Considerations for Clinical Trial Designs

John Jenkins, M.D.
Director
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

Outline

- Regulatory considerations for clinical studies
  - IND studies
  - Evidentiary standards for approval
- Examples
- Key points

Clinical Development Challenges

- Clinical development challenges in rare disease drug development programs
  - Rare disorders with few patients available for study
  - Often chronic, progressive, serious, life-limiting and life-threatening with unmet medical needs
  - Highly heterogeneous group of disorders
    - High phenotypic heterogeneity within disorders
  - Natural history often not well (or incompletely) understood
  - Endpoints, outcome measures, tools, instruments, biomarkers usually lacking

Clinical Trial Objectives

- Primary goal of a clinical trial is to establish cause and effect
  - Isolate the effect of a treatment and rule out factors that could lead to misleading findings (bias)
  - Establish a favorable risk-benefit profile for a new drug
- Development and testing demands high standards, scientific rigor and safety monitoring

Objectives (2)

- Overall objectives for all drugs (Orphan and non-Orphan) - to determine that:
  - Drug is safe and effective for its proposed use
    - Benefits outweigh the risks
  - Drug's proposed labeling is appropriate to allow for its intended use
  - Methods used in manufacturing are adequate to preserve the drugs identity, strength, quality and purity
- That is, development program should tell the drug's whole story

IND Studies

- Initial Investigational New Drug Applications (INDs)/first-in human studies
  - primary objectives are to assure the safety and rights of subjects participating in the clinical trial (*312.22)*
- FDA's role
  - Clinical trials in US conducted under INDs
  - At each stage of development, FDA will focus on
    - Assuring safety and rights of subjects
    - Scientific quality of the clinical investigations
    - Likelihood that the investigation will yield data capable of meeting statutory standards for marketing approval

IND (2)

- IND submissions required elements (312.23)
  - General investigational plan
  - Protocol
  - Investigator Brochure
  - CMC, animal toxicology, previous human experience, and other information, as applicable
    - Non-clinical information (e.g., animal toxicology) is necessary to assure that it is reasonably safe to conduct the proposed clinical investigation(s) [312.23(a)(8)]

IND (3)

- After submission of Initial IND application, study may not proceed for 30 days
  - If no hold imposed after 30 days, study may proceed
  - Most common reasons for clinical hold [312.42(b)(1)]
    - (i) “subjects… would be exposed to an unreasonable and significant risk of illness or injury”
    - (iv) “IND does not contain sufficient information required …to assess the risks to subjects”
  - Common safety barriers
    - Lack of characterization of drug/biologic (CMC)
    - Lack of pre/non-clinical data
      - E.g., Animal toxicology

Evidentiary Standard for Approval

- Regulatory Challenge:
  - For approval, Orphan drugs held to same evidentiary standard as non-Orphan drugs
  - Orphan drugs must:
    - Demonstrate **substantial evidence of effectiveness/clinical benefit** (21CFR 314.50)[1,2]
    - 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)
  - Clinical benefit:
    - The impact of treatment on how patient feels, functions or survives
      - Improvement or delay in progression

Adequate and Well-Controlled Study

- Must incorporate generally accepted scientific principles for clinical trials
  - 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
    - Method of selection of subjects
    - Method of assigning patients to treatment/control groups
    - 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

"Flexibility"

- Regulations provide room for flexibility in reviewing treatments for rare diseases
  - There are "many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards"
  - "…FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards."

(314.105)

Examples

CDER Orphan approvals in 2010 (as of Oct 8, 2010):

Product	Indication	AP Month 2010	Division	NDA/BLA
Dalfampridine (Ampyra™, Acorda)	Improve walking in Multiple Sclerosis	January	DNP	NDA
Collagenase (Xiaflex™, Auxilium)	Dupuytren's contracture	February	DPARP	BLA
Velaglucerase (VPRIV™, Shire HGT)	Gaucher disease	February	DGP	NDA
Carglumic acid (Carbaglu®, Orphan Europe)	NAGS deficiency (UCD)	March	DGP	NDA
Rifaximin (Xifaxan®; Salix Pharms)	Hepatic encephalopathy	March	DGP	NDA
Alglucosidase alfa (Lumizyme®, Genzyme)	Late-onset Pompe disease	May	DGP	BLA
Glycopyrrulate (Cuvposa™, Shionogi)	Drooling in children with neurologic disorders (e.g., cerebral palsy)	July	DNP	NDA
Pegloticase (Krystexxa™, Savient Pharma)	Chronic gout not responsive to conventional therapy	September	DPARP	BLA

Approval history

- Dalfampridine (improve walking in Multiple Sclerosis)
  - 2 R, DB, PC trials, n=540
- Collagenase (Dupuytren's contracture)
  - 2 R, DB, PC trials, n = 374
- Velaglucerase (Gaucher disease):
  - One pivotal study → R, DB, parallel dose-group, n =25
  - Total program → 3 studies, n=99
- Rifaximin (hepatic encephalopathy)
  - One R, DB, PC trial, n=299
  - Efficacy supplement, prior approval for traveler's diarrhea, so previous extensive exposure history in patients
- Alglucosidase alfa (late-onset Pompe disease):
  - One R, DB, PC trial, n=90
  - Additional supportive information from related experience in infantile-onset Pompe disease from a post-marketing registry, n=15
- Carglumic acid (NAGS deficiency):
  - OL, historically-controlled, retrospective case series, n=23
- Glycopyrrolate (drooling in children with neurological disorders)
  - One pivotal study → R, DB, PC, parallel, 8-week study, n=38
  - Total program → 2 studies, n=151
- Pegloticase (chronic gout in adult patients who do not respond to conventional therapy)
  - 2 R, DB, PC 6-month trials, n=212

Orphan Highlights 2010

- Diverse collection of diseases/populations studied
  - MS, Dupuytren's contracture, genetic disorders (3), hepatic encephalopathy, gout, pediatric neurological disorder
- Range of study designs
  - R, DB, PC
  - OL, historically-controlled
- Program sizes
  - Dalfampridine n=540
  - Carglumic acid n=23
- Scope of studies needed to provide sufficient evidence
  - E.g., single study – carglumic acid → step-wise programs for most others
  - Totality of evidence will be considered
- Endpoints accepted
  - Novel and established/well-described
  - Meaningful, interpretable, well-defined and reliable
  - "Fit for Purpose"

Key Points for Orphans

- No one right way to do things for rare diseases
  - Clinical development program must be based on a solid scientific foundation
    - Mechanism of action, underlying pathophysiology of disease well-understood
    - Disease natural history needs to be defined
  - Study design considerations based on population under study, drug/product and disease characteristics, etc.
    - E.g., relapsing remitting vs. chronic progressive
    - Potentially curative vs. ameliorating an aspect of disease
    - Other available therapies
  - Still need to demonstrate substantial evidence of effectiveness
    - Flexibility in how that is achieved
    - Multiple pathways defined in existing guidance
      - E.g., single study with:
      - Pharmacologic/pathophysiologic endpoints
      - Multiple endpoints, different events (measures)
      - Statistically persuasive findings

Key Points (2)

- Much of work done before (pivotal) study starts
  - Map out clinical develop program as early as possible
  - Recommend doing a natural history study early on
  - Early phase trials very important to inform design pivotal trial(s) – even if very small
- Safety is always an important concern for drug development throughout the entire drug development process

Key Points (3)

- Strong communication with FDA increases chances of a successful outcome
  - Meet early and often (formal meetings)
  - 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)
  - Contact the Review Division
    - Consistent point of contact is the Regulatory Project Manager in the OND Review Division
  - Formal policies and procedures for meetings
    - Guidance document: "Formal meetings between the FDA and sponsors or applicants"[8]

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

Summary

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

In Conclusion

- Successful clinical development of treatments for rare diseases possible and a growing area of research and development
- To improve chances of success of rare disease clinical development programs
  - Strong communication and collaboration are necessary
    - Recommend FDA involvement in planning as early as possible

References

1. FDA website
www.fda.gov
2. Many Guidances available, many topics, not specific to rare diseases
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

Some Guidances:
3. Formal meetings between the FDA and sponsors or applicants
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf
4. Content and format of investigational new drug applications (INDs) for Phase1 studies of drug
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071597.pdf

References (2)

5. Providing clinical evidence of effectiveness for human drug and biological products
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf
6. E10 Choice of control group and related issues in clinical trials
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073139.pdf
7. Statistical principles for clinical trials
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073137.pdf

References (2)

Other:

8. Code of Federal Regulations: (21CFR, Food and Drug Law)

   http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

   - IND regulations 312
   - NDA 314
   - Biological products 600

9. Office New Drugs home page

   http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm184426.htm