U.S. FOOD & DRUG ADMINISTRATION

Quality Considerations for Developing Complex Generics

Best practices for successful pre-ANDA meetings and mid-cycle review meetings (MCRM), from the product quality perspective

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A quality product of any kind consistently meets the expectations of the user – drugs are no different.

Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is assuring *every* dose is safe and effective, free of contamination and defects.

It is what gives patients confidence in their *next* dose of medicine.

Overview

- Pre-ANDA program objectives- Product Development Meeting (PDEV)
- Program metrics and trends
- Best practices in preparing the meeting package
- MRCM (GDUFA III)
- Conclusion

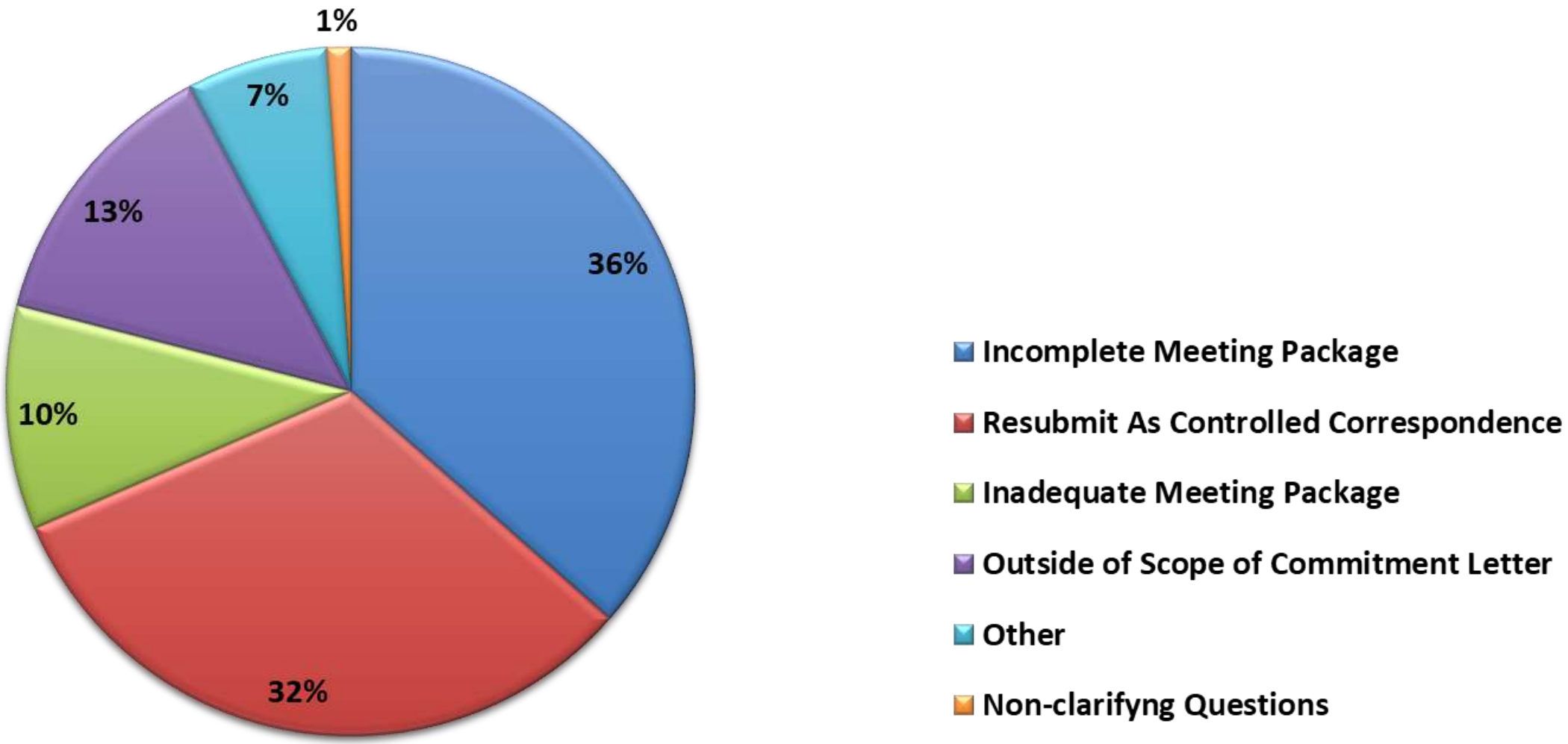
Pre-ANDA Program for Complex Generic Products

Controlled Correspondence	ANDA applicants can submit written inquiries to request information on a **specific element** of generic drug development.
Product Development Meeting (PDEV)	ANDA applicants can submit written inquiries/specific proposals to request the Agency's input **on scientific and regulatory issues in generic drug development of a complex drug product**
Pre-Submission Meeting (PSUB)	ANDA applicants can present unique or novel data or information that will be included in the upcoming ANDA submission.
Product-Specific Guidances	PSGs identify the most appropriate methodology for developing generic drugs and generating evidence needed to support generic approval.

Pre-ANDA Development (PDEV) Program

- Clarify regulatory expectations for prospective applicants early in product development
- Assist applicants to develop more complete submissions
- Promote a more efficient and effective ANDA review process
- Reduce the number of review cycles required to obtain ANDA approval, particularly for complex products

Common Reasons for Denial



What is a Complex Product?

Complex Active Pharmaceutical Ingredient	API sameness, higher order structure, etc. E.g., Glatiramer Acetate Injection
Complex Dosage Forms/ Formulations	Characterization of Formulation E.g., Doxorubicin HCl Liposomes
Complex Routes of Delivery	Q3 sameness for in-vitro BE approach E.g., Cyclosporine Emulsion
Complex Drug-Device Combinations	Complex drug-device combination products E.g., Drug product in autoinjector

Potential OPQ Topics for PDEV Meeting

- Studies on characterization of complex API, higher order structure, aggregation, etc.
- Impurity thresholds for products not covered under ICH guidance, immunogenicity assessment
- Proposed physicochemical and structural characterization tests to demonstrate Q3 sameness
- Dissolution testing and other analytical methods
- Quality information for device or container closure system
- Design of stability studies

Complex API

- Can the Agency clarify whether the proposed physicochemical and structural characterization and analytical techniques/methods are considered acceptable for demonstrating API sameness between the test product and the RLD?

Complex API

- Based on the initial studies, the ABC method could not be used for the determination of the aggregation profile of test product. We propose to use the following methods. Does the Agency agree?
- The following studies were performed to demonstrate the immunogenicity risk of the test product is low. Does the Agency agree with the conclusion or are any additional *in silico* or *in vitro* immunogenicity studies required?

Analytical Methods and Impurities

- The purity of this radiopharmaceutical will be evaluated using a validated ABC and DEF method with X-ray vision detection. Does the Agency agree that this combined method will adequately demonstrate radiochemical and chemical purity of Kryptonite Injection?
- In the absence of ICH guidance on impurities for radiopharmaceuticals, and because of the low content in the drug product, we propose to derive a control strategy based on ABC guidance. Does the Agency agree that this control strategy is adequate to establish acceptance criteria for Purity of Kryptonite Injection?

Q3 Sameness

- Can the Agency clarify whether the proposed physicochemical and structural characterization and analytical techniques/methods are considered acceptable for demonstrating Q3 sameness between the test product and the RLD?
- We believe that the proposed *in-vitro* study design is adequate to demonstrate the bioequivalence of proposed test product against the RLD for the intended ANDA submission. We request the Agency's feedback on whether the proposed studies are adequate or additional *in-vitro* characterization studies are required to demonstrate the bioequivalence of test product against the RLD.

Device

- Based on the these studies, we feel that the minor difference in the proposed device between test product and RLD arise from the difference in manufacturer. Would the Agency confirm if our proposed evaluation for the packaging component is adequate, and that no additional evaluation is required to demonstrate the suitability of the proposed packaging component?

Stability Studies

- Would the Agency please clarify if our proposal for placing the vial (containing drug product) and PFS (containing Water for Injection) onto stability (at accelerated and long term condition) as individual packs and not as a co-pack is acceptable?

Recommendations for Pre-ANDA Submission

- Familiarize yourself with all applicable guidance and standards
- Ask **specific questions** about your development plan, proposed approach / method, study design, etc.
- Include adequate justification and preliminary data (as needed) to support your proposals
- No need for data dumping
- Refrain from asking review issues

Mid-Cycle Review Meeting (MRCM)

- An opportunity for the applicant to ask for the rationale for any deficiency identified in the mid-cycle DRL(s),and/or to ask questions related to FDA's assessment of the data or information in the ANDA.
- The applicant may not present any new data or information at this meeting
- No change in goal date. Relevant DRL(s) response due date will be extended to 15 days after the MCRM is held.

Enhanced Mid-Cycle Review Meeting (EMRCM)

- An opportunity for the applicant to ask questions related to a proposed scientific path to address possible deficiencies identified in the mid-cycle DRL
- An applicant may ask questions about potential new data or information to address any possible deficiencies identified in the mid-cycle DRL
- GDUFA goal date will be extended by 60 days
- Will extend the response due date for the relevant DRL(s). Due date will be recalculated from the date of the meeting.

Challenge Question #1

Does the Agency agree that our characterization studies to demonstrate Drug Product equivalence to the RLD based on the FDA's Product Specific Guidance are in line with FDA expectations?

Is this an appropriate question for a PDEV?

A. Yes

B. No

Challenge Question #2

The applicant plans to submit a PDEV for a generic product of a synthetic peptide injection solution. Which question is not suitable for a PDEV?

A. Does the Agency agree on the proposed protocol for the adaptive and innate immunogenicity study?

B. Does the Agency agree on the proposed limit for Impurity Z?

C. Does the Agency agree on the proposed comparative studies to characterize the aggregation profile of test product and RLD?

Summary

- Understand all applicable guidance and standards to prepare meeting packages
- Choose the correct pathway and ask specific questions appropriate for the specific pathway
- Provide sufficient supporting information to justify your proposed plan

Resources

- Guidance for Industry: Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA (October 2022)
- MAPP: Evaluating Requests for and Conducting Product Development and Pre-Submission Pre-ANDA Meetings (October 2022)
- MAPP: Classifying Approved New Drug Products and Drug-device Combination Products as Complex Products for Generic Drug Development Purposes (April 2022)
- GDUFA III commitment letter

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Questions?