U.S. FOOD & DRUG ADMINISTRATION

# Pre-ANDA Meetings for Complex Drug Products

## Do's and Don'ts from the Quality Perspective

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# Overview

- Strategic use of the right communication for Pre-ANDA Communication
- What Makes a Drug Product Complex
- Pre-ANDA Meeting Package Contents and Stages
- Do’s and Don'ts for PDEV and PSUB Meetings
- Summary

# What Makes a Drug Product "Complex"

- **Complex Active Ingredient**
  - The active ingredient is not a simple, single chemical entity, *e.g.*, glatiramer acetate, protamine sulfate
- **Complex Formulation**
  - The drug is delivered via a sophisticated formulation or physical form, *e.g.*, iron sucrose, propofol
- **Complex Route of Delivery**
  - Locally acting drugs, *e.g.*, desonide emulsion, prednisolone acetate suspension, brimonidine gel
- **Complex Dosage Form**
  - Transdermal systems, *e.g.* fentanyl patches; metered-dose inhalers, e.g. albuterol MDI
- **Complex Drug-Device Combination**
  - The product consists of both a drug and a device, where the device is integral to the drug's delivery, safety, or effectiveness, *e.g.*, epinephrine auto-injector, fluticasone nasal spray

**Note**: Products may fall into multiple categories

# Pre-ANDA Communications

| Review Product-Specific Guidances (PSGs) | Submit a Controlled Correspondence (CC) | Request a Formal Meeting |
|---|---|---|
| Recommendations on bioequivalence (BE)/ pharmaceutical equivalence (PE) studies | For targeted scientific questions not answered in the PSG | For complex issues requiring in-depth dialogue and data review |
| Your foundational resource for established FDA recommendations | Best for narrow, specific scientific or regulatory questions that do not require in-depth data review or discussion. | Reserved for when CC is not adequate, or when meetings would improve assessment efficiency |
| **Always check here first** | **Be specific and focused** | **Come prepared with data** |

# PDEV & PSUB Meeting Package Contents

## Product Identification:

- Pre-assigned ANDA number
- Established name
- Reference Listed Drug (RLD) and application number
- Brief statement of purpose and objectives of the meeting, including background of the issues
- Chemical structure
- Dosage form, route of administration, and dosing regimen (frequency and duration)
- Proposed indications (e.g., if not seeking approval for all RLD indications)

## Meeting Request Information:

- Brief statement of purpose and objectives of the meeting, including background of the issues
- Brief statement indicating how the product meets the criteria for a complex product
- Requested format (face-to-face, videoconference, or written response only)

## Development Background:

- Brief history of the development program
- Status of product development

Guidance for Industry: *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022)

# Pre-ANDA Meeting Stages

| | Product Development Meeting | Pre-Submission Meeting |
|---|---|---|
| **Grant/Deny decision notification** | 14 days | 30 days |
| **Format** | Face to Face, Videoconference or Written response only | Face to face or Videoconference |
| **Schedule** | 120 days from grant | 60 days from request |
| **Eligibility** | • Complex products without a PSG<br>• Complex products with PSG but an alternative equivalence evaluation | Applicants that have had a PDEV meeting for the same complex generic product |
| **Request When** | • A controlled correspondence response would not adequately address the questions<br>• The meeting would significantly improve ANDA assessment efficiency | 6-8 months before anticipated ANDA submission |
| **Official Meeting Minutes** | 30 days from the meeting | 30 days from the meeting |

# PDEV: The Do's and Don'ts

- Focus on your development strategy and data
- Present preliminary data with adequate justification to support your proposal
- Ask a series of specific questions requiring targeted scientific advice on BE/PE study design

- Request a meeting for non-BE/PE specific elements of generic drug product development
- Ask about review issues
- Bring new data or surprises at last minutes after meeting package submitted
- Expect definitive approval of your approach

# Common Reasons for PDEV Meeting Request Denials

- Question is too broad or vague
- Question seeks assessment decision
- Question is better suited for Controlled Correspondence
- Insufficient data provided to support discussion
- Product does not meet criteria for complex product
- Question not relates to BE/PE issues

# PSUB: The Do's and Don'ts

- Provide information per the PSUB meeting presentation outline template
- Present **unique or novel** data or information that will be included in the ANDA submission
- Include regulatory history and summary of generic drug development
- Have had a prior PDEV meeting for the same product

- Treat this as a question-based meeting
- Use this as an opportunity to determine whether the application is acceptable for receipt
- Request a PSUB without a previously granted PDEV meeting
- Request a PSUB for non-complex products

# Sample Appropriate PDEV Question

**Applicant Question:**

*"Can the Agency clarify whether the proposed physicochemical characteristics and analytical techniques/ methods are considered acceptable for demonstrating sameness between the proposed test product and the RLD?"*

**FDA Response:**

- The general approach proposed for the comparative characterizations appears to be consistent with the draft product specific guidance (PSG).
- However, the adequacy of the characterization methods is an assessment issue and will be determined during the ANDA assessment.
- We have the following additional recommendations for you to consider: [Specific recommendations would follow]

**Key Takeaway:** This question is appropriate because it seeks clarification on approach, not definitive approval.

# Are These Appropriate PDEV Questions?

- Does the Agency agree with our approach for comparative physicochemical analyses of the test product and the RLD?

- Can the Agency confirm that the choice of sample preparations for comparative physicochemical analyses of the test product and the RLD are considered suitable?

# Are These Appropriate PDEV Questions?

- Does the Agency agree that the proposed parameters for the drug product specification are sufficient to control drug product characteristics at release and throughout the shelf life?

- Does the Agency agree that test A is performed only as part of the comparative characterization between the test drug product and the RLD and not as part of the routine release and stability testing?

- Can the Agency clarify whether the proposed in-use testing parameters are sufficient to confirm compatibility of the drug product with the diluent to establish the in-use storage period?

# Challenge Question

An applicant is developing a complex generic product. Which question is not suitable for a PDEV?

A. Does the Agency agree our proposed approach of using CD/FTIR to evaluate the secondary structure of Peptide A in the test DP and RS, with respect to active ingredient sameness?

B. Can the Agency clarify whether the proposed in-use stability study protocol for an implant device is considered reasonable to demonstrate compatibility?

C. Does the Agency agree on the proposed limit for Impurity X?

# An Important Reminder

- Please be advised that the final decision regarding the adequacy of any supporting data and information will be determined once the ANDA submission is received and reviewed by the Agency.
- Additional information may be requested on these specific issues during the application review process.

# Resources

- GDUFA III Commitment letter (2022)
- Guidance for Industry: *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022)
- Guidance Document: *Controlled Correspondence Related to Generic Drug Development* (March 2024)
- Product-Specific Guidances (PSGs): www.fda.gov/generic-drugs
- GDUFA Information: www.fda.gov/GDUFA

# Summary

**Key Takeaways:**

- Use Product-Specific Guidance, Controlled Correspondence, and formal meetings (PDEV/PSUB) strategically for effective FDA engagement.
- Prevent denials by generating robust data and asking targeted, science-based questions.
- Use PDEV meetings for scientific discussion on BE/PE approaches during development
- Use PSUB meetings to present unique or novel information that will be included in the ANDA submission.

**Remember**: Final decisions on adequacy of data and information are made during ANDA review