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

Christine Le, PharmD, PMP
Commander, United States Public Health Service
Regulatory Research Officer/Project Manager
Office of Research and Standards
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Generic Drug Forum

April 3, 2019

Outline

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

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

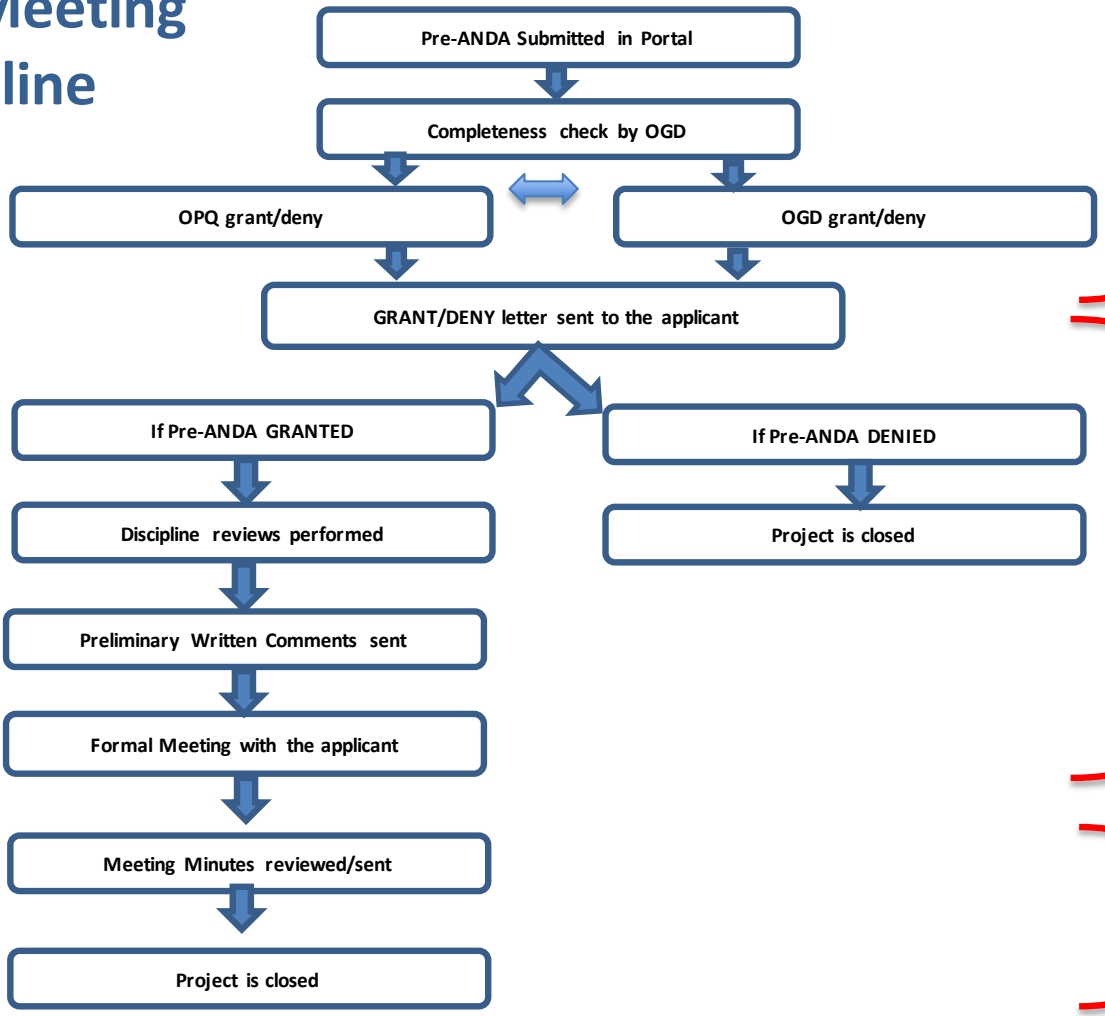
  https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm114027.htm

- 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

Take-Aways

- Use the portal to submit Pre-ANDA meeting requests
- Read the draft Guidance for Industry (October 2017)
  - "Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA"
- Choose the correct pathway
  - Product Development Meeting, Pre-Submission Meeting, or Controlled Correspondence
- Provide sufficient information/data

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