ANGI ROBINSON
Executive Director, Scientific Account Leader, Premier Research

Angi Robinson has been with Premier Research for over 12 years and has provided executive oversight and full management support for numerous studies, including global studies with a focus in paediatrics and rare diseases. Ms. Robinson has supported FDA Pre-IND meetings, IND submissions and BLA & NDA directorship. Ms. Robinson’s experience includes multiple study designs including PK/PD, adaptive design, FDA Fast Track designations and she has directed several studies requiring the oversight of Data Safety Monitoring Boards and Data Monitoring Committees. She has supported NDA submissions, including a pivotal studies resulting in product approval. Ms. Robinson is the Global Project Director for Good Clinical Practice Journal’s (GCPj) 2008 Clinical Research Team of the Year for a pivotal clinical trial in a rare disease.
CHARLENE SANDERS
Vice President, Global Regulatory Affairs & Pediatric Strategic Consulting, Premier Research

Dr. Sanders’ brings extensive regulatory expertise including more than 18 years of pharmaceutical management experience to Premier Research. Her experience in drug development and regulatory affairs includes interactions with both regulators and major pharmaceutical companies. Dr. Sanders’ therapeutic experience in oncology, neuroscience, pain and pediatrics is well aligned with Premier Research’s therapeutic focus and prowess in executing clinical trials targeting rare diseases and orphan drug status. She trained in pediatrics and has had post-doctoral specialty fellowships. She has held teaching faculty appointments at the Children’s Hospital of Los Angeles, Morgan Stanley Children’s Hospital (Columbia University Medical Center), Children’s Hospital of Boston (Harvard University) and Yale University. She received her Medical Degree from the University of Pennsylvania School of Medicine and has practiced clinical and research medicine for three decades.

Dr. Sanders is able to leverage her career experiences, both in global regulatory strategy and medical practice, by bringing her extensive knowledge to the Premier Research team. Dr. Sanders has recurrent success in providing clinical design input and direct protocol review that overcome regulatory hurdles associated with research trials, as well as broad regulatory, clinical and translational research expertise in US regulatory healthcare policy environments. She is an expert in pediatric regulatory requirements and orphan drug regulatory pathways. She has strong familiarity with non-US healthcare delivery and regulatory research models used by European and Australian pharma and biotech industry organizations, as well as experience in Pan-Pacific regulatory and business environments.
OUR WEBINAR WILL BEGIN SHORTLY.

In the meantime, download a copy of our white paper The Science of Hope.

www.premres.com/rare
OUR WEBINAR WILL BEGIN SHORTLY.

Later, watch John Orloff of Novartis and Phil Vickers of Shire HGT discuss rare disease and orphan drug development strategies.

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PROVEN STRATEGIES FOR RARE DISEASE AND ORPHAN DRUG DEVELOPMENT IN THE US

Angi Robinson and Charlene Sanders
16th July 2013
WHAT IS AN “ORPHAN DRUG”?  

“Orphan drugs” are medicinal products intended to treat diseases so rare that sponsors are reluctant to develop them under usual marketing conditions.

- Between 5,000 and 8,000 distinct rare diseases exist today, affecting between 6% and 8% of the population in total i.e. 27 – 36 million people in the European Union.

- 250 new rare diseases are identified each year, 80% are genetic in origin and 50% affect children.

- 460 new medicines are currently in clinical trials for treating rare diseases.
ORPHAN MARKET FACTS
SINCE THE ORPHAN DRUG ACT

- Orphan Market Facts Since The Orphan Drug Act
  - Prior to 1982 FDA approved 10 orphan treatments
- From 83’-04’ over 325 orphan drugs approved
  - About 1/3 of all approvals
- Over 3,000 compounds received “designation”
- Market Size: Approx. $90B in 2011 growing to $112B by 2014
  - Over 40 drugs hit $1B in global sales
  - Most drugs developed by small biotech/specialty pharma
  - 2009 “big pharma” accounted for 70% market share
- Cost of treatment high
- 6,800 rare diseases for which no therapies exist
COMPARISON OF DISEASE PREVALENCE REQUIRED TO OBTAIN ORPHAN STATUS

- EU: 5 per 10,000 individuals in the EU (< 253,000 patients per year)

- USA: < 200,000 patients per year in the US (7.5 per 10,000 individuals)

- Japan: < 50,000 patients per year in Japan (4 per 10,000 individuals)

- Australia: < 2,000 patients per year or (1 per 10,000 individuals)
PATHWAY TO DEVELOPMENT IN RARE DISEASE

Larissa Lapteva, Rare Diseases Program, CDER, FDA

B:R Assessment

Clinical Evidence to Establish Safety and Efficacy Science—Based Primary Endpoints

Leveraging of Pharmacology Toxicology Data to Support Clinical Program

Assurance of Consistent Product’s Quality and Manufacturing

Understanding of Product’s Proposed Mechanism of Action

Knowledge of Disease’s Natural History
Orphan Drug Designation Application Review Time Measures

- Ensure timely review of orphan drug designation applications
  - Total number of orphan drug designation reviews completed in the month
    - 4Q2012 = 83
  - Percentage of orphan drug designation reviews completed in 90 days or less
    - 4Q2012 = 84%
  - Percentage of orphan drug designation reviews completed in 120 days or less
    - 4Q2012 = 98%
  - Total number of orphan drug designation decisions that resulted in orphan designation in the month
    - 4Q2012 = 49
RARE/ORPHAN DISEASES CONSIDERATIONS

Research Advances for Rare Diseases and Orphan Products

- Implementation of Registries for Rare Diseases
- Genomic Models Research: Patient-Researcher Relationships/Role of Crowd Sourcing in Rare Disease Research
- Challenges of Developing Novel Orphan Medicines for the Global Market
- Rescuing and Repurposing Drugs: Challenges and Opportunities
- Rare Disease Development Challenge of Demonstrating Value
FDA FINALIZES CHANGES TO ORPHAN DRUG REGULATION, EMPHASIS ON CLARIFYING EXISTING POLICIES

POSTED: 11 JUNE 2013

- FDA would substitute the term “medically plausible” for a definition to stop companies from potentially “gaming” approvals.
- Under the new definition, FDA explains that a subset is taken to mean the drug is appropriate when used in the subset, but use in a broader population would be inappropriate “owing to some property(ies) of the drug,” such as toxicity or the mechanism of action.
- FDA said that while it “understands the concern,” it is more concerned about an orphan subset being “artificially narrow.” It will not require the same scientific proof for the negative population that it does for the positive one.
- Even if a single drug is used to treat multiple applications that would cause it to treat more than 200,000 patients, FDA said it will still see the drug as an orphan treatment for the purposes of the Orphan Drug Act so long as each patient population is under 200,000.
- FDA conceded that new dosage forms – some of them, anyway – may be clinically superior to previously approved dosage forms and “thus eligible for their own seven-year period of orphan exclusive approval.”
PRACTICAL CONSIDERATIONS IN PLANNING RARE DISEASE STUDIES
STRATEGIC APPROACH TO RARE DISEASE TRIAL

- Study Startup
  - Country/Site distribution
  - Regulatory start up

- Enrollment

- Study Execution
COUNTRY / SITE DISTRIBUTION APPROACH

GLOBAL:
- Approvals
- IMP
- Insurance
- Translations

SINGLE/LIMITED REGIONS:
- Enrollment
- Retention
- Relocation

premier research
GLOBAL CONSIDERATIONS

- RA/EC Approvals
  - Clear Strategy for implementation: Region → Country → Local
  - Replication of documents: sequential vs. reinventing the wheel

- IMP Supply
  - Utilize depots thoughtfully: supply drug “on demand”

- Insurance
  - Understand minimum requirements: terms, limits
  - Inquire about EC/RA requirements for implementation timelines

- Translations
  - Know what must be translated vs. submitted in English
  - Quality Control: ensure documents are accurate prior to translation
SINGLE/LIMITED REGION CONSIDERATIONS

• Relocation
  • Challenges with rapid disease progression, subject stability, willingness to move
  • Requirements/logistics: visa, insurance, accommodations

• Enrollment
  • Consider geographical distribution/subject prevalence
  • Consider maximum work load per selected site

• Retention
  • Costs incurred for long term relocation
  • Loss of subject interest due to travel/time commitments
REGULATORY/ETHICS CONSIDERATIONS

- Regulatory approval timelines may be rate limiting
  - *Important factor in country consideration*
  - *Approval timeline vs. study timelines*
  - *Disease prevalence should be considered*

- Best case ≠ reality
  - *Rare disease studies may create further challenges*
  - *Study may not be approved in all countries*
APPROVAL CONSIDERATIONS

• Challenges
  • Lack of familiarity with disease
  • Limited human data
  • No physician expertise
  • No standard of care

• Solutions
  • Publications
  • PI attendance at meetings
  • Establish “norms”
SITE SELECTION CONSIDERATIONS

- KOLs may have limited pivotal trial research experience
  - *Clinical research and GCP accreditation may be needed*

- Referral physicians and large patient encashment sites may access to broad patient base but have limited disease knowledge
  - *Disease and protocol training may be needed*

- Standard practices may vary widely
  - *Consultation with investigators during study planning and protocol writing is essential*

- Local site start up process may greatly impact the timeline
  - *Understand site specific processes*
ENROLLMENT

- Metric based enrollment metrics are widely unavailable
- Most sites may enroll 0-1 patient
  - Back-up and/or extra sites may be prudent as enrollment is often unpredictable
- Continual learning and reevaluation of enrollment assumptions is critical
- Thoughtful recruitment planning is essential
  - Develop site specific recruitment plan including data mining and outreach planning
  - Collaborations with PAGs (patient advocacy groups)
  - Accessing/creating patient registry
  - Providing study information materials and/or disease information
  - Utilizing call centers
  - Physician outreach and referral planning
  - General promotion of disease awareness
  - Conference / awareness participation
STUDY EXECUTION CONSIDERATIONS

- Long term plan
  - Plan twice, execute once
  - Manage the program; not just the study
  - Proactive accounting for any interim data needs

- Study design requirements
  - Specialty testing
  - IMP/Study Supply
  - Plan for long term studies

- Proactive approach to study closeout
  - Identify data challenges
    - Local labs, retrospective data collection, high AE/ConMed rate
  - Implement clean data reviews, include data transfers
  - Interim data transfers and cleaning