# GDUFA II: Pre-ANDA Program and Meetings for Complex Generic Products

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Generic Drug Forum

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# Outline

- The Pre-ANDA Program
  - Three Pre-ANDA Meeting Types for Complex Products
  - Controlled Correspondence
  - Product-Specific Guidances
- The Pre-ANDA Meeting Process and the Meeting Package
- The Pre-ANDA Program Tips for Success

# The Pre-ANDA Program

- The Pre-ANDA Program was established by GDUFA II to
  - Clarify regulatory expectations for prospective applicants early in product development
  - Assist applicants to develop more complete submissions
  - Promote a more efficient and effective review process
  - Reduce the number of review cycles required to obtain ANDA approval of Complex Products

- Pre-ANDA meetings accelerate access to generics of complex products through early engagement with the FDA
  - Product development meeting
  - Pre-submission meeting
  - Mid-review cycle meeting

# Complex Products

| COMPLEX of: | Complex Product Type | Drug Products |
|---|---|---|
| Active Pharmaceutical Ingredients (APIs) | peptides, complex mixtures of APIs, naturally sourced ingredients | Glatiramer acetate injection, Sevelamer carbonate tablet/powder, Conjugated Estrogens tablet |
| Formulations/Dosage Forms | liposomes, colloids, transdermals, extended-release injectables, implantables | Doxorubicin HCl Liposome injection, Cyclosporin ophthalmic emulsion, Etonogestrel implant, Lidocaine patch |
| Routes of Delivery | locally acting drugs such as dermatological products, complex ophthalmological products | Acyclovir topical cream/ointment, Prednisolone acetate ophthalmic suspension |
| Drug-Device Combinations | dry powder inhalers, metered dose inhalers, nasal sprays, auto-injectors | Mometasone furoate nasal spray, Fluticasone propionate and Salmeterol inhalation powder, Epinephrine auto-injector |
| Other products | complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement | Abuse deterrent opioid formulations |

Generic Drug User Fee Amendments (GDUFA) II Commitment Letter:
https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

# Product Development (PDEV) Meeting

- A meeting involving a scientific exchange to discuss specific issues or questions
- FDA will provide targeted advice regarding an ongoing ANDA development program
- Timing: Anytime during product development stage

# Pre-Submission (PSUB) Meeting

- A meeting to discuss and explain the format and content of an ANDA to be submitted
- Pre-submission meetings will not include a substantive review of summary data or full study reports
- Timing: ANDA expected to be submitted within 6-12 months

*Guidance for Industry: ANDA Submissions- Content and Format (September 2018)*
https://www.fda.gov/downloads/drugs/guidances/ucm400630.pdf

# Mid-Review-Cycle Meeting

- Scheduled for those applicants with prior PDEV and/or PSUB meetings
- Generally occurs at the mid-point of the review plus

  30 days
- Provides the applicant with an update on the status of the review of their application and next steps forward

# GDUFA II: Controlled Correspondence (CC)

- Standard CC review and respond within 60 calendar days
  - Information on a specific element of generic drug development
- Complex CC review and respond within 120 calendar days
  - Clinical content and bioequivalence protocols for reference listed drugs (RLDs) with risk evaluation and mitigation strategies (REMS) or with elements to assure safe use (ETASU)
  - Alternate bioequivalence approach within the same study type (e.g. in vivo pharmacokinetic, in vitro, and clinical)
- Clarification of ambiguities CC review and respond within 14 calendar days

*Draft Guidance for Industry: Controlled Correspondence Related to Generic Drug Development (November 2017)*
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm583436.pdf

# Product-Specific Guidances (PSGs)

- For general questions about PSGs - use the controlled correspondence process
- Alternative bioequivalence approach to issued PSG
  - Complex controlled correspondence process (120 calendar days)
  - Pre-ANDA meeting process
- No PSG for Complex Product
  - Pre-ANDA meeting process
  - FDA must grant meetings for complex products with no PSG
- Almost 1700 PSGs are currently available as of February 2019

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

# Submitting the Meeting Request

- Obtain a pre-assigned ANDA number

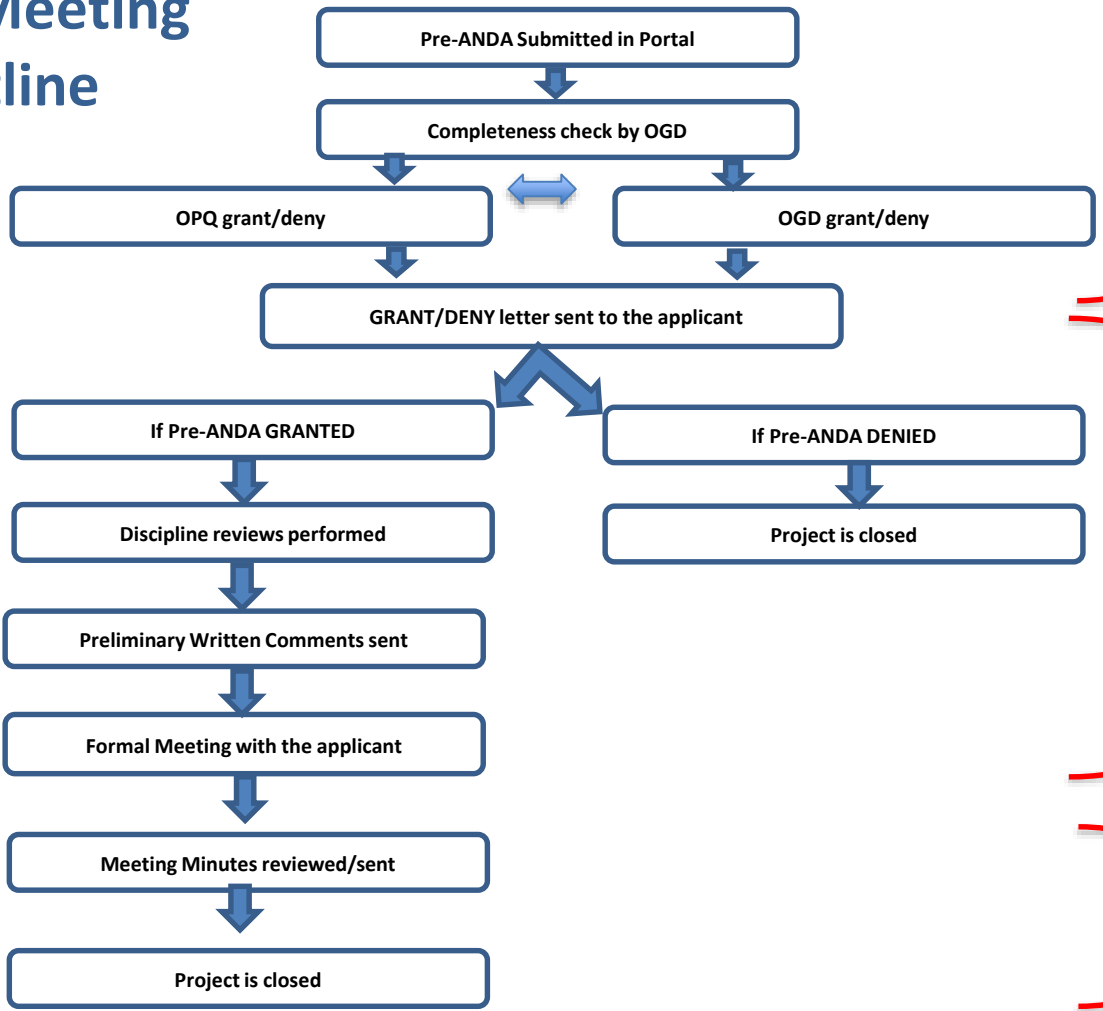
  https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm114027.htm

- Submission via the CDER Direct NextGen Collaboration Portal
  - The Portal website https://edm.fda.gov
- Meeting package for PDEV
  - Provide clear and specific questions that are supported by appropriate data
- Meeting package for PSUB
  - Outline the unique, novel or complex aspects of upcoming ANDA submission to be presented at the meeting
  - Provide appropriate background material and data for specific questions regarding the submission

# Meeting Package Format & Content

- Refer to the draft Guidance for Industry (October 2017)
  - *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*
- Each question is followed by a corresponding justification, rationale or data to support discussion as applicable
- List of questions grouped by discipline (e.g. Bioequivalence, CMC etc. )
- Each question clearly numbered (e.g. 1,2,3 without sub-questions)

# Pre-ANDA Meeting Process Outline




**Stage 1**
**(30 days)**
**Will be 14 days starting Oct 1st 2019**

**Stage 2**
**(120 days)**

**Stage 3**
**(30 days)**

# Pre-ANDA Meeting Package Assessment

- A project manager from the Office of Research and Standards (ORS) is assigned as the point of contact
- The FDA staff will assess the meeting package, request consults if needed, and send information requests (IRs)
  - Prospective ANDA Applicant responds to any IRs via the Portal
- The FDA will strive to send preliminary written comments at least five calendar days prior to the meeting

# Meeting Day

- After receiving preliminary written comments from the FDA, prospective ANDA applicant should optimize and submit the meeting agenda and/or slides via the Portal
  - Pre-ANDA meetings are typically one hour
  - Agenda should be focused on clarification or further discussion around the preliminary written comments
- Meeting participants discuss the questions and the data provided to assist the prospective ANDA applicant's complex product development program
- **FDA will not address or discuss new data or questions not presented in the original meeting package**

# Post-Meeting

- FDA will issue official minutes within 30 calendar days of the meeting
- If prospective ANDA applicants would like the FDA to consider their meeting summary:
  - Submit within 7 calendar days of the Pre-ANDA meeting
  - Must be submitted via the portal

# GDUFA II: Pre-ANDA Program Tips for Success

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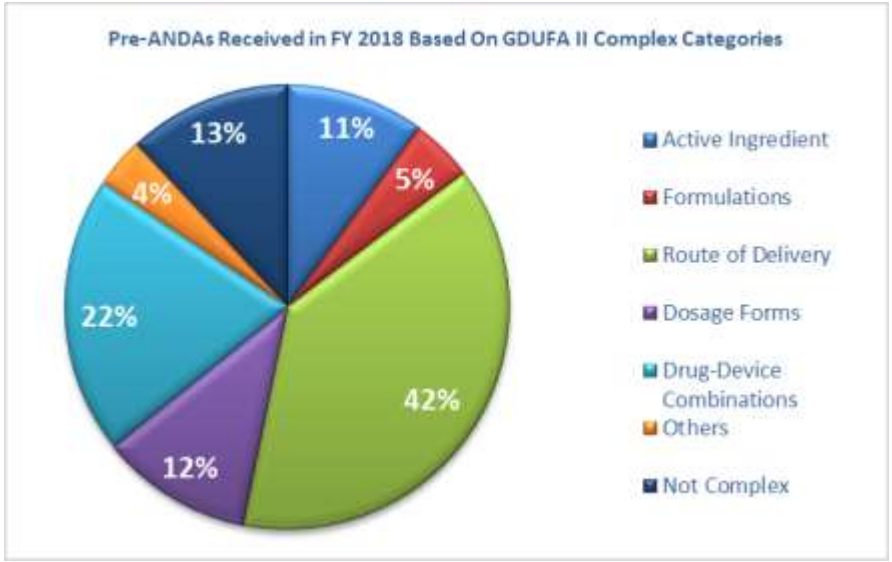
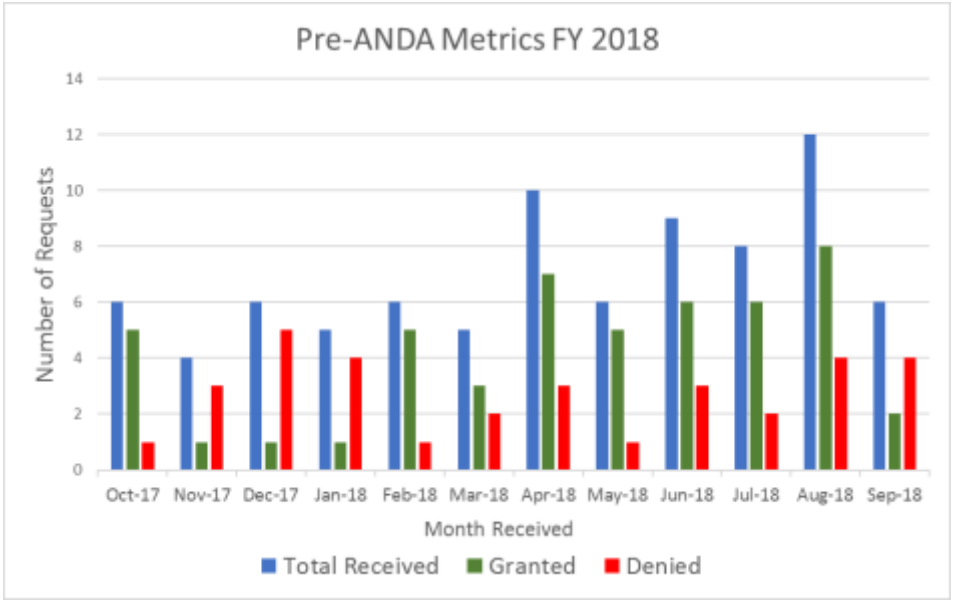
# GDUFA II Pre-ANDA Metrics

- In Year 1
  - 83 total Pre-ANDA Requests
  - 48 Meetings Granted
  - 13 Meetings cancelled due to sponsor satisfied with the preliminary written response

# GDUFA II Pre-ANDA Metrics



# Common Reasons for Denial

- Incomplete meeting packages
- Not a complex product
- Wrong meeting type chosen – PDEV vs PSUB
- Should be a controlled correspondence
- PSG is available and not asking for an alternate bioequivalence route

# Helpful Tips

- Provide sufficient data to review question in the meeting package
- Q1/Q2 questions where not required by regulation or recommended in a PSG—yes this is the pathway
  - Submit a meeting request that proposes a BE approach for a specific formulation
  - FDA will provide feedback on the BE approach
  - If you know you are not Q1/Q2, include your justification

# Helpful Tips-Submitting Devices

- Read the guidance on Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA
  - AKA: Comparative Analyses Guidance
- Consider when and how to submit your device
  - As part of a meeting request or as a control?
  - Prototype or final design?
  - What about 3D printed devices?

# Am I a Pre-sub or Prod-dev Meeting?

- Product Development meetings are for discussion of specific scientific issues
  - Proposed study design, alternative approach, additional study expectations
- Pre-submission meetings are for 6-12 months before submission
  - You are ready to submit
    - Do you have your stability batches started?
  - Discuss format and content of ANDA
    - Not a filing review

# Am I a Controlled Correspondence or Prod-Dev?

- Standard controls reviewed in 60 days
  - Use for guidance clarification and rapid input into development programs
- Complex controls reviewed in 120 days (new in GDUFA II)
  - Clinical input (protocols for Safety determination letters)
  - Alternate BE approach (within the same class)
- Consider timelines – how soon will I get my answer?
- Pre-ANDA meetings are best for multidisciplinary questions
- Controls are for single questions or a small group of closely related questions

# Examples of Useful Questions

- NOT- Please review the protocol
  - Instead submit specific questions regarding your protocol
- NOT- What tests should I do?
  - Instead propose your development plan with appropriate justification
- NOT- Is my PK study acceptable?
  - Instead identify the point of uncertainty and ask a specific question
- NOT- Is my specification acceptable?
  - Instead ask a specific question about this complex product and your understanding of how you will control the CQA of your product

# Example Pre-ANDA Questions

- Are there additional critical material attributes or critical process parameters that FDA feels we should address?

- Does the Agency agree that, on the basis of the data presented, the proposed physicochemical tests are acceptable to support comparative physicochemical characterization?

- Does the Agency agree with the approach we designed to compare the overall particle size distribution of API particles in the test and RLD product by means of MDRS and SEM-EDS?

# Example Pre-ANDA Questions

- Based on above mentioned observations, XXX believes that drug substance used by XXX to manufacture the submission batches either does not have amorphous material or could be present at an insignificant level which doesn't affect product performance. XXX believes that XRD Test at drug substance release test would be sufficient to show the crystalline purity. Is it acceptable to the agency?

- Does FDA agree with the proposed manufacturing process and controls including in-process tests?

- Does FDA agree with XXX's assessment that all the potential impurities listed in the table provided can be controlled in the drug substance consistent with the limits recommended in pharmacopeia and ICH Q3A(R2) guidance?

# The Pre-ANDA Program: Lessons Learned

- No run-on questions please!
- Group questions based on discipline (BE, CMC, Regulatory, Biopharmaceutics etc.)
- Provide adequate supporting information for each question
  - Prevents the Pre-ANDA from being denied
  - Allows FDA to provide the best response
  - Avoids information requests

# Point of Contact

- Meeting Project Manager
  - ➢Point of contact for prospective applicants/US Agents
- Email PreANDAhelp@fda.hhs.gov (Pre-ANDA Meetings)
- Email GenericDrugs@fda.hhs.gov
- Email Druginfo@fda.hhs.gov

# Take-Aways

- Use the portal to submit your meeting requests
- Read the guidance to help develop a the meeting package
  - "Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA"
- Choose the correct pathway
  - Product Development, Pre-submission, or Controlled Correspondence
- Ask specific questions
- Provide sufficient information to address your question
- We look forward to working with you!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