Clinically Relevant Specifications
FDA Perspective

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The link to the patient...
Expectations for Quality

Patients and caregivers assume that their drugs:

- Are safe, efficacious, and have the correct identity
- Deliver the same performance as described in the label
- Perform consistently over their shelf life
- Are made in a manner that ensures quality
- Will be available when needed
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 correlations between quality attributes and clinical performance

Adapted from M. Nasr’s “Setting Specifications in the 21st Century”/PQRI Workshop, March 16, 2005
Clinical Relevance

• Quality attributes
  – Critical – with proper clinical linkage
  – Others – to assure robustness and performance of manufacturing process and patient expectations
  – Possible surrogate markers of intended clinical performance

• Clinical considerations
  – Urgency (BT, otherwise expedited)
  – NTI
  – Pediatric

• IVIV correlation/relationship
  – Dissolution testing

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ONDP Strategic Priorities (2016-21)

• Enhance the team-based review process
• Proactively support continuous improvement – review quality
• Proactively support continuous improvement – review efficiency
• Facilitate effective, transparent and risk-based communication
• Enhance robust discussions linking quality to clinical performance
• Achieve excellence through a skilled, knowledgeable and collaborative workforce
Clinical Relevance in Quality Review

Incorporates a robust and broad dialog
- Clinical framework (e.g. urgency)
- Regulatory framework (review deliverables)
- Supporting technical information
- Appropriately considers prior knowledge
- Strong collaboration for common understanding
- Lifecycle management considerations
- Other aspects of “the patient at the table”
- Transparent and effective risk-informed discussions
  - One Quality Voice
Clinically Relevant Specifications (CRS)

- Similarly broad and robust discussion
- Begins with supporting data platform
- Discussion considers needs of stakeholders
  - What do we get?
  - Will not or can not?
  - Nice to know or need to know?
- Takes existing knowledgebase into account
  - IVIVC/R
  - Dissolution method/criteria
  - Physiology/physicochemical properties
  - Safety data (e.g. qualification data for impurities)
Clinically Relevant Specifications (CRS)

• Discussion transparently addresses uncertainty
  – What do we know?
  – What are we uncertain of?
  – What is the impact of the uncertainty?
• Considers whether/how uncertainty can be mitigated
• Considers whether uncertainty needs to be mitigated
• Considers the possibility of mitigating outside of specification adjustments
Clinical Relevance - Impurities

- Existing CMC guidances provide significant recommendations based on clinical relevance associated with impurities:
  - *ICH Q3A: Impurities in New Drug Substances*
  - *ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*
Clinical Relevance - Impurities

• Current ICH Q3A Guidance (Impurities in New Drug Substances):
  o “Higher or lower thresholds for qualification of impurities can be appropriate for some individual drugs based on scientific rationale and level of concern, including drug class effects and clinical experience…. a higher qualification threshold can be appropriate for individual drugs when the level of concern for safety is less than usual based on similar considerations (e.g., patient population, drug class effects, clinical considerations).”
  o The standard identification and qualification thresholds described in this guidance are inversely proportional to the maximum daily dose of the drug (i.e., the higher the maximum daily dose, the lower the threshold values).
Clinical Relevance - Impurities

- Current ICH M7 Guidance (Assessment and Control of Mutagenic Impurities):
  - “There may be some cases where a drug substance intended for other indications is itself genotoxic at therapeutic concentrations and may be associated with increased cancer risk…exposure to a mutagenic impurity would not significantly add to the cancer risk of the drug substance.”
  - Higher acceptable intakes may be justified:
    - when human exposure to the impurity is much greater from other sources e.g., food, or endogenous metabolism (e.g., formaldehyde)
    - in cases of severe disease, reduced life expectancy, late onset but chronic disease, or with limited therapeutic alternatives
    - based on a risk/benefit analysis when control efforts cannot reduce levels below the acceptable limit
Example 1 – ICH M7 Case Study (Mock)

**Treatment duration: < 1 day**

- Parent drug is a short-acting intravenous anaesthetic agent used for the induction of general anesthesia for short procedures such as reduction of dislocated joints and tracheal intubation
- *Acceptable daily intake 120 μg/day*

**Treatment duration: Lifetime**

- Parent drug is indicated for the symptomatic relief of allergy such as hay fever (allergic rhinitis), urticaria (hives), and other skin allergies.
- *Acceptable daily intake 1.5 μg/day*
Example 2 – Impurity Levels

- Dosage form – solid oral tablet, 200 mg (daily)
- Conventional manufacturing process
- Impurity X present at levels of up to 0.3% (DS) in clinical and stability batches
- Impurity X qualified at 1.0% by previous safety studies
- Acceptance criterion for Impurity X proposed as NMT 0.9% in the dossier
- Path forward in regulatory review?
Example 3 - Stability

• Stability data package expectations often tied to clinical relevance
  – Historically, if the stability data package in an original submission does not conform to the recommendations in ICH Q1A with regard to the amount of stability data, the review team can consider the NDA incomplete upon receipt
  – However, on a case-by-case basis, the review team will decide if an NDA with such a stability package will be filed:
    • potential public health impact
    • intended use of the product (e.g., chronic versus rescue use, administration by medical practitioner versus patient)
    • known or potential stability failure modes
    • product design aspects
Linking to the Patient/Clinical Relevance

• Focus/align on “Why does it matter to the patient?” or “What is the impact on overall quality?”
• Most effective when discussions are *timely*, transparent, and robust
• Multiple collaborators often involved (e.g., clinical review division, Applicants, other offices)
• Can be framed by anyone
• Occurs within the appropriate regulatory framework (e.g. PDUFA deliverables, application urgency)
• End result – using sound science and technical expertise to identify/discuss major risks to quality, while communicating effectively regarding necessary mitigation and/or potential impact to the patient
The Big Picture…

“Link to the Patient”

**Technical**

- ICH and other guidances
- CQAs
- Lifecycle Management
- Assumptions of quality
- Control Strategy
- CFR

**Patient**

- Labeling
- QRM
- Product Design

**Clinical Relevance**

**Risk Communication**
Thank you!

Questions? CDER-OPQ-Inquiries@fda.hhs.gov