Orphan Drugs: An American Success Story

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Intro to Orphan Drugs --- How to get from here to there

- The Orphan Drug Act: Rationale, Realization and Rewards.
- Medically Relevant subsets
- Examples: the scope of orphan drugs?
- Question time....
Economic Realities: 1982

- Rare diseases = Few potential pill buyers
- 1973-1982: 10 new drugs for rare diseases
- \( \approx 7,000 \) rare diseases; 25 million people
- Congressmen/Senators regularly besieged by requests for assistance/research
Abbey Myer:
Grassroots Political Mover

“They are like orphans in that they require special care.” Henry Waxman
The New Deal of the ODA

- Get a drug designated as an “orphan drug”
  - Show (with data) that it’s “promising”
  - For treating <200,000 person in the US

- Do the clinical trials/get marketing approval

- Receive incentives:
  - MARKET EXCLUSIVITY
  - Tax credits
  - Fee exemptions
ODA: A MAJOR SUCCESS

- 361 Approved Drugs
- ≈2,250+ Designated Orphan Drugs
- 2008: 38% of all FDA-approved NMEs were Orphans
The US Orphan Drug Act has been HUGELY Successful
The Diseased Populations Served have been VERY Small

Distribution of Orphan Designations and Approvals by Size of Patient Population

US Prevalence (in thousands) of Disease for which Orphan Product Designated

Source: FDA/OOPD, M. Braun et al
Life table analysis of Progression from Designation to Market Approval
And all human pathology is targeted by designated orphan drugs*
Orphan Designation and IND Status

- Independent processes
- Orphan drugs must proceed through IND and NDA/BLA to become marketed
- Orphans not treated differently in review: safety/efficacy still required but flexibility is common practice.
Orphan drugs are part of medicine’s personalization.

Personalized medicine is better than impersonal medicine
Can diseases be subset?

“Salami slicing” is frowned upon
But subsets are permissible.

Question #1---What is the disease?

Question #2---Could the drug be useful for treating the disease outside the subset?

Example: mAb for Breast cancer: YES

Example: 2\text{nd} line therapy for renal cancer: NO

Example: Stage IIb-VI melanoma
So what is a typical orphan drug?
A JOURNEY OF 2,755.8 MILES BEGINS WITH A SINGLE BOUNCE.

LIFE IS AN ADVENTURE. DON’T BLOW IT.
Example: Adagen for ADA

Population: $1:2 \times 10^5$ to $1:1 \times 10^6$ born with homozygous mutation.

Causes Severe Combined Immunodeficiency

Adagen is one of the first orphan drugs (based on n=12!); enzyme replacement therapy. Designated in 1984.
Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency

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ABSTRACT

Background We investigated the long-term outcome of gene therapy for severe combined immunodeficiency (SCID) due to the lack of adenosine deaminase (ADA), a fatal disorder of purine metabolism and immunodeficiency.

Methods We infused autologous CD34+ bone marrow cells transduced with a retroviral vector containing the ADA gene into 10 children with SCID due to ADA deficiency who lacked an HLA-
Naglazyme for MS Type VI (Maroteaux-Lamy syndrome)

- Mucopolysacharridosis, liposomal storage disorder.
- Estimated only 1,100 persons world-wide.
- Enzyme replacement can prevent these changes
Lysosomes—Intracellular Organelles
These membrane-bound structures contain numerous hydrolytic enzymes responsible for degrading a variety of cellular components, including polysaccharides, polypeptides, lipid-linked glycosyl groups, and damaged organelles.

- Complex material is broken down
- Lysosome containing complex material
- Complex material is excreted or can be reused
- Nucleus
Enzyme Replacement Therapies

- Some of the most extraordinarily expensive treatments in the history of mankind (some $≈ 400,000/pt/yr).
- FDA does not regulate price.
- Radically transformative beneficial to patients lives.
- Exclusivity lasts 7 years; knowledge is eternal.
ExPTPA and Radiogardase for Radiologic Poisonings

- Chelation for highly-specific indications; current zero prevalence.
Example: Eflornithine for African sleeping sickness

- Extremely rare disease in the US and Europe
- Treatment would be highly personalized, based on travel history
OOPD Grants Program

- $16 Million/yr
- Grants are up to $400,000/yr x 4 yrs
- Only for clinical testing of orphan drugs, phase I-III
- Manage about 60 grants, 10-15 new ones awarded annually
- About 30% of submissions are funded
- 47 have gone on to full market approval
Summary

- Basics of the Orphan Drug Act
- A bit about subsetting
- Wide variety of applications
- Much more to come
Questions?