FDA Regulation and Review of Small Clinical Trials

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Disclaimer: The views expressed in this talk represent my opinions and do not necessarily represent the views of the FDA
Clinical Development Challenges

- Orphan disorders
  - Rare disorders with few patients available for study
    - Statute defines Orphans as <200,000 patients in US
    - Particularly challenging for “ultra-Orphans” (e.g., IEMs)
  - Many disorders are chronic, progressive, serious, life-limiting and life-threatening
  - Highly heterogeneous group of disorders
    - High phenotypic heterogeneity within disorders
  - Natural history often not well understood
  - Endpoints often not defined
    - Need outcome measures, tools, instruments, biomarkers
  - Tissue targeting (e.g., many treatments don’t enter CNS)
Regulatory Challenge

• Orphan Drug Act mainly provides financial incentives

• What ODA doesn’t do:
  – Hold Orphan drugs to a different standard than non-Orphan drugs

• Orphan drugs must:
  • Demonstrate substantial evidence of effectiveness/clinical benefit (21CFR 314.50)
  • Substantial evidence of benefit requires:
    – Adequate and well-controlled clinical study(ies) (§314.126)
Substantial Evidence of Effectiveness

• Adequate and well-controlled study:
  – Study has been designed well enough so as to be able “to distinguish the effect of a drug from other influences, such as spontaneous change…, placebo effect, or biased observation” (§314.126)
Adequate and Well-Controlled Study

• Major elements of the study design:
  – Clear statement of purpose
  – Permits a valid comparison with a control
    • Concurrent: placebo, no-treatment, active, dose-comparison
    • Historical
  – Adequate measures to minimize bias
  – Methods of assessment of response are well-defined and reliable
  – Analysis of the results is adequate to assess the effects of the drugs
Major Barriers to Clinical Development

• #1: Lack of pre-clinical data
  – CMC
  – Pharmacotoxicology

• #2: Disorder being treated is not well understood or well characterized
  – Impacts heavily on study design considerations - endpoints, outcome measures, assessment tools and instruments

• #3: Evidence of effectiveness not well described in pivotal clinical trial
Regulatory Challenge #1: Bench to Bedside Hurdle

- Phase 1/first-in human/first-in-disease state clinical trial, primary objectives are to assure the safety and rights of subjects participating in the clinical trial (§312.22)

- Common safety barriers for getting into Phase 1:
  - Early/Pre-IND Phase
    - Lack of characterization of drug/biologic (CMC)
    - Lack of pre/non-clinical data
      - E.g., Animal toxicology
      - Animal studies required prior to first-in-human dosing (and possibly first-in-disease state)
Safety

- Toxicology* – Key considerations to determine if drug is safe to administer to study subjects:
  - What are the dose limiting toxicities?
    - What organ systems are at risk
    - What should be monitored in clinical trials
    - Are toxicities reversible
  - How will drug be administered – dose, duration, route?
  - What is the dose-escalation plan
  - What is the target population (e.g., children, infants)
  - What is the safe starting dose in light of the above considerations

  - Adequate safety support needs to be completed in a timely manner or can delay clinical program

Safety (2)

• Clinical Trials
  – Usually medically-fragile patient population
    • Tolerate toxicities poorly
  – Study population very small
    • Limited opportunity to assess safety profile and appropriate dosing
  – Vulnerable patients, require special protections ("Medically Disadvantaged” Declaration of Helsinki, Article 8)
    • Informed consent
Regulatory Challenges #2 & 3: Common Efficacy Barriers

• Inadequate planning
  – Overall development plan should be drafted prior to any human exposure, if at all possible
  – Communicate plan with the Review Division as early as possible, preferably pre-IND
    • Very early † Office of Translational Sciences (e.g., biomarkers)
    • Anytime ‡ Office of Orphan Product Development
Common Efficacy Barriers (2)

• Inadequate pivotal study design
  • For rare/ultra-rare diseases, often only get one chance at an adequate and well-controlled study (often no confirmatory trial)
  • Prospectively define objectives/hypothesis, endpoints, population for study
  • Need to have control arms or comparators
    – Published literature likely inadequate
    – Serial “case studies” are hard to interpret for efficacy
  • Absent data or poor use of data from early phase trial(s)
    – First/early studies predominantly for safety, PK/PD, and exploratory efficacy to inform pivotal study
    – Often, there is no dose finding, poor PK information and efficacy assessment not well informed
Areas for Development

• Natural history studies*
• Outcome measure development*
  – Tools and instruments (e.g., PROs, composite scales and indices)
  – Biomarkers (e.g., imaging, biologic markers)
**These take years – can be ongoing whether or not potential candidates have been identified
• Repurposing (old drug, new indication)
• Translational Science
  – Animal models, biomarker qualification, pharmacogenomics, pharmacometrics, computational modeling, adaptive study designs
Current Legislation/Regulations Available for Serious Disorders

– Fast Track Designation
  • Combination of a drug product intended to treat serious/life-threatening condition and a claim that addresses an unmet medical need
  • Scheduled meetings
  • Rolling review

– Accelerated Approval based on surrogate endpoint
  • Subpart H - drugs (21 CFR 314.500)
  • Subpart E – biologics (§601.40)

– Priority Review
  • 6-month NDA/BLA PDUFA goal date instead of std 10-month
Communication

• Early and frequent communication with FDA
  – Encouraged by FDA to “aid in the evaluation of the drug and in the solution of scientific problems…” “Free, full, and open communication…” (§312.47)
  – Better communication with the review Division increases chances of a successful outcome

• Opportunities for Communication:
  – Formal meetings
    • Type A: dispute resolution, e.g., Clinical Hold, Refuse-to-File (RTF)
    • Type B: clinical stages, e.g., pre-IND(§312.82), EOP2 and pre-NDA/BLA (§312.47),
    • Type C: not type A or B
  – Informal meetings
  – Special Protocol Assessments (SPAs)
Summary

• To improve chances of success of rare disease treatment development:
  – Much of the work should be done before the clinical study starts. Need better:
    • Translational science/animal data
    • Disease characterization
    • Endpoints and outcome measures
  – Strong communication and collaboration are necessary
    • Recommend FDA involvement in planning as early as possible (i.e., pre-IND)
References