GDUFA III
Maximize the Impact of the Redesigned PSUB Meetings on Generics Approvals

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SBIA Webinar: Redesigned Pre-Submission Meetings in GDUFA III: Benefits for ANDA Submission and Approval
May 9, 2024

Disclaimer

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

Outline

- Pre-submission (PSUB) meeting requests: why, how, and what
- Case Examples
  - Products applied on the skin (topical semisolid dosage forms)
  - Orally inhaled drug products (OIDPs)
- Conclusions

Why = The Purpose

- To provide a preview of complex issues in a prospective ANDA to better prepare FDA assessors.
- To help the prospective applicant to better prepare the ANDA submission to avoid potential major deficiencies due to unawareness of certain expectations.

➢ Reduce potential major deficiencies, thus, more streamlined review process

How = The Process

Complex issues for considering a PSUB request when the prospective ANDA involves:

- New analytical methods and/or orthogonal analytical approaches
  - Drug products containing complex active pharmaceutical ingredient (API)
  - Novel/new manufacturing processes
- Alternative bioequivalence (BE) approach for supporting BE
  - In vitro performance and characterization testing based BE approach vs comparative clinical BE studies recommended in the product-specific guidance (PSG)
  - Modeling and simulation (M&S) to support BE
- New or complex study design/ guidance implementation or data analysis challenges
  - Immunogenicity study design for peptide drugs
  - In vitro release testing (IVRT) and/or in vitro permeation testing (IVPT)
  - Statistical analysis of in vitro and/or in vivo BE data
  - Comparative human factor studies for device evaluation

What = The Result

Potential outcomes of PSUB requests

- FDA assessors:

  Better understanding of the identified complex issues

- ANDA applicants:

  Ensure feedback received in previous regulatory inquiries is properly understood and executed

  Ensure understanding of the PSG recommendation and implementation is on the right track

  Additional feedback from FDA to facilitate preparation of final ANDA submission

Example 1: Active Ingredients D and E topical gel approved for indication X

PSG recommendations

- In vitro characterization approach
  - Test (T) product meeting the “no difference” criterion,
  - Reference (R) and T sameness in physicochemical and structural attributes,
  - equivalent in vitro release of D and E between R and T,

Challenges during implementation

- In vitro characterization approach
  - T product meeting the “no difference” criterion,
  - R and T sameness in physicochemical and structural attributes, new analytical method for characterization of particle size distribution of active ingredients suspended in the gel
  - equivalent in vitro release of D and E between R and T, challenges observed during method validation (selectivity study)

Example 1: Active Ingredient D and E topical gel approved for indication X (Cont.)

- New analytical method for characterization of particle size distribution of active ingredients suspended in the gel

How: Clearly outline your strategy for developing and validating analytical method(s) that were used to simultaneous characterize the particle size distribution of two active ingredients suspended in the gel.

What: When feasible, the Agency can clarify if additional data/ data presentation may be helpful to facilitate the scientific assessment

- Challenges observed during method validation (selectivity study)

How: Clearly outline what approaches were utilized to validate the selectivity of the method, and the differences compared to method validation approach in general guidance.

What: When feasible, Agency can clarify if additional solubility/ release data may be helpful to facilitate the scientific assessment

Once all studies are complete, a PSUB can be requested.

PSUB Package: M&S Analysis

- Orient FDA assessors in preparation for review of your upcoming ANDA submission
  - Previous product development (PDEV) meeting, model-integrated evidence (MIE) meeting and FDA-EMA Parallel Scientific Advice (PSA) Program meeting: summary of regulatory recommendations
  - Controlled correspondence: summary of FDA recommendations
  - Unique or novel data or information to be included in the ANDA submission
- Placement of modeling in eCTD: identification of modeling approach, datasets supporting the approach, reports documenting the approach
  - analysis report under Module 5.3.1 or other relevant module

PSUB Package: M&S Analysis

- M&S approaches supporting alternative BE approaches should be properly documented
  - Level of detail in the Modeling Analysis Plan (MAP)/ Report (MAR) should allow the Agency to reproduce the analysis
- MAP and MAR
  - Role of the proposed model within the ANDA clearly stated
  - Justifications and limitations clearly stated
  - Model development/validation process clearly described
  - VBE assessment and results: clearly presented with interpretation and type I/II error analysis

PSUB Package: M&S Analysis

- Orientation File: list of version-controlled model files and supporting datasets, their sources (applicant-generated, literature) and their role in the ANDA
  - Model file(s) developed to support the M&S approach
    - Model 1, 2, …
  - Datasets utilized in the M&S approach
    - Clearly identified in the submission
    - Describe their relationship with studies supporting the ANDA submission
  - Literature and other sources of information

PSUB Package: M&S Analysis

- Orient FDA assessors on the data utilized to support the M&S approach and their role in the regulatory submission
  - Data generated by the applicant within the scope of this ANDA
  - Other relevant datasets provided by the applicant in support of their M&S approach
  - Protocols, study reports referring to the datasets utilized, and analysis performed
  - Literature sources

PSUB Package: M&S Analysis

Outside the scope of the PSUB meeting:

- Specific questions on
  - the filing acceptability of the M&S approach in the ANDA
  - the overall acceptability of an alternative BE approach if applicable
- Substantive assessment of any part of the ANDA submission

However,

- "… FDA will identify items or information that should be clarified before submission of the ANDA."
- Productive exchange during the meeting

M&S Example 2: Active Ingredient Y OIDP

PSG recommendations

- Combined in vitro and in vivo BE approach
  - Qualitative (Q1) and quantitative (Q2) sameness for reference listed drug (RLD) and test (T) products,
  - Device similarity,
  - Multiple in vitro tests,
  - In vivo pharmacokinetics (PK) study in fasting condition for both strengths with healthy volunteers,
- In vivo comparative clinical endpoint or pharmacodynamic study with patients

Applicant's alternative BE approach

- Combined in vitro and in vivo BE approach
  - Q1/Q2 sameness for RLD and T products,
  - Device similarity,
  - Multiple in vitro tests,
  - In vivo PK study in fasting condition for both strengths with healthy volunteers,
- Alternative in vitro and in silico studies, including in silico regional deposition model

M&S Example 2: Active Ingredient Y OIDP

PSUB Meeting leveraged to ensure that critical components of the M&S approach within the alternative BE approach are accurately captured

- Context of use for proposed model in the alternative BE approach
- Data generated by the applicant within the scope of this ANDA
  - aerodynamic particle size distribution [APSD] with realistic mouth-throat models, dissolution, plume geometry, in vivo PK data, among others
  - Other supporting material
    - relevant datasets, protocols, study reports referring to the datasets utilized and analysis performed, literature sources

M&S Example 2: Active Ingredient Y OIDP

- Validation of the proposed model for its intended purpose
  - In vivo nuclear imaging data, including gamma scintigraphy, single photon emission computed tomography (SPECT)/computed tomography (CT), and positron emission tomography (PET)/CT studies
  - Observed data on systemic PK of active ingredient Y in the OIDP of interest (pilot study, literature sources, etc., if available)
  - Validation of the computational framework utilized for building the model (if applicable)
- Model application for assessing regional drug delivery
  - Virtual bioequivalence (VBE) assessment study: study design, virtual healthy and asthmatic patients, statistical analysis
  - Establish biorelevant limits for bioequivalence comparison of key recommended studies for BE establishment

M&S Example 3:
Active Ingredient Y topical cream

PSG recommendations

- In vitro characterization approach
  - T product meeting the “no difference” criterion,
  - R and T sameness in physicochemical and structural attributes,
  - equivalent in vitro release of Y between R and T,
  - ~~equivalent rate and extent of Y permeation through excised human skin between R and T~~
- In vivo BE study with PK endpoints in healthy volunteers

Applicant’s alternative BE approach

- In vitro characterization approach
  - T product meeting the “no difference” criterion,
  - R and T sameness in physicochemical and structural attributes,
  - equivalent in vitro release of Y between R and T,
  - equivalent rate and extent of Y permeation between R and T within the scope of an in silico IVPT study
- In vivo BE study with PK endpoints in healthy volunteers

M&S Example 3:
Active Ingredient Y topical cream

PSUB meeting leveraged to:

- Summarize previous meeting outcomes:
  - Pilot IVPT study demonstrated high inter-donor variability
    - advised to increase the number of donors
  - Bioanalytical methodology for API Y
    - advised to increase the sensitivity of the method (LLOQ)
  - Challenges in showing discriminatory capability of the IVPT methodology
    - advised to explore several applied product amounts per FDA guidances (PSG and general guidances)
  - In silico IVPT model was underpredicting Y skin permeation and not capturing inter-donor variability observed in the pilot IVPT study
    - advised to validate the IVPT methodology applied and increase number of donors/replicates as explained above to ensure that future model refinement is performed against reliable IVPT data

M&S Example 3: Active Ingredient Y topical cream

- Ensure that IVPT study issues identified in previous meetings have been addressed
  - Number of donors, bioanalytical method validation, applied drug product doses
- Orient FDA assessors on the data utilized to support the M&S approach and their role in the regulatory submission
  - Data generated by the applicant within the scope of this ANDA
    - in vitro characterization, pilot IVPT study data for model validation, in vivo PK data, among others
    - Other supporting material
      - relevant datasets, protocols, study reports referring to the datasets utilized, and analysis performed, literature sources

M&S Example 3:
Active Ingredient Y topical cream

- PSUB Meeting leveraged to ensure that critical components of the M&S approach within the alternative BE approach are accurately captured
  - Role of the proposed model in the alternative BE approach without a pivotal IVPT study
  - Validation of the proposed model for its intended purpose
    - Pilot IVPT study data under this ANDA and other IVPT datasets available in the literature or provided by the applicant
    - Validation of the computational framework utilized for building the in silico IVPT model (if applicable)
  - VBE assessment IVPT study: study design, virtual population (sample size, sex), statistical analysis, type I/II error analysis

Conclusions

- Focus meeting package on describing principal areas of interest.
- Use the presentation format in the guidance
- Highlight any novel/unique data/approaches
- A PSUB meeting can be requested when all studies are complete for the identified complex issue(s)

Refer to guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA Guidance for Industry*

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Questions?


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