Experiences from Post-Complete Response Letter (CRL) Scientific Meetings in GDUFA III

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Learning Objectives

- An overview of post-Complete Response Letter Scientific Meeting Requests (post-CRSMRs) per the GDUFA III Commitment Letter

- Learn when and how to utilize post-CRSMR to support generic drug development

Outline

- 2022 GDUFA III Commitment Letter (CL)
- Post-CRSMRs: Grant scenarios
- Complex generic products
- Analysis of post-CRSMRs submitted from 10/01/2022 to 12/31/2024
- Case studies
- Post-CRSMRs: Common reasons for meeting request denial
- Post-CRSMRs: Expectations for the meeting package
- Post-CRSMRs: Summary

CL: Options For Engaging FDA Prior to Responding to the CRL

1. Post-CRL Clarification Meeting Request (Post-CRCMR)

To seek clarification concerning deficiencies identified in a CRL

2. Submission of a Controlled Correspondence (CC)

To seek regulatory and/or scientific advice after issuance of a CRL

3. Post-CRL Scientific Meeting Request (Post-CRSMR)

To request scientific advice on possible approaches to address deficiencies identified in a CRL related to establishing equivalence

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Post-CRSMRs: Grant Scenarios

FDA **will grant** the post-CRSMR if the following criteria are met:

- Complex generic product or in FDA's judgment the request raises issues that are best addressed via post-CRSMR and cannot be adequately addressed through CC; and
- Relates to one or more of the following:
  - A new equivalence study needed to address the deficiencies in the design identified in the CRL,
  - An approach that is different from that submitted in the ANDA, e.g., a change in study type from in vivo to in vitro,
  - A new comparative use human factors study, or
  - A new approach to demonstrating sameness of a complex active ingredient

Post-CRL scientific meeting provides an applicant scientific advice on possible approaches to address deficiencies identified in a CRL related to establishing equivalence

Complex Generic Products

Complex Products – generally include:

1. Products with complex active ingredients (e.g., peptides, polymeric compounds, complex mixtures of APIs, naturally sourced ingredients); complex formulations (e.g., liposomes, colloids); complex routes of delivery (e.g., locally acting drugs such as dermatological products, complex ophthalmological products, and otic dosage forms that are formulated as suspensions, emulsions or gels) or complex dosage forms (e.g., transdermal systems, metered dose inhalers, extended release injectables)

2. Complex drug-device combination products (e.g., pre-filled auto-injector products, metered dose inhalers); and

3. Other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement

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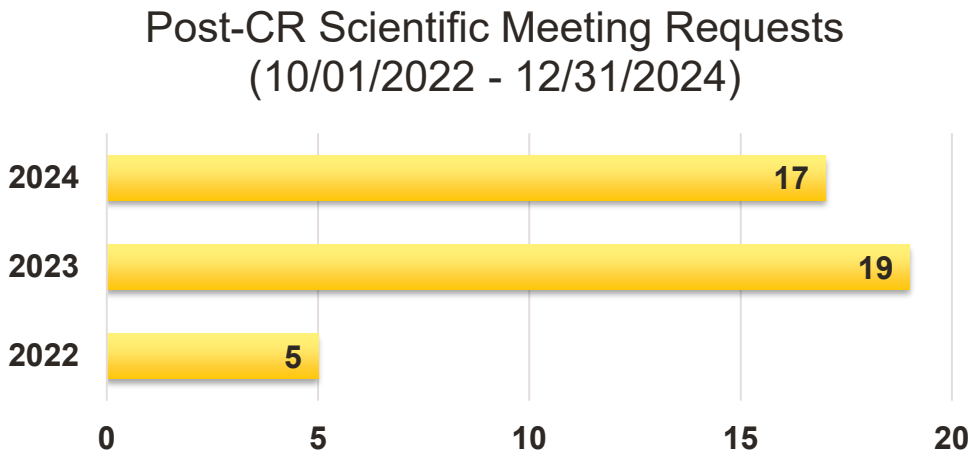
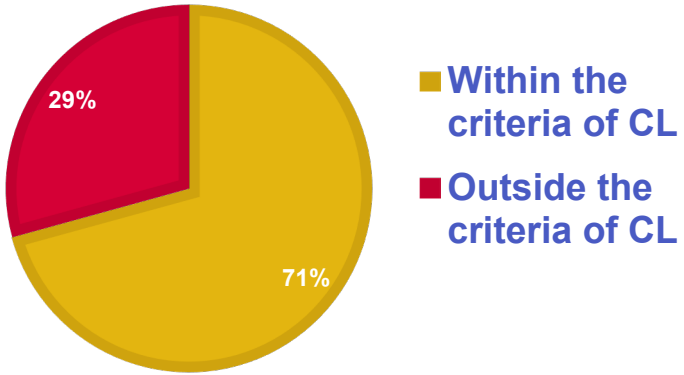
Submitted Post-CRSMRs

- A total of **41** post-CRSMRs were submitted between October 2022 and December 2024



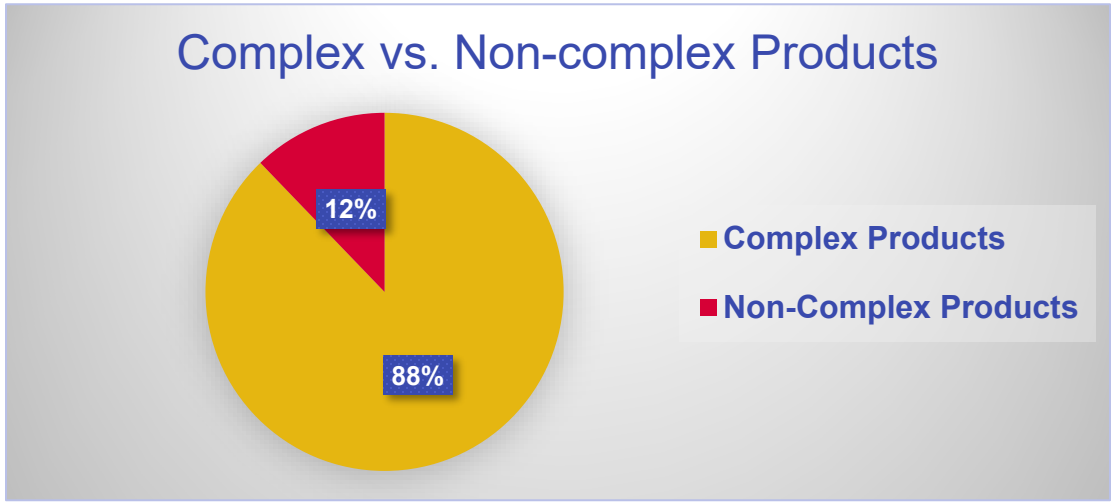
Data for 2022 is only for 3 months (Oct – Dec)

Percentage of Post-CRSMRs Within or Outside the Criteria of the CL



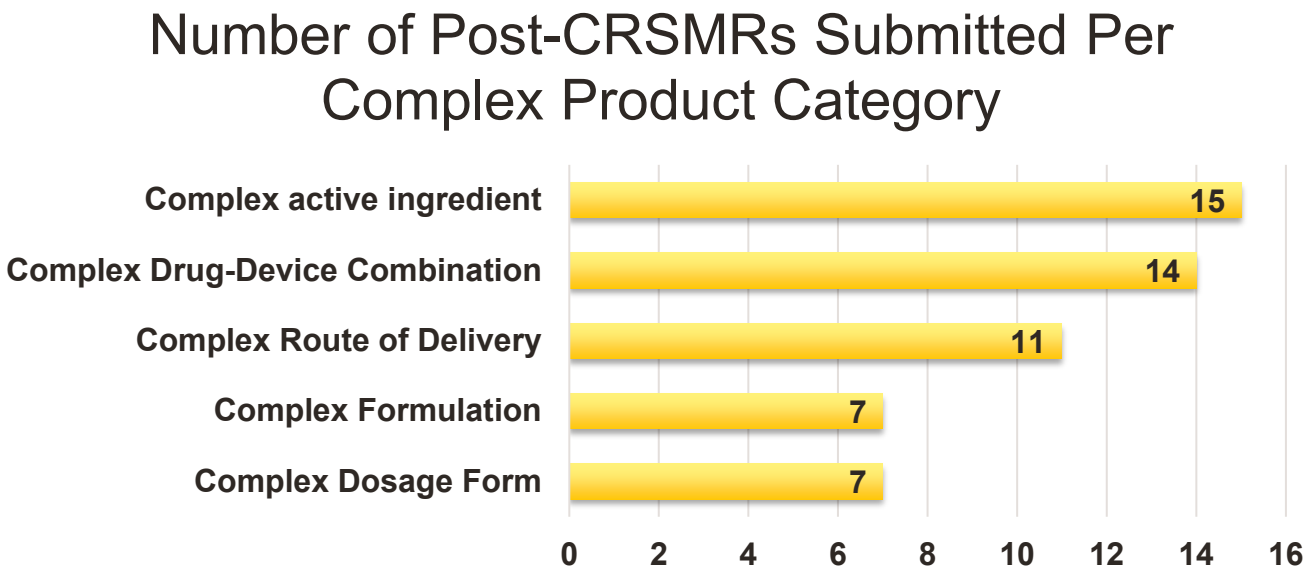
- Based on criteria of the CL (mentioned in Slide 5), out of total 41 submitted post-CRSMRs, 29 (71%) were submitted within the criteria of the CL and 12 (29%) were submitted outside the criteria of the CL

Post-CRSMRs: Complex vs. Non-Complex Products



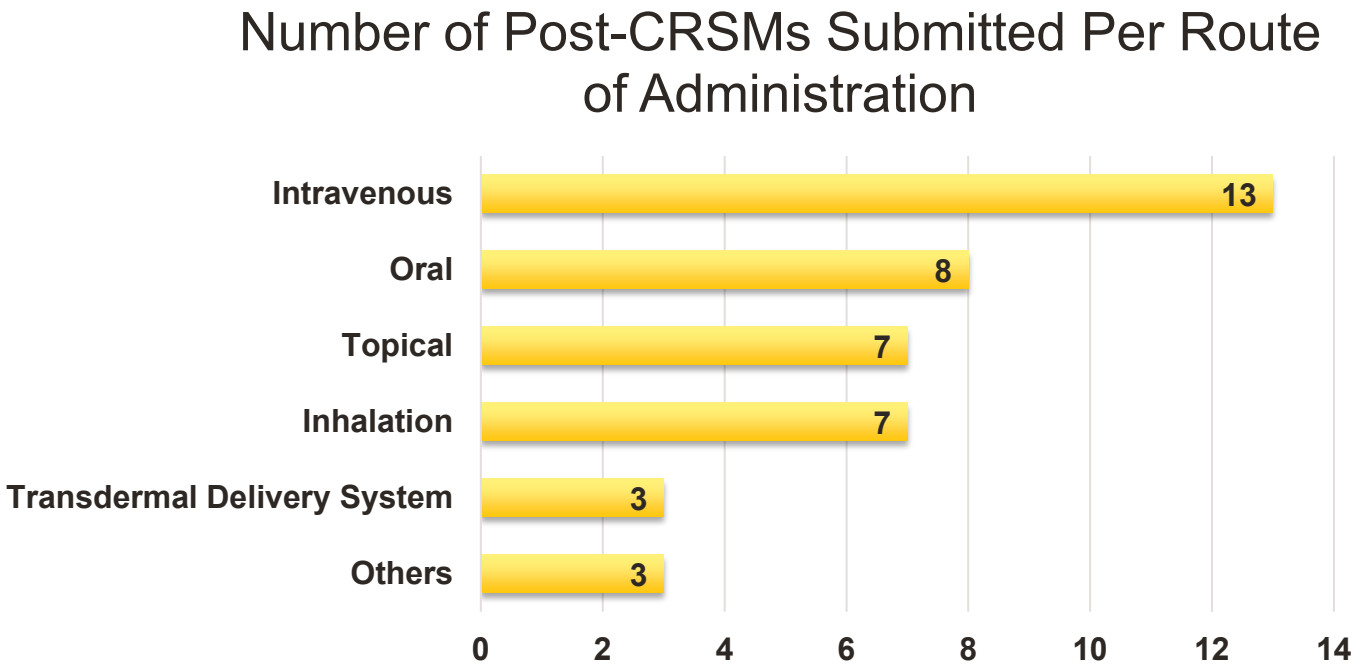
- Out of total 41 submitted post-CRSMRs, 36 (88%) were for complex drug products and 5 (12%) were for non-complex drug products

Post-CRSMRs: Per Complex Product Category



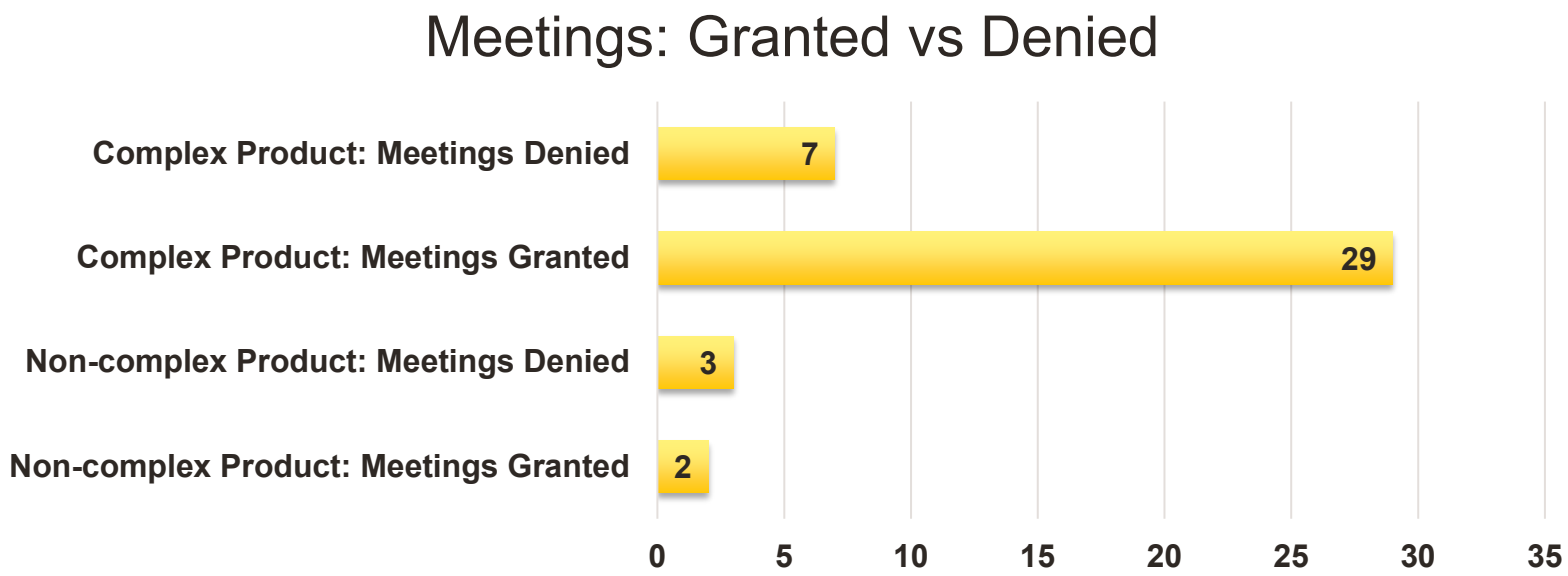
- The total number (54) exceeds 36 submitted meeting requests for complex products as some products qualified for more than one category

Post-CRSMRs: Per Route of Administration



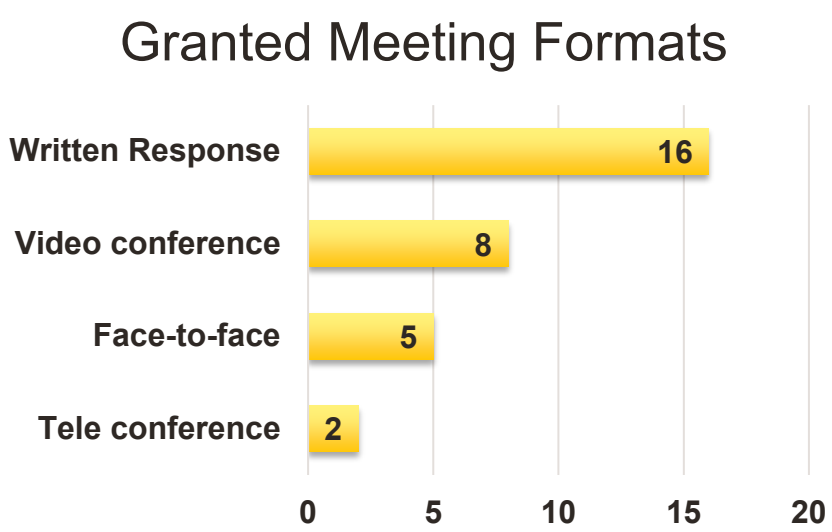
- Out of total 41 submitted meeting requests

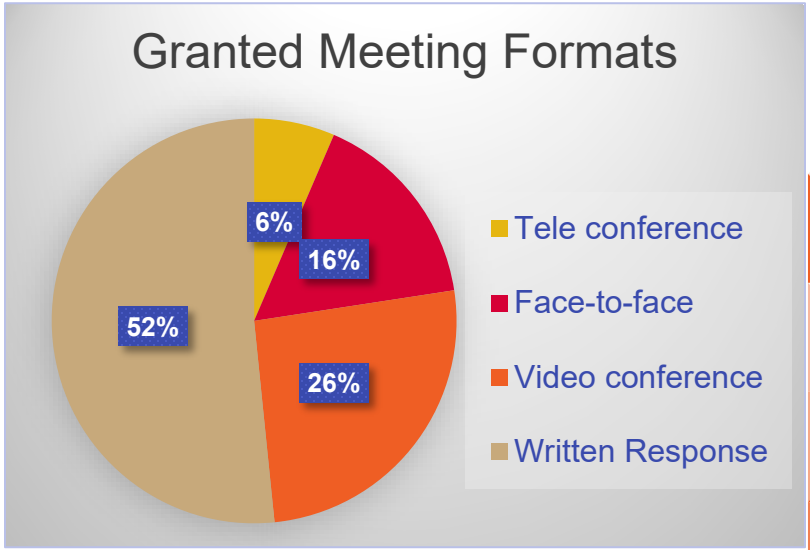
Post-CRSMRs: Granted vs Denied



- Out of total 10 denied meeting requests, 6 were recommended to submit controlled correspondence

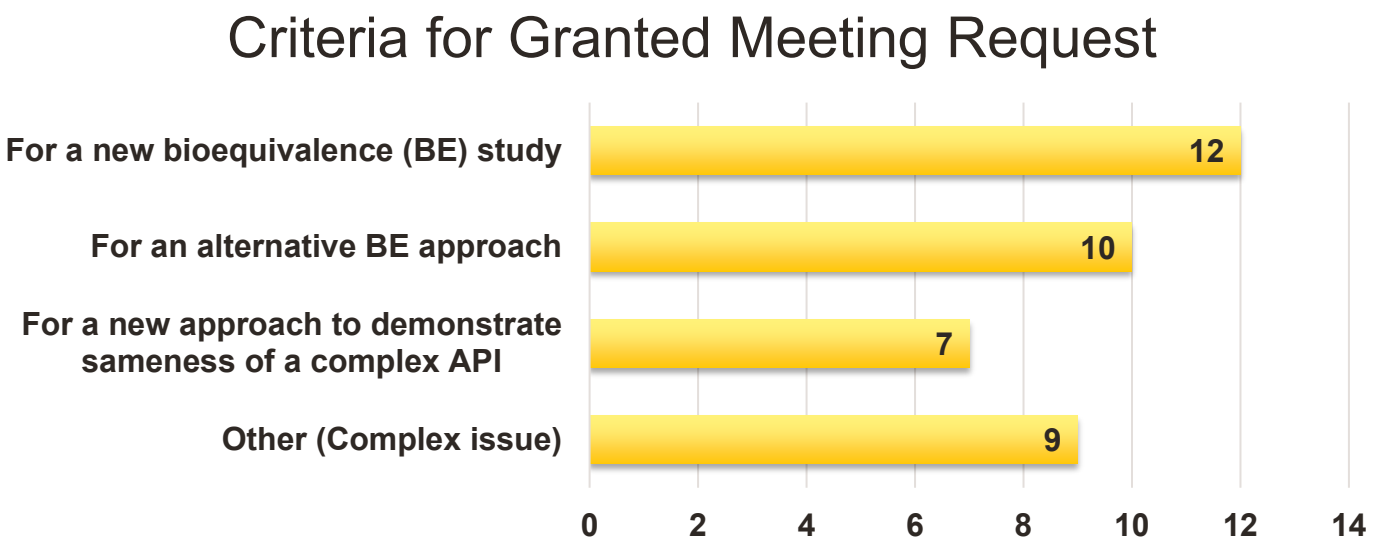
Post-CRSMRs: Granted Meeting Formats





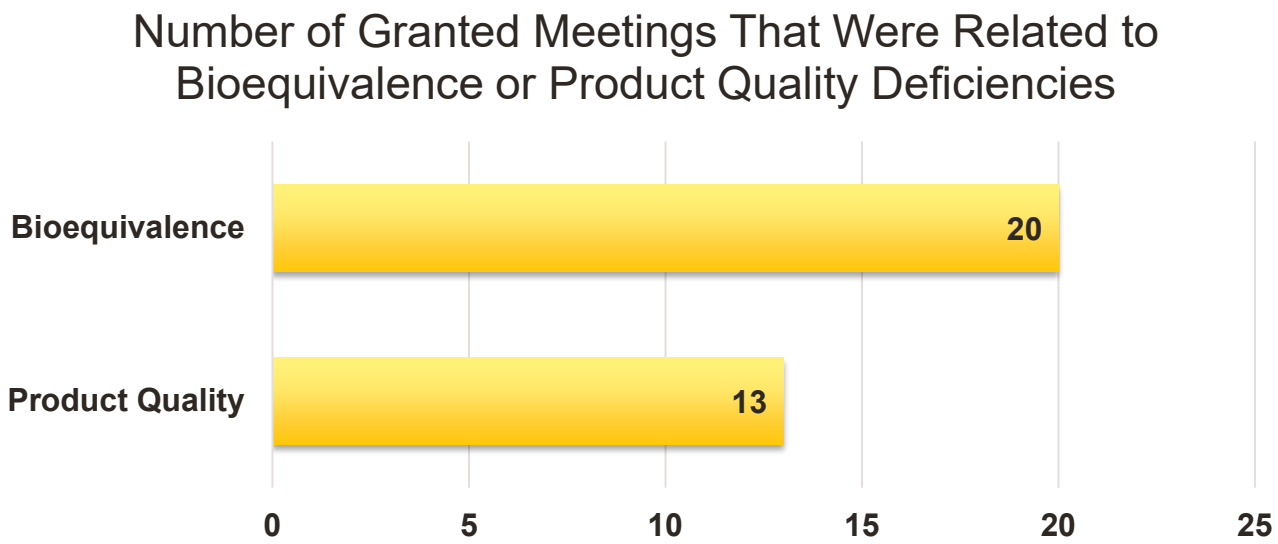
- A total of 31 post-CRSMRs were granted out of 41 submitted post-CRSMRs

Post-CRSMRs: Criteria for Granted Meeting Requests



- The total number (38) exceeds 31 granted meeting requests as some meeting requests met more than one request criteria

Post-CRSMRs: Number of Granted Meetings That Were Related to Bioequivalence or Product Quality Deficiencies



- The total number (33) exceeds 31 granted meeting requests as some post-CRSMRs contained questions for more than one discipline

Post-CRSMRs Granted: Case Studies Pertaining to BE

Oral Immediate-Release Tablets

➢ Non-complex drug product; complex issues

- Questions related to in vitro study design

Oral Immediate-Release Powder

➢ Complex drug product; complex API

- Questions related to establishment of maximum binding (showing attainment of plateau) in the in vitro equilibrium binding study

Post-CRSMRs Granted: Case Studies Pertaining to BE

Oral Extended-Release Tablets

➢ Non-complex product; an alternative BE approach

- Applicant was requested to reformulate the test product and conduct new in vivo BE studies due to pharmacokinetic (PK) issues. The applicant instead proposed a population PK modeling approach to address the issues

Intravenous Injectable Product

➢ Complex drug product; an alternative approach

- The applicant proposed an alternate approach for statistical evaluation of the PK/BE study

Post-CRSMRs Granted: Case Studies Pertaining to BE

Topical Drug Products

- Complex drug products; complex dosage forms/route of delivery

Case 1: PSG recommends conducting an in vivo BE study with clinical endpoints. However, the applicant proposed a characterization-based in vitro approach for establishing BE

Case 2: Applicant proposed physiologically based pharmacokinetic (PBPK) modeling in lieu of in vitro permeation testing (IVPT)

Case 3: Applicant provided justification that IVPT is not suitable for establishing BE for this specific topical drug product

Post-CRSMRs Granted: Case Studies Pertaining to BE

Inhalation Drug Products

- Complex drug products; complex drug-device combinations

Case 1: Applicant proposed new pivotal in vitro BE studies from batches manufactured at an alternate manufacturing site to bridge with batches manufactured at the original site

Case 2: Applicant proposed in silico model to support realistic aerodynamic particle size distribution (rAPSD) testing

Case 3: Applicant proposed a statistical approach other than population BE (PBE) to evaluate rAPSD data

Post-CRSMRs: Common Reasons for Meeting Denial

- Incomplete meeting package
- The product does not meet the criteria for a complex product
- The meeting request does not meet one or more of the criteria per GDUFA III CL as mentioned in Slide 5
- In FDA's judgment, the request raises issues that can be adequately addressed through a controlled correspondence
- Submitted questions are considered as review issues or responses to CRL deficiencies
- Submitted information needs pre-review of new data or in vivo BE study protocols

Post-CRSMRs: Expectations of the Meeting Package

- The cover letter should clearly identify that it is a "*Post-Complete Response Letter Scientific Meeting Request*"
- Clearly state if it is a complex/non-complex drug product, and include any rationale or justifications for why the product meets the criteria for a complex product, if applicable
- Clearly state which of the criteria (as mentioned in Slide 5) relating to establishing equivalence the meeting request is focusing on
- Clearly state the requested format (i.e., in-person face-to-face, videoconference, or written response only)
- Specify approaches to address CRL deficiencies, grouped by discipline, with data to support the discussion

https://sbiaevents.com/files2023/GDF-2023-Day-1-Slides.zip
https://www.fda.gov/media/107626/download

Post-CRSMRs: Summary

- Post-CRSMRs are for requesting scientific advice on possible approaches to address deficiencies identified in a CRL related to establishing equivalence

- Applicants should clearly specify the GDUFA III Commitment Letter criteria that justify their meeting request along with the requested meeting format

- To effectively leverage post-CRSMRs, applicants should be mindful to avoid common reasons for meeting request denials discussed in this presentation

Acknowledgements

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