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Bioequivalence and Complex Generics: How to Get Pre-submission Advice

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Bioequivalence

- Generic Drugs must be bioequivalent to their RLD
- No significant difference in rate and extent of exposure at the site of drug action
- Most common approach: Pharmacokinetics
  - Compare AUC and Cmax

Product Specific Guidance

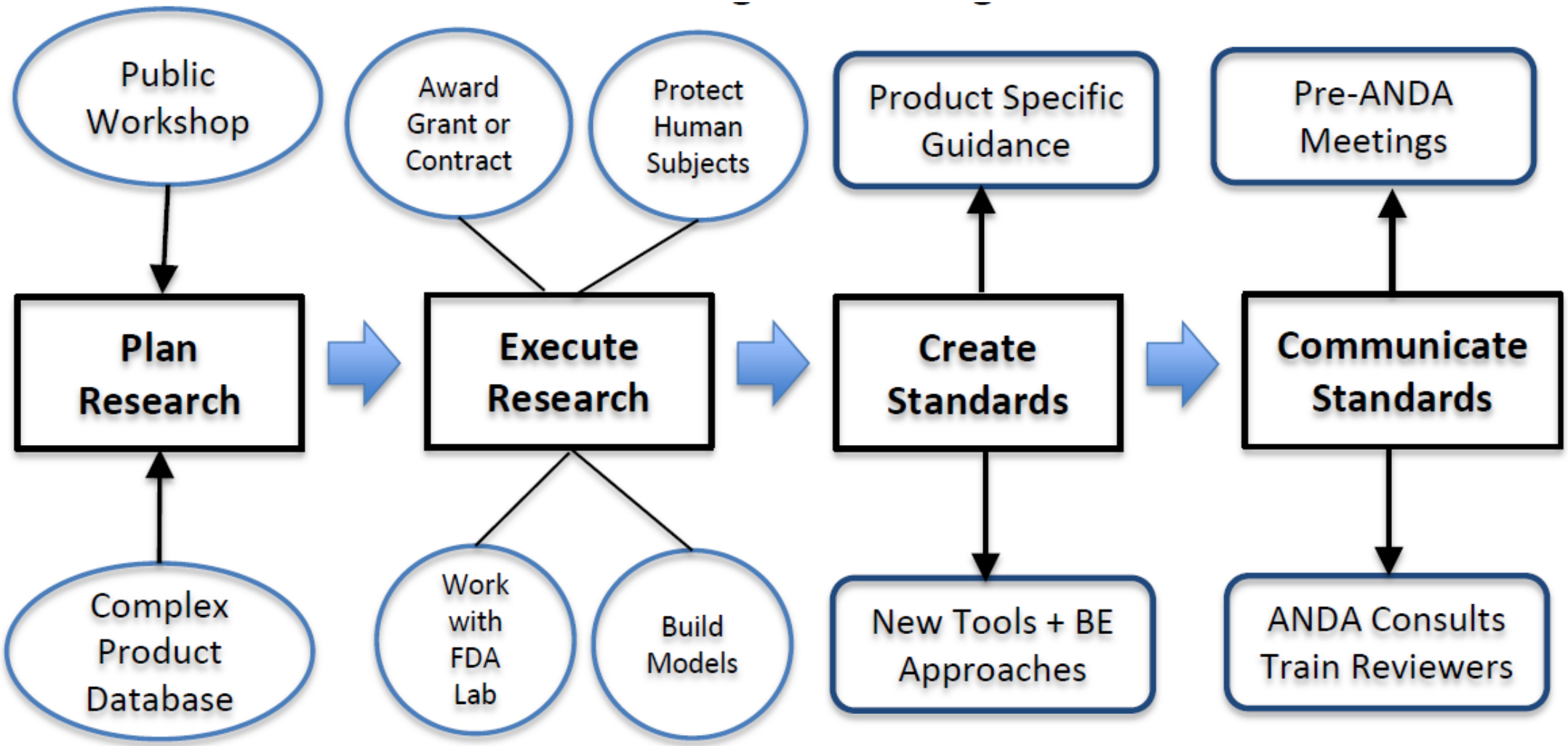
- Product Specific Guidance (PSG) provide clear and direct advice to ANDA applicants for a specific RLD
  - What study, what dose, what analytes, what endpoints, what population
  - https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm
- Over 1500 available with quarterly updates
- PSG are critical to the high first cycle acceptable rate for the OGD bioequivalence review
- GDUFA II goal: non -complex PSG will be available 2 years after NME approval

Complex Generics

- "Complex Product" is a defined term in the proposed GDUFA II Commitment Letter.
  - products with complex active ingredients, formulations, routes of delivery or dosage forms
  - complex drug-device combinations
  - other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement
- Complex products often need different approaches to demonstrate bioequivalence
- GDUFA II includes aspects to accelerate the development of complex products
  - Research
  - Pre-ANDA meetings

Complex Generics Research

ORS is a multidisciplinary **Office** that plans and conducts **Research** and translates the results into generic drug **Standards**



Pre-ANDA Meetings

- Clarify regulatory expectations for prospective applicants early in product development
- Help applicants develop more complete submissions
- Promote a more efficient and effective review process
- Reduce the number of review cycles necessary to obtain ANDA approval of complex products
- Three types
  - Product Development
  - Pre-Submission
  - Mid-Review-Cycle

Pre-ANDA Meetings

- FDA will grant Product Development Meetings if
  - The request concerns development of a complex product for which
    - FDA has not issued a product specific guidance or
    - The applicant proposes an alternative bioequivalence method of a different class
- Within 30 days (year one and two) or 14 days FDA will grant or deny the meeting
- After granting, FDA will offer a meeting date within 120 calendar days of granting the request

Pre-ANDA Meetings

- Pre-Submission Meetings
  - Provide an opportunity for the applicant discuss and explain content and format of the ANDA to be submitted
  - Provide an opportunity to give advice that will enable efficient review and improve the chance of first cycle approval
  - Identify items or information for clarification before submission
- Mid-Review-Cycle Meetings
  - If you had a pre-ANDA meeting on a complex product and use the same pre-assigned ANDA number to submit an ANDA
  - After you submit your ANDA the RPM will contact you to arrange a mid-review-cycle teleconference with the FDA staff reviewing your application

Thank You

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