Unveiling the Data: Post-Complete Response Letter Scientific Meeting Requests under GDUFA III

Generic Drugs Forum (GDF) 2024:
Regulatory Considerations to Enhance Generic Drug Access
CDER Small Business & Industry Assistance (SBIA)
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Disclaimer

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

Learning Objectives

- ✓ An overview of post-complete response letter (CRL) scientific meeting requests (MRs) under GDUFA III
- ✓ Summary of the historical information
- ✓ Case studies on the effectiveness of post-CRL scientific MRs

Post-CRL Scientific Meetings

- **Purpose:** To provide an applicant with scientific advice on possible approaches to address deficiencies identified in a CRL related to establishing equivalence
- **Criteria:**
  - Complex product or in FDA's judgment, the request raises issues that are best addressed via this meeting process
  - Include one or more of the following for discussion as it relates to establishing equivalence
    - A. A new equivalence study needed to address the deficiencies identified in the CRL
    - B. An approach that is different from that submitted in the ANDA
    - C. A new comparative use human factors study
    - D. A new approach to demonstrate sameness of a complex active pharmaceutical ingredient

GDUFA III Commitment Letter Section IV.C

Likely Deny Scenario

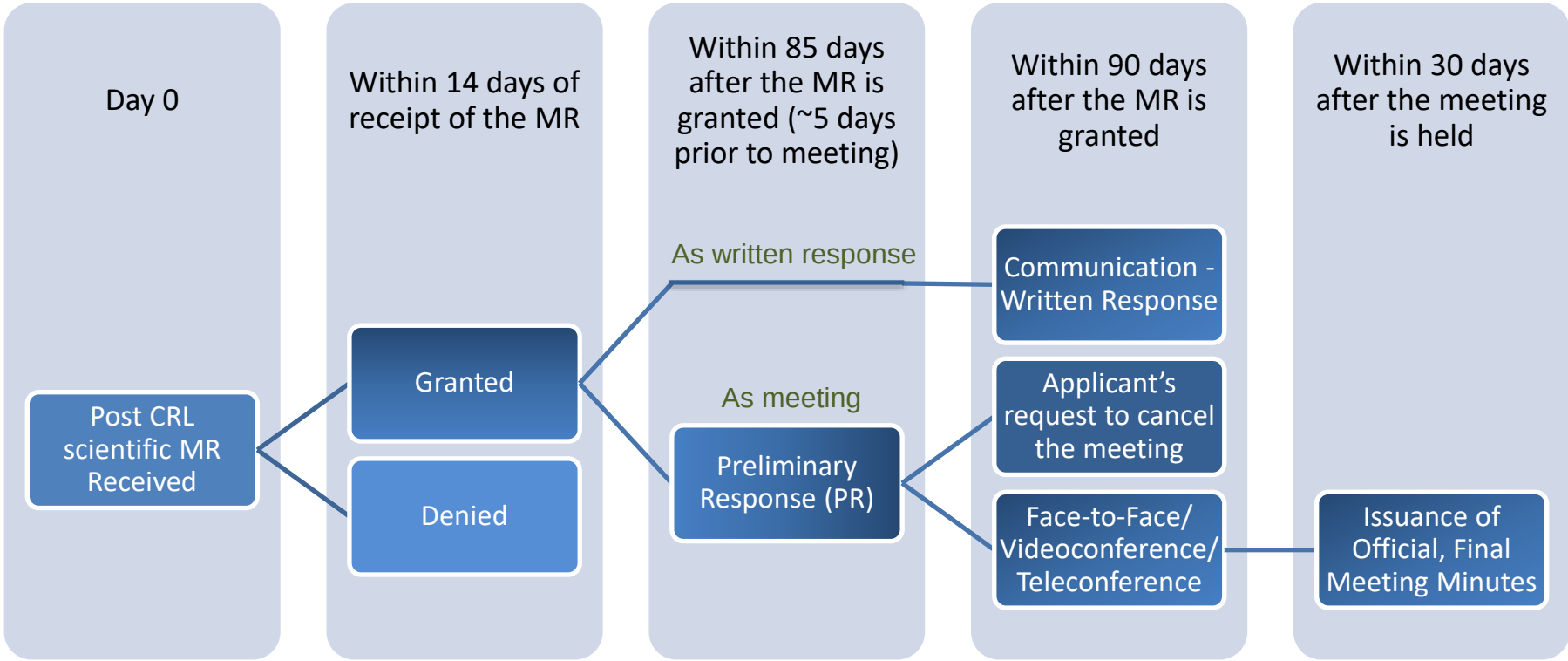
- In FDA's judgment, questions that can be more adequately addressed through controlled correspondence
- Incomplete meeting package
  - Ideally, the complete meeting package includes but not limited to
    - List of questions and their relevant criteria, per GDUFA III commitment letter, with supporting rationale or data, as applicable
    - Supporting information about the drug product (e.g., complex vs. non-complex)

Additional Remarks…

- Applicants are eligible to request a post-CRL scientific meeting even if
  - There was no prior product development meeting for respective ANDA
  - They already submitted a post-CRL clarification teleconference to seek clarification concerning deficiencies identified in a CRL
- If an applicant has additional questions after a post-CRL scientific meeting, they may submit a controlled correspondence (preferred) or request another post-CRL scientific meeting (based on eligibility)
  - Same question(s) should not be asked through multiple avenues

General Timeline

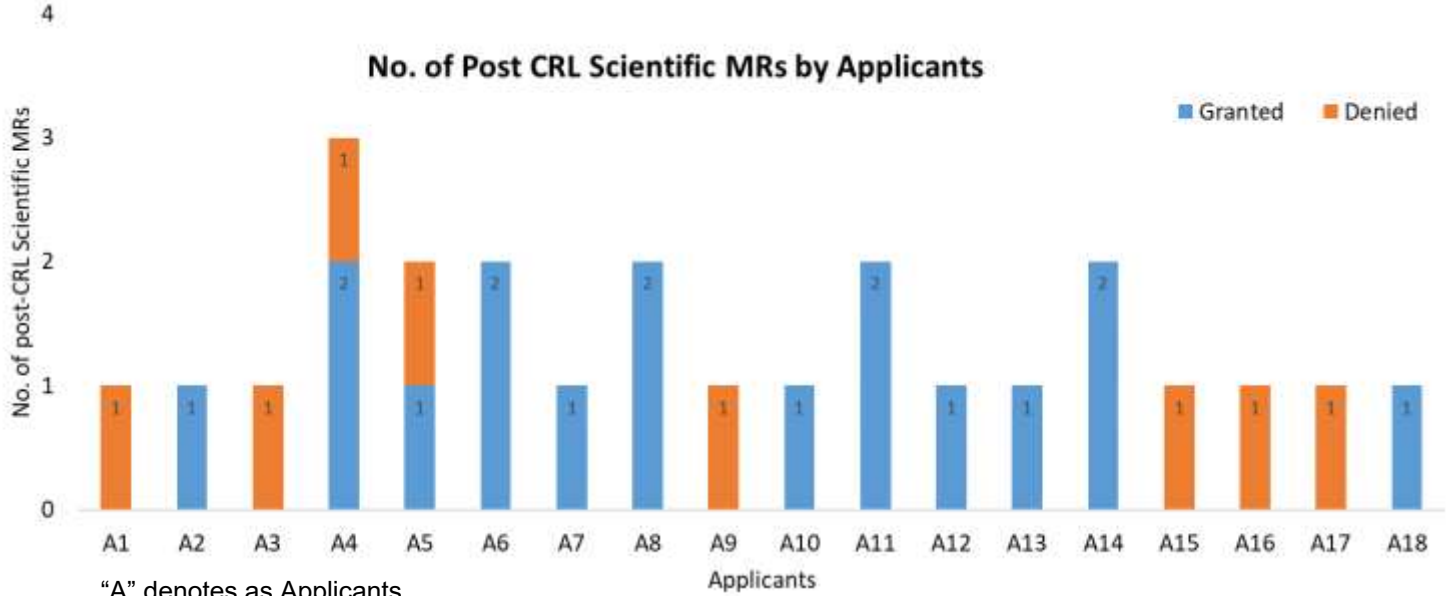
ANDAs in "Complete Response" status that meet eligibility requirements



If a due date falls on a weekend or federal holiday, it will be moved to the preceding business day

Post-CRL Scientific MRs: Synopsis

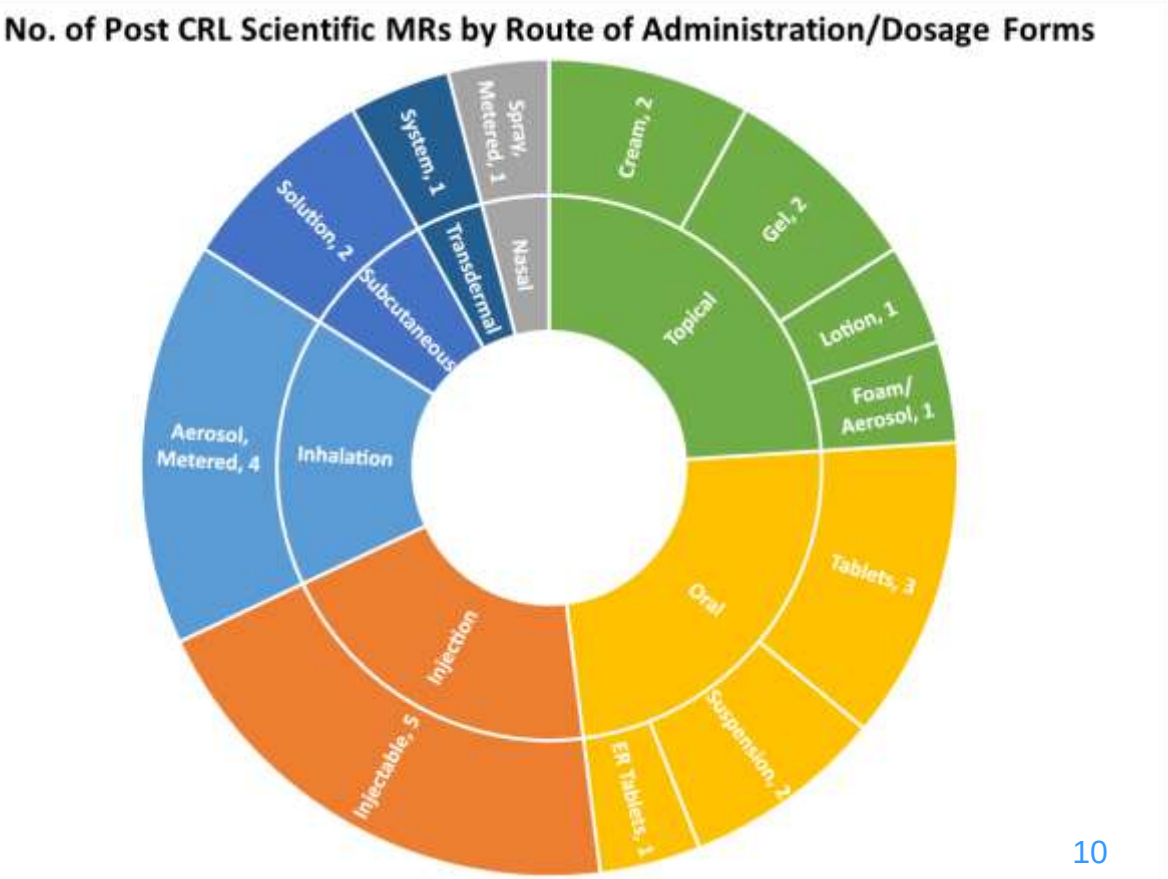
- 25 Post-CRL scientific MRs has been received between Oct. 2022 and Jan. 2024
  - 20 MRs were for complex products, and 5 MRs were for non-complex products
  - 17 MRs were granted, and 8 MRs were denied



"A" denotes as Applicants

Utilization of MRs

- MRs included wide range of dosage forms with different routes of administration for generic drug products



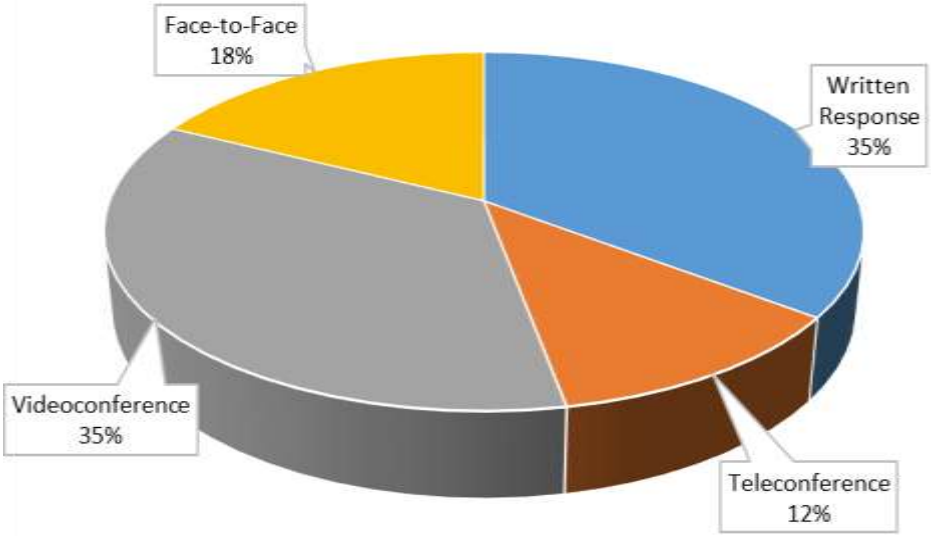
Post-CRL Scientific MRs: A Closer Look

Category	Granted Meetings		Denied Meetings
No. of MRs	17		8
Type of Drug Products	16 Complex products 1 Non-complex product		5 Complex products 3 Non-complex products
Basis/ Criteria	Criteria A: 5 MRs Criteria B: 7 MRs Criteria D: 2 MRs	• Alternative approach • Complex issues • Non-complex product met one of the criteria • Inter-office collaboration is needed	• Outside the scope • Appropriate for controlled correspondence • Same question(s) at multiple avenues

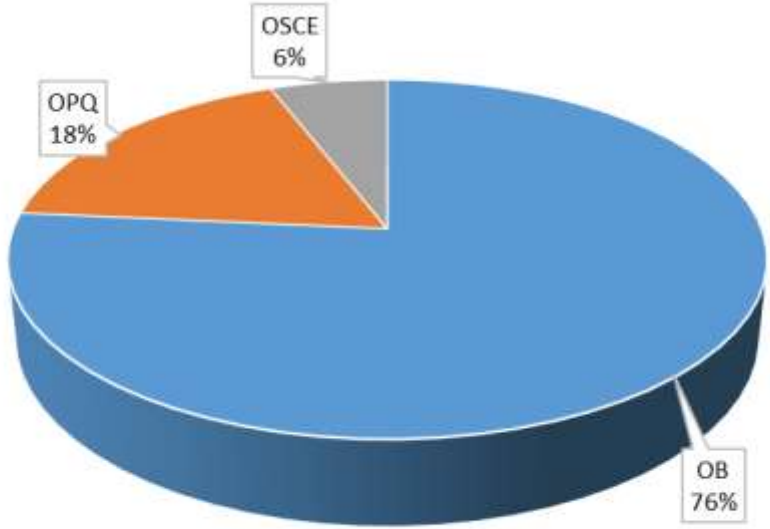
A: A new equivalence study needed to address the deficiencies identified in the CRL
B: An approach that is different from that submitted in the ANDA
D: A new approach to demonstrate sameness of a complex active ingredient
Note: Some of the MRs were qualified under more than one criteria

Post-CRL Scientific MRs: Distribution

- **Format of granted MRs**



- **Lead Offices of granted MRs**



Lead Offices are the ones who chaired the post-CRL meetings when granted. However, different offices were collaborated across disciplines to address the questions as applicable.

OB: Office of Bioequivalence
OPQ: Office of Pharmaceutical Quality
OSCE: Office of Safety and Clinical Evaluation

Case Studies: Granted MRs

- **Category:** Complex product + a new equivalence study was needed
- Example 1: Metered Aerosol Inhalation Product
  - Inadequacy about Realistic Aerodynamic Particle Size Distribution (rAPSD) and computational fluid dynamics (CFD) modeling study
  - The applicant proposed a detailed study design to address the deficiencies identified in the CRL
- Example 2: Intravenous Injectable Product
  - Recommendations to conduct a new pivotal in-vitro particle size distribution (PSD) study using adequate exhibit batches
  - The applicant sought the feedback on the proposal of manufacturing three batches of test product at commercial scale and utilize modified approach to support bioequivalence (BE), compared to the product-specific guidance (PSG) recommendations

Case Studies: Granted MRs

Continued..

- **Category:** Complex product + a different approach from the submission in ANDA

- Example 3: Topical Aerosol/Foam Product
  - Recommendations to conduct in-vivo BE study with clinical endpoints, per the PSG
  - The applicant proposed to pursue in-vitro characterization-based BE approach

- Example 4: Topical Lotion Product
  - Recommendations to conduct one of the in-vitro bioequivalence study [i.e., in-vitro permeation test (IVPT)] under characterization-based BE approach
  - The applicant proposed physiologically based pharmacokinetic (PBPK) modeling approach

Case Studies: Granted MRs

Continued..

- **Category:** Complex Product + a new equivalence study was needed + a different approach from the submission in ANDA

- Example 5: Metered Aerosol Inhalation Products
  - Same drug product with two different strengths submitted in two different ANDAs from the same applicant
  - Similar deficiencies were communicated for both applications due to similar scientific issues
  - The applicant sought clarification and concurrence for a series of repeated/new equivalence studies to address deficiencies identified in the CRLs for respective ANDAs
  - To ensure efficiency, a two-hours combined meeting was granted to discuss both applications

Case Studies: Granted MRs

Continued..

- **Category:** Complex product + an alternative approach
- Example 6: Intravenous Injectable Product
  - The applicant proposed an alternate approach for statistical evaluation of the pharmacokinetic BE study to address the deficiency in the CRL
- **Category:** Non-complex product + an alternative approach
- Example 7: Oral Extended-Release Tablets
  - The applicant proposed an alternative approach (i.e., utilization of population pharmacokinetic approach) to address the deficiency comments related to T_{lag}, observed in the submitted data

Case Studies: Granted MRs

Continued..

- **Category:** Non-complex product + complex issues

- Example 8: Oral Immediate-Release Tablets

  - The applicant sought the Agency's input for utilization of the alternatative study design compared to the recommendations in the general guidance for Biopharmaceutics Classification System-Based Biowaivers and relevant challenges (e.g., Complexity and instability of active ingredient in acidic media)

Common Observations for Denial of MRs

- Non-complex products and outside the scope of a post CRL scientific MR
- More than one meeting requested to discuss a particular issue(s) or question(s) at different avenues
- Question is more appropriate to be addressed through Controlled Correspondence
- Disputes regarding the relevance of deficiency comment(s)
- Request to evaluate/re-consider the data

Take Home Message

- The purpose of post-CRL scientific MRs is to provide scientific advice on possible approaches to address communicated deficiencies in a CRL related to establishing equivalence
- FDA will not pre-review any specific scientific data submitted in the meeting package within the scope of post-CRL scientific MR
  - However, it is encouraged to provide supporting data for the proposed approach, as applicable
- In general, the acceptability of any proposed new approach along with study data is assessed upon submission of an ANDA amendment with relevant data and information

Challenge Question #1

- If an applicant has additional questions after a post-CRL scientific meeting, the applicant may request a subsequent post-CRL scientific meeting or submit a controlled correspondence.

A. True

B. False

Challenge Question #2

- Since the applicant did not have product development meeting, the application is not qualified for post-CRL scientific meeting request, despite it is a complex product and meet one of the four criteria outlined in the GDUFA III commitment letter.

A. True

B. False

Resources to Refer…

- GDUFA Commitment Letter
- Draft Guidance for Industry: Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA

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Thank you

Questions?

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