Patient Focused Specifications

Susan Kirshner

Director, Division of Biotechnology Review and Research 3

Office of Biotechnology Products

CASSS North America Strategy Forum
July 18, 2023

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Overview

- Patient focused drug development

- Manufacturing control strategy

- Specifications

  - Selection of tests

  - Selection of analytical procedures

  - Acceptance criteria

- Summary

Patient Focused Drug Development

- In 2012 FDA established the patient focused drug development initiative to more systematically obtain patient perspective on specific diseases

- **Patient focused** (also referred to as patient-centered): Ensuring that patients' experiences, perspectives, needs, and priorities are meaningfully incorporated into decisions and activities related to their health and well-being.[1]

[1] Patient-focused Drug Development Glossary https://www.fda.gov/drugs/development-approval-process-drugs/patient-focused-drug-development-glossary

Patient Focused Drug Development

- **Patient-focused drug development (PFDD)** (also referred to as patient focused medical product development): A systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are meaningfully incorporated into medical products throughout the medical product life cycle. [1]

- PFDD helps ensure the acceptability and usability of the drug for the patient and promote appropriate use of the drug

[1] Patient-focused Drug Development Glossary https://www.fda.gov/drugs/development-approval-process-drugs/patient-focused-drug-development-glossary

Pharmaceutical Quality

A quality product of any kind consistently <u>meets the expectations of the user.</u>

Pharmaceutical Quality

A quality product of any kind consistently <u>meets the expectations of the user.</u>

Drugs are no different.

Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is assuring *every* dose is safe and effective, free of contamination and defects.

FDA

It is what gives patients confidence in their *next* dose of medicine.

Manufacturing Control Strategy

- The manufacturing control strategy is designed to ensure the consistent production of a product of required quality

- Specifications are a component of the control strategy

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

Patient Focused Specifications

Foundations for Patient Focused Specifications Include:

- Patient focused quality target product profile
  - Safety, purity, potency
  - Usability (e.g. pill size, syringe or autoinjector design)
- Well characterized quality attributes
  - Understand the impact of process- and product- purity and impurity on product safety and effectiveness
- Mature quality system [CDER Quality Management Maturity | FDA](#)

For the purposes of this talk assume these are established

Specifications

- Specification, as used in § 601.12 of this chapter, means the quality standard (i.e., **tests, analytical procedures, and acceptance criteria**) provided in an approved application to **confirm the quality** of products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a product. For the purpose of this definition, acceptance criteria means numerical limits, ranges, or other criteria for the tests described.

21 CFR 600.3(kk)

Specifications

- **No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such product**. Each applicable test shall be made on each lot after completion of all processes of manufacture which may affect compliance with the standard to which the test applies. The results of all tests performed shall be considered in determining whether or not the test results meet the test objective, except that a test result may be disregarded when it is established that the test is invalid due to causes unrelated to the product.

21 CFR 610.1 Tests prior to release required for each lot

Selection of Tests

- Test selection is product specific
- Confirm quality of the product
  - Select tests based on quality target product profile
    - Examples:
      - 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)

Selection of Tests

– Informed by product understanding

- May not test for tri-sulfide bonds with evidence that they reform to disulfide bonds in vivo[2,3,4]

- C- terminal lysine in MAbs generally does not impact structure, FcRn binding, PK, potency, is rapidly removed in vivo[3,4,5,6] and is not specifically tested for

[2] Wang T et al. Investigation of antibody disulfide reduction and re-oxidation and impact to biological activities. Journal of Pharmaceutical and Biomedical Analysis. 102 (2015):519 – 528.
[3] Liu H et al. Modifications of recombinant monoclonal antibodies in vivo. Biologicals. 59 (2019):1 – 5.
[4] Liu H et al. In vitro and in vivo modifications of recombinant and human IgG antibodies. mAbs 6(2014)(5):1145 – 1154.
[5] Schuster J et al. Protein stability after administration: A physiologic consideration. J Pharm Sci. 112(2023): 370 – 376.
[6] Brorson K and Jia A. Therapeutic monoclonal antibodies and consistent ends: terminal heterogeneity, detection, and impact on quality. Current Opinion in Biotechnology. 30(2014):140-146.

Selection of Tests

– 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

Selection of Tests

- Tested attributes generally include[7]:
  - 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)

7ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

Selection of Analytical Procedures

- Selection is based on the attributes being tested
- Orthogonal methods may be needed for an attribute
  - 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 may patient-focused acceptance criteria be set?

Acceptance Criteria

FDA

- 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 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

- "In general, the types of data and information should be guided by the consideration of clinical impact of impurity levels, as opposed to manufacturing process capability, to ensure the acceptance criteria are clinically relevant."
- For biotechnology products the relationship of impurities to stability, potency, adverse clinical events may not be clear.
- In such cases there may be greater consideration for manufacturing process capability.

Impurity Acceptance Criteria MAPP 5017.2

- Acceptance criteria supported by a risk assessment
  - Impact of impurity on activity, PK/PD, safety, and immunogenicity[8]
  - Sources of data: clinical, non-clinical (e.g. in vitro, animal), prior knowledge, publicly available information
  - Uncertainty may be a factor in the risk assessment

[8] 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

Impurity Acceptance Criteria

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

Acceptance Criteria

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

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
- 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 or in vivo data
  - Prior knowledge
  - Publicly available information
- If uncertainty is not adequately addressed, there may be greater consideration for manufacturing process capability when setting acceptance criteria

U.S. FOOD & DRUG ADMINISTRATION