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

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Outline

- Overview of the pre-abbreviated new drug application (pre-ANDA) program
- Pre-ANDA meeting process
- Program metrics and trends
- Tips for success

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

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

www.fda.gov

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 Components

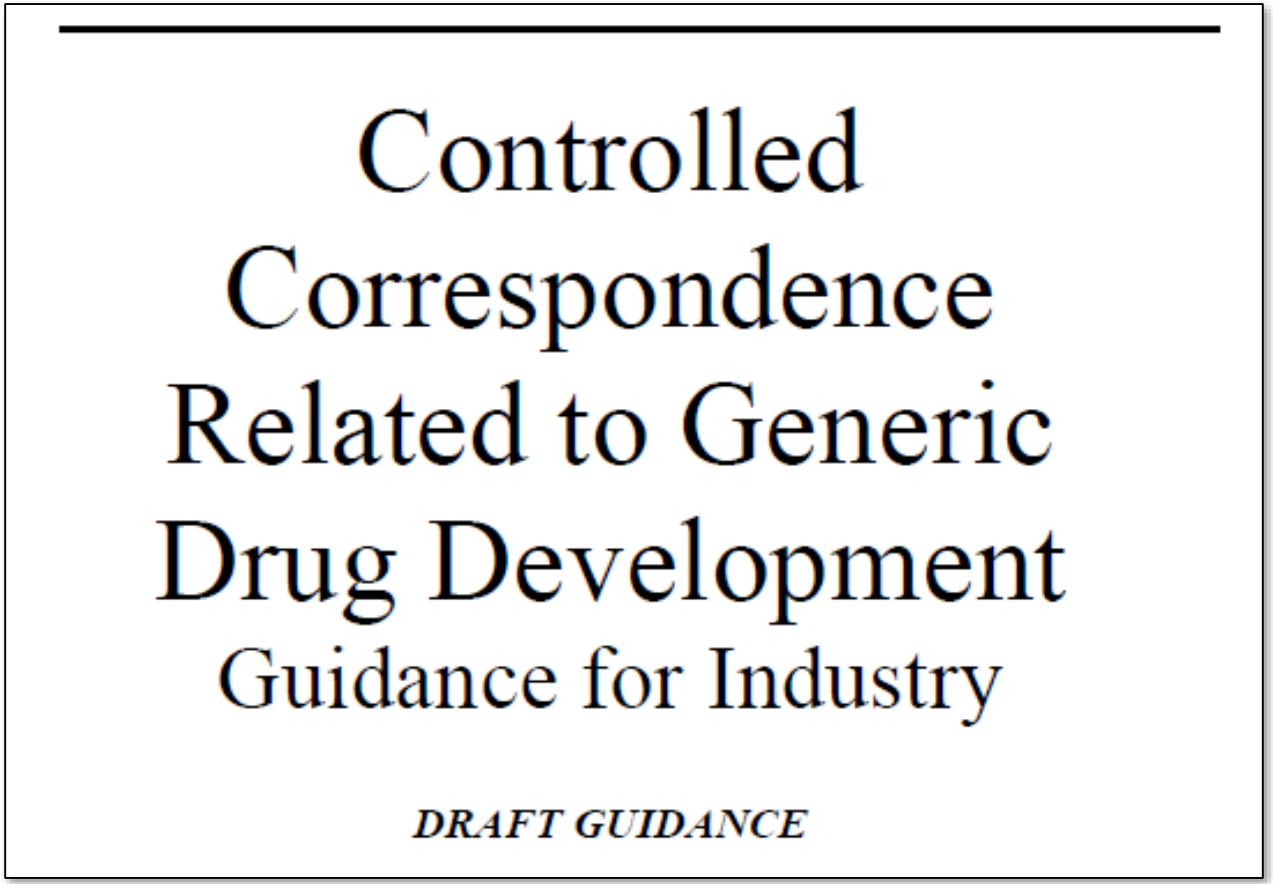
- Research
- Product-Specific Guidances (PSGs)
- Controlled Correspondence
- Meetings for ***complex*** products

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 1700 PSGs are currently available as of July 2019
  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


Controlled
Correspondence
Related to Generic
Drug Development
Guidance for Industry
DRAFT GUIDANCE

Controlled Correspondence (CC)

- **Standard CC (60 calendar days)**
  - Specific element of generic drug development
- **Complex CC (120 calendar days)**
  - Clinical content
  - Bioequivalence (BE) protocols for 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)
- **Clarification of ambiguities (14 days)**
  - Submit within 7 days of reviewing FDA's response

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 study reports
- ANDA is anticipated to be submitted ˜6 months of meeting date

GDUFA II Meetings: After ANDA Submission

Mid-Review-Cycle Meeting (MRCM)

- For applicants with prior PDEV and/or PSUB meetings
- Generally mid-point of review plus 30 days
- Update on status of review and next steps

CC or PDEV Meeting?

- Controlled Correspondence
  - Single or small group of closely related questions
  - Response within 60 (standard) or 120 (complex) calendar days
- Pre-ANDA Meeting
  - Best for multidisciplinary questions
  - Meeting held within 120 days of being granted

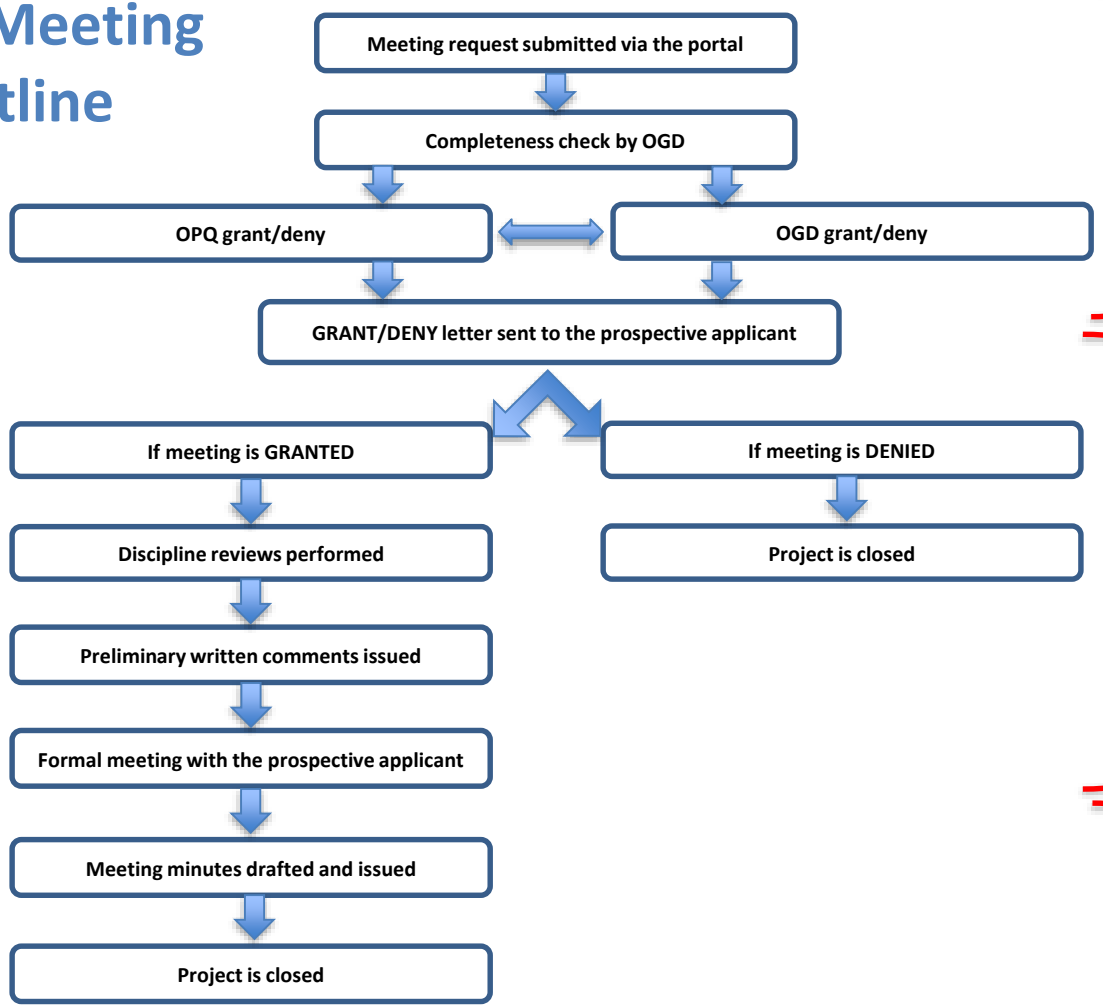
FDA will grant a PDEV or PSUB meeting for a complex product, if:

- 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
- 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)

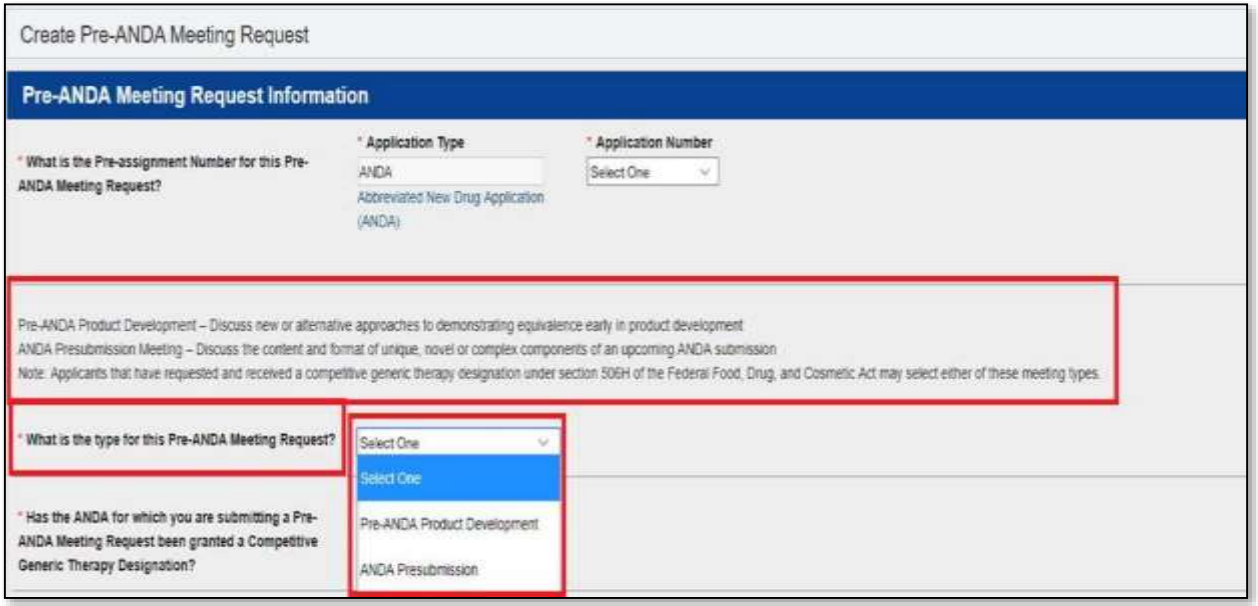
Stage 3
(30 days)

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 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., 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 Office of Generic Drugs (OGD) and Office of Pharmaceutical Quality (OPQ)
  - Assessment team reviews the product details, contents and submitted questions
  - OGD and OPQ coordinate to provide a unified response

My Meeting Was Granted

- Typically granted as face-to face meeting, though the applicant can request a written response or teleconference
- Written responses and teleconferences still qualify you for a mid-review-cycle meeting
- A project manager from the Office of Research and Standards (ORS) is assigned as the point of contact

Pre-ANDA Meeting Package Assessment

- FDA staff will review the meeting package, request consults and send information requests (if 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
  - 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 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 be eligible for a MRCM

Meeting Day

- Meetings are typically 1 hour
- Discussion should be focused 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

Competitive Generic Therapy

- New pathway for drugs with “inadequate generic competition”

- Eligible for PDEV and PSUB meetings
  - Includes both complex and non-complex products
  - Provide documentation of Competitive Generic Therapy designation with meeting request
  - Does **not** provide for an expedited meeting timeline

- FDA will consider the following, among other factors, to determine whether to grant or deny a meeting request with CGT:
  - Complexity of developing an ANDA for a specific drug
  - Potential public health impact (e.g., severity of the condition treated, size of impacted patient population)
  - Impact on FDA resources and other workload commitments

GDUFA II: Pre-ANDA Program Metrics and Tips for Success

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Complex Generic Drug Product Development Conference
Sep 25, 2019

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

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A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


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

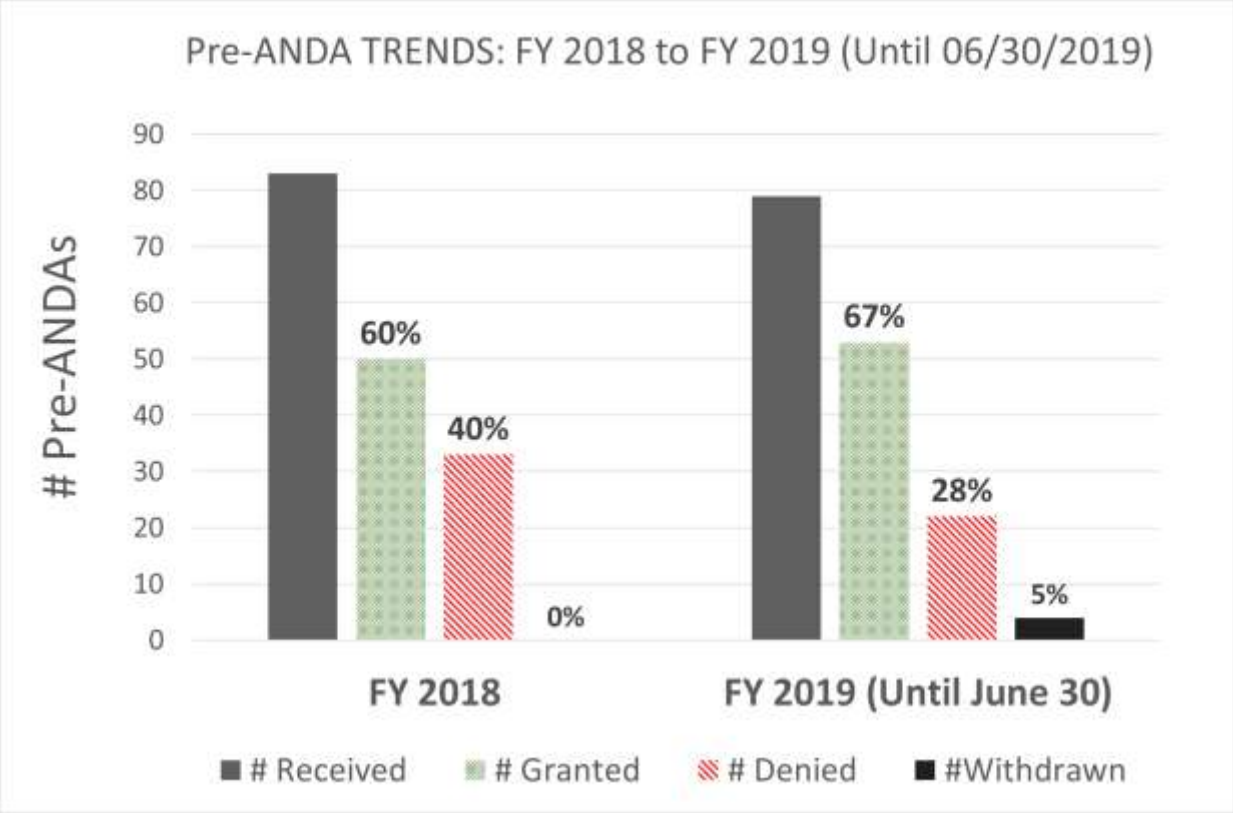
Pharmaceutical quality is

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

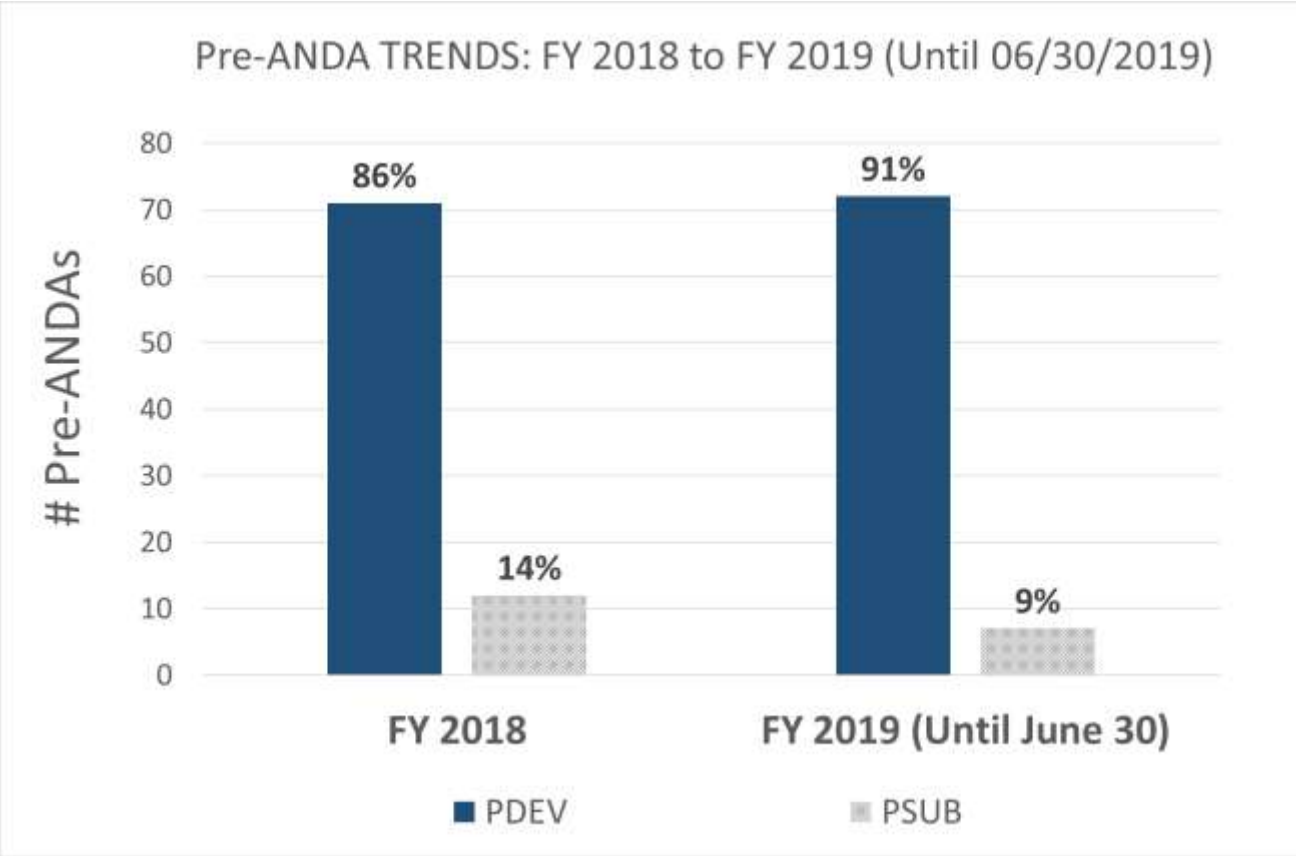

It is what gives patients confidence in their *next* dose of medicine.

GDUFA II Pre-ANDA Metrics

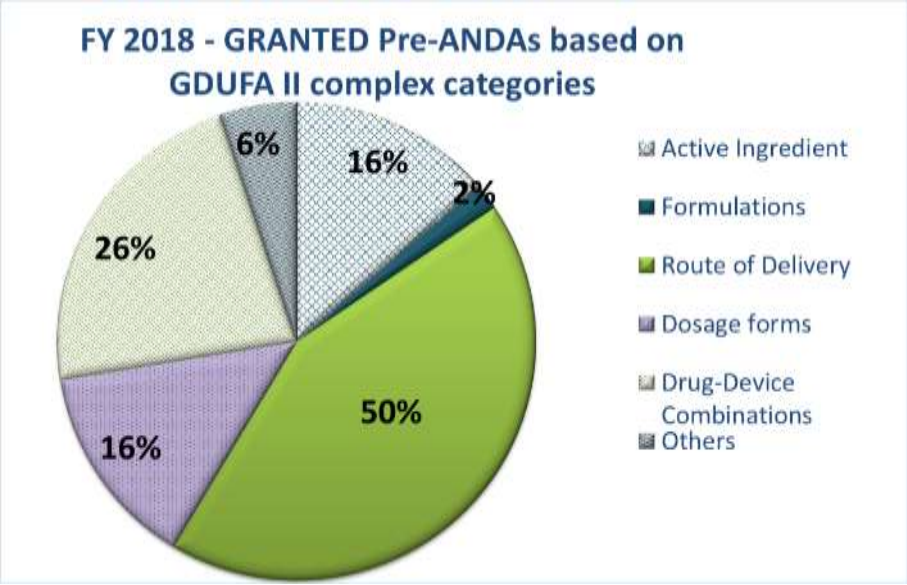
PRE-ANDA TRENDS: GRANT/DENIAL

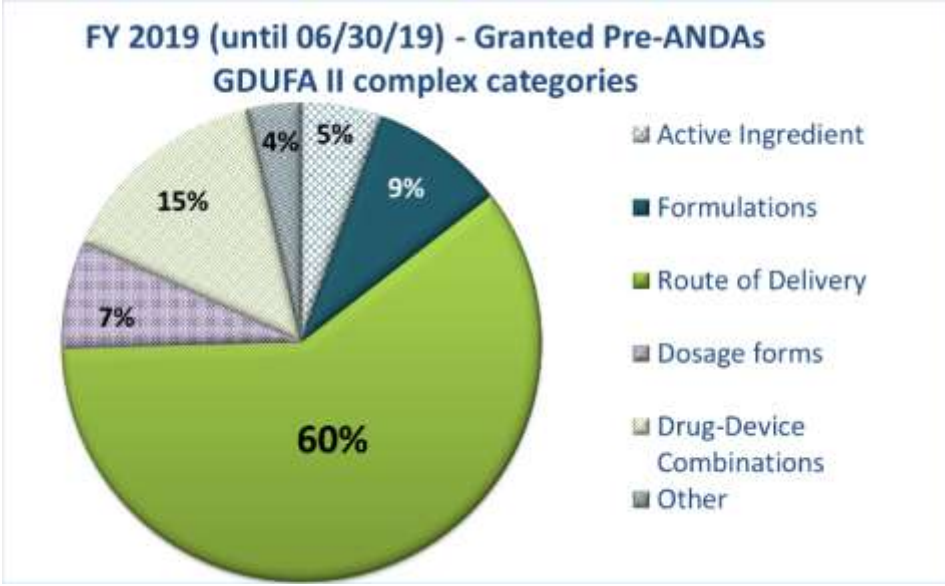


PRE-ANDA TRENDS: PSUB vs PDEV



PRE-ANDA TRENDS: BY COMPLEX CATEGORY (Granted)

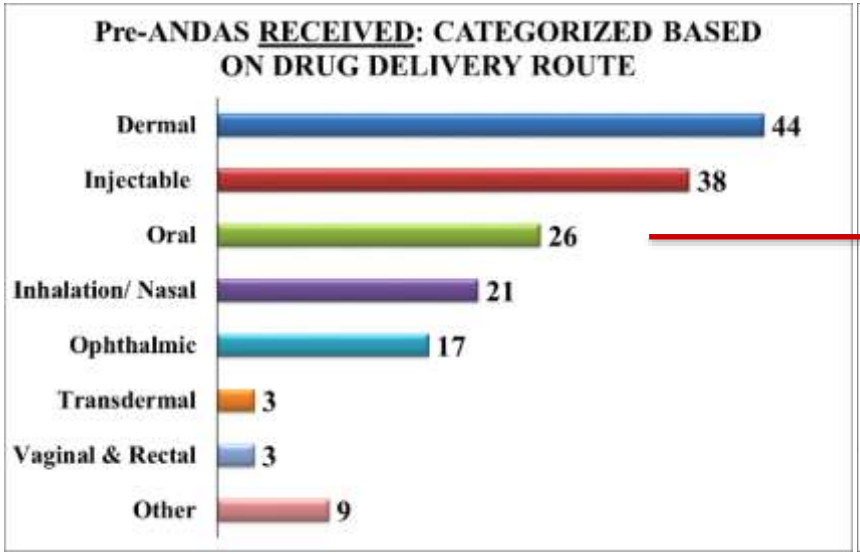


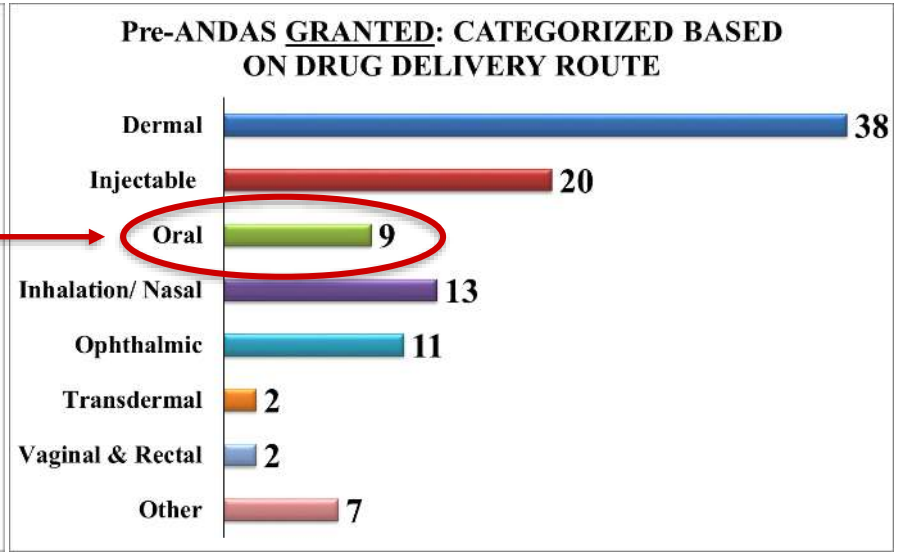


Route of Delivery includes mostly topicals and ophthalmics

PRE-ANDA TRENDS: By Drug Delivery Route

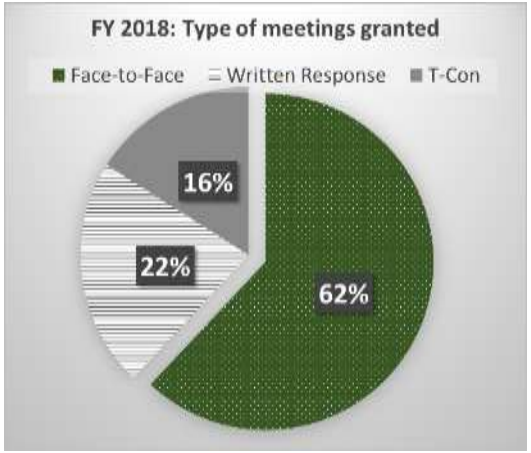
FY 2018 and FY 2019 (until June 30th)



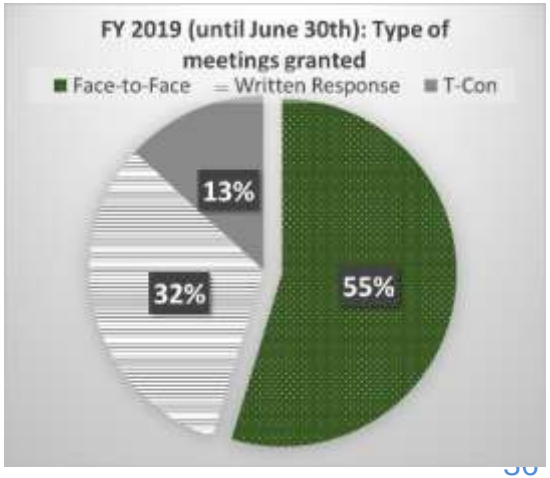


Type of Meetings Granted

- Year 1 Submissions- 50 Grants
  - Predominantly Face-to-Face
  - 13 Cancelled (applicant satisfied with preliminary written response)



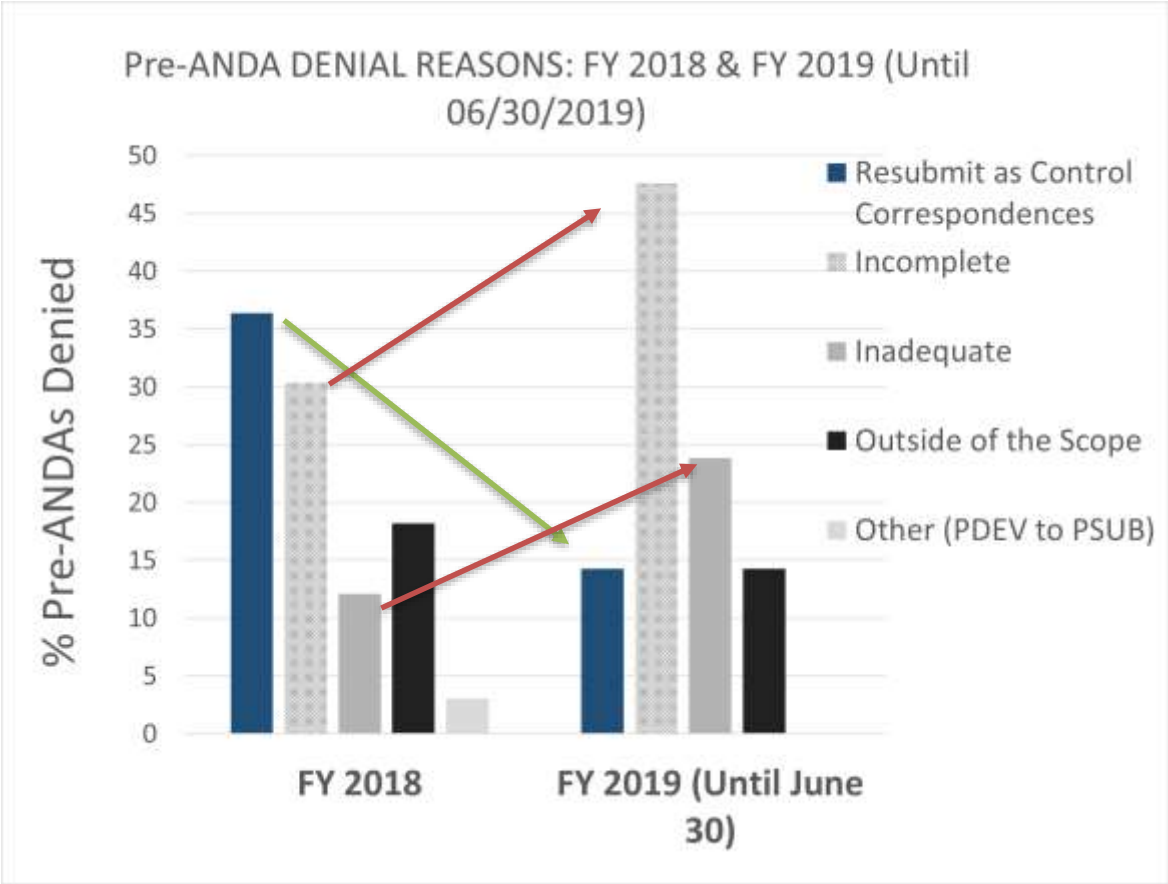
- Year 2 submissions (Until June 30th) - 53 Grants
  - Predominantly Face-to-Face
  - 6 Cancelled (applicant satisfied with preliminary written response)



Common Reasons for Denial

- Incomplete meeting packages
- Inadequate meeting package
- Should be a controlled correspondence
- Wrong meeting type chosen – PDEV vs PSUB
- Out of Scope of GDUFA-II commitment letter
  - Not a complex product
  - Not a 505 (j) route
  - ANDA already received
  - PSG is available and not asking for an alternate bioequivalence route

Pre-ANDA Trends: Denial reasons



Deny letter – Path forward

- For Incomplete meeting packages
  - What is missing
- For Inadequate meeting packages
  - What justification is insufficient
- Others
  - Appropriate for controlled correspondence route
  - Non 505 (j) route (out of scope)
  - Type of meeting (PDEV vs PSUB)

Deny letter – Path forward

- Incomplete Meeting Package - Example
  - The Agency has made the decision to deny your product development meeting because the meeting package is considered ***incomplete*** due to the ***absence of specific questions and information*** to support your development plan and your proposed bioequivalence approach. Therefore, **we recommend you include the following** information in a new meeting request:
    - ….
    - ….
    - ….

Deny letter – Path forward

- Inadequate Meeting Package - Example
  - There is ***insufficient information*** in your meeting package to establish whether the rate and extent of bioavailability at the local site of action (e.g., in the skin) correlates with the systemic pharmacokinetics. ***Specific information and data* is needed** that may provide information about how you expect to demonstrate that the cutaneous pharmacokinetics for your proposed generic product would be bioequivalent to that of the reference product. The Agency would then be able to comment about whether such an approach may be appropriate for establishing the bioequivalence.

Do’s and Dont’s

for a successful Pre-ANDA submission

Helpful tips

- Provide in your meeting package
  - preliminary data to support your approach
  - specific questions about your development plan, grouped by discipline
  - justification to support proposed approach and methods used

- Composition similarity questions (where not required by regulation or recommended in a PSG)—yes, this is the pathway
  - Propose an alternate BE approach for a specific formulation
  - FDA will provide feedback on the alternate BE approach
  - If you know you do not have compositional similarity, include your justification

Examples: Effective 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 appropriate to support comparative physicochemical characterization?

Examples: Effective Pre-ANDA Questions

- Does FDA concur with proposed alternate in-vitro approach to demonstrate bioequivalence? A d*etailed approach with justification and characterization data is provided.* Are there any additional in-vitro characterization studies recommended by the Agency?

- Does the Agency agree with the approach we designed to compare the overall particle size distribution of active pharmaceutical ingredient particles in the test and reference listed drug product by means of morphologically directed Raman spectroscopy and scanning electron microscopy-energy dispersive X-ray spectroscopy?

Example: Agency's response

Question: Does the Agency concur with adequacy of the current controls in the finish product specification? Are there any additional controls/studies recommended by the Agency?

Agency Response: The adequacy of current controls in the finish product specification will be an ANDA assessment issue. Please note that the need for additional physicochemical properties tests may be identified during the ANDA assessment process.

In addition, we have following comments for your drug release method for the purpose of quality control…

Example: PSUB questions

- Does FDA agree the BCS-Based Study Summary and Formulation tables should be provided in Section 2.7 and the study reports provided in Section 5.3.1.2.

- Does FDA agree that the design controls information to be filed in the above mentioned ANDA Sections is sufficient in support of the combination product requirements? Does FDA requires design history files of the prefilled syringe in the ANDA, and in which section?

- Does FDA agree that the full details and reports of active pharmaceutical ingredient characterization and sameness studies can be referenced to Section 3.2.S.3.1 of the DMF, no need to place the same information and reports once more in the ANDA?

Example: Controlled Correspondence questions

- For release and stability testing, the applicant proposes to conduct the chemical and microbial test on drug product filled cartridges without assembling in a pen whereas device performance tests will be carried out on the final assembled pen device. Does the Agency concur?

- The applicant proposes a x% overage of XYZ in the formulation to compensate the losses during the manufacturing process. Does the Agency concur?

Example: NOT 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?

ANDA assessment issues

Take-Aways

- 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 critical quality attributes of your product

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 (group the questions by discipline)
- Provide sufficient information to address your question
- We look forward to working with you!

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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