

Patient Focused Specifications

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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

Specifications

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

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

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

¹Wang 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 immunogenicity¹
 - 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

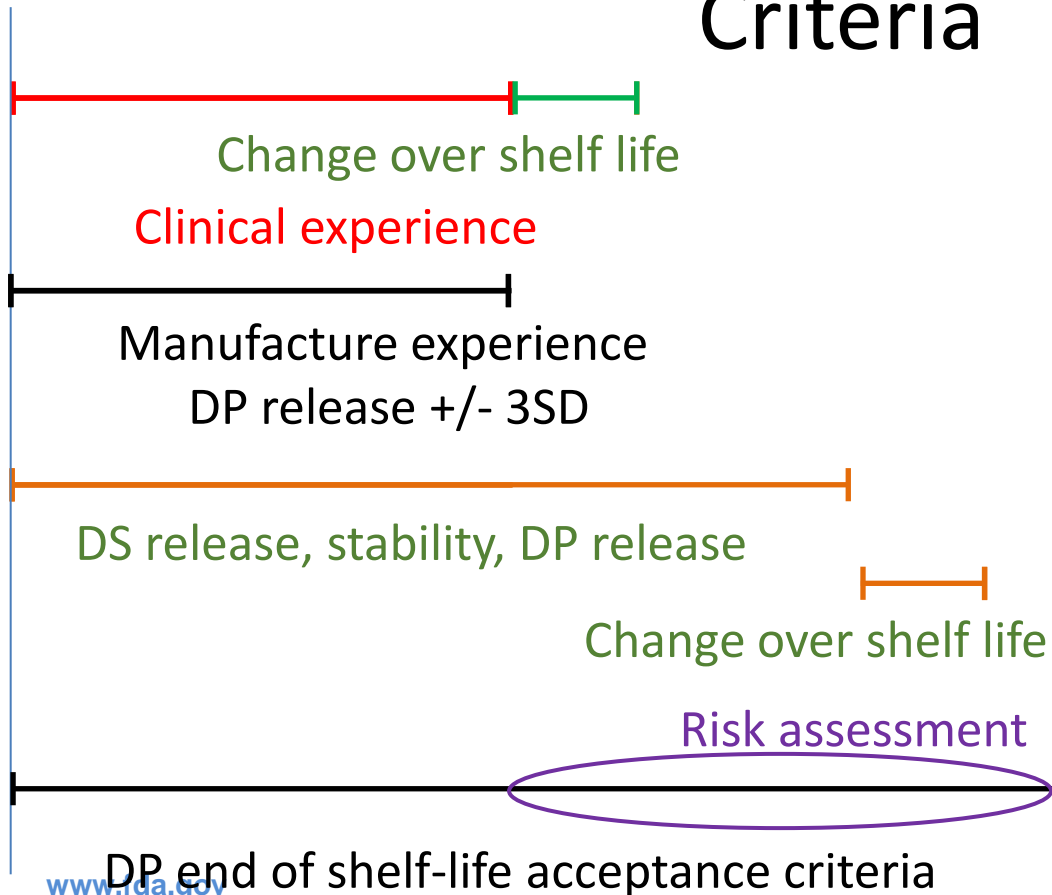
- Sources of uncertainty
 - Strength of the data to understand the clinical effect
 - Analytical capability
- Apply risk management principles e.g. as described in ICH Q9 in managing uncertainty
- ICH Q9
 - Use risk-based decision making
 - Address uncertainty through **the use of knowledge**

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

