Considerations for Clinical Trial Designs

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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 drug’s 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 \((21\text{CFR 314.50})^{1,2}\)
    – 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)
### CDER Orphan approvals in 2010 (as of Oct 8, 2010):

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

Some Guidances:
3. Formal meetings between the FDA and sponsors or applicants
4. Content and format of investigational new drug applications (INDs) for Phase1 studies of drug
References (2)

5. Providing clinical evidence of effectiveness for human drug and biological products

6. E10 Choice of control group and related issues in clinical trials

7. Statistical principles for clinical trials
References (2)

Other:
   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