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

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Overview Pre-ANDA Program Components

- Research
- Product-Specific Guidances (PSGs)
- Controlled Correspondence (CC)
- Meetings for ***complex*** products

ANDA – abbreviated new drug application

Research

Scope

- FDA conducts internal and external research to support fulfilment of submission assessment and pre-ANDA commitments

Public Workshops

- Annually, FDA conducts a public workshop to solicit input from industry and stakeholders for inclusion in an annual list of GDUFA II Regulatory Science initiatives
- Interested parties may propose regulatory science initiatives via email to genericdrugs@fda.hhs.gov
- FY 2021 Generic Drug Science and Research Initiatives Public Workshop will be held on June 23, 2021: https://www.fda.gov/drugs/news-events-human-drugs/fy-2021-generic-drug-science-and-research-initiatives-public-workshop-06232021-06232021
- After considering industry and stakeholder input, FDA posts a list of research priorities on FDA's website
- Industry GDUFA II regulatory science working group
    - Meets with FDA twice yearly on current and emerging challenges and concerns

Research

Reporting

- FDA prepares annual reports on the extent to which GDUFA science and research-funded projects support:
  - the development of generic drug products
  - evidence needed to support efficient assessment and timely approval of ANDAs
  - the evaluation of generic drug equivalence

https://www.fda.gov/drugs/generic-drugs/generic-drug-research-related-guidances-reports

https://www.fda.gov/drugs/fy-2019-gdufa-science-and-research-outcomes

Product-Specific Guidances (PSGs)

- Agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent to specific reference listed drugs

- Approximately 1,900 PSGs are currently available as of April 2021 https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

- Upcoming New or Revised PSGs for Complex Generic Drug Product Development

  https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-complex-generic-drug-product-development

- Plan to attend the SBIA PSG Webinar on May 5, 2021 FDA Product-Specific Guidances: Lighting the Development Pathway for Generic Drugs - 05/05/2021 - 05/05/2021 | FDA

How Often Does FDA Publish New and Revised PSGs?

- FDA issues new and revised PSGs on a quarterly and as-needed basis
- The published PSGs are announced in the Federal Register and made available to the public on FDA's website

Product-Specific Guidance Drive Pre-ANDA Process

Controlled Correspondence (Controls)

- Questions on the guidance for Complex products and alternatives to the guidance
  - Within the same study type

Pre-ANDA Meetings

- Complex product and no guidance
- Complex product and alternative to guidance
  - Different study type

Controlled Correspondence (CC)

- **Standard CC (60 calendar days)**
  - Requesting information on specific element of generic drug development
  - Post approval submission requirements not covered by guidance on post approval changes and not specific to an ANDA
- **Complex CC (120 calendar days)**
  - Evaluation of clinical content
  - Bioequivalence (BE) protocols for reference listed drugs (RLDs) with risk evaluation and mitigation strategies (REMS) with elements to assure safe use (ETASU)
  - Alternate BE approach within the same study type (e.g., pharmacokinetic, in vitro, and clinical)

Controlled Correspondence Related to Generic Drug Development, December 2020

GDUFA Reauthorization Performance Goals & Programs Enhancements Fiscal Year 2018-2022

Clarification of Ambiguities

- Controlled correspondence response, in FDA's judgment, merits further clarification
- The request should be submitted within 7 calendar days of issuance of FDA's controlled correspondence response
- A request received after 7 calendar days from issuance of the controlled correspondence response is considered a new controlled correspondence

Challenge Question

Bioequivalence (BE) protocols for reference listed drugs (RLDs) with risk evaluation and mitigation strategies (REMS) with elements to assure safe use (ETASU) is an example of which type of controlled correspondence?

Complex controlled correspondence

Complex Products

Complex active pharmaceutical ingredient (API)	• Any drug product containing a complex API, regardless of administration routes and dosage forms. e.g., Conjugated Estrogen Tablet, Glatiramer Acetate Injection
Complex routes of delivery	• Any non-solution drug product with a non-systemic site of action (e.g., topical, ophthalmic, local gastrointestinal (GI) action) e.g., Cyclosporine Emulsion, Acyclovir Cream
Complex dosage forms/formulations	• Any non-oral complex formulation/dosage form product where there are often two or more discrete states of matter within the formulation e.g., Doxorubicin HCl Liposomes, Leuprolide Acetate for Depot Suspension
Complex drug-device combinations	• Where the drug constituent part is pre-loaded in a product-specific device constituent part or is specifically cross-labeled for use with a specific device, in which the device design affects drug delivery to the site of action and/or absorption e.g., Epinephrine Injection (autoinjector)
Other products	• Any solid oral opioid drug products with FDA approved labeling for that show properties (and thus gaining their labeling) to meaningfully deter drug abuse e.g., Hydrocodone Bitartrate ER Tablet

Lionberger R. Innovation for Generic Drugs: Science and Research Under the Generic Drug User Fee Amendments of 2012, Clinical Pharmacology & Therapeutics (CPT), 2019, Vol.105(4), p.878-885

Pre-ANDA Program Goals

- Clarify regulatory expectations for prospective applicants early in product development
- Assist applicants to develop more complete submissions
- Promote a more efficient and effective ANDA assessment process
- Reduce the number of review cycles required to obtain ANDA approval, particularly for ***complex*** products
  - MAPP 5220.8: Evaluating Requests for and Conducting Product Development and Pre-Submission Pre-ANDA Meetings https://www.fda.gov/media/130874/download

GDUFA II Meetings: Before ANDA Submission

Product Development (PDEV)

- Scientific exchange to discuss specific issues or questions (e.g., a proposed study design, alternative approach, or additional study expectations)
- Targeted advice regarding ongoing ANDA development program

Pre-submission (PSUB)

- Discuss and explain content and format of the ANDA to be submitted
- Advice to enable efficient review and improve chances of first cycle approval
- Does ***not*** include substantive review of summary data or full study reports
- ANDA is anticipated to be submitted ~6 months after meeting date

GDUFA II Meetings: After ANDA Submission

Mid-Review-Cycle Meeting (MRCM)

- Held during first review cycle with prior PDEV and/or PSUB meetings
- Generally mid-point of review plus 30 days
- Update on status of review and next steps
- Applicants should not submit meeting requests for the MRCM, the Regulatory Project Manager will contact the applicant to schedule the meeting

Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA Guidance for Industry

CC or PDEV Meeting?

- **Controlled Correspondence**
  - Single or small group of closely related questions
  - Response within 60 (standard) or 120 (complex) calendar days
  - Following a PDEV meeting, applicant seeking further clarification or has new question related to what was discussed at the meeting
- **Pre-ANDA Meeting**
  - Best for multidisciplinary questions
  - Do not submit the same question through CC and pre-ANDA meeting
  - New information, data, or questions that will not be adequately addressed in a controlled correspondence
  - Meeting held within 120 days of being granted
  - Recommend one request for a product development meeting for the specific complex product per year

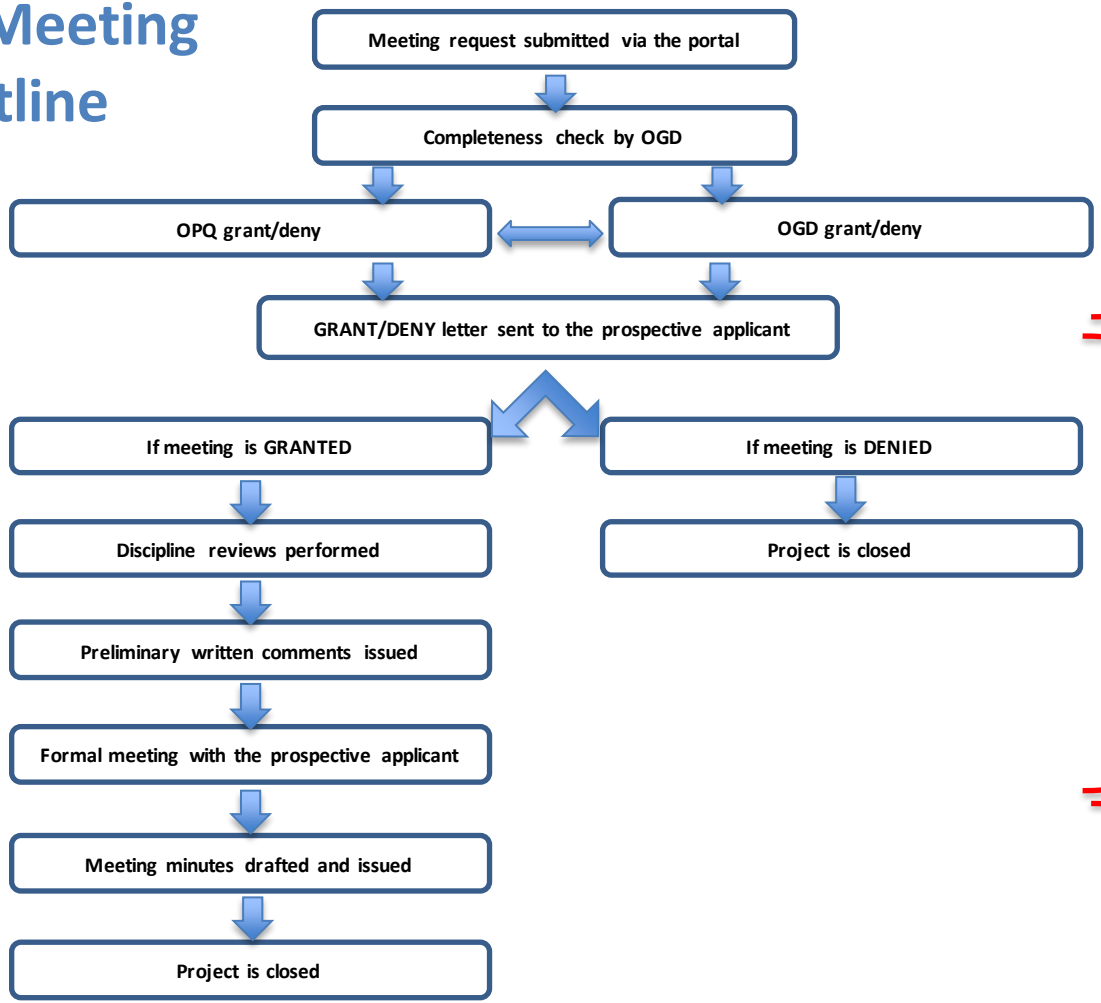
FDA will Grant a PDEV or PSUB Meeting for a Complex Product, if:

- No PSG available
- Proposing an alternative BE approach to the PSG
  - Change in study type (e.g., in vitro instead of in vivo approach)
- Meeting package is complete
- Questions could not be adequately addressed through a CC
- A meeting would significantly improve ANDA review efficiency

Depending on Available Resources, FDA may Grant if, in FDA's Judgment:

- Concerns complex product development issues
- Meeting package is complete
- Questions could not be adequately addressed through a CC, and
- May grant a meeting for non-complex product
- A meeting would significantly improve ANDA review efficiency

Pre-ANDA Meeting Process Outline



Stage 1
(14 days*)
***As of Oct 1st 2019**

Stage 2
(120 days)

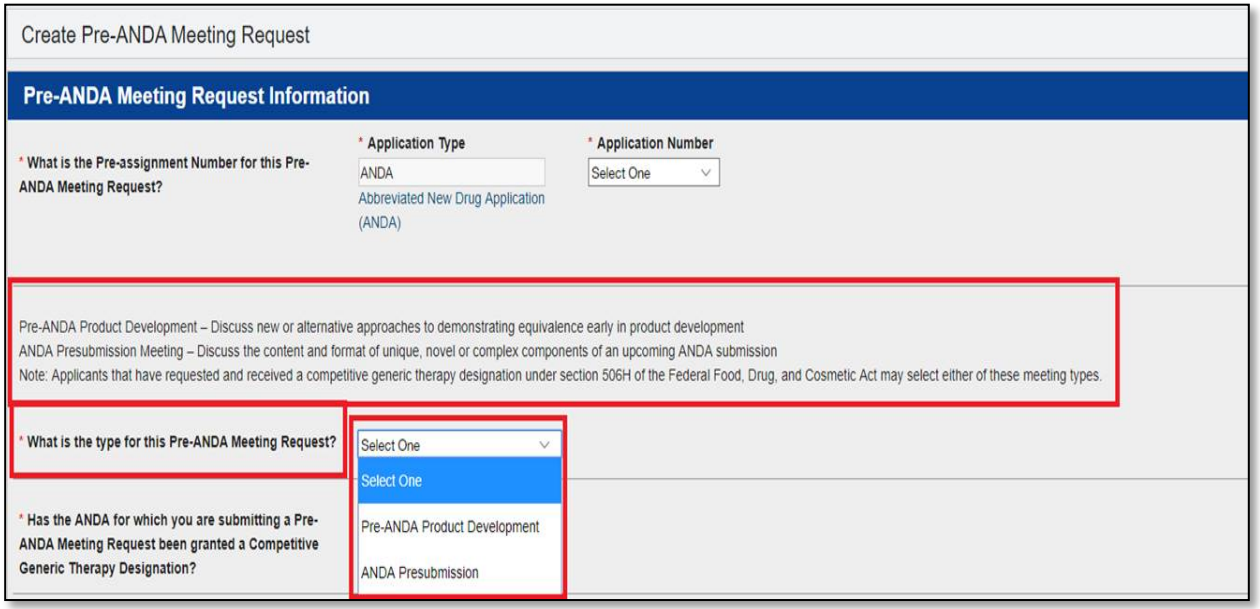
Stage 3
(30 days)

Submitting Your Meeting Request

- Obtain a pre-assigned ANDA number

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

- Submit via the CDER Direct NextGen Collaboration Portal



Submitting Your Meeting Request

- Meeting package for PDEV
  - Provide specific proposals and questions supported by appropriate data and scientific justification
- Meeting package for PSUB
  - Outline the unique, novel, or complex aspects of your upcoming submission
  - If you have specific questions, provide appropriate background material and data related to those questions

Meeting Package Format and Content

- Refer to the final Guidance for Industry (November 2020)

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

Meeting Request Evaluation

- Parallel assessments of the meeting request by the Office of Generic Drugs (OGD) and the Office of Pharmaceutical Quality (OPQ)
  - Meeting request assessment team reviews the product details, contents, and submitted questions
  - OGD and OPQ coordinate to provide a unified response

Your Meeting Was Granted

- Typically granted as face-to-face (FTF) meeting, though the applicant can request a written response or teleconference
  - During the pandemic, FTF are converted to t-con
  - You will be notified 4-6 weeks before the meeting
- Written responses and teleconferences still qualify you for a mid-review-cycle meeting
- A project manager from the Office of Research and Standards (ORS) or OPQ is assigned as the point of contact

Pre-ANDA Meeting Package Assessment

- After the meeting is granted, FDA staff will review the meeting package, request consults and send information requests (as needed)
- Information Requests (IR)
  - Sent to prospective applicant through the portal
  - FDA strives to send early in the process, but can be sent at any point
  - Prospective applicant responds to the IR through the portal
- Preliminary responses are based upon the Agency's current thinking and knowledge
  - May change with available data or research, etc.

Preliminary Responses

- Preliminary written comments will be sent via the portal approximately 5 calendar days before your scheduled meeting
- Your opportunity to focus your meeting
  - Submit presentation materials (not required)
  - Submit a revised agenda
  - Submit these through the portal at least 48 hours prior to scheduled meeting
- Should NOT generate the submission of new questions
- You can cancel your meeting if you feel the preliminary responses adequately address your questions
  - Still eligible for a MRCM

Meeting Day

- Meetings are typically 1 hour
- Discussion should focus on clarification of the Agency's preliminary written comments
- Meeting participants discuss the data, questions, and the responses 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

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

Cancelled Meetings

- If a meeting is cancelled, a subsequent request to schedule a meeting is considered a new request
- A product development or pre-submission meeting may be cancelled:
  - Applicant withdraws the meeting request
  - Applicant determines questions adequately answered by the preliminary written comments
  - FDA issues PSG on establishing BE to the RLD that is the basis of submission for the prospective ANDA applicant

Resolution of Dispute About Meeting Minutes

- Applicant requesting additional clarification of meeting minutes should contact the assigned FDA point of contact (i.e., the FDA PM for the meeting)
- Submit in writing to FDA within 10 calendar days of receipt of official meeting minutes
- Addresses issues with the meeting minutes only

Challenge Question

Which type of pre-ANDA meeting request does ***not*** include substantive review of summary data or full study reports?

Pre-submission meeting request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