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

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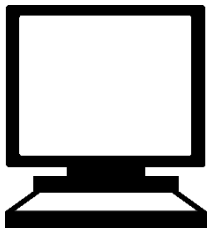
Pharmaceutical Quality

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



Pharmaceutical Quality

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.

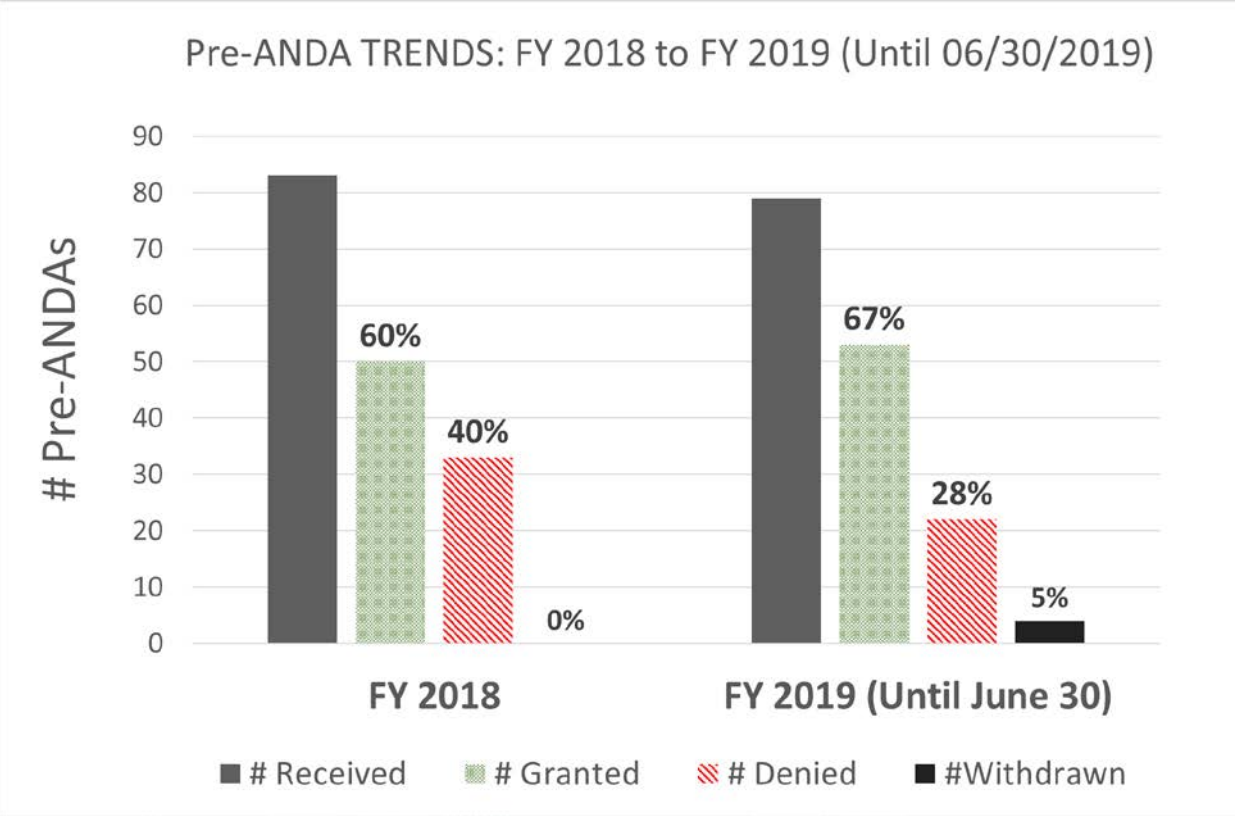
Pharmaceutical quality is

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

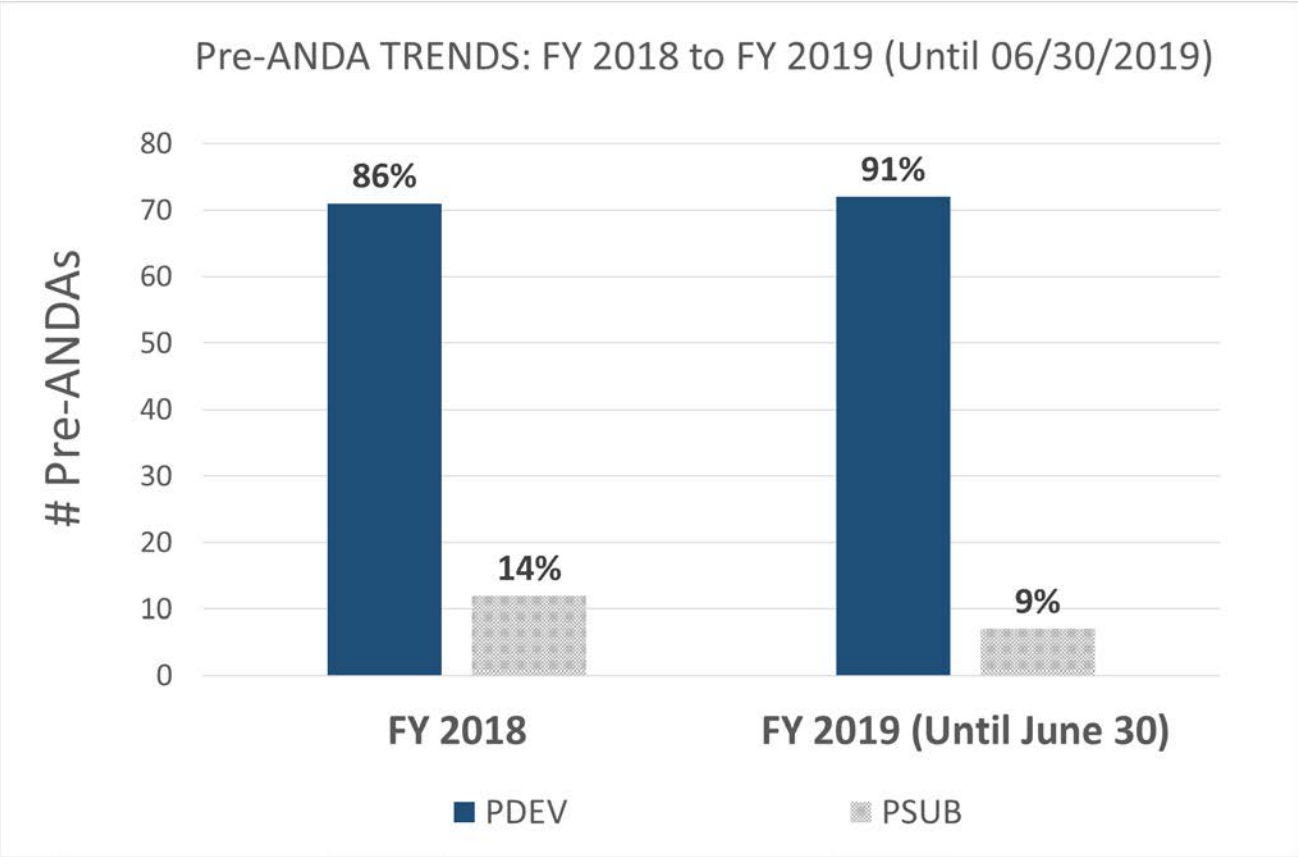

It is what gives patients confidence in their *next* dose of medicine.

GDUFA II Pre-ANDA Metrics

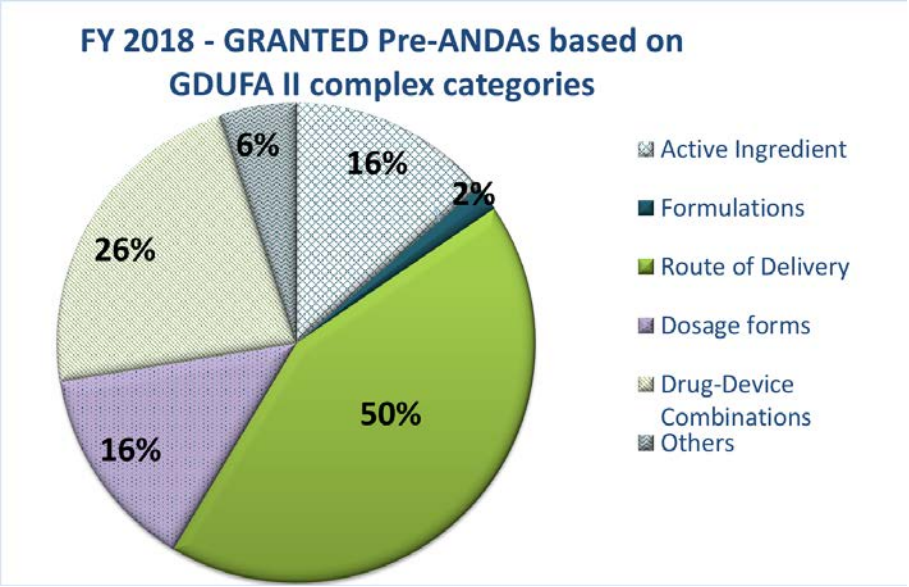
PRE-ANDA TRENDS: GRANT/DENIAL

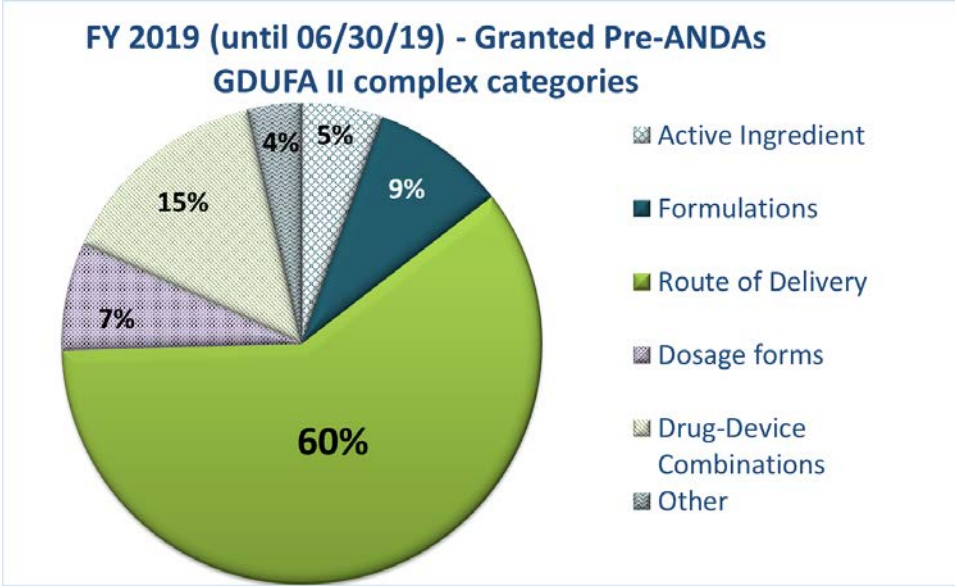


PRE-ANDA TRENDS: PSUB vs PDEV



PRE-ANDA TRENDS: BY COMPLEX CATEGORY (Granted)

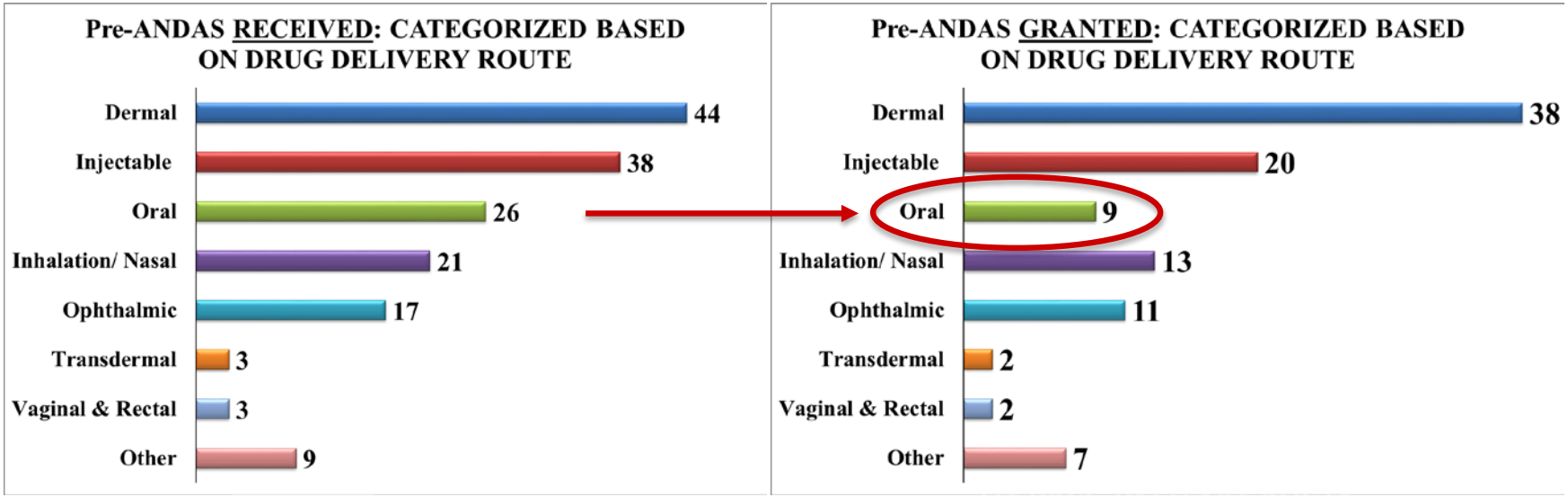




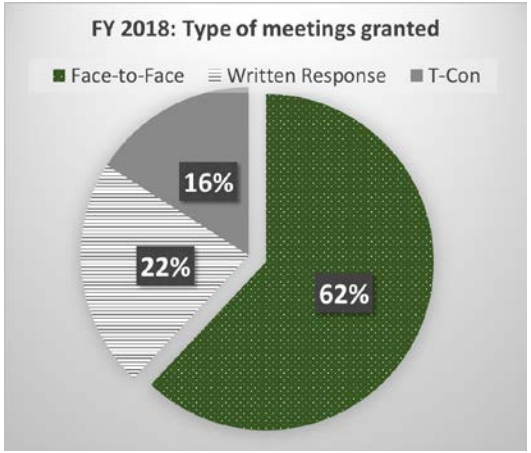
Route of Delivery includes mostly topicals and ophthalmics

PRE-ANDA TRENDS: By Drug Delivery Route

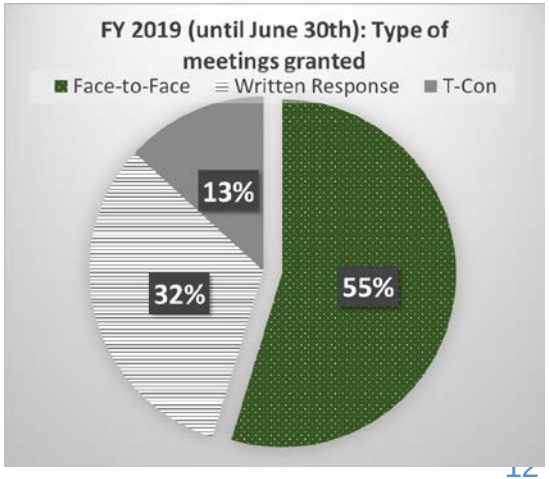
FY 2018 and FY 2019 (until June 30th)



Type of Meetings Granted



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

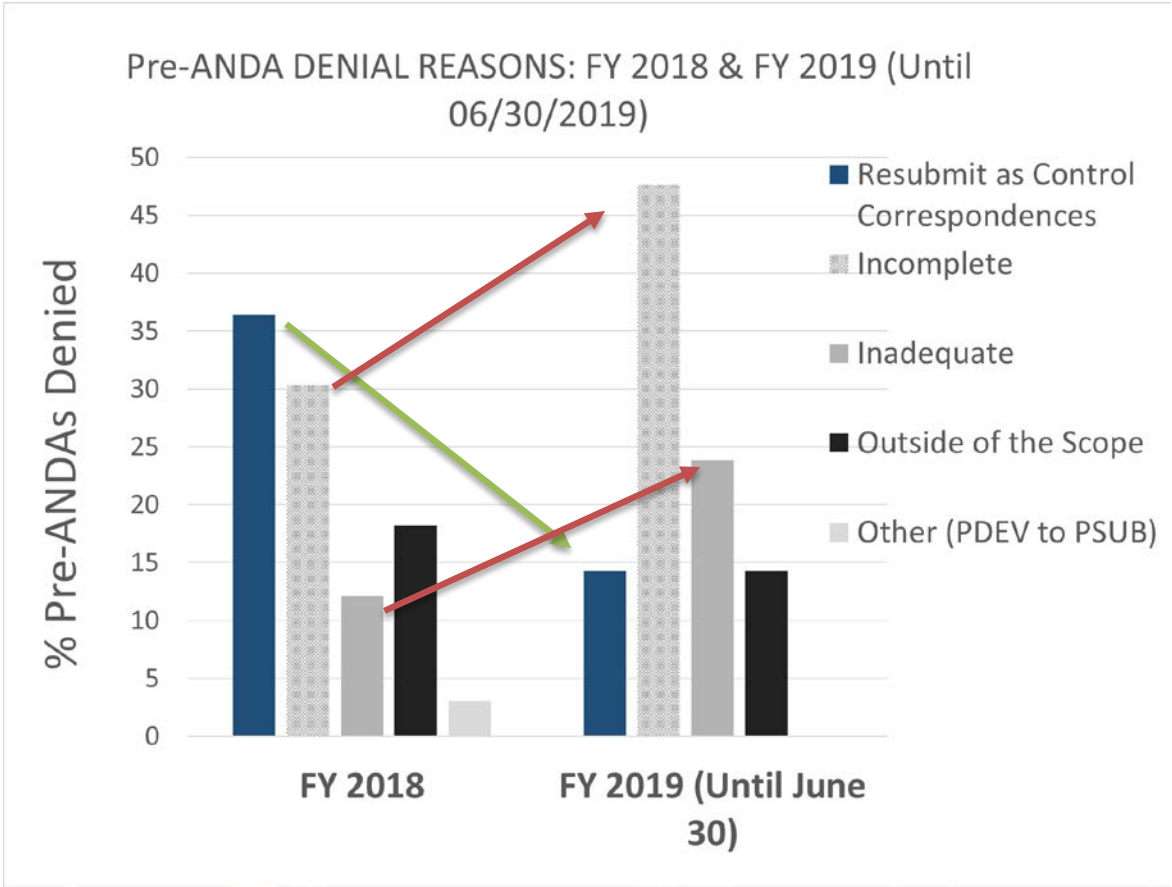


- Year 2 submissions (Until June 30th) - 53 Grants
  - Predominantly Face-to-Face
  - 6 Cancelled (applicant satisfied with preliminary written response)

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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