Considerations for Morphologically Directed Raman Spectroscopy (MDRS) Study Information Submitted in Nasal Suspension ANDAs

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SBIA Generic Drug Forum – April 12 – 13, 2023

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Learning Objectives

- Explain the alternative approaches to the Comparative Clinical Endpoint (CCEP) study for locally acting nasal suspensions
- Considerations for a high-quality submission for an MDRS study
- Identify submission-related common deficiencies for an MDRS study

FDA BE Recommendations for Locally Acting Nasal Suspensions: Weight-of-Evidence Approach

Equivalent In Vitro Performance

Equivalent Systemic Exposure

Equivalent Local Delivery:
Comparative clinical endpoint study or
Alternative BE approach

Formulation Sameness and Device Similarity

- Challenges of a comparative clinical endpoint study: high variability, low sensitivity, and longer study duration

BE: bioequivalence

Recommendation of Alternative BE Approach for Nasal Suspensions

Alternative approach to the comparative clinical endpoint BE study in product-specific guidances (PSG) for Nasal Suspension products (i.e., Fluticasone Propionate and Mometasone Furoate)

*For example, PSG for **Mometasone Furoate Monohydrate Nasal Spray states:***

A comparative clinical endpoint BE study is recommended for T mometasone furoate nasal spray product because of an inability to adequately characterize drug particle size distribution (PSD) in aerosols and sprays using commonly used analytical methods. Drug PSD in suspension formulations has the potential to influence the rate and extent of drug availability to nasal sites of action and to systemic circulation. If drug PSD in the T and R products can be accurately measured using a validated analytical method such as morphology-directed Raman spectroscopy or any other advanced methodology, prospective applicants may submit comparative particle size distribution data as part of their drug characterization within their ANDA application.

MDRS Study Submissions

- Increasing trend of nasal suspension product submissions containing MDRS study in recent years.
- Many MDRS study deficiencies are related to incomplete submissions.
- Deficiencies related to incomplete MDRS study submission may be classified as major.

What and In Which Module to Submit

- Module 2.7.1
  - BE summary tables
  - MDRS study eCTD summary tables are under development. Please check fda.gov for the current recommendations

  https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/abbreviated-new-drug-application-anda-forms-and-submission-requirements
- Module 5.3.1
  - MDRS Method Development and Validation Reports
    - MDRS method development report
    - MDRS method validation report including standard operating procedures (SOPs)/protocol with predefined acceptance criteria that were effective at the time of study.
  - MDRS pivotal study report
    - Raw Data
    - PBE analysis on D_{50} and Span

Depending on the data submitted and upon evaluation of the said data, additional information may be requested during ANDA assessment.

Submission-Related Common Deficiencies – MDRS Method Development

- Sample Preparation
- Image and Size Characterization

Deficiencies Related to Sample Preparation

- Incomplete submission of detailed procedure and validation/optimization data on
  - Selection of dispersion technique
  - Method of spraying and its impact on PSD (particle size distribution)/batch to batch variability
  - Volume of sample used
  - Sample concentration
  - Particle settling time
  - Data on deagglomerated particles
  - Use of surfactant (if any)
  - Cover-slip and its placement
  - Sealant used
  - Number of sprays used in sample preparation

Deficiencies Related to Image and Size Characterization

- Incomplete submission of validation/optimization data and procedure on:
  - Optical magnification selection
  - Threshold value selection data
  - Raman particle count data
  - Morphology filter selection
  - Elongation filter selection data
  - Circular equivalent (CE) diameter selection data
  - Validation data on selection of Raman correlation score
  - Orthogonal method selection and execution
  - Optimization data on selection of pre-processing settings

Submission-Related Common Deficiencies – MDRS Method Validation and Pivotal Study

Deficiencies Related to MDRS Method Validation and Pivotal Study

Method Validation

- Missing validation data for MDRS method on:
  - Reproducibility of the method and accuracy
  - Robustness of the method including:
    - Sample Volume
    - Scan Area
    - Percent Overlap
    - Morphology Filters (CE diameter, convexity filter, and solidity filter)
    - Threshold Selection
    - Particle Settling Time

Pivotal Study

- Missing 100% raw data
- Missing PBE analysis on D_{50} and Span

Summary

- The number of ANDA submissions containing MDRS study has increased in recent years.
- Common MDRS submission deficiencies observed are related to method development, validation, and pivotal studies.
- Many MDRS study deficiencies are preventable by providing supporting development and validation data.

Challenge Question #1

Which of the following statements is TRUE?

A. Potential challenges of a CCEP study include high variability and longer study duration.

B. Number of ANDA submissions containing MDRS study has increased in recent years.

C. Many MDRS study deficiencies are related to incomplete submissions.

D. All of the above.


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