Complex Drug Substances: A Generic Perspective

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Outline

- Complex Drug Substances
  - Regulatory path
  - Examples
- Review Concerns
  - DS definition
  - Sameness
  - Process and process development
  - Analytics
  - Acceptance criteria

Complex Drug Substances

- Complex drug substances in generic drug products
  - Generics pathway 505(j)
  - Generated by synthetic routes

Examples of Complex Drug Substances (DS)

- Low molecular weight heparins (LMWHs)
  - Enoxaparin Sodium
- Peptide mixtures
  - Protamine sulfate
- Polymers
  - Glatiramer acetate
- Co-ordination complexes
  - Iron sucrose complex

Complex DS

1. Lack of well defined structure

   e.g.

   - Glatiramer acetate
   - LMWHs

- DS is a heterogeneous mixture

2. Lack of structure-activity relationship

- biological activity not attributed to any one or specific structural epitopes

Complex DS in Generic DP: Approaches to Establish Sameness

- Characterization challenge
  - Can't identify all structures
    - Millions of molecules in a mixture such as Glatiramer acetate or Enoxaparin
  - Identify Unique structural signatures
  - Identify Structural motifs that act as process signatures for entire peptide or polysaccharide or polymer chain can be used in sameness determination

Complex DS in Generic DP: Approaches to Establish Sameness

- Process signatures are structural fingerprints of innovator's manufacturing process
- Once identified they can be used to reverse engineer innovator's manufacturing process and effectively enable one to conclude that the manufacturing process and underlying chemistry including kinetics, reaction biases in effect are the same between RLD and generics

Complex DS Manufacturing Process and Process Development

- Manufacturing process directly affects molecular structure of DS
  - Establish process-structure relationships
  - Define process signatures
  - Identify critical process parameters (CPPs) and optimize the CPPs based on DS structure
  - Implement in-process controls (IPCs) to ensure batch to batch consistency

Complex DS Manufacturing Process and Process Development

- Manufacturing process development challenges
  - Scarcity of publicly available information
  - Limited availability of reference product

Complex DS Manufacturing Process and Process Development

- Some helpful approaches
  - Identification of process signatures and CPPs and their optimization using DOE
  - Mechanistic studies, mathematical models
  - Comparing resultant final DS with the RLD
  - Iterative process
  - Process validation

Complex DS: Analytics

- Sufficiency
  - Orthogonal tests sufficient to cover all process signatures to completely capture innovator's process
- Specificity
  - Tests can differentiate between process signatures of correctly formed material vs similar but nonequivalent

Complex DS: Analytics

- Sensitivity
  - Tests can measure changes in process signatures as a function of small changes in CPPs

Approaches to address Analytics challenges

- Sufficiency: Cover all aspects of the molecular structure
  - Primary attributes/ process signatures
    - Specific functional groups affected by process
  - Secondary attributes/ general properties
    - Physico-chemical properties
  - Supplementary characteristics
    - Bioassay
    - Higher order structures

Approaches to address Analytics challenges

- Specificity/ Selectivity
  - Evaluate analytical method specificity used for analysis of process signatures with the use of negative controls
    - Material similar to the DS in fundamental aspects of structure such as molecular weight but with some differences in process signatures

Approaches to address Analytics challenges

- Sensitivity
  - Validate analytical technique for sensitivity to the measured process signatures by testing against process negative controls
    - DS like material manufactured by same process with small changes in CPPs
      - Can be within or at the borderline of the design space

Robust Analytics

- Develop reference standard based on reference product
- Use of state of art analytical tools for characterization and sameness determination
- Analyze batch to batch variability in generic DS and RLD
- Develop sameness criteria using RLD data

Impurities in Complex DS

- How to determine what structures are part of DS and what are related substances/ impurities?
- Analysis of reference product
  - Multiple lots within expiry
- Address Immunogenicity concerns

Acceptance Criteria

- Analysis of reference product
  - Multiple lots within expiry
  - In some cases adoption of artificial factors such as 90% RLD min. to 110% RLD max. to cover inherent variability within the reference product maybe acceptable
    - Method sensitivity, precision
  - Use of existing guidance if applicable

Summary

- Complex DS in generic drug products
- Defined by structural signatures and physico-chemical properties
- Manufacturing process development is critical aspect
- Robust and relevant analytics
- Comprehensive sameness determination

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