



# Is Your Treatment Ready for 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.

# Study Challenges in CNS/IEMs

- IEMs
  - Rare disorders with few patients available for study
  - 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, outcome measures, tools, instruments, biomarkers usually lacking
  - Tissue targeting

# Outline

- Regulatory considerations for initiating clinical studies and moving clinical development forward
- Common safety and efficacy barriers encountered when evaluating INDs
- Where we see the near- and longer-term needs are for advancing clinical development
- Opportunities for collaboration and communication

# Rare Disease: Definition

IEMs are Orphan Diseases. Rare/Orphan disease defined as:

"...the term rare disease or condition means any disease or condition which (a) affects less than 200,000 persons in the U.S..." (21CFR 316)

# Orphan Drug Act (ODA)

- Many treatments for IEMs receive Orphan Drug designations under the Orphan Drug Act
- Orphan Drug Act
  - 25<sup>th</sup> Anniversary in 2008
  - Predominantly financial incentives
  - Pre ODA: ~10 approved drugs
  - Post ODA: >300

# Regulatory Challenge

- What Orphan Drug Act 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)

# Regulatory Challenge (2)

- 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)

# The Bench to Bedside Hurdle

- Common safety barriers:
  - 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)
      - Especially challenging for affects on CNS

# Safety

- Toxicology\* – Key considerations to determine if drug is safe to administer to study subjects:
  - Identify initial “safe dose” for clinical trials, margin of exposure
  - Dose-escalation plan and safe stopping dose
  - What organs/systems are at risk?
  - Dose limiting toxicities – what should be monitored in clinical trials? Are toxicities reversible?
  - How will drug be administered – dose, duration, route?
  - Target population (e.g., children, infants)
  - Make sure adequate safety support is done in a timely manner or can delay clinical program

\*From: Jacobson-Kram D, OND/CDER. Preclinical Safety Testing of Drugs. Presentation to the Israel Chapter of PDA. July 15-16, 2008.<sup>10</sup>

# 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
    - Consider use of safety committee (e.g., DSMB)

# 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

# Common Efficacy Barriers

## #1 Poor planning

- Draft overall development plan prior to any human exposure, if at all possible
- Please come in and discuss the overall plan with us pre-IND
  - Considering IND → Review Division (likely DNP or DGP)
  - Very early → Office of Translational Sciences (e.g., biomarkers), Office of Orphan Product Development

# Common Efficacy Barriers (2)

## #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
- Poor use of early phase trial(s)
  - First/early studies predominantly for safety, PK/PD, and exploratory efficacy to inform pivotal study

# Areas for Development

- Natural history studies
- Outcome measure development
  - Tools and instruments
    - E.g., patient reported outcomes, composite scales and indices
  - Biomarkers
    - E.g., Imaging, biologic markers
- These take years – can be ongoing whether or not potential candidates have been identified

# Areas for Development (2)

- Repurposing
  - Old drug, new indication
- Translational science
  - Animal models, animal studies
  - Biomarkers qualification process
  - Pharmacogenomics, pharmacometrics, computational modeling
  - Adaptive study designs

# Directions for the Future

#1 Best access for patients to an effective therapy is an approved drug

- For approval, treatments must demonstrate substantial evidence of effectiveness
  - Substantial evidence of effectiveness requires design and execution of at least one adequate and well-controlled clinical trial
    - To design an adequate and well-controlled clinical trial requires well-described disease (natural history), and acceptable endpoints, outcome, measures, tools, instruments and/or biomarkers to adequately assess the intervention

# Directions for the Future (2)

## #2 Much of the work should be done before the clinical study starts

- Map out clinical development program as early as possible
  - Endpoints and outcome measures, patient population, etc.
  - Use everything you have
    - Early phase trials can be very valuable, even if data are very limited
    - Translational science

# Directions (3)

## #3 Collaboration more likely to result in success

- FDA involvement as early as possible (i.e., pre-IND)
  - Better communication with the review Division increases chances of a successful outcome
  - Reach agreement on clinical trial design, endpoints, population for study, length of study, comparators, etc. prior to initiating study
  - We are looking for more translational-period opportunities to interact--important area for the future