Practical Issues
(Phase 3 in Rare Diseases)

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Multiple Perspectives

• Pulmonary / Critical Care Physician
• Academic medicine
  – Cleveland Clinic Foundation, 1995 - 1999
• Division of Pulmonary and Allergy Products, CDER
  – Medical Officer / Team Leader / Deputy Director
  – 1999-2006
• Chief Medical Officer, United Therapeutics and Lung Rx
  – 2006 – 2012
• Principal, EJS Consulting, LLC (current)

• Lymphangioleiomyomatosis (LAM) Foundation
  – Scientific Advisory Board, Board of Directors
UT / Lung Rx

• United Therapeutics (UT)
  – Founded in 1996 by Martine Rothblatt following the diagnosis of her daughter with a rare, fatal condition called pulmonary arterial hypertension (PAH)
  – Publicly traded company with approximately 500 employees
  – Marketed products:
    • treprostinil for PAH (IV, SC, Inhalation)
    • tadalafil for PAH (oral)
  – Focused on the development of products to address unmet medical needs of patients with chronic, life threatening conditions (cardiovascular, oncology, infectious disease)
  – Lung Rx / Lung LLC is a wholly owned subsidiary of UT
The LAM Foundation

- Founded in 1995 by Sue Byrnes, following the diagnosis of her daughter with lymphangioleiomyomatosis (LAM), a rare, fatal lung disease
- Advocacy, patient support / education, research funding
  - Peer review process for funding fellowships and pilot projects.
  - Research aim: advance the science; provide resources to generate data that would support grants from larger funding agencies (e.g. NIH R01 grant)
  - Recent focus on infrastructure development for future clinical trials and research to support translational trials (e.g. biomarker development)
- MILES Trial (Multicenter, International Lymphangioleiomyomatosis Trial of the Efficacy and Safety of Sirolimus) (NEJM, 2011)
  - Based on insights into the molecular pathobiology of LAM generated through research funded in part by the LAM Foundation
  - PI: Frank McCormack MD (Director, Div of Pulmonary, Critical Care and Sleep Medicine, University of Cincinnati; Scientific Director, LAM Foundation)
  - Funding from various sources, including LAM Foundation, NIH (Rare Lung Disease Consortium), FDA Office of Orphan Products Development
Phase 3 in Rare Diseases: The Task

• Same as for anyone else:
  – Generating substantial evidence of a clinically meaningful benefit
  – Generating a safety database that is adequate to allow a reasonable understanding of the risk profile

• Research in rare diseases presents unique challenges in accomplishing the task.
  – Some may be obvious, but the magnitude of their collective effect on drug development may not be.
Recent big pharma forays into the orphan arena notwithstanding, rare disease research has typically been conducted by and probably will continue to be conducted by small firms.

– The demise of the “blockbuster” model, thinning pipeline and expiring patents may attract serious interest of big pharma (e.g. some firms setting up orphan groups), but we’ll see...
Resources

• Small firms involved in rare disease research may lack resources in several areas.
  – **People**: Firms may be founded based on a particular promising therapeutic approach to a rare disease. The leadership may be quite passionate and dedicated to the disease, but lack significant drug development experience.
  – **Operational Machinery**: Small firms generally lack the operational machinery and depth of experience found at larger companies (biometrics, clinical monitoring, clinical writing, etc.).
  – **Financial**
    • Orphan Drug Act incentives certainly help to attract investors who see potential value in small markets. Still, these may be high risk undertakings because of the uncertainties involved (development, marketing challenges, reimbursement challenges, etc.).
    • Often the case that small firms have no revenue and are therefore reliant on an uncertain flow of investor capital.
Few Patients

- By definition, the number of patients available to study is limited. These small numbers impact the ability to establish safety and efficacy, as compared to common diseases.
- In some cases, competing studies may compound the problem (e.g. Pulmonary Arterial Hypertension).
- Hinders optimal Phase 2 development. Too few patients to optimally explore dosing interval, dose ranging, etc.
- Hinders collection of robust safety database.
- Hinders successful implementation of study.
  - Slow recruitment
  - Patients often live far from study sites
    - Requires outreach to identify potential subjects
    - Logistical challenges (travel costs, etc)
    - Potential subjects may be reluctant to travel to study sites frequently
  - Many sites required – each with small numbers of subjects
    - increases cost and administrative burden
    - presents challenges to QC and assuring consistency across sites
Few Patients

- Small numbers available for P3 makes it difficult to achieve highly statistically significant results except in instances where the effect size is dramatic.
  - Statistical Significance is a function of
    - the variance intrinsic to the measure (primary endpoint)
    - the magnitude of the effect size
    - number of subjects / observations
  - In one sense, this could be seen as an unintended consequence of the application of a common statistical standard: a de facto “different standard” for rare diseases in terms of an effect size.
Scientific advancements have led to new insights into the molecular mechanisms of various rare diseases and identified potential therapeutic targets.

Firms developing drugs for rare diseases may be particularly reliant on the scientific and clinical expertise of a small number of physicians/scientists with relevant experience.

Physicians who care for these rare conditions have a unique understanding of the disease and its manifestations and impact on the patient. They should participate in the design and conduct of clinical studies.
Expert Physician Consultants

• The challenge relates to the fact that, in many cases, these expert physicians/scientists don’t have substantial drug development experience.
  – Appreciation of the importance of Phase 2
  – Understanding of issues around the demonstration of efficacy (e.g. biomarkers, surrogate endpoints, clinically meaningful endpoints)
  – Experience in the conduct of complex, multinational clinical trials
  – Understanding of the importance of Good Clinical Practice

• With more common diseases the expert advisors often have prior experience so they “speak the same language.”

• In the absence of good data, physicians caring for patients with rare diseases may have adopted certain therapeutic practices that may interfere with study design (e.g. LAM, Idiopathic Pulmonary Fibrosis).
The Diseases

• May be slowly progressive
  – Require long studies to establish benefit
  – Difficult to establish proof-of-concept
  – Difficult to dose-range

• Rare, so
  – Natural history may not be well described
  – Useful biomarkers may not be known
  – Likely no established surrogate endpoints
  – Prior data to inform expected effect size / powering may be lacking
Regulatory Uncertainty

• Uncertainty regarding how the “standard” expectations of regulatory authorities might be applied to very rare conditions
  – No overarching policy
  – In the absence of experience with a specific disease, review divisions may be reluctant to commit to specific expectations
  – Quantity of evidence to support effectiveness, size of safety database, etc
• No historical successes (or even failures) to guide program
  – Primary endpoints: acceptable and sensitive to drug effect
  – Secondary endpoints: informative, supportive
  – Study design: scientifically sound and capable of demonstrating drug effect
Regulatory Uncertainty

• Uncertain potential for additional, post-marketing data collection
  – Additional safety follow-up or REMS
  – Supplementary evidence of efficacy
  – Requires resources, continued access to patients, etc.
Addressing the Challenges

- Many of the challenges can’t be addressed by FDA reviewers
  - Some challenges are intrinsic to rare diseases
  - Some challenges relate to resources
    - Period of exclusivity: 7 vs. 10 years
    - Reimbursement issues
  - Some proposed solutions would require structural / administrative changes
    - “Division of Orphan Products” to review all orphan applications?
    - “Orphan Specialist” within each review division?

- Must maintain assurance that approved drugs are effective and have an acceptable safety profile, while doing our best to ensure that patients with rare diseases have access to safe and effective therapies.
Addressing the Challenges

• Communication between firms and the FDA is key.
  – FDA may assume that the firm knows what it is thinking.
    • Less cumulative experience and “regulatory intelligence”, so even relevant publicly available information may not be identified
  – The firm may assume that FDA knows details of its product, existing literature, the specific rare disease

• Where there are no established clinical endpoints – need to discuss and agree on what can be clinically meaningful and also achievable
  – This takes more effort than areas where endpoints / study designs are well established.
  – Agency reviewers who may have dealt with a large number of rare disease programs may be able to offer creative approaches to study design.
Addressing the Challenges

• Additional meetings / communications?
  – “Pre-pre-IND” (as in CBER) would allow early read on feasibility / cost.
  – Teleconferences and direct communication with reviewers during development would help to address issues in real time.
  – Clear communication of “need to have” vs. “nice to have”

• Agreement among regulatory bodies in various regions
  – Even more critical for rare disease programs – need to be sure to address all requirements in each study.
  – Extended timelines to achieve input and agreement from all relevant authorities are less well tolerated by small firms.
  – Differing opinions are hard to avoid, but interagency communication would help.