Understanding the Needs of CDER Drug Review Divisions

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CDER Review Divisions

• Evaluate efficacy and safety of new drug applications for specific indications by Sponsors

• Agency involvement & advice often begins early during drug development

• Agency involvement continues post-marketing to further assess safety
New Drug Development

IND Phases

- Clinical Phase 1: Safety/Tolerability and Pharmacological Studies
- Clinical Phase 2 (proof-of-concept): Early Efficacy Testing & Dose Determination
- Clinical Phase 3: Safety and efficacy Studies

Non-Clinical: Research Lab & Animals

- Discovery & chemical synthesis
- Clinical Outcomes Assessments & Natural History Studies

pre-IND

post-marketing

IND

NDA/BLA
Level of Evidence of Efficacy: Legal Requirements

• 1962 Drug Amendments to the Food Drug & Cosmetic Act:
  – Required establishment of effectiveness of the drug as a prerequisite for marketing approval
  – Effectiveness established by “Substantial Evidence”
  – Substantial evidence consists of “Adequate & Well Controlled Investigations”
What are Adequate and Well-Controlled Studies?

• Studies that have 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” (21 CFR 314.126)

• Adequate and well controlled trials have:
  – **Appropriate control for valid comparisons**
  – Appropriate selection of subjects
  – **Well-defined and reliable methods of assessing response**
  – Adequate measure to minimize bias
  – Prospectively planned analyses designed with rigor
Defining Clinical Benefit

• Treatment benefit occurs when a drug positively effects
  – How a patient **feels** (e.g. symptoms)
  – How a patient **functions** (e.g. walks)
  – How a patient **survives** (e.g. improved mortality)

• Clinical effect must be clinically meaningful in the context of a given disease
Challenges in Drug Development for Rare Diseases

• Small population  
  – Limited opportunity for study & replication

• Often Heterogeneous  
  – Study population size limits statistical analysis

• Incomplete understanding of disease manifestations

• No precedent for drug development  
  – Lack established endpoints, outcome measures & tools/instruments for the population
Drug Development:
(Especially for Rare Diseases)

Start with the end in mind: Obtain clinically meaningful evidence of benefit in how patients feel, function or survives from adequate and well controlled trial(s)
What Can Patient Organizations do to Facilitate Drug Development?

• Perform Natural History Study

• Provide Patient Experience Data

• Develop and Validate Qualitative and/or Quantitative Assessment Methods

• Encourage enrollment in randomized, controlled trials
Natural History Studies

• Comprehensive study characterizing a disease or subset of disease over time

• Identify variables that correlate with disease progression and outcomes in the absence of experimental treatment
  • Demographic, genetic, environmental

• Cohort
  • Prospective or Retrospective
  • Include all stages of disease from pre-symptomatic to death/cure/non-progressive chronic disability
Why are Natural History Studies Important?

• Scientific framework for rigorous investigation
  – Understanding disease outcomes and variability
    • Endpoints
    • Population
    • Sample Size

• External control population for pivotal trial*
  – Reserved for special circumstances in which there is a dramatic treatment effect & disease course is highly predictable & endpoints are objective
    • Population & efficacy assessments comparable to interventional study populations

Natural History Studies within the Regulatory Framework of Rare Disease Development
Patient Experience Data

• Inform Clinical Endpoints
  – Ensure bothersome signs and symptoms assessed
  – Ensure impact of condition on functioning and quality of life assessed

• Inform Benefit-Risk Assessment
  – Patient preference and tolerance for side effects
Assessment Tools

- Design and validate novel patient reported outcome measures
- Design and validate novel observer reported outcome measures
- Validate accuracy and reliability of tools originally developed for other disease populations
Clinical Trial Participation

- Patient participation is necessary for clinical trials & new drug development
  - Individual patients need to decide whether they are willing to undertake the burdens and potential risks associated with clinical trial participation
- Randomized, placebo/standard of care, controlled clinical trials are the most informative as they control bias
Conclusions

• Best access for patients to an effective therapy is an approved drug.

• Patient engagement early & throughout development process is important to informing drug development and regulatory decision making.

• You can help the FDA by early engagement and use of scientifically sound methods to collect representative patient data for natural history studies and endpoint selection and measurement.