Rare and Orphaned Disease Drug Products: Convergence of Scientific and Regulatory Paths Leading to Successful Approval

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Lecture Overview

• Orphan Drug Act
• Rare Disease (RD) Definition and Impact
• RD Research Challenges
• NIH Programs for RD Research
• Progeria Discussion
• Special Guest
January 4, 1983: The Orphan Drug Act is passed to stimulate the development of drugs and biological products for the treatment of rare diseases.
Orphan Drug Act (ODA)

- Ronald Reagan signed the ODA 30 years ago
- In the decade leading up to the passage of the ODA, only 10 industry-supported products for rare diseases were brought to market
- Monumental legislation because it created—for the first time—incentives to develop desperately needed medical products for Americans suffering with rare diseases
- Amended several times since to reach current form
“As FDA commemorates the passage of this important legislation…”

- >2700 products in development have been designated as orphan drugs through the Orphan Drug Designation Program.
- >$290 million has been awarded to clinical studies through the Orphan Products Grants Program.
- >400 orphan products for rare diseases have been brought to market.
ODA 30th Anniversary 1-7-2013

-Recognition of the “Rare Disease Community”…

• **Patient Advocates**… who spur national **awareness** about RDs and support families, educate the community, and drive research into their diseases;

• **Legislators**… who worked to champion the passage of the ODA and subsequent legislation/funding;

• **Research Community**… leverage scarce resources and foster collaborations among **academia** and **industry**;

• **Clinicians**… who support the medical needs of patients with RDs and their families; and

• **Industry**… including pharmaceutical and biotech companies, research organizations, angel investors, and venture capitalists who, in the spirit of the ODA, have come together to develop products for RDs
What is a “Rare Disease”?

Definition of “rare” varies depending on the policies and legislation enacted by each region:

- USA: <200,000 per Orphan Drug Act of 1983*
- EU: <1/2,000*
- Japan: <50,000*
- Australia: <2,000/year*
- Singapore: <20,000*
- WHO: 0.65-1/1,000*
- China: <1/10,000 newborns or <1/500,000 general pop.
- India…???

Impact of “Rare Disease”

- Affects 6-8% or more of the world’s population
- 600-700 million people worldwide
- >7000 rare diseases currently recognized as such
- ~250 added per year
- <5% have effective drug therapies available
- **Broad spectrum of illness and etiology…**
  - Genetic, rare cancer, congenital malformation, autoimmune, toxic, infectious, degenerative, etc.

“Rare Disease” Facts

- Majority, 80%, are genetic based
- 75% affect children
- Urgency…30% of all pts with RDs will die before age 5 yrs
- Biochemical vs. anatomic defects…clinical concerns
- Unpredictable physiologic responses
- Mandatory neonatal screening for treatable disorders
- Rare cancers are the most studied… most orphan drug designations/approvals are for rare cancers (30-40% of all in US and EU)
- Currently, 400+ approved orphan drugs
- >450 medicines for RDs currently in clinical trials

Advancements in Gene Sequencing Technology Offers Huge Promise

Discovery of Gene Mutation causing Sturge-Weber Syndrome, Port-Wine Stain Birthmarks Offers Hope

Thursday, May 09, 2013

- Baltimore, Md. -- In new findings published today in the *NEJM*, researchers from the Kennedy Krieger Institute reveal the discovery of the cause – a **genetic mutation that occurs before birth** – of Sturge-Weber syndrome (SWS) and port-wine stain birthmarks. SWS is a rare disorder affecting approximately one in 20,000 births, while port-wine birthmarks are more common, affecting approximately one million individuals in the United States.


See also SWS Foundation/SWS International Registry
Exciting Times in Rare and Orphaned Disease Drug Research

Thanks in large part to the ODA, development of drug and biologic products intended to treat rare (orphan) diseases is one of the fastest growing areas of clinical research...

...and one of the most challenging
Obvious Challenges in Rare Disease Research

- Small number of patients by definition
- Widely dispersed geographically
- Often inadequate patient registry system
- Lack of information availability for families and providers
- Different definitions and regulations from region to region

Disease Prevalence Can Change

Examples…

- AIDS was a “rare disease” in the 1980’s but would not qualify as one today.
- Lymphomas were once lumped into a single category. However, since 2007 they have been identified according to the WHO classification system which allows drugs for certain types of lymphoma to qualify for orphan status designation.
Unique Challenges in Rare Disease Research

- Lack of animal disease models
- Diverse disease pathophysiology
- Poorly understood natural history
- Lack of historical data
- Variable age of onset
- Limited number of qualified biomarkers and surrogates
- Vague definitions of clinical endpoints
- Uncertain durations of therapy
- Heterogeneity in treatment effects
- Absence of placebo controls

Overall Purpose of Clinical Investigation in RD

The principles associated with clinical development of orphan drugs do not differ from non-orphan drugs in this regard...

1. Determine the **effectiveness** of a drug in the treatment or prophylaxis of a disease or condition
2. Assess the **risk and safety profile** of the drug
3. Determine the **overall risk-benefit** to patients who will be treated with the drug for a given condition
4. Provide data capable of meeting statutory standards for marketing approval
Speeding Up Drug “Discovery”*

- >10,000 drugs have been tested in clinical medicine
- Public domain databases can be used to create a virtual library (using HTS techniques, etc...)
- Cross-reference drugs against targets (enzymes, receptors, ion channels, transporters, etc...) known to be involved with a particular RD process
- Several new uses for FDA-approved drugs have been identified by screening academic or commercially available libraries of drugs or off-patent molecules (eg. Mycophenolate approved as immunosuppressive has also been found to inhibit angiogenesis)

Existing Drugs Are Often Effective in RD

- Drug “**repositioning**” or “**repurposing**”…new uses for existing drugs beyond their initially approved therapeutic indications
- Often occurs by **serendipity**…(eg. Sildenafil)
- **Resurrection** of a withdrawn medication… (eg. thalidomide in multiple myeloma)
- **Combinations** of approved drugs can be tried looking for synergy (eg. CA, HIV, TB)

Database Guided Repurposing of Drugs for Rare Diseases

- Rare Disease Repurposing Database (RDRD)
- Facilitates the repurposing of drugs for use in RDs
- Matches FDA orphan designation database to FDA drug and biological product approval lists
- Offers sponsors a new tool for finding special opportunities to develop niche therapies for RD patients

“Repurposing” Provides Advantages in RD*

- Known “druggable” targets with demonstrated efficacy in some clinical context
- Availability of materials and data such as long term toxicology profile
- Clearly described manufacturing controls
- May facilitate the regulatory process
- **Time saving** and **cost-effective** relative to bringing a new molecular entity to market

"Now, that's product placement!"
Sildenafil

• Pfizer compound UK-92, 480
• First clinical trials in Morriston Hospital in Swansea

• IUPAC name:

1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl) phenylsulfonyl]-4-methylpiperazine
Sildenafil

• Original Phase I clinical trials in HTN and angina
• Patented in 1996.....PDE5/c-GMP
• FDA approved for ED on March 27, 1998
• Repurposed:
  FDA approved as an orphan drug for adult PAH in June 2005...marketed as Revatio (20mg PO tid)

FYI...Tadalafil was FDA approved for adult PAH on May 22, 2009...marketed as Adcirca (40mg PO qd)
Sildenafil in Cardiac Transplantation

Sildenafil Allows Successful Heart Transplantation in Patients With CHF, Pulmonary Hypertension: Presented at CCC

- VANCOUVER -- October 30, 2011 -- Sildenafil therapy decreases pulmonary vascular resistance (PVR) and the transpulmonary pressure gradient, even in patients with “fixed” pulmonary hypertension, allowing them to undergo heart transplantation, according to a study presented here October 27 at the 12th Annual Canadian Cardiovascular Congress (CCC).

This retrospective study originating from the Laval group demonstrated that peri-heart transplant sildenafil therapy was well tolerated and decreased MPAP, PVR, and TPG in patients with fixed secondary pulmonary hypertension in the absence of ventricular assist device support. **Excellent early and late survival comparable to patients without significant pulmonary hypertension was demonstrated.** Duration of therapy was 163±116 days before heart transplant. Sildenafil was reintroduced early after transplant.
Sildenafil in Kids with PAH?


- Elegant discussion describing a **pharmacometric**
  approach to determine how best to evaluate the effects
  of sildenafil in the **pediatric PAH population (RD)**
- Recommended using $\Delta$ PVRI from baseline as a
  **surrogate clinical endpoint of efficacy**
- **However**, clinical studies revealed that the
  improvement in the 6-min walk distance seen in adults
  was not the case for the **pediatric PAH population**……
Sildenafil in Kids with PAH?

- FDA Drug Safety Communication: FDA recommends against use of Revatio (sildenafil) in children with pulmonary hypertension

- [8-30-2012] The U.S. Food and Drug Administration (FDA) is recommending that Revatio (sildenafil) not be prescribed to children (ages 1 through 17) for pulmonary arterial hypertension (PAH; high pressure in the blood vessels leading to the lungs). This recommendation against use is based on a recent long-term clinical pediatric trial showing that: (1) children taking a high dose of Revatio had a higher risk of death than children taking a low dose and (2) the low doses of Revatio are not effective in improving exercise ability. Most deaths were caused by pulmonary hypertension and heart failure, which are the most common causes of death in children with PAH.

“Innovation Stagnation”-March 2004

“Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products”

This landmark FDA report, identified reasons for the widening gap between scientific discoveries and their translation into innovative medical treatments.

• CPI 2004…Critical Path Initiative
• ARS 2010…Advancing Regulatory Science Initiative
“Innovation Stagnation” - NIH Response
NIH → NCATS → ORDR → TRND

*Therapeutics for Rare and Neglected Diseases “TRND”* (est’d 5/2009)… $24M trans-NIH initiative

*National Center for Advancing Translational Sciences “NCATS”* (est’d 11/2011)… FY 2014 budget request $665M

• **TRND** is specifically intended to stimulate research collaborations with academic scientists working on rare illnesses.

• The **NIH ORDR** oversees the program.

• TRND's laboratory operations are administered by the **National Human Genome Research Institute** (NHGRI), which also operates the **NIH Chemical Genomics Center** (NCGC), a principal collaborator in TRND.
Bench-to-Bedside Awards

- Rare diseases bench-to-bedside medical research projects designed to speed translation of promising laboratory discoveries into new medical treatments

The Rare Diseases Clinical Research Network

- A clinical research network supported by NIH Institutes and Centers and the ORDR
Rare Diseases Human Biospecimens/Biorepositories (RD-HuB)

- A searchable database of biospecimens collected, stored, and distributed by biorepositories in the United States and around the globe.

Undiagnosed Diseases Program

- The Undiagnosed Diseases Program provides answers to patients with mysterious conditions that have long eluded diagnosis and advanced medical knowledge about rare and common diseases.
Global Rare Diseases Patient Registry and Data Repository (GRDR)

• A pilot project to establish a data repository of de-identified patient data, aggregated in a standardized manner, to enable analyses across many rare diseases and to facilitate various research projects, clinical studies, and clinical trials…(http://www.grdr.info)
Main Goals of the GRDR…

• Develop a set of **Common Data Elements** (CDEs) to facilitate data collection into the GRDR in a standardized and meaningful manner;

• Assist organizations with no patient registry to establish their own registry and be able to contribute their data into the GRDR or other databases;

• Facilitate harmonization between the many sources of patient information.

http://www.grdr.info
www.grdr.info
“Rare diseases have no borders”
www.grdr.info

“They don’t affect individuals they affect entire families”
Hutchinson-Gilford Progeria Syndrome…HGPS
~100 children in 37 countries
2003…collaborative effort discovered the genetic basis for progeria
Silent point mutation in the LMNA gene…long arm chromosome #1
Defective nuclear membrane stability …defective scaffolding/laminar protein
Caused by addition of a farnesyl group to the Lamin A protein
• Abnormal protein formation…progerin…also part of normal aging!!
• First clinical trial 2007-2009…promising research involving FTI’s (farnesyl transferase inhibitors) such as lonafarnib
• Current three drug trial in progress…lonafarnib, pravastatin and zoledronic acid
• Future studies…rapamycin/sirolimus, etc…
“Life According to Sam”
2013 Sundance Film Festival/HBO
“Life According to Sam”  
2013 Sundance Film Festival/HBO

Tells the story of Sam Berns and his family….

• takes you on their journey starting from the diagnosis in 1998, when little existed in the way of information or medical care for progeria,

• through their efforts culminating in the publication in September 2012 of the results of the first-ever clinical trial for children with progeria…
Progeria Research Foundation…
• Founded March 1999
• 2003 identified genetic basis of the syndrome
• Definitive diagnostic testing possible
• 2007 start of first clinical trial
• 2012 publication of study results and identification of first treatment for the disease

“Possible organizational and working model for other RD research groups”
• Executive Director…Ms. Audrey Gordon