Assessing Product Quality Attributes Utilizing Appropriateness Criteria and Efficacy and Safety Inputs to Establish Clinically-Relevant Specifications

John D. Ayres, M.D.
Pharma Safety Solutions, LLC
Disclaimer

The presenter is a clinician.
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BACKGROUND
Acceptance criteria should be established and justified based on data obtained from lots used in *preclinical and/or clinical studies*, data from lots used for *demonstration* of manufacturing consistency and data from *stability studies*, and *relevant development* data.

2. International Conference on Harmonisation: Specifications: Test Procedures And Acceptance Criteria For Biotechnological/Biological Products Q6B
ICH Q6A/B Guidance on Specifications

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described.

For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release.

21 CFR §211 Subchapter C et. seq
NOW THAT ACCEPTANCE CRITERIA HAVE BEEN DETERMINED WHAT IS THE RELEVANT FRAMEWORK FOR ASSESSING CLINICAL RELEVANCE?
Clinical Relevance

• Definition of adequate quality: delivers clinical performance described in drug label and is not contaminated

• Clinically relevant specifications: based on risk to clinical performance, not what can be achieved by process

• Clinically relevant manufacturing standards: deviation should have clear link to risk of substandard clinical performance

• Standards should include human factors analysis—end user is very important for medicines

Evolution in FDA’s Approach to Pharmaceutical Quality
Janet Woodcock, MD
Clinical relevance: understanding impact to clinical performance (safety and efficacy)

Evolution in FDA’s Approach to Pharmaceutical Quality

- Clinically relevant specifications: based on risk to clinical performance, not what can be achieved by process

"Fit-for-Use" = is product safe, effective and not contaminated.

"Fit-for-Sale" = does product meet all established quality attributes.

What Are Clinically Relevant Specifications (CRS)?

- CRS are those specifications that take into consideration the clinical impact of variations in the critical quality attributes (CQA) and process parameters assuring a consistent safety and efficacy profile

Clinical Relevance

- Product quality = the foundation upon which clinical safety and efficacy assessment depend
- Integration of quality and clinical assessment
- Without clinical linkage, acceptance criteria could be too wide, too tight or irrelevant
- A product is "fit for use" by meeting established quality attributes (purity, potency/strength, identity, bioavailability/delivery, labeling/packaging, etc.)
- Strive to establish appropriate, preferably quantitative, correlations between quality attributes and clinical performance

Adapted from M. Nester’s “Setting Specifications in the 21st Century” PCRI Workshop, March 15, 2005

Establishing Clinically Relevant Drug Product Specifications: FDA Perspective

Sandra Suarez Sharp, Ph. D.
FDA/CDER/QIT
2012 AAPM Annual Meeting and Exposition
Chicago, IL, October 16, 2012

Clinically Relevant Specifications
Where Are We Now?

FDA/CDER Conference 2018
September 30, 2018
Sarah Pope Mikusek, Ph.D.
Office of New Drug Products

A look at FDA perspectives
How do we establish ‘clinically relevant’ specifications absent pivotal trial exposure yet batches produced in a qualified cGMP setting can be anticipated to fall...?
Clinical experience:
the range of attribute values corresponding to the batches that have been given to patients as part of a clinical trial

Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency and data from stability studies, and relevant development data. [ICH Q6A/B Guidance on Specifications]
Clinically Relevant Specifications

Exploring the Barriers to Adoption
Over a decade later: what have been the barriers inhibiting realization of this vision?

1. Institutional culture and reluctance to change:
   - **Lack of incentive** for early adopters
   - Status quo familiar and comfortable

2. Submitters driven primarily by **short term rewards**:
   - **It’s all about Approval**
   - Expectations of the market
   - Expectations of management
   - Impact of outside funding (hedge funds) seeking ROI

3. **Uncertainty anxiety**:
   - When in doubt push limits of **process capability**
   - **Dramatizing the literature** – National Enquirer vs NEJM
   - How good is the data?

4. **Intuitive thinking** verses science
   - Understanding the capabilities of CTs
   - Over-reliance on Phase 3 data

5. Benefit-Risk Assessment
   - **Emotional biases** impacting Risk:Benefit
     - Oncology vs addiction disorders
   - Diversity in trial population
   - Lack of **pragmatic trials** assessing CQAs with CT outcomes/companion diagnostics
   - Social utility and patient input often missing
   - Distinguishing safety from tolerability

6. **Hesitancy to adopt** disruptive technologies
   - Predictive modeling
   - Integrated process control and monitoring

MANAGING COMPLEX CHANGE REQUIRES
VISION + SKILLS + INCENTIVES + RESOURCES + ACTION PLAN

Clinically Relevant Specifications

Adopting clinically driven paradigms
Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization.

Clinically relevant specifications: based on risk to clinical performance, not what can be achieved by process

Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency and data from stability studies, and relevant development data.

ICH Q6A/B Guidance on Specifications

Janet Woodcock, MD – Evolution in FDA’s Approach to Pharmaceutical Quality
ICH Q8R2 – Quality Target Product Profile

Forms the basis of design for the development of the product. QTPP considerations might include:

- Intended use in clinical setting, route of administration, dosage form, delivery systems;
- Dosage strength(s);
- Container closure system;
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the drug product dosage form being developed;
- Drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product.

QTTP: A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.
Consider The Challenge with Biotherapeutics

Characterization of structure and heterogeneity is not enough:

- Host Cell Proteins
- Aggregates
- Charge Heterogeneity
- Potency
- Endotoxin
- Complex Raw Materials
- Primary Packaging Component Interactions
- Environmental Stress and Sheer
- Dose Escalation

Each of these attributes should be weighted depending upon a number of clinical factors such as route, frequency and duration of administration; clinical indication; and patient population, etc.
Setting Clinically Relevant Specifications

• Step 1: Identify the *critical* quality attributes
  • Does the attribute directly link to the QTPP?
  • Does failure to meet the prescribed range *directly and adversely* impact the benefit/risk profile?
  • Does the attribute display 1\textsuperscript{st} order impact to the product’s clinical utility?
  • Clinically Relevant – not what can be achieved by process

• Step 2: Establish *clinically-relevant* acceptance criteria range
  • Pivotal phase 3 clinical trial outcomes data
  • Define range of inherent process and analytic variability
    • In-silico, pre-clinical and stability data
    • Demonstration/registration and early phase studies batch data
    • Platform knowledge, impact ranking and biologic plausibility
## Impact Ranking

<table>
<thead>
<tr>
<th>Impact Score</th>
<th>Biological Activity</th>
<th>PK</th>
<th>PD/Efficacy</th>
<th>Immunogenicity</th>
<th>Safety &amp; Tolerability</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (9)</td>
<td>&gt; 50 – 100% Change OR No data</td>
<td>Significant change in PK is linked to quality attribute OR Significant change in PK with no connection with quality attribute OR No change in PK detected but metabolism results in significant loss of PD linked to quality attribute OR...</td>
<td>Significant Impact on PD that appears to be attributed to specific quality attribute OR Significant change in PD with no clear link to specific quality attribute OR...</td>
<td>ADA(^1) detected that appears to be linked to specific quality attribute and has a significant impact on PK/PD/Safety OR ADA detected that has no specific link to the quality attribute but has a significant impact on PK/PD/Safety OR No data available on ADA in relation to specific quality attribute OR...</td>
<td>No Data Available OR No margin of safety OR Cytokine Release Syndrome Grades 3-5 (see Appendix 1) OR...</td>
<td>Data suggests that the attribute affects the conduct/interpretation of the toxicology study (i.e. presence of aggregates). OR The test article has a less than typical margin of safety to clinical doses. OR...</td>
</tr>
</tbody>
</table>

Incorporates attribute’s *impact* to pharmacological properties and the *knowledge basis* used to determine the impact (i.e. uncertainty).
Discharging Uncertainty

Four (4) mechanisms to obtain clinical exposure of batches falling within anticipated variability but beyond pivotal trial exposure:

1. Release material in normal course of distribution and monitor via routine product complaint and pharmacovigilance processes.
2. Introduce in an on-going or conventional clinical trial.
3. Introduce material in normal course of distribution and follow with an observational study.
4. Introduce material in normal course of distribution and implement a post-approval, batch-specific surveillance study utilizing disproportionality algorithms linked to analytic data.
1. Release material in normal course of distribution and monitor via routine product complaint and pharmacovigilance processes.
   • Generally not a desirable option
   • Monitoring not routinely conducted to correlate inputs to specific batches or attributes
   • Low level safety signals might be subsumed by data from batches already marketed
Discharging Uncertainty

2. Introduce in an on-going or new ‘conventional’ clinical trial.
   • If introduced in on-going study, difficult to determine if event results from new product or a latent effect of previous exposure.
   • Co-mingling of product batches at trial sites
   • Lack of complete dataset
   • Small incremental exposure to attribute (when evaluated against pivotal trial exposure [x to x+y]) would likely require significant trial population, drug naïve, to identify clinically relevant attribute-related event.
3. Introduce material in normal course of distribution and follow with an observational study.

- Utilize large insurance databases
- Relevant data inputs notoriously compromised (incorrect and missing data, lack of batch numbers, multiple concomitant medications)
- High potential for bias.

4. Introduce material in normal course of distribution and implement a post-approval, batch-specific surveillance study utilizing disproportionality algorithms linked to analytic data.

- Can be biased by reporting directives (lawsuits, recalls, DHCP letters)
- Driven by spontaneous reporting
- High volume of reports permit earlier opportunity to identify issues
- Batch numbers can be solicited during report
- Datamining algorithms can be linked to biologic plausibility to support findings

Use of Automated Signal Detection

- Pharmacovigilance Maps (PVmaps)
- Proportional Reporting Ratio (PRR)
- Empirical Bayes Geometric Mean (EBGM)
- Lower-bound of the EBGM’s 90% Confidence Interval (EB05).
### Proportional Reporting Ratio (PRR)

#### Use of Automated Signal Detection

<table>
<thead>
<tr>
<th>• Batch-to-Batch Disproportionality</th>
<th>• Aggregated Batches</th>
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</thead>
<tbody>
<tr>
<td>– Environmental Impact</td>
<td>– Potential API Pass-through Effect</td>
</tr>
<tr>
<td>– Container-closure</td>
<td>– Manufacturing Process Change</td>
</tr>
<tr>
<td>– Undetected Manufacturing Issue</td>
<td>– Scale Up (Process A → B → C)</td>
</tr>
<tr>
<td>– Counterfeit/Adulterated</td>
<td>– Technical Transfer</td>
</tr>
<tr>
<td></td>
<td>– Site change</td>
</tr>
</tbody>
</table>

#### Proportion of AE “Y” among all AEs for batch “X” = \(\frac{a}{a+b}\)

#### Proportion of AE “Y” among all AEs for all other batches = \(\frac{c}{c+d}\)

#### Formula:

\[
P RR = \frac{A/(A+B)}{C/(C+D)}
\]

Reports with AE “Y”  
Reports following Batch “X”  
Reports following Other Batches  

<table>
<thead>
<tr>
<th>Reports with AE “Y”</th>
<th>All Other AE reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>c</td>
<td>d</td>
</tr>
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</table>

### Batch-to-Batch Adverse Event and Product Complaint Surveillance

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
<th>L</th>
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<tbody>
<tr>
<td>Cases Reported</td>
<td>Events</td>
<td>Month</td>
<td>Three</td>
<td>Current Month</td>
<td>FF6E19A</td>
<td>FF85AS7A</td>
<td>-FF85F1</td>
<td>FF6E69A</td>
<td>FF6E69A</td>
<td>FF6E70A</td>
<td>FF6E70A</td>
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<tr>
<td>Lots used</td>
<td>Total</td>
<td>Curr</td>
<td>Past</td>
<td>-n/yr-</td>
<td>1509</td>
<td>1509</td>
<td>126</td>
<td>126</td>
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<td>Past three months</td>
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<td>398</td>
<td>282</td>
<td>282</td>
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<td>266</td>
<td>266</td>
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<td>211</td>
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<tr>
<td>106</td>
<td>Allergic Conditions Nec.</td>
<td>33</td>
<td>9</td>
<td>24</td>
<td>22</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>107</td>
<td>Allergic Conditions Nec.</td>
<td>13</td>
<td>3</td>
<td>10</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>1</td>
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<td></td>
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<tr>
<td>108</td>
<td>Application and Instillation Site Reactions</td>
<td>6</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>1.31</td>
<td>1.59</td>
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<td>2.17</td>
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<td>109</td>
<td>Isolation and Instillation Site Reactions</td>
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<td>1</td>
<td>4</td>
<td>3</td>
<td>1.31</td>
<td>1.59</td>
<td>1.65</td>
<td>2.17</td>
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<tr>
<td>110</td>
<td>Bacterial Infections Nec.</td>
<td>13</td>
<td>3</td>
<td>10</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>1</td>
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<tr>
<td>111</td>
<td>Death and Sudden Death</td>
<td>26</td>
<td>9</td>
<td>17</td>
<td>25</td>
<td>1.69</td>
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<tr>
<td>112</td>
<td>Device Related Complications</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>1.37</td>
<td>1.37</td>
<td>1.37</td>
<td>1.37</td>
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<tr>
<td>113</td>
<td>Fever</td>
<td>46</td>
<td>13</td>
<td>33</td>
<td>25</td>
<td>1.24</td>
<td>1.24</td>
<td>1.24</td>
<td>1.24</td>
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<tr>
<td>114</td>
<td>Medication Errors Nec.</td>
<td>141</td>
<td>28</td>
<td>113</td>
<td>74</td>
<td>1.03</td>
<td>0.73</td>
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<td>1.40</td>
<td>0.74</td>
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<tr>
<td>115</td>
<td>Sepsis, Bacteremia and Viralna</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>1.31</td>
<td>1.31</td>
<td>1.31</td>
<td>1.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>116</td>
<td>Therapeutic and Nontherapeutic Responses</td>
<td>63</td>
<td>18</td>
<td>45</td>
<td>48</td>
<td>1.49</td>
<td>0.48</td>
<td>2.06</td>
<td>0.55</td>
<td>0.66</td>
<td>0.66</td>
</tr>
</tbody>
</table>

CASSS • CMC Strategy Forum
The Mayflower Hotel, Washington, DC
January 28, 2019
### Proportional Reporting Ratio (PRR)

#### Batch-to-Batch Product Complaint Data Set

<table>
<thead>
<tr>
<th>Case</th>
<th>Total</th>
<th>Current</th>
<th>Past</th>
<th>n / p-</th>
<th>FF6E70A</th>
<th>FF6E9A</th>
<th>FF5A87A</th>
<th>-FF6F51</th>
<th>FF6D19A</th>
<th>-FF6E78</th>
<th>FF6H26A</th>
<th>FF6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Surveillance data provided are hypothetical and do not represent actual cases or events.
Stability finding increased related substances post-primary container change

Aggregate Batch Data Comparing “Suspect” to “Control” Batches
## Discovery of Drug Induced Illness – Clinical Uncertainty

<table>
<thead>
<tr>
<th>Rate of Suspected Drug Induced Illness</th>
<th>Background Rate</th>
<th>Method(s) of Discovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Low</td>
<td>Clinical Observation</td>
</tr>
<tr>
<td>Low</td>
<td>High</td>
<td>Not discoverable</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Clinical observation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limited Formal research</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>Formal research</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Formal research</td>
</tr>
</tbody>
</table>

Adapted from Jick H. NEJM. 296(9):481-5 (1977)
Assessing the Unexpected Event

Protamine Sulfate Supply Disruption

• As a result of the March 2011 Tōhoku earthquake and tsunami the Japanese fishing industry was unable to operate in their former fishing grounds off Honshu.

• To maintain a protamine supply the fishing grounds for wild Chum salmon were moved northward to Hokkaido Island.

• “New peak” reported in Hokkaido R-protamine

Protamine is an arginine-rich, strongly basic naturally occurring nuclear protein used in insulin to form an insoluble protamine-insulin salt complex and as an antagonist used to reverse heparin’s anticoagulation effects.
Clinical Assessment Approach

1. A comprehensive assessment of both Hokkaido and Honshu-sourced protamine confirmed the inherent composition variability characteristic of natural source materials and the historical presence of transient peaks.

2. The literature identifies that a large number of both chronic protamine-containing insulin users and individuals exposed to a single large intravenous bolus infusion of protamine will develop antibodies to the material.

3. Significant hypersensitivity reactions can and do occur but most reactions are mild and not life-threatening.

4. A review of adverse event database—evaluating adverse event reports from 329 insulin batches utilizing from 9 different protamine batches and where the chromatograms have shown some peak-profile variability—identified no discernable differences in adverse event profiles.
In summary what is the path forward to (1) define clinical relevance and (2) establish the appropriate range for specifications?

- Culture shift needed for both manufacturer and regulator
- Link the Design Space to the Patient via QTPP
- Pragmatic clinical trials should include assessment of quality attributes relative to clinical endpoints and outcomes
- Batches reflecting anticipated inherent variability desirable for CT use
- Incorporate in-silico, developmental, stability, pre-clinical, early phase and pivotal trial data into acceptance criteria assessment
- Parallel adoption of companion diagnostics for appropriate patient selection
- Post-approval batch-specific surveillance programs for on-going monitoring of CQAs including site and manufacturing process changes.
Questions?

Thank you.

John D. Ayres, M.D.
Pharma Safety Solutions, LLC
jayres@pharmasafetysolutions.com