Advice on Preparing For Pivotal Studies-Product

- Understand critical product characteristics & have the controls in place to maintain consistency
- Have meaningful potency assay in place
- Lock down procedures and acceptance criteria based on development experience
- Protocol for stability of Phase 3 material in place, based on earlier stability data
- Shipping qualification

Lot Release Specifications- are you there?

- Guidance: ICH Q6B, Q6A
- Step-wise approach:
  - Phase 1: safety, quality manufacture
  - Phase 2: safety, tightening specifications
  - Phase 3: safety, specifications defined
  - BLA:
    - Validated assays
    - Statistical analyses
- Inability to understand critical product characteristics can impact ability to analyze clinical data

Pre-Clinical

- Scientific basis for conducting clinical trial
- Data to recommend initial safe dose & dose escalation scheme in humans
- Proof of Concept Studies in relevant animal models
- Toxicology Studies in relevant animal species
  - Identify, characterize, quantify the potential local and systemic toxicities

Clinical: Early Phase Considerations

- Optimal dose and administration
  - Starting dose level/dose escalation scheme
  - Route of administration
  - Dose schedule
- Define appropriate patient population
- Staggering of dose escalation
- Safety Monitoring plans
- Safety Reporting requirements

Planning Later Phase Clinical Studies

- End of phase 2 meeting with FDA
  - Justify dose, regimen for phase 3
  - Preliminary safety profile established
  - Target population
    - Specific proposed indication
    - Assays required for eligibility
    - Prior therapy
  - Proposed control arm
  - Statistical considerations
  - Assessments
  - Preliminary evidence of activity/effect size
- Estimate patient effect size for phase 3 planning
  - Interpretation of time to events is problematic in single arm studies
    - Leads to over optimistic interpretation of effect size

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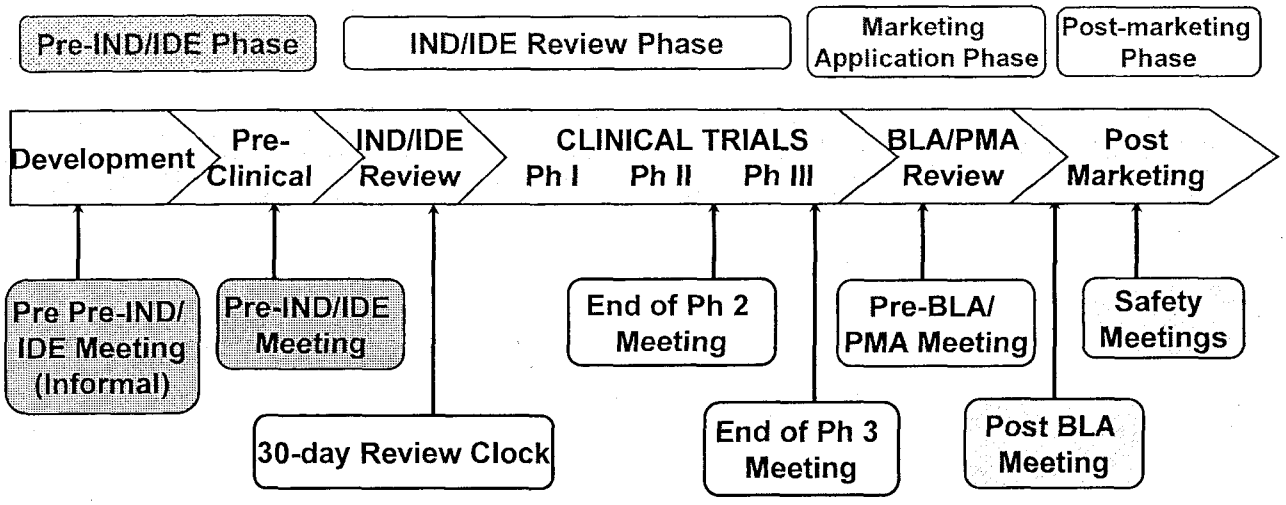
Interactions with FDA Throughout the Product Lifecycle



Product development is an iterative process, with frequent FDA and sponsor interaction

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Legal Standard for New Drug Approval

- Adequate tests of safety under the conditions prescribed, recommended or suggested in labeling
- Substantial evidence of effectiveness under the conditions prescribed, recommended or suggested in labeling
- Manufacturing, processing and packing is adequate to assure identity, strength [potency], quality and purity

-- Section 505(d)

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Examples of mechanisms for ensuring product safety and efficacy

- License application review
- Clinical data auditing and site inspections
- Pre-approval and biennial manufacturing facility inspections
- Appropriate product labeling
- Post marketing commitments and requirements
- Monitoring of adverse event and product deviation reporting

OCTGT Resources & Contact Information

- References for the Regulatory Process for OCTGT:
  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm
- Guidance Documents for Cell and Gene Therapies:
  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm
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