CLINICALLY RELEVANT SPECIFICATIONS

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Outline

CMC variables (critical quality attributes) affecting clinical outcomes

Clinically relevant specifications
Definition
Importance

Traditional approach in setting clinically relevant specifications

Approaches for setting dissolution specifications
Approach 1 (no data linking in vitro dissolution with bioavailability)
Approach 2 (established ranges of bioequivalent release characteristics)
Approach 3 (robust and predictive IVIVC)

Role of IVIVC in setting clinically meaningful dissolution specifications

Challenges in developing clinically relevant dissolution specifications

Summary and conclusions
Examples of CMC Variables Affecting Clinical Outcome

- Impurity profile (safety profile)
- Content uniformity (consistent dose)
- Biopharmaceutics related properties
  - Drug release rate (affecting BA)
    - Particle size
    - Polymorphism
    - Hardness
    - Release controlling excipients

What are Clinically Relevant Specifications?

Specifications that take into consideration the clinical impact on the patient assuring consistent safety and efficacy profile.
Traditional Approach For Setting Specifications

Based on in vitro considerations
Understanding batch to batch variability
Considered only as a quality control measure
Analytical capability in terms of accuracy, precision and bias
Using clinical, marketed and stability data

Importance of Establishing Clinically Relevant Specifications (CRS)

Establishing CRS guarantees:
Consistent safety and efficacy profiles for the marketed product relative to those achieved by the clinical trial formulation
Delivery of the intended dose to the patient
Optimal rate of delivery
Optimized drug therapy to the patient
Decreased inter/intra-lot variability
Setting Clinically Relevant Specifications

Choice of acceptance criteria is no longer made based on the in vitro results, but on pre-determined clinical acceptable outcomes.

Understanding the relationship between the in vitro measures and the clinical outcomes may provide greater regulatory flexibility.

What are the Approaches for Setting Dissolution Specifications?

Approach 1:
No data linking in vitro dissolution to plasma levels (least desirable scenario)

Approach 2:
Established range of release characteristics resulting in bioequivalence (also applicable to BCS Class I)

Approach 3:
Predictive and robust in vivo in vitro correlations
APPROACH 1
NO DATA LINKING DISSOLUTION TO PLASMA LEVELS

Approach 1

Least desirable approach
Clinical relevance may not always be assured.
Dependent on the data available to set the specifications

Decisions based on in vitro considerations only
Specifications may not be reflective of the "relevant" product quality

Limited regulatory flexibility resulting in tighter specifications
Decreased risk by assuring similar release characteristics in vitro
Dependent on the discriminating ability of the dissolution method
If adopted, it may result in a tighter manufacturing design space with a limited regulatory flexibility
Dissolution Profiles of 91 Batches

680 out of 4095 comparisons show f2 less than 50.
The proposed acceptance criterion 75% at 45 minutes accommodate the lowest.

Dissolution Profiles of 91 Batches (continued)

Removing 6 lowest and 4 highest batches.
Out of 3240 pairs, 184 pairs with f2 less than 50
About 6%
Approach 2

**Clinical relevance is always assured**

Decisions are based on in vitro and in vivo considerations

Regulatory flexibility may result in wider dissolution specifications

If adopted it will result in wider manufacturing design space with regulatory flexibility
Over-Discriminating Dissolution

**In Vitro**

- % Dissolved vs. Time (h)
- Comparison of Target, Variant 1, Variant 2, and Variant 3

**In Vivo**

- Plasma Conc (ng/mL) vs. Time (h)
- Comparison of Target, Variant 1, Variant 2, and Variant 3

**APPROACH 3**

*SETTING OF DISSOLUTION SPECIFICATIONS BASED ON TARGETED CLINICALLY RELEVANT PLASMA CONCENTRATIONS*
Role of IVIVC

Enable dissolution to become a surrogate for the in vivo bioavailability of the drug product

Cumulative Dissolution and Dissolution Rate
Challenges in Establishing Clinically Relevant Dissolution Specifications

**Silo approach to drug development**

Lack of communication between formulator, analytical scientist, manufacturing scientist, clinical pharmacology and pharmacometrician

**Prospective planning of manufacture and study of formulations with different release characteristics in vivo**

Available software do not take into account formulation variables and manufacturing processes

**Lack of in vitro dissolution methods that are discriminating and predictive of in vivo performance**

Lack of clear criteria for the acceptability of mechanistic models and most acceptance criteria proposed to date are very wide or loose

Perception that clinical relevant dissolution specifications will lead to tighter specifications

Perceived lack of incentives from the industry perspective
Steps to Increase the Success of Achieving Clinically Relevant Specifications

Multidisciplinary team is a must to achieve clinically relevant specification
More effort needed to develop in vitro method that are more discriminating and more predictive of the in vivo performance
Regulatory agencies should promote the use of quantitative modeling approach of setting specifications and evaluating the quality of the drug product
Provide increased regulatory flexibility for the use of predictive models

Conclusion

Establishment of an IVIVC is one of the very few instances where a regulatory action can be obtained using modeling and simulations
The setting of clinically relevant specifications will not necessary result in tighter specifications
Clinically relevant specifications is one of the many tools available to provide the most optimal therapeutic benefit to the patient
Clinical pharmacologists as well as pharmacometricians should increase their collaboration with the CMC and manufacturing scientists and play a more important role in setting the specifications of a drug product.