

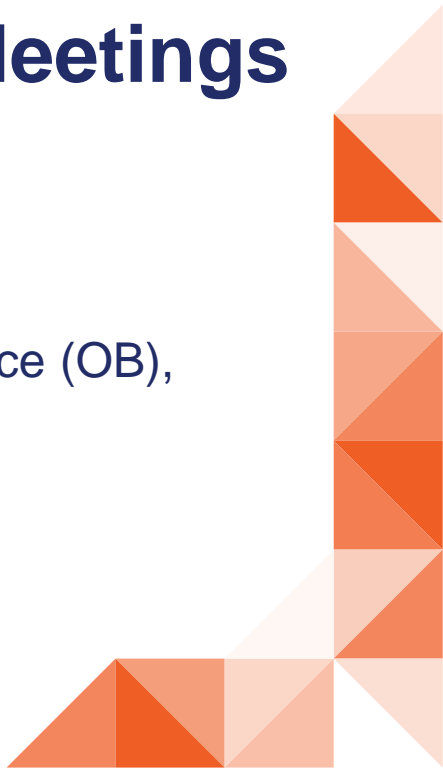
# Experiences from Post-Complete Response Letter (CRL) Scientific Meetings in GDUFA III

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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-CR**C**MR)

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-CR**S**MR)

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

<https://www.fda.gov/media/153631/download>

# 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



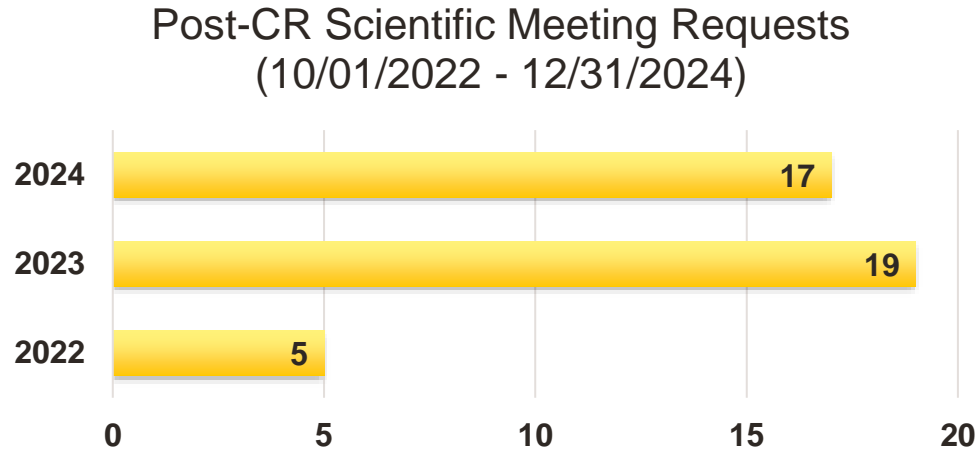
**Complex Products** – generally include:

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

# Submitted Post-CRSMRs



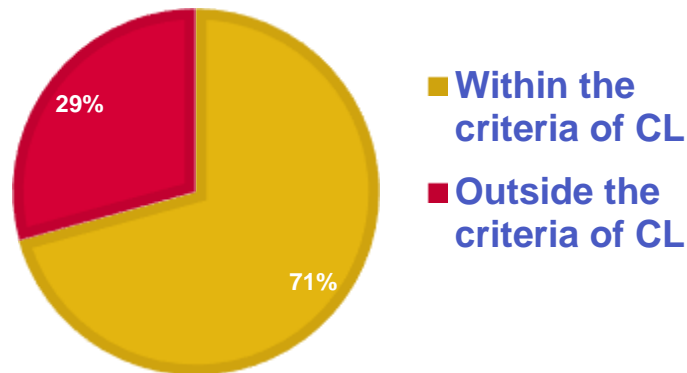
- A total of **41** post-CRSMRs were submitted between October 2022 and December 2024



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

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

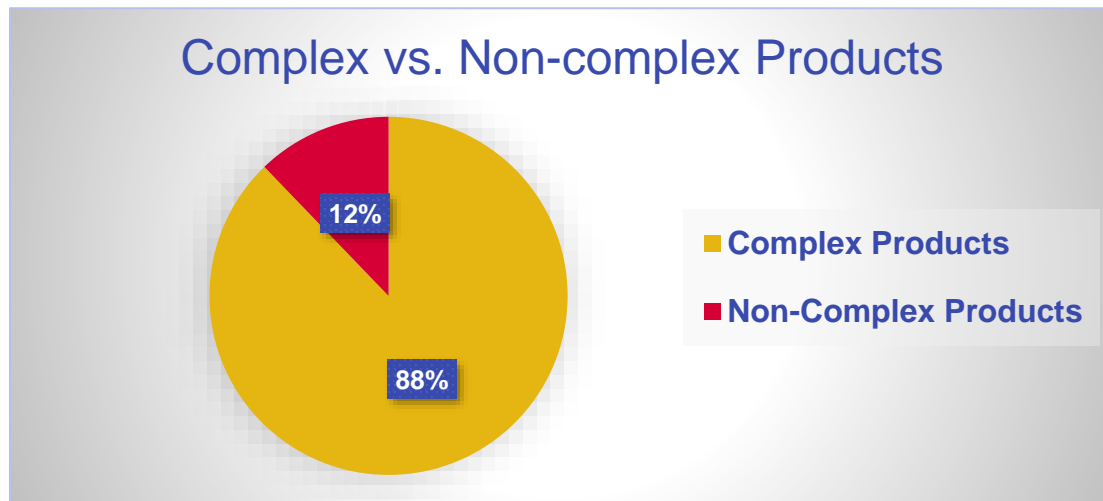
PERCENTAGE OF POST-CRSMRS WITHIN  
OR OUTSIDE THE CRITERIA OF THE CL



- ❖ 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

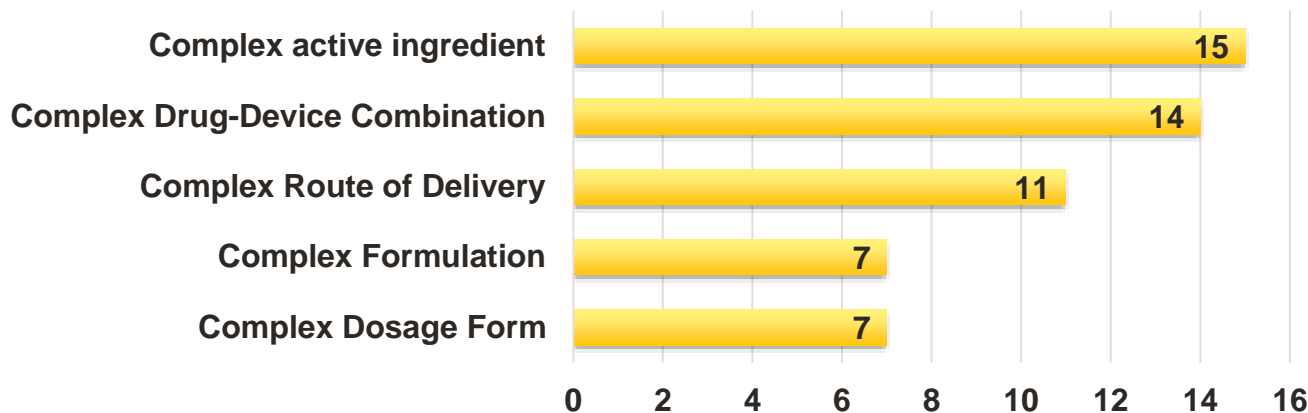


- ❖ Out of total 41 submitted post-CRSMRs, 36 (88%) were for complex drug products and 5 (12%) were for non-complex drug products

# Post-CRSMRs: Per Complex Product Category



## Number of Post-CRSMRs Submitted Per Complex Product Category

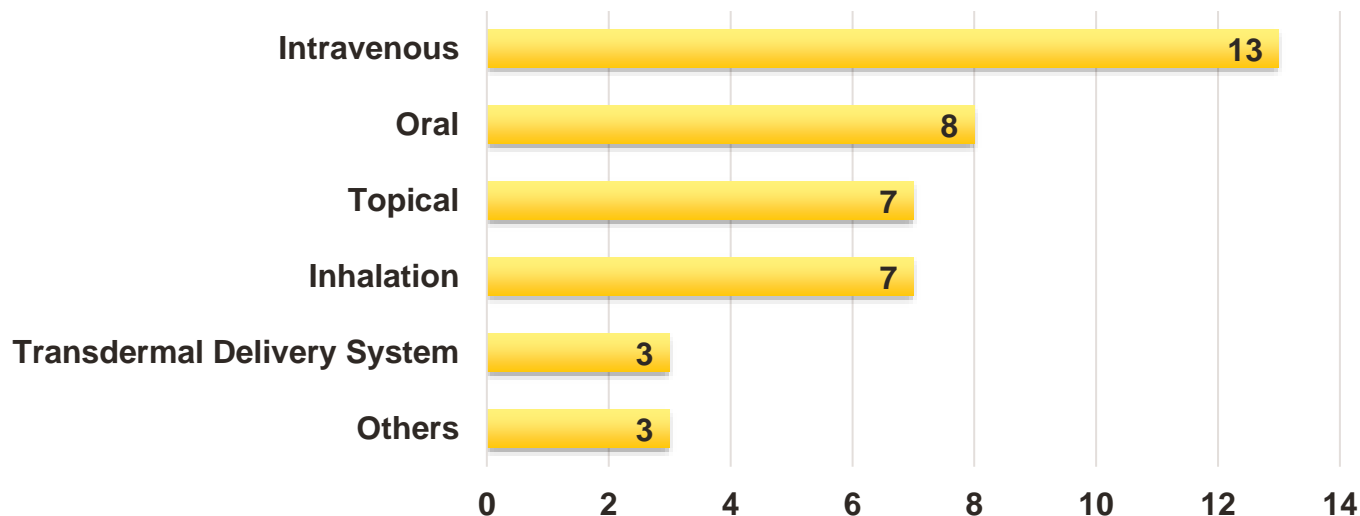


- The total number (54) exceeds 36 submitted meeting requests for complex products as some products qualified for more than one category

# Post-CRSMRs: Per Route of Administration



Number of Post-CRSMs Submitted Per Route of Administration



➤ Out of total 41 submitted meeting requests

# Post-CRSMRs: Granted vs Denied



## Meetings: Granted vs Denied

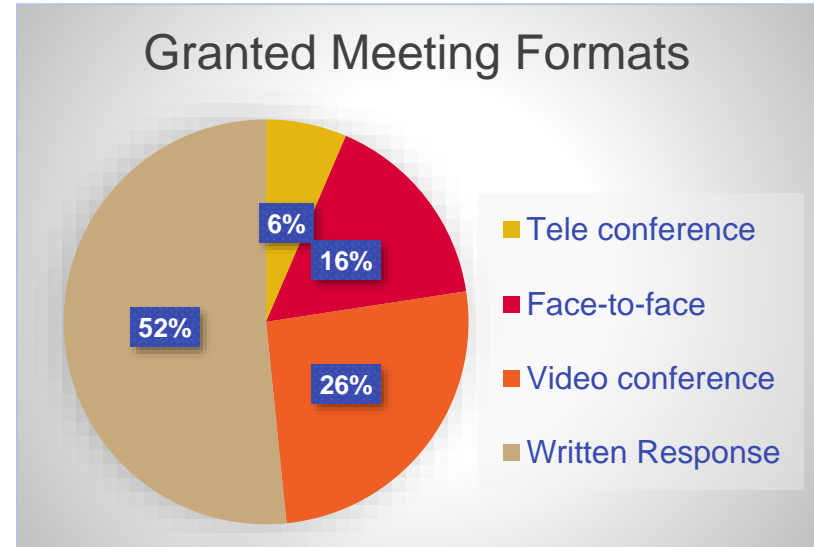
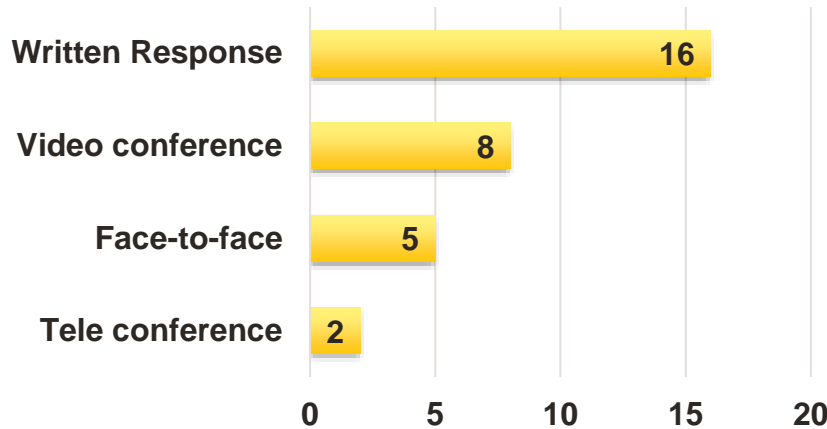


- Out of total 10 denied meeting requests, 6 were recommended to submit controlled correspondence

# Post-CRSMRs: Granted Meeting Formats



## Granted Meeting Formats

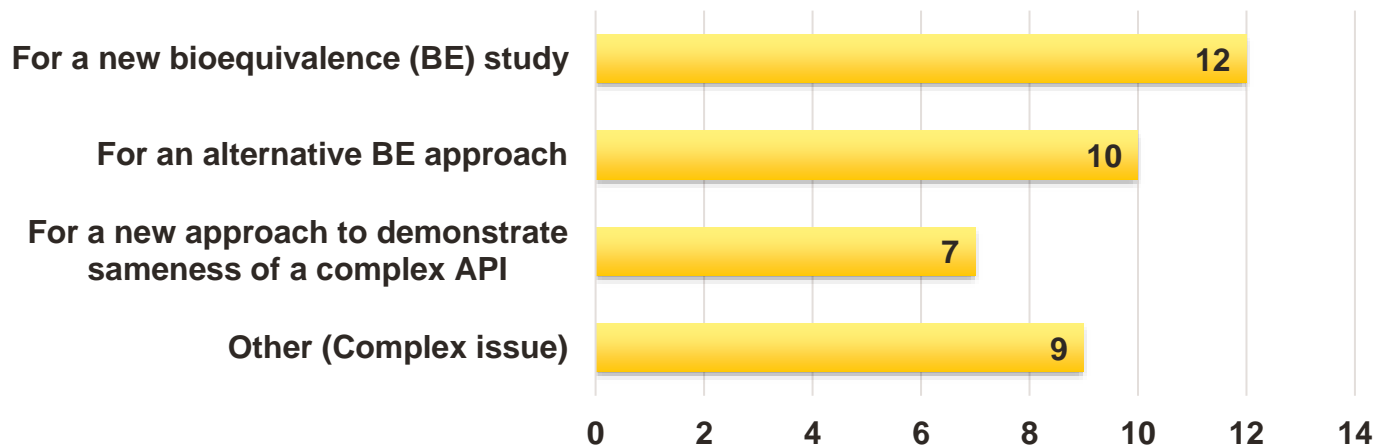


- A total of 31 post-CRSMRs were granted out of 41 submitted post-CRSMRs

# Post-CRSMRs: Criteria for Granted Meeting Requests



## Criteria for Granted Meeting Request

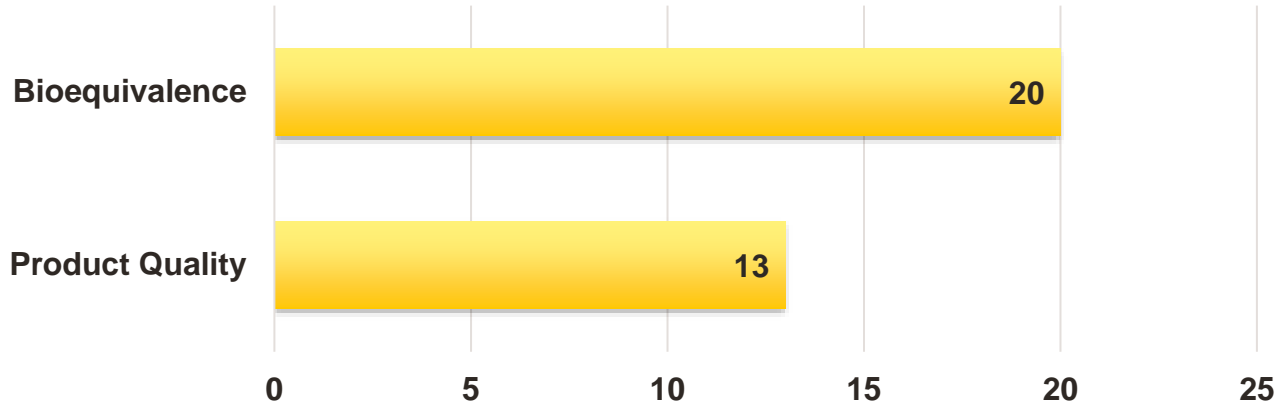


- The total number (38) exceeds 31 granted meeting requests as some meeting requests met more than one request criteria

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



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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