Pre-ANDA Meeting or Controlled Correspondence?

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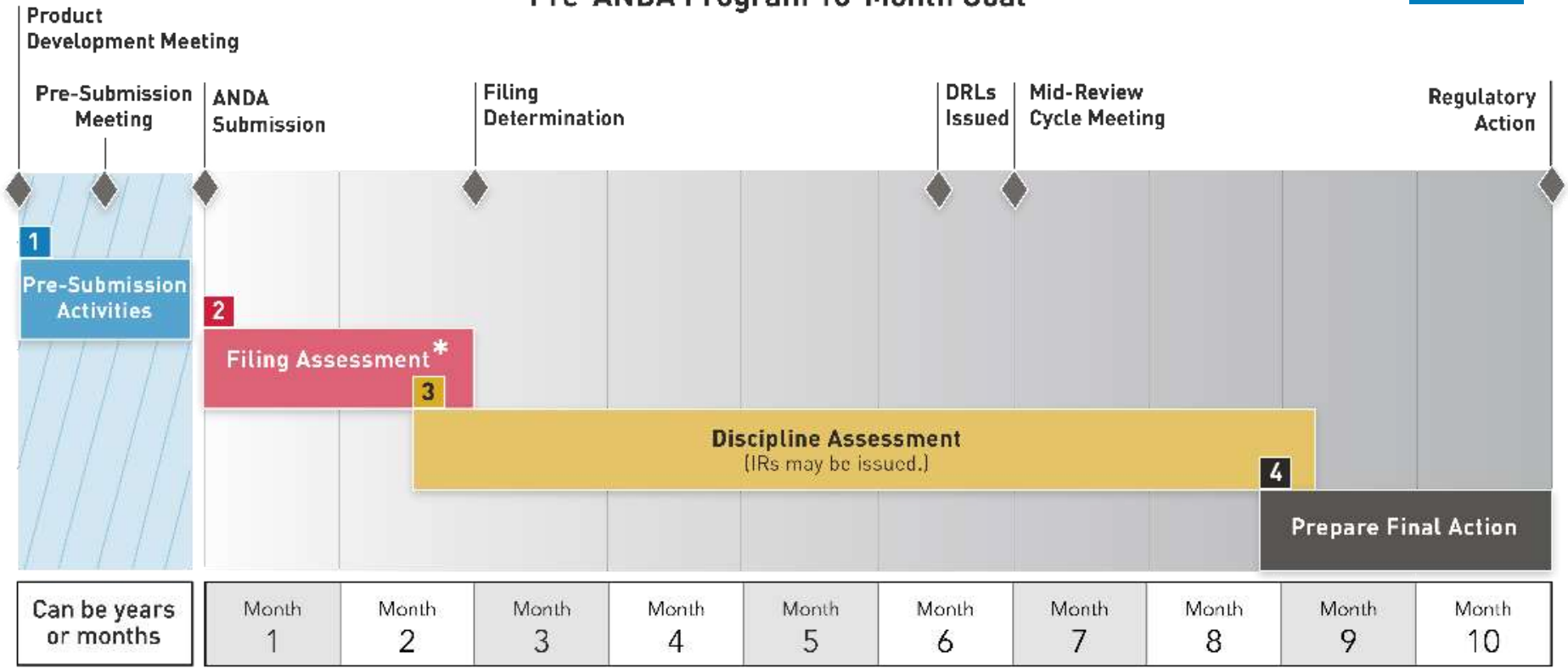
Early Engagement with the Agency for ANDAs

- Controlled Correspondence
  - Standard controlled correspondence
  - Complex controlled correspondence
- Meetings for complex products
  - Pre-ANDA meetings accelerate access to generics of complex products through early engagement with the FDA

Abbreviated New Drug Application (ANDA) Review Timeline+

Pre-ANDA Program 10-Month Goal



+ Each ANDA assessment progresses in a unique and iterative way. This is one example and is not reflective of every ANDA assessment.

* Good ANDA Assessment MAPP

The Different Meanings of Complex

- Complex products are not the same as complex controls
  - Complex products generally include:
    - Products with complex active ingredients
    - Complex drug-device combinations
    - Other products where early engagement could be beneficial
  - Complex controls must meet specific criteria regardless of whether the drug product is complex or not

Standard Controlled Correspondence

- Answered within 60 days of submission
  - Generally 1 to 2 questions requesting information on a specific element of generic drug product development or certain post approval submission requirements
  - You are permitted to ask for a clarification if you feel your response is ambiguous (14 day turn-around time)

Complex Controlled Correspondence

- Answered within 120 days of submission
  - The control involves clinical content
  - Bioequivalence protocols for RLDs with REMS ETASU
  - Evaluation of alternative bioequivalence approaches within the same study type
- Clarification of ambiguities also allowed

Product Development Meetings

- A meeting involving a scientific exchange to discuss specific issues or questions
  - Early engagement in your individual product development program
  - A novel proposed study design
  - Alternative bioequivalence approach
  - Additional study expectations
- FDA will provide targeted advice regarding an ongoing ANDA development program

Meetings We Will Grant

- FDA will grant a prospective applicant a Product Development Meeting if, in FDA's judgment:
  - The meeting concerns development of a complex product for which FDA has not issued product-specific guidance (PSG) or proposes an alternative equivalence evaluation (i.e., change in study type, such as in vitro to clinical) for a complex product for which FDA has issued a PSG

Meetings We May Grant

- Dependent on available resources, a product development meeting may be granted if the meeting concerns complex product development issues other than those identified in the previous slide
  - For example, FDA has developed a product-specific guidance and the prospective ANDA applicant is not proposing an alternative equivalence evaluation, but the request raises complex issues better suited for a meeting format

Pre-Submission Meetings

- Ready to or close to submitting your application
- A meeting to discuss and explain the format and content of an ANDA to be submitted
- Applicants can obtain advice that will enable efficient review and improve the chance of first cycle approval
- Pre-submission meetings will not include substantive review of summary data or full study reports
- ANDA expected to be submitted within 6-12 months

For All Meetings

- The prospective applicant should submit a complete meeting package, including a data package and specific proposals;
- A controlled correspondence response would not adequately address the prospective applicant's questions; and
- A Product Development Meeting would significantly improve ANDA assessment efficiency.

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)
  - Evaluation of clinical content
  - BE Protocols for RLDs with REMS ETASU
  - Alternate BE approach (within the same class)
- Clarification of ambiguities are allowed – see

Controlled Correspondence Related to Generic Drug Development Draft Guidance for Industry

Optional Meeting or Control?

- Meetings are best for multidisciplinary questions
- Controls are for single questions or a small group of closely related questions
- Consider timelines – how soon will I get my answer?

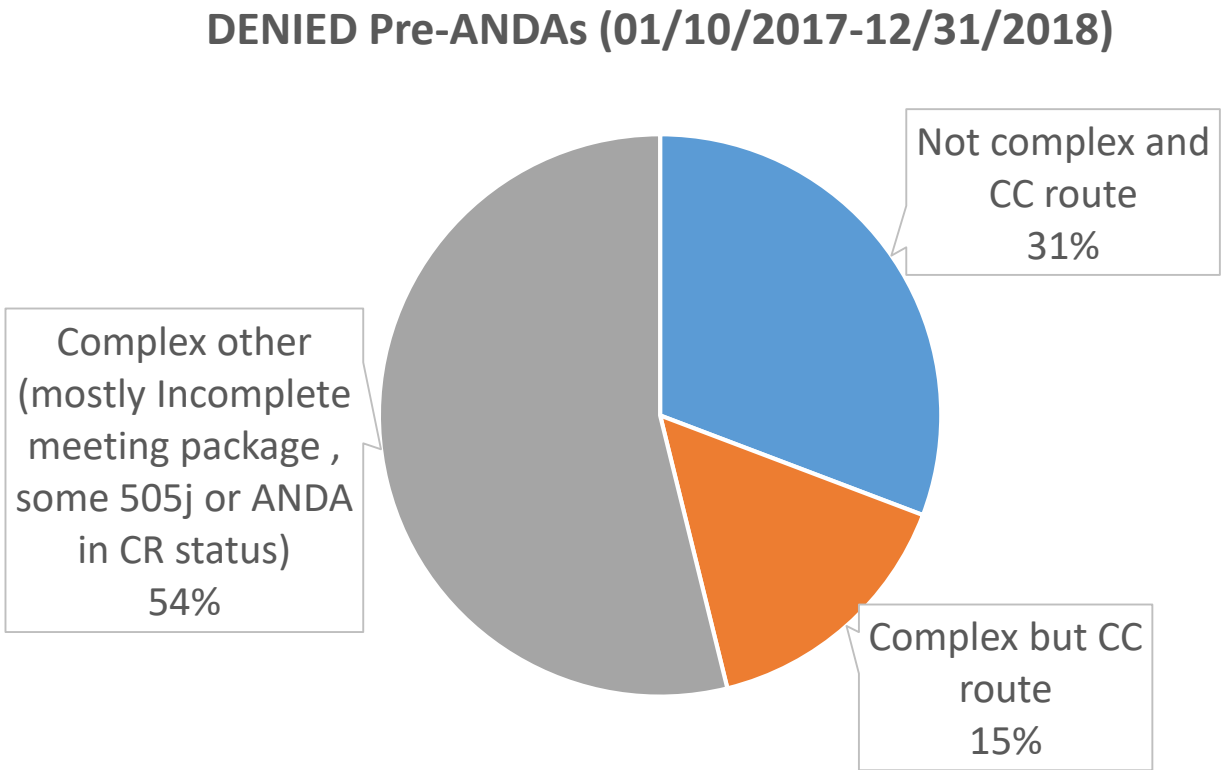
Pre-ANDA Meetings vs. Controlled Correspondence

- Pre-ANDA Meetings
  - Complex Products (as defined in GDUFAII commitment letter)
  - Other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement
  - Multiple questions
- Controlled correspondence
  - All products
  - Single question or closely related questions

OPQ Triage for Pre-ANDA Meeting Requests

- Complex product as defined in GDUFAII commitment letter
- Complete meeting package
- Meeting package includes issues assessed by OPQ
- Availability of guidances that cover issues included in the meeting package
- Meeting package contains questions in which a Pre-ANDA will enhance assessment efficiency

Pre-ANDA Metrics (Denied Pre-ANDAs)



Non-complex Products

- Common non-complex products include
  - Oral IR tablets / capsules
  - Oral MR tablets / capsules
  - Injections (solutions)

- Pre-ANDA meetings are likely to be denied; controlled correspondence is recommended

Non-complex Products

- Typical OPQ related controlled correspondences for non-complex products include:
  - Size and shape of oral dosage forms
  - Stability protocols and data requirements
  - Exhibit batch (size, scale, sites) and packaging requirements
  - In use and dilution studies
  - Two API sources
  - Excipient choice / levels
- Strongly recommended to follow FDA guidances, ICH guidelines, RLD label information and applicable compendial standards

Non-complex Products: Controlled Correspondence

- Example: Size of an oral MR tablet / capsule larger than the recommendations in FDA guidance on Size, Shape and Other Physical Attributes of Generic Tablets and Capsules (2015)
- Common justifications that are inadequate by themselves
  - There are approved generic products of similar size
  - Only “slightly larger” than RLD
  - Different formulation technology compared to RLD (e.g., matrix vs. osmotic)
- Deviation from guidance recommendation needs to be justified based on impact on patient considering the following (as applicable)
  - Target population
  - Indication
  - Patient compliance
  - Dosing recommendation including length of treatment
  - Medication errors

Complex Products

Case Study 1: Request for PDEV meeting for an ophthalmic emulsion

Triage summary

- Complete meeting package provided
- Is it a complex product as per GDUFA II commitment letter?: Yes
  - Complex route of delivery
- Does the meeting package involve issues assessed by OPQ?: Yes
  - Drug distribution between different phases
  - Stability testing plan
  - Clarification of characterization tests vs. routine release tests

Complex Products

Case Study 1: Request for PDEV meeting for an ophthalmic emulsion

Triage summary

- Does the meeting package contains at least one OPQ question in which a PDEV meeting would significantly enhance assessment efficiency?: No
  - All OPQ questions are straightforward and can be answered using controlled correspondence with faster response time

OPQ decision

- Decline PDEV meeting request

Complex Products

Case Study 1: Request for PDEV meeting for an ophthalmic emulsion

OGD Decision

- Decline PDEV meeting request
  - PSG is available for this complex product and the firm is not proposing an alternative equivalence approach
  - Firm is requesting PSG clarification, which can be answered through a control without need for a meeting

- Meeting request was denied; firm advised to submit controlled correspondence

Complex Products

Case Study 2: Request for PDEV meeting for a vaginal ring

Triage summary

- Complete meeting package provided
- Is it a complex products per GDUFA II commitment letter?: Yes
  - Complex dosage form, complex drug-device combination
- Does the meeting package involve issues assessed by OPQ?: Yes, multiple questions
  - Microbiology
  - Drug product facility (cGMP / inspections)
  - Scale up proposal
  - Device related issues (biocompatibility , E/L, and specifications)
  - Excipient controls
  - Drug release test for long acting product

Complex Products

Case Study 2: Request for PDEV meeting for a vaginal ring

Triage summary

- Does the meeting package contains at least one OPQ question in which a PDEV meeting would significantly enhance assessmemt efficiency?: Yes
  - Complex drug device product with limited experience and questions for multiple OPQ sub-offices
- Does the PSG or CMC guidances cover the concerns in the meeting package?
  - No, mainly because this is a complex drug-device combination product

OPQ decision

- Grant PDEV meeting request with OGD concurrence

Complex Products

Case Study 3: Request for PDEV meeting for a nasal spray

- Single question: Can the firm use Purified Water, USP and a preservative when the RLD uses Water for Injection, USP and aseptic processing?

OPQ and OGD Triage

- Incomplete meeting package
  - No product development plan provided
  - No formulation information or justification for the proposed preservative provided
  - No BE strategy provided
  - No device information provided
- Meeting request was denied with request to re-submit with complete meeting package

Conclusion

- Pre ANDA meetings and controlled correspondences are useful pathways for prospective applicants to get targeted feedback on product development and ANDA submission
- Prospective applicants should:
  - Select the appropriate pathway to get feedback from FDA depending on complexity of product, development stage, and number of questions
  - Submit a complete meeting package, including a data package and specific proposals / questions
  - Read all applicable guidances and standards
  - Justify proposed deviations from applicable guidances and standards using scientific and patient-centric approach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