standardization (International Standards Organization)
Terminology

- **Method** – the wet chemistry
- **Procedure** – format of the reportable value
  - FDA Guideline treats these as synonymous
- **Reportable value** – the result of measurement or amalgamation of measurements which are held to an acceptance criterion
  - **Release** – average of assays
  - Stability – linear regression line
  - Method transfer – difference in means between laboratories
- **Analytical target profile (ATP)** – the performance requirements for an analytical method
- **Uncertainty** – from ISO *Evaluation of measurement data — Guide to the expression of uncertainty in measurement*
  - “Uncertainty (of measurement): parameter, associated with the result of a measurement, that characterizes the dispersion of the values that could reasonably be associated with the measurand.”

Distinction is important to method transfer, bridging and validation.
Lifecycle stages

– **Stage 1** – Method design, development and understanding
  – Method *selection and optimization*

– **Stage 2** – Procedure performance qualification
  – “. . . confirms the analytical procedure is *capable of delivering reproducible data that consistently meet the performance criteria defined in the ATP* while operated subject to the noise variables that may be experienced.”

– **Stage 3** – Procedure performance verification
  – “. . . *routine monitoring* of the analytical procedure's performance and evaluation to determine if the analytical procedure, as a result of any *change*, is still *fit for purpose*.”
Risk based vision

- How to develop, validate, transfer and maintain a procedure to ensure it will continuously produce results that are fit-for-use?

Development

Validation

Transfer/bridge

Routine

Stage 1

Stage 2

Stage 3

d from Boulanger, De Montfort  QbD for Biopharmaceuticals, 13Jan2015
Building quality into a procedure

- The “reportable value” is the composite of assays performed in replicate
  - Reportable values are associated with uncertainty
    - Expressed as confidence/tolerance intervals
    - Managed through design
  - Assays x reps
  - Other design (assay) factors:
    - Analysts
    - Instruments

- VC’s can be used to design other studies in the most effective/efficient manner

\[
SE = 100 \cdot \left( e^{\frac{\text{Var(Assay)}}{n} + \frac{\text{Var(Rep)}}{nk}} \right) - 1
\]

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<th>Number of assays (n)</th>
<th>Reps (k)</th>
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<th>3</th>
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The analytical target profile (ATP)

- “The procedure must be able to quantify [Analyte] in [presence of X, Y, Z] over a range of A% to D% of the nominal concentration with an accuracy and uncertainty such that the reportable result falls within ±B% of the true value with at least a P probability determined with C confidence.”

- B-content tolerance interval
  - “The estimated β-content tolerance interval to contain P% of future inaccuracies with C% confidence must be contained within the range of +/- U.”

- Other “requirements”
  - High throughput, transferable, cost, etc.
The ATP (cont.)

- What about other “reportable results”?
  - Stability line or slope
  - Difference between laboratories
  - Calibration factor
  - Process factor effect

- The concept of the ATP should extend to all uses of measurement data to make decisions
  - Requirements for reportable results should drive the design of the “procedure”
  - Most acceptance criteria are driven by specifications
Uses of methods

- Batch release
- USP <1033> utilizes a process capability index to address ATP
  - Probability of out-of-specification (OOS)

\[
C_{pm} = \frac{U \text{pper Speci}ficationLimit - L \text{ower SpecificationsLimit}}{6 \cdot \sqrt{\sigma^2_{\text{Product}}} + RB^2 + \sigma^2_{\text{Release}}}
\]

where \(\sigma^2_{\text{Product}}\) is an estimate of product variability, \(RB\) is relative bias, and \(\sigma^2_{\text{Release}}\) is release assay variability.

\[\begin{align*}
\text{Spec} & \quad \text{LSL} & \quad \text{USL} \\
\text{Sigma} & \quad -4 & \quad -3 & \quad -2 & \quad 2 & \quad 3 & \quad 4 \\
\text{Cpm} & \quad -1.3 & \quad -1.0 & \quad -0.7 & \quad 0.7 & \quad 1.0 & \quad 1.3 \\
\text{P(OOS)} & \quad & \quad & \quad & \quad & \quad & \quad \sim 0.1\%\quad \sim 0.001\%
\end{align*}\]
Uses of methods (cont.)

- Method changes (transfer, technology, new standard)
- A margin ($\Delta$) can be established which is associated with low risk of an OOS if the margin is reached (manufacturer's risk) while the patient is protected by the release limit
- The “comparability study” design addresses the risks of making a bad decision
- An equivalence test (or noninferiority) is performed to demonstrate conformance to the equivalence margin (upper confidence bound falls within the equivalence margin)
Uses of methods (cont.)

- Comparing stability after a process change
- Using accelerated stability and an extension of Arrhenius
- Design elements include #temps, #lots, sampling/testing strategy
- Bayesian methods to leverage historical experience

\[ C_T(t) = C_0 - k_{298}e^{\frac{E_a}{R} \left( \frac{1}{298} - \frac{1}{T} \right)} \cdot t \]

Use nonlinear mixed model (King-Kung-Fong) to generate Effect Size plots

Binbing Yu, Evaluating the comparability of stability at long-term storage temperature using accelerated stability data, IABS, September 29-30 2015
Summary

- A quality by design approach to assays enlists statistical methods and metrological concepts to help build quality into the procedure and to manage risks.
- Key to a QbD approach is “fitness-for-use” which forms the basis for the analytical target profile.
- Advanced statistical approaches such as Bayesian analysis provide further opportunities to develop and validate a method through posterior predictive probability, the risk associated with fitness-for-use.
  - Also addresses the small dataset issue.
Thank you