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Industry Perspective of Orphan Diseases Drug Development

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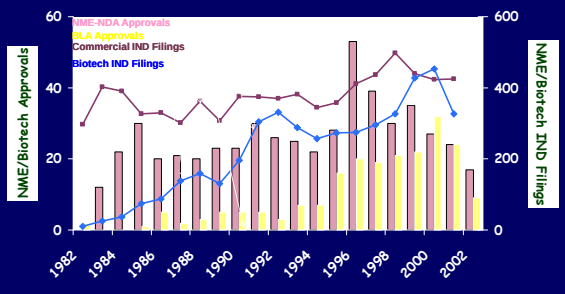
The Rising Cost of New Drug Development*

- $54 million (1976$) - Hansen 1985
- $231 million (1987$) - DiMasi et al. 1991
- $802 million (2000$) - DiMasi et al. 2003

** Includes cost of failed compounds and cost of capital*

Declining IND Filings and NME and Biotech Approvals



Source: FDA

Orphan Drug Development: Introduction to Legislation

- US 1983
- Japan 1993
- EU 2000

→ **ICH Countries**

- Australia 1998
- Taiwan 2000
- Korea 2005
- Singapore 2006

Orphan Drug Development: Patient Access

- Most countries have process for allowing patient access to drugs for rare diseases
- Including some countries where orphan legislation does NOT exist
  - e.g. Argentina, Brazil, Chile, Mexico, Columbia, Peru, Canada

Orphan Drug Development: R&D Incentives

US
- 50% tax credit on clinical research, grants for clinical research

EU
- No authority - can be implemented by member states

Japan
- Up to 50% of R&D costs for up to 3 years, tax deductions

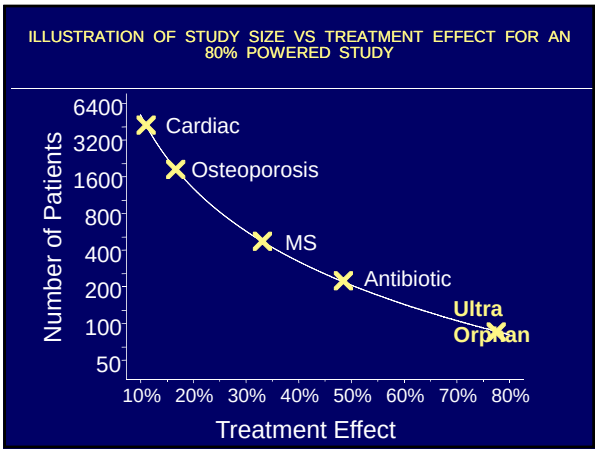
Australia
- N/A

Orphan Drug Development: Patient Numbers

- US
  - Prevalence <200,000 or
  - R&D costs cannot be recovered in 7 years
- Japan
  - Prevalence <50,000
- EU
  - Incidence <5/10,000 or
  - Product unlikely to be developed without incentives
- Australia
  - Prevalence <2000
- Taiwan
  - Prevalence <0.01% births

Why Should a Biopharmaceutical Company Be Interested in Orphan Diseases

- Orphan Drug Act
  - Financial incentives
  - 7 years exclusivity in US (10 years in EU)
- Potentially less competition
- More likely to have a single gene defect with known mechanism of action



Trial Design Issues:
CHALLENGES FOR APPROVAL OF ULTRA -ORPHAN DRUGS

- Must Understand Clinical-Pathologic Correlations:
  - Slowly Progressive Diseases: Duration of Study?
  - Disease Heterogeneity: Selection of Clinical Endpoints
  - Neurodegenerative Diseases: Do Imaging Endpoints Predict Clinical Benefit?
- Clinical versus Surrogate Efficacy Endpoints:
  - Accept Causal Pathophysiology: Primary Genetic & Metabolic Defects
    - Use of Primary Biochemical & Pathologic Markers as Surrogate Endpoints
    - Neurodegenerative Diseases May Have Difficult Endpoints
- Phase 4 Post-Marketing Clinical Verification Studies:
  - Multiple Trial Design Issues: Placebo-Controlled? Duration? Value of Registries? What if Study Fails?
- Labeling: Who to Treat?
  - Only Symptomatic Patients? Issue of Prevention

SURROGATE MARKERS & ENDPOINTS

Surrogate Marker:

A Laboratory or Clinical Measurement, Believed by Current Knowledge to Share a Causal Mechanism with the Clinical Outcome.

Surrogate Endpoint:

A Pre-Defined Change in a Surrogate Marker that Is Expected to Predict Clinical Benefit.

Example of Gaucher Disease

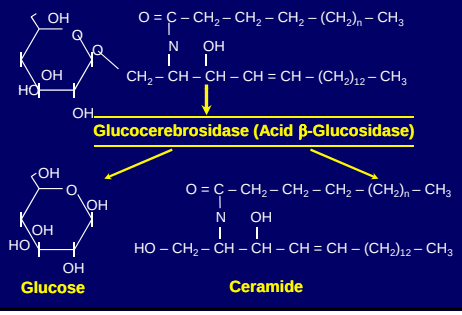
Gaucher is an Orphan Disease

- Qualified for Orphan Disease status in the US: less than 200,000 patients
- Orphan Diseases status is also applicable to Europe, Japan, Australia, Canada in addition to other countries
- Small population with limited patients available for clinical trials

Biochemical Defect Identified

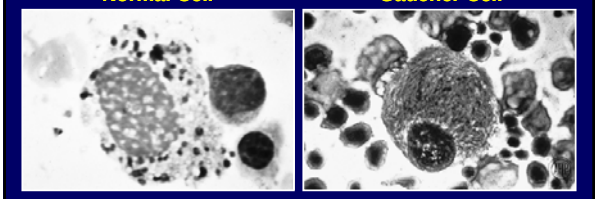
Glucocerebroside (Glucosylceramide)

Glucosyl **Ceramide**

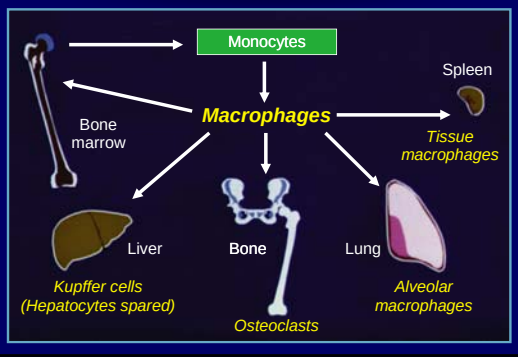


Gaucher Disease

Normal Cell **Gaucher Cell**



Clinical Manifestations Reflect Cellular Sites of Substrate Storage



Historical Timelines

PCE Gaucher: Clinical Case
Aghion: Glucocerebroside Accumulation
DeDuve: Lysosome
Brady: Glucocerebrosidase Deficiency
Beutler; Ginns: Glucocerebrosidase Gene
Barton; Brady: Placental ERT—Ceredase® (alglucerase injection)
Grabowski, Barton, Pastores, Brady: Recombinant ERT—Cerezyme® (imiglucerase for injection)

1882 1932 1955 1965 1985 1991 1994

Ceredase Clinical Development

- Results of original trial on only 12 patients in 1991 using Ceredase (placentally derived enzyme)
  - Splenomegaly and hepatomegaly reduced in first 6 months of therapy
  - Hematological deficiencies of hemoglobin, hematocrit, erythrocyte and platelet count significantly improved

Cerezyme Clinical Development

- US pivotal study (RC91-0110): Study in 30 patients comparing Ceredase with Cerezyme (recombinantly produced) over 6 months showed no difference in safety or efficacy between products (1992)
- US Extension Study (RC92-0501): Continuation of safety and efficacy evaluation from pivotal study population for an additional 20 months (1994)
- Israeli Study (R92-0301): 10 patients were studied in two dosing schedules over 2 years with improvements in hemoglobin and platelet counts and reductions in liver and spleen size (1994)

Global Approval Status of Cerezyme

- United States
  - Ceredase (placenta derived): approved by FDA in 1991
  - Cerezyme approved as an Orphan Drug in 1994
- Europe Union
  - Approved as an Orphan drug in 1997
- Approved in 55 countries in total

Why Would an Academic Group Work with the Biopharmaceutical Industry on an Orphan Disease Treatment?

- Ability to confirm pre-clinical observations
- Provide assistance in performing pre-clinical toxicology
- Provide GMP grade drug substance and product
- Assist in regulatory fillings
- Provide intellectual and financial support clinical trials
- Provide help in clinical trial design
- Reduce the time to clinic

What is Industry Looking at Prior to Investing in an Orphan Disease Product?

- Establish unmet medical need
- Is there and animal model and/or proof of concept experiment
- Is the pathophysiology and pathobiology of the disease understood?
- Is natural history understood?
- Is there a network of experts who are likely to identify patients and can perform clinical research
- What is the geographic/ethnic distribution of patients
- Intellectual property rights protection vs. public domain knowledge
- If no IP, is orphan disease status likely

What Should Academics Look for in a Partner?

- Is there a true commitment to this disease
- What is the experience that this company brings
- Do they have the appropriate resources to complete the drug development (How deep are their pockets)
- What is science, clinical, regulatory depth of the partner
- How far are they willing to fund the program
- What is the track record

CHALLENGES FOR ORPHAN DRUG DEVELOPMENT FOR SMALLER COMPANIES

- Raising capital
  - venture capital, resource and human constraints
- Manufacturing costs for small quantities but at clinical GMP grade for use in clinical trials and toxicology
- Market data re numbers of patients and locations, reimbursement often very vague

CHALLENGES FOR THE CLINICAL DRUG DEVELOPMENT FOR ORPHAN DISEASES

- Poor understanding or documentation of natural history
- No prior pathways to follow
- Clinical endpoints often unclear in effect
- Sample size limited
- Patient enrollment challenging
- Must educate investigators and regulators

What can an Academic Group do to Improve the Chances of a Successful Drug Development?

- Understand the natural history of the disease
- Understand the mechanism of disease
- Identify the heterogeneity and the likely population to study
- Know the centers of excellence throughout the world
- Establish a clinical research network
- Form a partnership with the patient organizations

CLINICAL TRIALS FOR ORPHAN DRUGS

- Chronic progressive disorders
  - Heterogenous
  - Reversibility vs stopping progression
- Trial design issues
  - Heterogenous vs homogenous: subsets?
  - Large treatment effect required
    - Type 2 error becomes the issue
  - Placebo use sometimes difficult
  - Endpoint selection
  - Duration

What Makes for a Happy Academic/Industry Relationship?

- Understand each others needs
  - Academics deal in different currency (publications)
  - Industry must get a return on investment in a reasonable time frame
- Pre-nuptial agreement - spell out what are the expectations
  - Material transfer agreement
  - Designated preclinical experiments
  - Clinical site contract
  - Advisory capacity
  - Royalty agreement

Conflict Resolution-Let the Data Speak

- "**Truth is great** and will prevail if left to herself. She is the proper and sufficient antagonist to error, and has nothing to fear from the conflict, unless, by human interposition, disarmed of her natural weapons, free argument and debate "
  - Thomas Jefferson, 1779

Is There an Orphan Disease Too Rare to Treat Through the Usual Pathways?

- Difficulties in running a meaningful clinical trial
- Costs of Drug Development remain high no matter how small the population
- Recovery of costs and return difficult despite exclusivity and tax credits
- Premium prices necessary
- Access for patients
  - Reimbursement becomes an issue
  - Distribution channels difficult
  - Which patients to treat: all, some

Innovative Strategies for Very Rare Disease:

The example of GM2 Gangliosidoses Gene Therapy

- Government support of basic research in the UK
- National Health Service support for clinical trials in teaching hospitals in the UK
- International collaborative effort among academic institutions
- Patient organizations provide both monetary and patient support
- Eleemosynary support through private donors
- Genzyme to supply GMP grade material

Summary

- Academic benefits:
  - Manufacturing assistance
  - Trial design experience
  - Regulatory experience
  - Financial backing
- Industry benefits
  - Expert advice from the physicians
  - Access to patient populations
  - Assistance for regulatory fillings