Patient Focused Specifications

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Pharmaceutical Quality Symposium – October 31, 2023

Overview

- Patient focused drug development
- Specifications
  - What are specifications
  - Selection of tests
  - Selection of analytical procedures
  - Acceptance criteria
- Summary

Patient Focused Specifications

- Patient-focused specifications
  - a component of end-to-end patient focused product development
- End-to-end development includes :
  - Patient focused drug development
  - Manufacturing control strategy
  - Mature manufacturing quality systems

Patient Focused Drug Development

- **Patient focused** (also known as patient-centered)
  - Decisions and activities about health and well-being incorporate patients' experiences, perspectives needs, and priorities

Patient Focused Drug Development

- **Patient-focused drug development (PFDD)** (aka patient focused medical product development)
  - Systematic approach
  - Incorporates patients' experiences, perspectives, needs, and priorities into medical products
  - Medical product life cycle approach

Patient Focused Drug Development

- Patient focused drug development
  - Helps ensure acceptability and usability of the drug
  - Promotes appropriate use of the drug

Patient Focused Drug Development

- FDA established a patient focused drug development initiative in 2012
- Purpose: to more systematically obtain patient perspective on specific disease

Specifications and Manufacturing Control

- The manufacturing control strategy is designed to ensure the consistent production of a product of required quality
- Specifications are one part of the total control strategy

ICH Q8 (also see Q6, Q9, Q10, Q11, and Q12)

Specifications

- Specifications are standards for the product
- Product conformity to standards must be tested prior to lot release

21 CFR 610.1 and 21 CFR 600.3(kk)

Specifications

- Confirm the quality of:
  - Products
  - Intermediates
  - Raw materials
  - Reagents
  - Components
  - In-process Materials
  - Container closure systems
  - Other materials used in product production

21 CFR 600.3(kk)

Foundations for Patient Focused Specifications

- Patient focused quality target product profile
  - Ensures product meets user needs
  - Safe, pure, potent
  - Usability (e.g. pill size, syringe or autoinjector design)

Foundations for Patient Focused Specifications

- Well characterized quality attributes
  - Critical quality attributes are identified
  - Understand impact on safety and effectiveness of
    - process- related impurities
    - product- and related impurities
- Mature quality system
  - Focuses on outcomes that affect the patient or consumer

Specifications

- Specification components:
  - Test – e.g. purity or impurities
  - Analytical procedure – e.g. HPLC, SEC
  - Acceptance criteria
    - Used to decide whether to accept or reject a lot or batch
    - Numerical limits, ranges, or other criteria
    - Sampling plan

21 CFR 600.3(kk) and 21 CFR 210.3 (b)(20)

Test Selection

- Test selection is product specific
- Confirm quality of the product
- Tests should address the quality target product profile, e.g.
    - ADCC testing generally not needed when the target is soluble rather than membrane bound
    - Uptake assays included for enzyme therapies to intracellular targets (e.g. many inborn errors of metabolism) but not for targets that are in blood (e.g. gout)

Test Selection

- Informed by product understanding, e.g.
  - May not test for tri-sulfide bonds with evidence that they reform to disulfide bonds in vivo[1,2,3]
  - C- terminal lysine in MAbs generally does not impact structure, FcRn binding, PK, potency, is rapidly removed in vivo [2,3,4,5] and is not specifically tested for
- Include stability indicating tests

[1]Wang T et al. Journal of Pharmaceutical and Biomedical Analysis. 102 (2015):519 – 528. [2] Liu H et al. Biologicals. 59 (2019):1 – 5. [3] Liu H et al. mAbs 6(2014)(5):1145 – 1154. [4] Schuster J et al. J Pharm Sci. 112(2023): 370 – 376. [5] Brorson K and Jia A. Current Opinion in Biotechnology. 30(2014):140-146.

Test Selection

- Informed by process understanding, e.g.
  - Validated removal of impurities, such as methotrexate, insulin, anti-foam, host cell proteins, host cell DNA, can replace end-point testing
- For combination products tests should confirm device performance, e.g.
  - Break loose force and glide force for a pre-filled syringe

Test Selection

- Tested attributes generally include:
  - Appearance
  - Identity
  - Purity
  - Impurities (process- and product- related)
  - Potency
  - General tests (e.g. pH, osmolality)
  - Safety tests (depending on dosage form e.g. sterility, endotoxin)
  - Dosage form specific tests (e.g. volume in container, moisture content, break-force and glide force)

Selection of Analytical Procedures

- Selection is based on the attributes being tested
- Analytical procedures using different principles may be needed for test, e.g.
  - purity and impurity tests may include analytical procedures to detect size, charge, or hydrophobic variants
- The suitability of the analytical procedure should be established
  - Stability indicating, as needed
  - Accurate, reliable, sensitive, and reproducible detection of the attribute

Acceptance Criteria

- Numerical limits, ranges, or other criteria for the tests described
- How can patient-focused acceptance criteria be set?
  - MAPP 5017.2 Rev 1 (5/1/2020) Establishing Impurity Acceptance Criteria As Part of Specifications for NDAs, ANDAs, and BLAs Based on Clinical Relevance

Acceptance Criteria MAPP 5017.2

- Acceptance criteria set on a case-by-case basis because may be impacted by:
  - Risk to safety and efficacy
  - Clinical experience
  - Context of use, e.g. dosage form, dosing regimen, route and duration of administration, clinical indication, intended population

Impurity Acceptance Criteria MAPP 5017.2

- To ensure clinical relevance of acceptance criteria
  - Clinical impact of impurity levels should guide types of data and information needed
  - Understand relationship of impurities to stability, potency, adverse clinical events
  - May be greater consideration of manufacturing process capability when relationships are uncertain, e.g. biotech products

Impurity Acceptance Criteria MAPP 5017.2

- Acceptance criteria supported by a risk assessment
  - Impact of impurity on activity, PK/PD, safety, and immunogenicity[1]
  - Sources of data: clinical, non-clinical (e.g. in vitro, animal), analytical, prior knowledge, publicly available information
  - Uncertainty may be a factor in the risk assessment

[1] Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products (August 2014)

Impurity Acceptance Criteria MAPP 5017.2

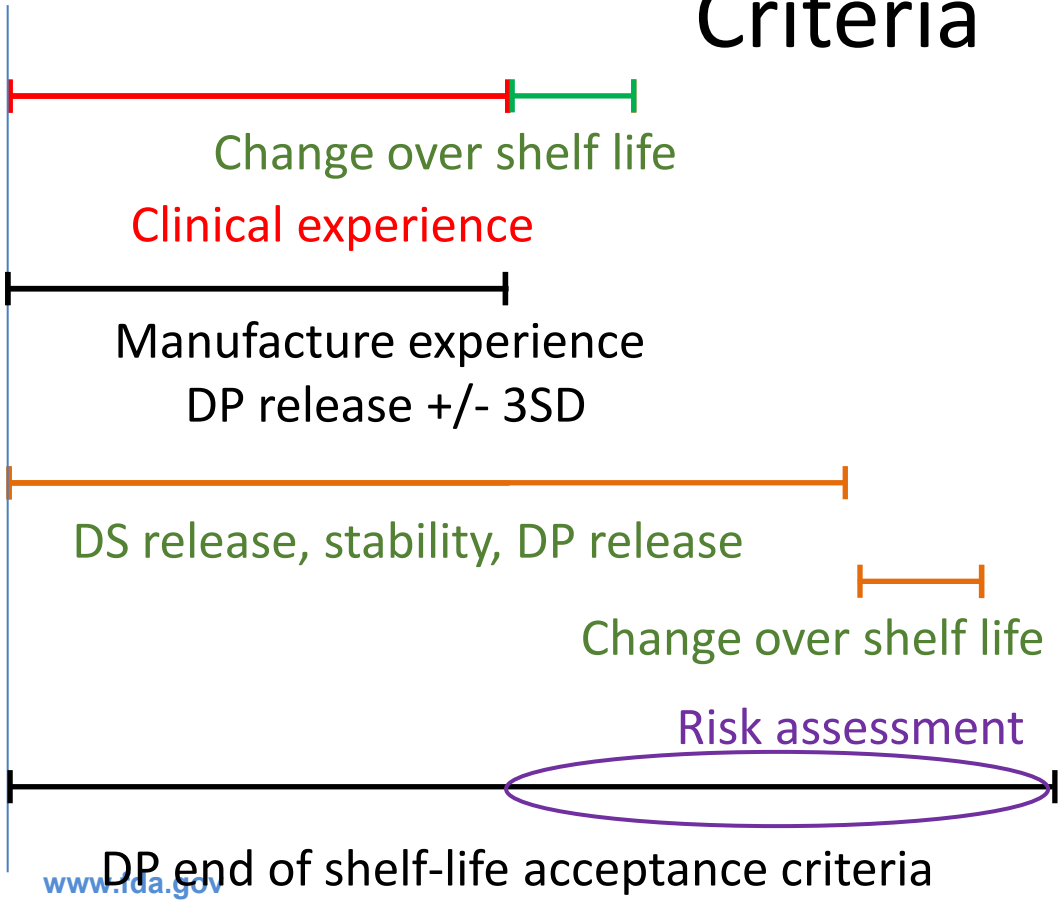
- Sources of uncertainty
  - Strength of the data to understand the clinical effect
  - Analytical capability
- Apply risk management principles e.g. as described in ICH Q9 in managing uncertainty

- ICH Q9
  - Use risk-based decision making
  - Address uncertainty through **the use of knowledge**

Acceptance Criteria - Summary

- To more fully implement patient-focused acceptance criteria, information is needed to bridge the gap between process capability and relevance to the patient

Case Study: Deamidation Acceptance Criteria



Applicant's Risk assessment on Deamidation:

- Ex vivo and in vivo studies indicates that the product rapidly deamidates in vivo
- Potency is not impacted by deamidation

Conclusion:

- The justification for DS and DP specifications of product related impurities and potency is adequate

Summary

- Patient-focused specifications are a component of end-to-end patient focused product development that includes:
  - Patient focused target quality product profile
  - Product characterization
  - Mature manufacturing quality systems
  - Manufacturing control strategy

Summary

- Patient-focused specification setting includes:
  - Selecting the appropriate tests
  - Using appropriate analytical procedures
  - Have product knowledge

Summary

- Uncertainty may arise when the relationship between an attribute and impact to patients is unclear.
- Risk assessments, supported by data and information, may be used to address uncertainty

Summary

- Sources of information and data may include:
  - Clinical data
  - In vitro, in vivo data, or ex vivo
  - Prior knowledge
  - Publicly available information
- May be greater consideration of manufacturing process capability when relationships are uncertain

Closing Thought

OPQ is committed to patient-focused drug development. We encourage sponsors to incorporate end-to-end patient focused product development information into their submissions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