Common Issues in Complex Drug Substance Review for Generic Drug Products

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Outline

- Scope
- Complex drug substances (DS) challenges
- Common deficiencies and possible solutions

Examples of Complex Drug Substances

- Peptides
  - Exenatide
- Complex mixtures
  - Low molecular weight heparins, e.g. Enoxaparin Sodium
  - Synthetic polypeptides, e.g. Glatiramer Acetate
- Polymers
  - Sevelamer Carbonate
- Molecular complexes
  - Iron Sucrose
- Naturally sourced ingredients
  - Conjugated Estrogens

Excluded in the Scope

- Biological DS
- Low molecular weight, well-defined small molecule DS

Basis for ANDA Approval

Federal Food, Drug, and Cosmetic Act Section 505(j): To obtain approval of a proposed generic drug, an ANDA applicant must demonstrate, among other things, that the proposed generic is:

- The same as its RLD in:
  - Active ingredient(s)
  - Strength
  - Dosage form
  - Route of administration
  - Condition of use
  - Labeling, with certain permissible differences
- Bioequivalent to RLD

Complex DS Challenges

- Identity
  - clearly defined?
- Strength
  - For DS as a mixture, strength may be expressed as a whole mixture
  - May require bioassay
- Purity
  - active ingredients, concomitants, or impurities?

Common Deficiencies

- Characterization
  - Identity and Physicochemical properties
  - Assay
  - Purity
- Control strategy
  - Starting materials, raw materials
  - Manufacturing process and controls
  - DS specification and analytical procedures
  - DS retest period

Identity/Physicochemical Properties

- Deficiency: insufficient data or inadequate acceptance criteria
- Possible solutions:
  - Utilize orthogonal advanced analytical techniques
  - For DS of complex mixtures:
    - Identify structural signatures
    - Use negative controls
  - Justify proposed acceptance criteria, e.g. analysis of multiple batches of RLD

Assay

- Deficiency: inadequate reference standard or its characterization
- Possible solutions:
  - Primary RS: for DS as a mixture, isolate API from RLD
  - Comprehensive characterization, including organic and inorganic impurities
  - Describe how potency is determined

Purity

- Deficiency: inadequate acceptance criteria or assessment of potential impurities
- Possible solutions:
  - Acceptance criteria: USP monograph, guidances, multiple batches of RLD, or pharm/tox study
  - Potential impurities
    - Acquire process knowledge
    - Demonstrate analytical procedure method specificity
    - Apply orthogonal analytical techniques

Starting Materials/Raw Materials

- Deficiency: inadequate designation of starting material(s) or specification
- Possible solutions:
  - Justification of SM per ICH Q11 and Q11 Q&As
  - SM specification:
    - Specific ID test(s)
    - Impurities: data to support proposed acceptance criteria

Manufacturing process and controls

- Deficiency:
  - Insufficient details
  - Inconsistent information in S.2.2, S.2.4, MBR
  - Inadequate in-process controls or intermediate specifications
  - CPPs not identified
  - Inadequate justification of CPPs ranges

Manufacturing process and controls (cont.)

- Possible solutions:
  - Clear, accurate, consistent information with sufficient details [21 CFR 314.50(d)(1)(i)]
  - Development study to identify CQAs and CPPs
  - Justification of CPPs ranges based on DS sameness data
  - List CPPs and ranges in S.2.4

DS specification

- Deficiency: Inadequate acceptance criteria or missing critical tests
- Possible solutions:
  - Acquire process knowledge
  - Include CQAs
  - Justify acceptance criteria: USP monograph, guidances, RLD data, etc.

Common Deficiencies- Example 1

- Lack of negative controls for DS as a mixture

To demonstrate the specificity and sensitivity of the analytics with respect to the structural signatures, it is important that you **develop sufficient negative controls that cover the manufacturing process parameters that can potentially affect the structural signatures**. The negative control batches are expected to meet the basic criteria for DS such as molecular weight specified in the RLD labeling, but the negative controls should fail at least some of the sameness characterization tests that capture the process signatures of individual manufacturing process steps. **Such negative controls are essential to demonstrate the discriminatory power and specificity of the analytical tests used in the characterization and release testing of your DS.** We recommend you apply the negative controls to all tests you used for sameness characterization.

Common Deficiencies- Example 2

- Impurity Controls for peptide DS

Potential diastereomers could be present in the drug substance due to the presence of the enantiomer in the Fmoc amino acid starting materials and/or racemization during the synthesis. **Please address the capability of your related substances analytical procedure for detecting potential diastereomers.**

Common Deficiencies- Example 3

- Inadequate acceptance criteria for DS Specification

We acknowledge that your proposed acceptance criterion of NMT 0.20% for each of the specified impurities at RRT 0.96-0.97, RRT 0.98-0.99, and RRT 1.03-1.05 is based on the impurities observed in the respective RRTs in three RLD lots. However, you neither identify nor characterize these impurities in both your drug substance (DS) and RLD. Therefore, it is not conclusive that these impurities in your DS are identical to those in the RLD. **Please provide structure characterization data for these impurities in both your DS and the RLD in order to justify your proposed acceptance criteria.**

Common Deficiencies- Example 4

- CPPs ranges not justified

We acknowledge that you have identified CPPs of DS synthesis and their acceptable ranges. However, there are insufficient data to support the proposed ranges. In particular, sameness characterization data for batches of DS that are manufactured using the proposed upper and lower limits of the CPPs have not been provided. **Please justify the acceptance ranges of the CPPs. The justification should include, but not be limited to, demonstration of equivalence of physicochemical properties, disaccharide building blocks, fragment mapping, sequence of oligosaccharides, as well as biological and biochemical assays.**

Common Deficiencies- Example 5

- Inadequate In-process controls

For Stage 2, your proposed limit of ≥ 40% for purity by HPLC appears to be too broad and not supported by your batch data (61-65%). **Please tighten the acceptance criterion.**

Common Deficiencies- Example 6

- Hold Times and Conditions

We acknowledge that the manufacturing process of DS involves isolation of several intermediates as well as purification fraction pools, which can be stored under specified storage conditions until further processing. **Please propose maximum holding times for each of the intermediates and fraction pools stored under the specified conditions, supported by data.**

Common Deficiencies- Example 7

- Missing yields for critical unit operations

We acknowledge that %yield limits have been proposed for all intermediates manufactured in Stages I-III. **Please provide the %yield limit for the final API. The yield should be based on the peptide content in the API.**

Common Deficiencies- Example 8

- Inadequate starting material specifications

The current specifications proposed for the Fmoc-AA starting materials are not acceptable. **Please include acceptance criteria for any specified, each unspecified, and total impurities by HPLC for all the Fmoc-AAs. Furthermore, please include two decimal place for the acceptance criterion of D-isomer.** For example, the limit for Fmoc-D-Lys(Boc)-OH should be revised from "≤ 0.1%" to "≤ 0.10%".

Final Remarks

- Identity, strength, quality, and purity
  - Critical to safety & efficacy
  - Basis for CMC approval recommendation


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