Orphan Drugs: Will they be Fostered by Biotech Alone?

Nabil Mouline, MBA, Consultant
Michael Rice, MS, MBA, Consultant

Defined Health’s Insight Series
Basking Ridge, NJ
Basel, Switzerland
Berlin, Germany
January 2008
The information in this presentation has been obtained from what are believed to be reliable sources and has been verified whenever possible. Nevertheless, we cannot guarantee the information contained herein as to accuracy or completeness.

All expressions of opinion are the responsibility of Defined Health and, though current as of the date of this presentation, are subject to change.
Orphan Diseases - What are They?

- 25 million Americans suffer from one of the approximately 5,000 identified rare diseases.
- Approximately 25 - 30 million Europeans are affected by rare diseases.
- 50% pediatric.
- 85% life-threatening or serious.
- No effective treatment available.
- Heterogeneous - many different diseases.
Misconception #1: Orphan Drugs = Biologics

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Small Molecules 80%</td>
<td>• Small Molecules ~ 80%</td>
</tr>
<tr>
<td>• Large Molecules 20%</td>
<td>• Biologics ~ 14%</td>
</tr>
<tr>
<td></td>
<td>• Devices ~ 5%*</td>
</tr>
<tr>
<td></td>
<td>• Medical Foods &lt; 1%</td>
</tr>
</tbody>
</table>

*FDA
Misconception #2: Orphan Drugs = Genetic Disorders

*Some medicines are listed in more than one category.

PhRMA
Misconception #3: Orphans Do Not Grow Up

WW Revenues 2006 ($ million)

Evaluate Pharma, DH Analysis

© Defined Health, 2008
History

1963  Kefauver-Harris Amendments “adequate and well-controlled studies”

1970’s  Orphanized Drugs
        Patient advocacy
        “Public Service Drugs”

1983  Orphan Drug Act

1990’s  Early years

2000’s  Modern era
History

1963  Kefauver-Harris Amendments “adequate and well-controlled studies”

1970’s  Orphanized Drugs
       Patient advocacy
       “Public Service Drugs”

1983  Orphan Drug Act

1990’s  Early years

2000’s  Modern era

Let me stress our belief that the private sector can work effectively to meet the challenge posed by rare diseases. The Pharmaceutical industry is prepared to work with interested private and public groups….and remove impediments to the development of more service drugs.

PMA (Now PhRMA) then President, Lewis Engman

Whittaker (Rep-Kansas): Do you believe that ODA might detract from your industry’s overall effort to obtain relief from the FDA regulations for all new drugs?

Hutt (PMA): …the best way to look for drugs for rare diseases is to look at all drugs for all diseases.
History

1963  Kefauver-Harris Amendments “adequate and well-controlled studies”

1970’s  Orphanized Drugs
        Patient advocacy
        “Public Service Drugs”

1983  Orphan Drug Act

1990’s  Early years

2000’s  Modern era
Original Law and Amendments

1983  The Orphan Drug Act (P.L. 97-414) was signed into law January 4
   •  Marketing Exclusivity (7 years), unless clinically superior
   •  Tax credit
   •  Research grant (40 marketed drugs - Remicade) protocol assistance

1984  200,000 patients or less

1985  Include patentable drugs

1986  Application prior to the filing

1990  Limit market exclusivity for profitable drugs (vetoed)
      Revise growth rate to calculate the 200,000 for AIDS (vetoed)

1991  FDA issues regulation

1997  Exemption from user fees ($0.5M)
      Extension of Tax credits (permanent)
FDA Application

Justifications for an Orphan Drug Request

(6) Where a drug is under development for only a subset of persons with a particular disease or condition,
(8) Documentation, with appended authoritative references, to demonstrate that:

(i) The disease or condition for which the drug is intended affects fewer than 200,000 people in the United States as specified in § 316.21(b),

or

(ii) For a drug intended for diseases or conditions affecting 200,000 or more people… there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States as specified in § 316.21(c).
History

1963  Kefauver-Harris Amendments “adequate and well-controlled studies”
1970’s Orphanized Drugs
    Patient advocacy
    “Public Service Drugs”
1983  Orphan Drug Act
1990’s Early years
2000’s Modern era
History

The Early Years

• Chenix (Solvay), Panhematin (Abbott), Opticrom (Fisons), Naltrexone (Dupont) applied for Orphan designation after marketing approval in an attempt to extend their patent life.

• Only 15 applications/10 designations in the first year - lack of interest.

• The first commercially significant products sparked litigation as to Orphan designation.
  – Interferons
  – EPO
  – Growth Hormone
Early Litigation

- Betaseron first approved (1993).
- Avonex approved (1996) on the basis of being superior.
  - Injection site necrosis associated with Avonex (0%) compared with Betaseron (5%).
  - 4% of Avonex patients experienced injection site reactions, compared to 85% of Betaseron patients.
- Rebif denied.
  - SubQ vs. IM.
  - Rebif comes in several doses.
Early Litigation

• EPO, Amgen’s first approved drug, obtains Orphan status (1989).
• Macrogen, Chugai/Genetics Institute apply for Orphan status.
  – Glycosylation pattern different from Amgen's Epogen.
  – FDA denies status - battle continues.
  – Chugai loses patent dispute.
Early Litigation

- Protropin, Genentech’s first drug, (with OODP grant).
- Humatrope (Lilly) applies for Orphan status.
  - Approved as drugs deemed different.
  - Genentech files a citizen petition and loses.
More Recent Litigation
-- Fabrazyme vs. Replagal

On grounds of similarity…

TKT to End Efforts to Seek U.S. Approval of Replagal

Fourth Quarter 2003 Replagal Sales Expected to Approximate Third Quarter Sales

CAMBRIDGE, Mass., Jan. 12 /PRNewswire-FirstCall/ -- Transkaryotic Therapies, Inc. (Nasdaq: TKTX) today announced that it will cease efforts to seek the approval of Replagal(TM) (agalsidase alfa) enzyme replacement therapy for Fabry disease from the U.S. Food and Drug Administration (FDA). TKT will continue to market and sell Replagal in countries where it is approved outside the United States, will continue its efforts to introduce Replagal in new markets in 2004, and will continue to supply Replagal to U.S. patients in its ongoing clinical trials.
History

1963  Kefauver-Harris Amendments “adequate and well-controlled studies”

1970’s  Orphanized Drugs
Patient Advocacy
“Public Service Drugs”

1983  Orphan Drug Act (and amendments)

1990’s  Early years

2000’s  Modern history
What Has Emerged - Market Stimulation

- From 1983 to 2006 - US
  - Over 2400 requests
  - Over 1700 designated
  - Over 300 approved Orphan products
# What Has Emerged - Serial Filers

Sponsors with multiple products, designations and approvals

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Products</th>
<th>Designations</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amgen</td>
<td>15</td>
<td>28</td>
<td>14</td>
</tr>
<tr>
<td>Genentech</td>
<td>10</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Orphan Medical</td>
<td>9</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Serono Laboratories</td>
<td>7</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>MedImmune</td>
<td>3</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Genzyme</td>
<td>12</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Biogen</td>
<td>3</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>8</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Novartis</td>
<td>5</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>14</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Roche</td>
<td>8</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>Pfizer</td>
<td>25</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>6</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Sanofi-aventis</td>
<td>9</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

[www.fda.gov/orphan/designat/list.htm](http://www.fda.gov/orphan/designat/list.htm)
What Has Emerged - Medical Advances

- **PEG-ADA (Enzon)**: Pegylation was first used in this Orphan product for enzyme replacement therapy for ADA deficiency in patients with severe combined immunodeficiency (SCID, 12 pts in the US).

- **Liposomal amphotericin B (Fujisawa)**: Early use of liposomal process in drug development.

- **Ceredase**: Enzyme replacement therapy.

- **Human Growth Hormone & Blood Coagulation Products**: Recombinant DNA Technology.

www.fda.gov; Company websites, Haffner 2002
What Has Emerged - Areas of Focus

Number of Drugs Approved by the FDA for the Top Seven Types of Rare Diseases/Conditions Addressed by Orphan Drugs

What Has Emerged - Market

Revenue from Drugs with Orphan Indications

Total Projected Pharma Market, 2009

EvaluatePharma, Visiongain, DH analysis

© Defined Health, 2008
### What Has Emerged - Blockbusters

<table>
<thead>
<tr>
<th>Product</th>
<th>Approved designation</th>
<th>Marketing Approval</th>
<th>Initial Approval (non Orphan)</th>
<th>2006 Sales</th>
<th>Additional Orphan indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enbrel</td>
<td>1998</td>
<td>1999</td>
<td></td>
<td>$4,379</td>
<td></td>
</tr>
<tr>
<td>Remicade</td>
<td>1995</td>
<td>1998</td>
<td></td>
<td>$4,253</td>
<td></td>
</tr>
<tr>
<td>Rituxan</td>
<td>1984</td>
<td>1989</td>
<td></td>
<td>$3,972</td>
<td></td>
</tr>
<tr>
<td>Neupogen/Neulasta</td>
<td>1990</td>
<td>1994</td>
<td>1991</td>
<td>$3,923</td>
<td>Severe chronic neutropenia</td>
</tr>
<tr>
<td>Gleevec</td>
<td>2001</td>
<td>2001</td>
<td></td>
<td>$2,554</td>
<td></td>
</tr>
<tr>
<td>EpoGen</td>
<td>1986</td>
<td>1989</td>
<td></td>
<td>$2,503</td>
<td></td>
</tr>
<tr>
<td>Topamax</td>
<td>1992</td>
<td>2001</td>
<td>1996</td>
<td>$2,027</td>
<td>Lenox gestaut</td>
</tr>
<tr>
<td>Lamictal</td>
<td>1995</td>
<td>1998</td>
<td></td>
<td>$1,982</td>
<td></td>
</tr>
<tr>
<td>Avonex</td>
<td>1991</td>
<td>1996</td>
<td></td>
<td>$1,707</td>
<td></td>
</tr>
<tr>
<td>Prograf</td>
<td>2005</td>
<td>2006</td>
<td>1994</td>
<td>$1,438</td>
<td>Heart transplant</td>
</tr>
<tr>
<td>Betsareron</td>
<td>1988</td>
<td>1993</td>
<td></td>
<td>$1,336</td>
<td></td>
</tr>
<tr>
<td>Zometa</td>
<td>2000</td>
<td>2001</td>
<td></td>
<td>$1,283</td>
<td></td>
</tr>
<tr>
<td>Erbitux</td>
<td>2000</td>
<td>2006</td>
<td>2004</td>
<td>$1,100</td>
<td>Head and Neck</td>
</tr>
<tr>
<td>Intron/Pegintron</td>
<td>1987</td>
<td>1988</td>
<td></td>
<td>$1,074</td>
<td></td>
</tr>
<tr>
<td>Kogenate</td>
<td>1989</td>
<td>1993</td>
<td></td>
<td>$1,070</td>
<td></td>
</tr>
<tr>
<td>NovoSeven</td>
<td>1988</td>
<td>1999</td>
<td></td>
<td>$1,028</td>
<td></td>
</tr>
<tr>
<td>Ceredase</td>
<td>1985</td>
<td>1991</td>
<td></td>
<td>$1,007</td>
<td></td>
</tr>
<tr>
<td>Botox</td>
<td>1984</td>
<td>1989</td>
<td></td>
<td>$983</td>
<td></td>
</tr>
</tbody>
</table>

*EvaluatePharma; FDA.*
### What Has Emerged - Strategies

<table>
<thead>
<tr>
<th>Regulatory Pathway</th>
<th>Dedicated Orphan</th>
<th>Repurposing Into Orphan</th>
<th>Life Cycle Management</th>
<th>Protection Strategy</th>
<th>Opportunistic / Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remicade (Centocor)</td>
<td>Cerezyme (Genzyme)</td>
<td>TOBI (Novartis)</td>
<td>Topamax (J&amp;J)</td>
<td>Epogen (Amgen)</td>
<td>Panhematin (Abbott)</td>
</tr>
<tr>
<td>Clolar (Genzyme)</td>
<td>Fabrazyme (Genzyme)</td>
<td>Lamictal (GSK)</td>
<td></td>
<td></td>
<td>Chenix (Solvay)</td>
</tr>
<tr>
<td>Zometa (Novartis)</td>
<td>Myozyme (Genzyme)</td>
<td>Erbitux (ImClone)</td>
<td></td>
<td></td>
<td>Subutex (Reckitt Benckiser)</td>
</tr>
<tr>
<td>Simulect (Novartis)</td>
<td>Thyrogen (Genzyme)</td>
<td>Prograf (Astellas)</td>
<td></td>
<td></td>
<td>Naltrexone (Dupont)</td>
</tr>
<tr>
<td>Neupogen (Amgen)</td>
<td>Elaprase (Shire)</td>
<td>Rebetol (Bayer-Schering)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituxan (Genentech)</td>
<td>Exjade (Novartis)</td>
<td>Enbrel (Amgen)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novoseven (Novo Nordisk)</td>
<td>Gleevec (Novartis)</td>
<td>Taxol (BMS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sandostatin LAR (Novartis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DH Analysis**  
*Defined Health Insight Series*  
January, 2008 – page 25  
© Defined Health, 2008
Ex-US Perspective – Comparing Legislation

<table>
<thead>
<tr>
<th></th>
<th>USA</th>
<th>EU</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrations involved</td>
<td>FDA / OOPD</td>
<td>EMEA / COMP</td>
<td>Ministry of Health, Labour and Welfare/ Organization for Pharmaceutical Safety and Research</td>
</tr>
<tr>
<td>Prevalence criterion of the disease for orphan status (per 10,000)</td>
<td>7.5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Market exclusivity (years)</td>
<td>7</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Funding</td>
<td>Grants for clinical research (pharma and academia eligible)</td>
<td>Framework Programmes for Research plus national measures only eligible</td>
<td>Grants for clinical and non-clinical research (pharma and non-clinical costs)</td>
</tr>
<tr>
<td>Tax credits</td>
<td>50% for clinical costs</td>
<td>Managed by member states</td>
<td>6% of both clinical and non-clinical costs</td>
</tr>
<tr>
<td>Protocol assistance</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Accelerated review</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reconsideration of orphan status</td>
<td>No</td>
<td>Yes (every 6 years)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Rinalid, 2005*
US – EU Common Application

The European Union and the FDA working together to create Common Application for Orphan Designation for Medicines

The European Commission, the European Medicines Agency (EMEA) and the United States (US) Food and Drug Administration (FDA) have adopted a common application form for sponsors seeking orphan designation of medicines in the European Union (EU) and US. This initiative is aimed at simplifying the process of obtaining orphan status for medicines intended for rare diseases in both jurisdictions.

About 30 million people living in the EU and 25 million Americans suffer from more than 6,000 rare diseases. Rare diseases are defined as those affecting fewer than five in 10,000 people in the EU and fewer than 200,000 people in the US. Due to the small number of patients, sponsors of medicines for rare diseases may expect relatively low profit from sales and, in some cases, a financial loss, when the costs of research and development of these drugs are taken into account.
Access Varies But Remains Available

- ODs are on a reimbursement list and thus benefit from systematic reimbursement in France, Germany, Spain, Holland and Sweden.

Number of Orphan Drugs on the National Reimbursement List in the EU 25
# Orphan Model - Alternative to an Endangered Model?

<table>
<thead>
<tr>
<th>Blockbuster Model</th>
<th>Orphan Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>$800 million per drug (or is it $1bn ?)</td>
<td>Application of Pharmacogenomics</td>
</tr>
<tr>
<td>8 - 12 years from the laboratory to the market</td>
<td>Short development time</td>
</tr>
<tr>
<td>Large studies: “Torcetrapibitis”</td>
<td>Small clinical studies</td>
</tr>
<tr>
<td>Very high attrition 5%-9%</td>
<td>Lower attrition rate</td>
</tr>
<tr>
<td>Limited efficacy - works in only half of the patients?</td>
<td>Higher tolerance for risk</td>
</tr>
<tr>
<td>Late onset of severe side effects: “VIOXXitis”</td>
<td>Wider availability of biomarkers/diagnostics</td>
</tr>
<tr>
<td>Exclusivity - less than 1 year ?</td>
<td>7-year exclusivity</td>
</tr>
<tr>
<td>Payer scrutiny</td>
<td>Higher profit margins - lower marketing cost</td>
</tr>
</tbody>
</table>

---

DH analysis, Rodman & Renshaw
Lower Attrition Rates

- Approval rates for drugs with Orphan indications are typically higher.

FDA, OPD
Shorter Timelines

• Both in Europe and in the US, decisions regarding Orphan designation are swift.

• Of the 18 Orphan Drug NMEs approved 2002-2005 in the US, 13 received priority review.

Source: European Medicines Agency (EMEA) Committee on Orphan Medicinal Products (COMP)
Longer Exclusivity

**Traditional Pharma Products**

**Orphan Drugs**

Orphan Drugs enjoy 7 years of marketing exclusivity while most non-Orphan Drugs face competition soon after launch.

Source: DiMasi, Paquette, Pharmacoeconomics 2004;22(Suppl 2):1-14
Genzyme: Early Adopter - The Focus

1981: Founded
1983: Cystic Fibrosis Clinical Program
1984: Ceredase Trials / Cerezyme research
1985: Ceredase Orphan Drug
1986: Test for CF, IPO
1988: Research on Fabry
1990: Gene Therapy
1994: Cerezyme (recombinant) approved - Ceredase ex US (Global)
1996: Research on Gene Therapy for Heart Disease
1997: Research in Cancer
1998: Thyrogen (Orphan status) and Synvisc approved
2001: Myozyme for Pompe disease - Orphan Status
2003: Fabrazyme approved - Orphan status
2006: Myozyme approved - Orphan status
Genzyme: Market Creator

• What does it take?
  – Good science that saves lives.
  – Do the leg-work:
    • Invent a Diagnosis/Test.
    • Find and know your patients (one by one).
  – Price accordingly.
### Genzyme: Patient Advocacy

<table>
<thead>
<tr>
<th>Benefit</th>
<th>To company</th>
<th>To patient group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Financial</td>
<td>Increased access to funding, which can often stimulate other sources of financing</td>
<td>Money directly employed in finding treatments; broad exposure and successful efforts often lead to additional funding in area</td>
</tr>
<tr>
<td>Public and political profile</td>
<td>Advocacy power useful for interactions with FDA and other regulators</td>
<td>Group recognized as contributor to search for new treatments</td>
</tr>
<tr>
<td>Advice and expertise</td>
<td>Increased access to patients, investigators and thought leaders</td>
<td>Receive information and nonfinancial support from companies</td>
</tr>
<tr>
<td>Research</td>
<td>Increased scientific knowledge in areas of commercial interest</td>
<td>Increased scientific knowledge of disease</td>
</tr>
<tr>
<td>Products</td>
<td>Opportunities to expand indications and markets for products that were previously unanticipated</td>
<td>Increased likelihood of products in disease areas of interest</td>
</tr>
<tr>
<td>Motivation</td>
<td>Human element inspires scientists to overcome challenges of drug R&amp;D</td>
<td>Empowers patients to feel they are directly contributing to search for a treatment</td>
</tr>
</tbody>
</table>
Genzyme: Early Adopter - Performance

Includes currently marketed products and follow on products (Synvisc/Synvisc-One, Renagel/Renvela) plus Mozobil.1 Includes Oncology and Thyrogen

Company Website, DH Analysis
Genzyme: Early Adopter – The Outperformer?

- Outperforming Biotech

Yahoo!Finance
A Word About Pricing - Orphan Pricing, Ultra-Orphan Pricing

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Generic Name</th>
<th>Developer/Sponsor</th>
<th>Mechanism of Action</th>
<th>Disease Indication</th>
<th>Disease Prevalence</th>
<th>Annual Cost</th>
<th>2006 sales</th>
<th>US approval date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naglzyme</td>
<td>galsulfase</td>
<td>BioMarin Pharmaceutical</td>
<td>Enzyme replacement</td>
<td>Mucopolysaccharidosis type VI (MPS-VI)</td>
<td>1 in 215,000</td>
<td>$300,000 - $400,000</td>
<td>$47MM</td>
<td>5/31/2005</td>
</tr>
<tr>
<td>Soliris</td>
<td>ecuclizumab</td>
<td>Alexion Pharmaceuticals</td>
<td>Immunomodulation</td>
<td>Paroxysmal nocturnal hemoglobinuria (PNH)</td>
<td>1 in 77,000</td>
<td>$355,000</td>
<td>Launched in April 2007</td>
<td>3/16/2007</td>
</tr>
<tr>
<td>Elaprase</td>
<td>idursulfase</td>
<td>Shire Pharmaceuticals / Genzyme</td>
<td>Enzyme replacement</td>
<td>Mucopolysaccharidosis type II (MPS-II) or Hunter syndrome</td>
<td>1 in 150,000</td>
<td>$300,000</td>
<td>$24MM</td>
<td>7/24/2006</td>
</tr>
<tr>
<td>Myozyme</td>
<td>Interferon beta-1b</td>
<td>Chiron &amp; Berlex Laboratories</td>
<td>Enzyme replacement</td>
<td>Pompe's disease</td>
<td>1 in 40,000</td>
<td>$270,000</td>
<td>$59MM</td>
<td>4/28/2006</td>
</tr>
<tr>
<td>Aidurzyme</td>
<td>iduronidase</td>
<td>BioMarin Pharmaceutical</td>
<td>Enzyme replacement</td>
<td>Gaucher's disease</td>
<td>1 in 115,000</td>
<td>$225,000</td>
<td>$95MM</td>
<td>4/30/2003</td>
</tr>
<tr>
<td>Cerezyme</td>
<td>Imiglucerase</td>
<td>Genzyme</td>
<td>Enzyme replacement</td>
<td>Types I, II, and III Gaucher's disease</td>
<td>1 in 100,000</td>
<td>$200,000</td>
<td>$1B</td>
<td>5/23/1994</td>
</tr>
<tr>
<td>Fabrazyme</td>
<td>Ceramide trihexosidase/alpha-galactosidase A</td>
<td>Genzyme (has US exclusivity until 2010)</td>
<td>Enzyme replacement</td>
<td>Fabry's disease</td>
<td>1 in 40,000</td>
<td>$200,000</td>
<td>$359MM</td>
<td>4/24/2003</td>
</tr>
<tr>
<td>Replagal</td>
<td>agalsidase alfa</td>
<td>Shire Pharmaceuticals (originally Transkaryotic Therapies)</td>
<td>Enzyme replacement</td>
<td>Fabry's disease</td>
<td>1 in 40,000</td>
<td>$200,000</td>
<td>$118MM</td>
<td>Approved only in EU in 2021</td>
</tr>
</tbody>
</table>

BioCentury
A Word About Pricing

Government Coverage of Orphan Drugs

Commentary by Clarke, J et al published in CMAJ September 4, 2001; 165 (5): In late 1992 the Ontario, Canada minister of health rejected appeals for public payment for Cerezyme because the cost per quality-adjusted life-year of treatment was above the level usually considered cost-effective. However, that decision was quickly reversed because of a “…widely publicized attack led by the National Gaucher Foundation of Canada. The foundation argued that the minister of health could not stand by and watch a very sick man suffer, when the means to relieve his suffering were at her fingertips. In consultation with advisors in the Ministry of Health, she eventually approved a province-wide program of selective reimbursement for enzyme replacement therapy for Gaucher’s disease.”

Connock, M. et al. in a report titled “Clinical Effectiveness and Cost-Effectiveness of Enzyme Replacement Therapy for Gaucher’s Disease: A Systematic Review” as published in Health Technology Assessment 2006; 10(24) concluded, “Although ERT for treating ‘average’ Gaucher’s disease patient exceeds the normal upper threshold for cost-effectiveness... some argue that since orphan drug legislation encouraged manufacture of Cerezyme... the NHS (National Health Service, UK) has little option but to provide it, despite its great expense.” “Moreover, if under equity considerations for orphan diseases the NHS feels it is important to provide the drug, regardless of its cost-effectiveness, then refining the precision of the [incremental cost-effectiveness ratio] estimate also becomes superfluous.”

Ferris, Baker Watts, Incorporated
Genzyme targets less-exotic diseases
It reports growth in core products

By Stephen Heuser, Globe Staff | May 16, 2006

If the future of medicine is making carefully targeted therapies for a carefully screened group of patients, then the future looks a lot like Genzyme Corp.

The 25-year-old Cambridge company, one of the largest and oldest biotechnology companies -- has long specialized in selling biologic drugs to patients with rare diseases. But in the past few years, it has begun diversifying into serving people with more widespread ailments, from leukemia to creaky knees.

Last year, Genzyme posted a 310.7 percent increase in profit margin over 2004, sending it to number three on the overall Globe 100 list. The company attributes much of its success to its purchase of Ilex Oncology Inc.

Genzyme has expanded steadily over the years, and unlike some firms it manufactures its flagship drugs in Massachusetts.

The company chronically faces potential public and political backlash over the prices of its drugs. Its cash cows are so-called ultra-orphan drugs for rare diseases, which cost $200,000-plus annually for each patient.

Patients have a love-hate relationship with Genzyme. Often, it is the only drug company developing or offering a therapy for their disease, but the price can leave them struggling to stay insured.
Can Big Pharma Emulate Genzyme?

• Some challenges:
  – Close relationship with patients…while making profits.
  – Charge Orphan price …while avoiding public outrage.
  – Learn to combine diagnostic testing and therapeutics.

• Some are daring…will they persist?
  – Shire
  – Novartis
Shire: The Latecomer

1986: Founded
1987: First deal
1996: IPO
1997: Acquire Pharmavene, Richwood
2005: TKT (Replagal, Dynepo, GA-GCB)
2007: Amicus deal (Amigal, Plicera, AT2220)

Will it pay off?
Novartis: The Jack of All (Drug) Trades?

1996: Merge Sandoz Ciba-Geigy
2005: Buy OTC (BMS portfolio)
2005: Buy Hexal (Generic)
2006: Buy Chiron (Vaccine + Orphan)

Another diversification move or is the timing just right?
Novartis on Orphan Drugs (aka Rare Diseases)

Welcome to Citizenship@Novartis

Patients

Rare diseases

As a responsible corporate citizen, Novartis has a duty to meet the needs of as many patients as possible. This includes undertaking research for new drugs to treat rare diseases - diseases which have been overlooked due to the high cost of research and development and the lack of a wide market. Novartis has already made major contributions to the treatment of rare disorders, for example, Gleevec® has been developed to treat a rare form of leukemia (CML), Sandostatin® is used to treat a rare form of carcinoid tumors and Exjade® is used to treat iron-overload in thalassemia.

Developing new medicines for rare disorders is an important part of the research strategy of the Novartis Institutes for Biomedical Research (NIBR). The idea is to test new medicines in “proof-of-concept” studies that include patients with well-defined, often rare and genetic diseases for which the disease mechanism is well understood. We have discovery and development efforts in several “niche” diseases such as Muckle-Well Syndrome, Tuberculous Sclerosis, and Cystic Fibrosis.

Muckle-Well Syndrome, for instance, is an inherited disease caused by a rare genetic mutation. It affects 10 000 people worldwide. The disease is characterized by a range of symptoms, from fever and chills to swollen, painful joints, hives and itchy skin. One of the disease’s severe complications, amyloidosis, is often fatal.
Orphan Diseases: Why Should Pharma Take Notice Now?

• Advancements in basic and translational science.
• Increased patient and physician awareness.
• Wider availability of genetic testing.
  – Over 600 CLIA approved testing centers.
• Government policy.
  – ODA.
  – Guidance on genetic testing and pharmacogenomics
• Successful Orphan precedents.
• Generic and regulatory pressure on the blockbuster model.
Fruits of the Human Genome Project?

**Timeline: The history of the Human Genome Diversity Project**

- **1991**: DOE and NSF fund planning workshops on the HGDP
- **1992**: Genome article calls for a Human Genome Diversity Project and HUGO appoints a HGDP Committee
- **1993**: DOE, NSF, and NIH award $2 million to the HGDP
- **1994**: DOE and NSF fund meetings at the University of Chicago and Stanford University
- **1995**: HUGO appoints a HGDP Committee
- **1996**: DOE, NSF, and NIH fund the HGDP
- **1997**: DOE, NSF, and NIH fund the HGDP
- **1998**: DOE, NSF, and NIH fund the HGDP
- **2000**: DOE, NSF, and NIH fund the HGDP

(CEPH, Centre d'Etude du Polymorphisme Humain; CSHL, Cold Spring Harbor Laboratory; DOE, Department of Energy; ELSI, ethical, legal and social implications; HGDP, Human Genome Diversity Project; HUGO, Human Genome Organisation; NIH, National Institutes of Health; NRC, National Research Council; NSF, National Science Foundation; RAFTI, Rural Advancement Foundation International; Penn State, Pennsylvania State University; SNF, single nucleotide polymorphism; UNESCO; UNESCO, United Nations Educational, Scientific and Cultural Organization.)
Early Development of Therapies for Monogenetic Diseases was Stunted by a Lagging Knowledge of Function and Lack of Investment

- Traditional deductive analysis from SNP genotyping data often fails.
- Microarray data doesn’t easily reveal genes that drive disease.
- Only ~3000 out of $3 \times 10^6$ SNPs are actually associated with disease (so far).
- A lack of effective tools for target validation.
- Which genes and which mutations are important and druggable?
2008: Will Genomic Enlightenment and Policy Change Reveal the Promised Fruits?

No Longer Just Looking under the Lamppost*

Francis S. Collins

...tending this meeting for excitement and exhilarating... It was a little different... The team and described... You know, it was exciting! I mean, you know, so... Equipped with faster, cheaper technologies for sequencing... The unveiling of the human genome almost 7 years ago... The human disease genes by... Then Uta Francke, later... The big news was triangulating variation... The number and order of genes...
Accelerating Number of HGMD Mutation Entries by Year of Publication

Total = 76,011

- Draft Human Genome Released
- Complete Genome Sequence Released
- HapMap Released
- Genome Released

Monogenetic Diseases as Therapeutic Targets

- Single gene defects, or mutations, are the underlying cause of many human diseases. These mutations may result in null, truncated, or dysfunctional enzymes.
  - Gross mutations predominately have null phenotypes, which completely lack enzyme activity.
  - Microlesions predominately cause minor changes in protein conformation, leading to partial enzymatic activity.
- Over 90% of mutations* responsible for human disease are microlesions resulting in production of truncated or subtly altered proteins, which have at least partial enzymatic activity.

* US Census Beureau (IDB) “World Vital Events” Incidence data CDC Wonder Database, Frequency of Inherited Disorders Database, OMIM.
### Annual Live Births By Therapeutic Indication (Projected 2007)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>GSD I (Von Gierkes)</td>
<td>0.0000167</td>
<td>69</td>
<td>226</td>
<td>2,151</td>
</tr>
<tr>
<td><strong>GSD II (Pompe)</strong></td>
<td><strong>0.0000250</strong></td>
<td><strong>103</strong></td>
<td><strong>338</strong></td>
<td><strong>3,221</strong></td>
</tr>
<tr>
<td>GSD III (Forbes, Cor)</td>
<td>0.0000050</td>
<td>21</td>
<td>68</td>
<td>644</td>
</tr>
<tr>
<td>GSD IV (Anderson)</td>
<td>0.0000200</td>
<td>82</td>
<td>270</td>
<td>2,576</td>
</tr>
<tr>
<td>GSD V (McArdle)</td>
<td>0.0000100</td>
<td>41</td>
<td>135</td>
<td>1,288</td>
</tr>
<tr>
<td>GSD VI (Hers)</td>
<td>0.0000050</td>
<td>21</td>
<td>68</td>
<td>644</td>
</tr>
<tr>
<td>GSD VII (Tauri)</td>
<td>0.0000100</td>
<td>41</td>
<td>135</td>
<td>1,288</td>
</tr>
<tr>
<td>Mucolipidosis I</td>
<td>0.0000100</td>
<td>41</td>
<td>135</td>
<td>1,288</td>
</tr>
<tr>
<td>Mucolipidosis II (I-cell disease)</td>
<td>0.0000250</td>
<td>103</td>
<td>338</td>
<td>3,221</td>
</tr>
<tr>
<td>Mucolipidosis III</td>
<td>0.0000010</td>
<td>4</td>
<td>14</td>
<td>129</td>
</tr>
<tr>
<td>Mucolipidosis IV (Moquio)</td>
<td>0.0000100</td>
<td>41</td>
<td>135</td>
<td>1,288</td>
</tr>
<tr>
<td><strong>Mucopolysacchaidosis I (Hurler)</strong></td>
<td><strong>0.0000100</strong></td>
<td><strong>41</strong></td>
<td><strong>135</strong></td>
<td><strong>1,288</strong></td>
</tr>
<tr>
<td>Mucopolysacchaidosis I (Scheie)</td>
<td>0.0000020</td>
<td>8</td>
<td>27</td>
<td>258</td>
</tr>
<tr>
<td>Mucopolysacchaidosis II (Hunter)</td>
<td>0.0000100</td>
<td>41</td>
<td>135</td>
<td>1,288</td>
</tr>
<tr>
<td>Mucopolysacchaidosis III A (Sanfilippo A)</td>
<td>0.0000010</td>
<td>4</td>
<td>14</td>
<td>129</td>
</tr>
<tr>
<td>Mucopolysacchaidosis III B (Sanfilippo B)</td>
<td>0.0000130</td>
<td>53</td>
<td>176</td>
<td>1,675</td>
</tr>
<tr>
<td>Mucopolysacchaidosis IV</td>
<td>0.0000040</td>
<td>16</td>
<td>54</td>
<td>515</td>
</tr>
<tr>
<td><strong>Mucopolysacchaidosis VI (Maroteaux-Lan)</strong></td>
<td><strong>0.0000050</strong></td>
<td><strong>21</strong></td>
<td><strong>68</strong></td>
<td><strong>644</strong></td>
</tr>
<tr>
<td>Mucopolysacchaidosis VII (Sly)</td>
<td>0.0000040</td>
<td>16</td>
<td>54</td>
<td>515</td>
</tr>
<tr>
<td>Mucopolysacchaidosis IX</td>
<td>0.0000001</td>
<td>0</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Gaucher</td>
<td>0.0000500</td>
<td>205</td>
<td>676</td>
<td>6,441</td>
</tr>
<tr>
<td>Fabry</td>
<td>0.0000250</td>
<td>103</td>
<td>338</td>
<td>3,221</td>
</tr>
<tr>
<td>Krabbe</td>
<td>0.0000100</td>
<td>41</td>
<td>135</td>
<td>1,288</td>
</tr>
<tr>
<td>GM1 Gangliosidosis</td>
<td>0.0000050</td>
<td>21</td>
<td>68</td>
<td>644</td>
</tr>
<tr>
<td>GM2 Ganglolosidosis (Tay Sach)</td>
<td>0.0000035</td>
<td>14</td>
<td>47</td>
<td>451</td>
</tr>
<tr>
<td>GM2 Ganglolsialidosis (Sandhoff)</td>
<td>0.0000010</td>
<td>4</td>
<td>14</td>
<td>129</td>
</tr>
<tr>
<td>Metachromatic Leukodystrophy</td>
<td>0.0000500</td>
<td>205</td>
<td>676</td>
<td>6,441</td>
</tr>
<tr>
<td>Niemann Pick C</td>
<td>0.0000100</td>
<td>41</td>
<td>135</td>
<td>1,288</td>
</tr>
<tr>
<td>Aldosterone Deficiency</td>
<td>0.0000010</td>
<td>4</td>
<td>14</td>
<td>129</td>
</tr>
<tr>
<td>Neuronal Ceroid Lipofuscinosis</td>
<td>0.0000500</td>
<td>205</td>
<td>676</td>
<td>6,441</td>
</tr>
<tr>
<td>Mannosidosis</td>
<td>0.0000020</td>
<td>8</td>
<td>27</td>
<td>258</td>
</tr>
<tr>
<td>Bardet-Biedl Syndrome</td>
<td>0.0000010</td>
<td>4</td>
<td>14</td>
<td>129</td>
</tr>
<tr>
<td>Wolman Syndrome</td>
<td>0.0000010</td>
<td>4</td>
<td>14</td>
<td>129</td>
</tr>
<tr>
<td>Farber’s Disease</td>
<td>0.0000010</td>
<td>4</td>
<td>14</td>
<td>129</td>
</tr>
<tr>
<td>Aultins’ disease</td>
<td>0.0000250</td>
<td>103</td>
<td>338</td>
<td>3,221</td>
</tr>
<tr>
<td>Canavan Disease</td>
<td>0.0000200</td>
<td>82</td>
<td>270</td>
<td>2,576</td>
</tr>
</tbody>
</table>


*Defined Health Insight Series © Defined Health, 2008*
Laboratory Directory: “Yellow Pages” of genetics labs
- 642 Clinical and research laboratories
- Offer tests for ~1,500 Inherited diseases
- ~1,219 clinical tests  ~289 research only

Growth of Laboratory Directory

- 36% Other Countries
- 64% U.S.
Awareness and Availability of Genetic Testing and Available Therapies are Likely to Expand Potential Niche Markets

1. Pre-gene discovery: Phenotype is narrowly defined.
   - Essential to gene discovery
2. Post-gene discovery: Phenotypic spectrum expands as patients are tested.
   - Essential to patient care
# Successful Precedents

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Generic Name</th>
<th>Developer/Sponsor</th>
<th>Mechanism of Action</th>
<th>Disease Indication</th>
<th>Disease Prevalence</th>
<th>Annual Cost</th>
<th>2006 Sales</th>
<th>US Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naglazyme</td>
<td>galsulfase</td>
<td>BioMarin Pharmaceutical</td>
<td>Enzyme replacement</td>
<td>Mucopolysaccharidosis type VI (MPS-VI)</td>
<td>1 in 215,000</td>
<td>$300,000 - $400,000</td>
<td>$47MM</td>
<td>5/31/2005</td>
</tr>
<tr>
<td>Soliris</td>
<td>eculizumab</td>
<td>Alexion Pharmaceuticals</td>
<td>Immunomodulation</td>
<td>Paroxysmal nocturnal hemoglobinuria (PNH)</td>
<td>1 in 77,000</td>
<td>$359,000</td>
<td>Launched in April 2007</td>
<td></td>
</tr>
<tr>
<td>Elaprase</td>
<td>idursulfase</td>
<td>Shire Pharmaceuticals / Genzyme</td>
<td>Enzyme replacement</td>
<td>Mucopolysaccharidosis type II (MPS-II) or Hunter syndrome</td>
<td>1 in 150,000</td>
<td>$300,000</td>
<td>$24MM</td>
<td>7/24/2006</td>
</tr>
<tr>
<td>Myozyme</td>
<td>interferon beta-1b</td>
<td>Chiron &amp; Berlex Laboratories</td>
<td>Enzyme replacement</td>
<td>Pompe’s disease</td>
<td>1 in 40,000</td>
<td>$270,000</td>
<td>$59MM</td>
<td>4/29/2006</td>
</tr>
<tr>
<td>Aldurazyme</td>
<td>imiglucerase</td>
<td>BioMarin Pharmaceutical</td>
<td>Enzyme replacement</td>
<td>Gaucher’s disease</td>
<td>1 in 115,000</td>
<td>$225,000</td>
<td>$95MM</td>
<td>4/30/2003</td>
</tr>
<tr>
<td>Cerezyme</td>
<td>imiglucerase</td>
<td>Genzyme</td>
<td>Enzyme replacement</td>
<td>Types I, II, and III Gaucher’s disease</td>
<td>1 in 100,000</td>
<td>$200,000</td>
<td>$1B</td>
<td>5/23/1994</td>
</tr>
<tr>
<td>Fabrazyme</td>
<td>ceramide trihexosidase/alpha-galactosidase A</td>
<td>Genzyme (has US exclusivity until 2010)</td>
<td>Reduce globotriaosylceramide deposition in kidney capillary endothelium</td>
<td>Fabry’s disease</td>
<td>1 in 40,000</td>
<td>$200,000</td>
<td>$359MM</td>
<td>4/24/2003</td>
</tr>
<tr>
<td>Replagal</td>
<td>agalsidase alfa</td>
<td>Shire Pharmaceuticals (originally Transkaryotic Therapies)</td>
<td>Reduce globotriaosylceramide deposition in kidney capillary endothelium</td>
<td>Fabry’s disease</td>
<td>1 in 40,000</td>
<td>$200,000</td>
<td>$118MM</td>
<td>Approved only in EU in 2001</td>
</tr>
</tbody>
</table>
Up-and-Coming Orphans

• Soliris (Alexion)
• Kuvan (PKU)- BioMarin
• Mipomersen (familial hypercholesterolemia)- ISIS/Genzyme
• Xenazine (HD) - Prestwick
• Amigal (Fabry)- Amicus/Shire
• Promacta (ITP)- GSK
• Advexin (Li Fraumeni) - Introgen
• EC Cystamin (nephropathic cystinosis, HD, Battens ) - Raptor Pharma
### Where Are They Now? 
Last Year's Top 10 Unpartnered CV Projects

<table>
<thead>
<tr>
<th>Developmental Agent</th>
<th>MOA</th>
<th>Phase</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Darusentan</strong> <em>(Myogen)</em></td>
<td><em>Endothelin A antagonist</em></td>
<td>III</td>
<td>Hypertension</td>
</tr>
<tr>
<td><strong>SLX 2101</strong> <em>(Surface Logix)</em></td>
<td><em>PDE 5 inhibitor</em></td>
<td>II</td>
<td></td>
</tr>
<tr>
<td><strong>FM-VP4</strong> <em>(Forbes Medi-Tech)</em></td>
<td><em>Cholesterol absorption inhibitor</em></td>
<td>II</td>
<td></td>
</tr>
<tr>
<td><strong>Mipomersen/ISIS 301012</strong> <em>(Isis Pharmaceuticals)</em></td>
<td><em>Apo B100 antagonist</em></td>
<td>II</td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td><strong>CK 1827452</strong> <em>(Cytokinetiks)</em></td>
<td><em>Cardiac myosin activator</em></td>
<td>I</td>
<td>AHF / CHF</td>
</tr>
<tr>
<td><strong>ATI-2042</strong> <em>(ARYx)</em></td>
<td><em>Amiodarone analog</em></td>
<td>II</td>
<td>Atrial Fibrillation</td>
</tr>
<tr>
<td><strong>VT 111</strong> <em>(Viron Therapeutics)</em></td>
<td><em>Serine protease inhibitor</em></td>
<td>II</td>
<td></td>
</tr>
<tr>
<td><strong>MC 1</strong> <em>(Medicure Inc.)</em></td>
<td><em>Vitamine B6 metabolite</em></td>
<td>III</td>
<td>Reperfusion Injury</td>
</tr>
<tr>
<td><strong>Acadesine</strong> <em>(PeriCor Therapeutics)</em></td>
<td><em>Adenosine agonist</em></td>
<td>III</td>
<td></td>
</tr>
<tr>
<td><strong>Elafin</strong> <em>(Proteo Biotech AG)</em></td>
<td><em>Leukocyte elastase inhibitor</em></td>
<td>I</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td><strong>DG 031</strong> <em>(deCODE genetics)</em></td>
<td><em>FLAP inhibitor</em></td>
<td>III</td>
<td></td>
</tr>
</tbody>
</table>

Isis Pharmaceuticals

Familial Hypercholesterolemia

Isis pharmaceuticals currently has Mipomersen (subcutaneous injection) in phase III and phase II development for the treatment of familial hypercholesterolemia and routine high cholesterol, respectively. Mipomersen is an antisense based therapy that inhibits the production of apolipoprotein B-100.

Familial hypercholesterolemia (FH), considered to be an ultra-orphan indication, is an autosomal dominant disorder characterized by significantly elevated levels of LDL-cholesterol ranging from 200mg/dl to greater than 600mg/dl. Individuals with FH are at high risk for premature coronary artery disease.

Non-pharmacotherapeutic treatment generally involves changes in diet, weight loss, and increasing activity levels. However, these efforts generally have only a modest effect on lowering LDL levels. Drug therapy focuses on the use of statins (often multiple). When target levels can not be achieved, patients become candidates for LDL apheresis, which cost between $50,000 and $75,000 per year.

By The Numbers (US)

| Homozygous Familial Hypercholesterolemia (HoFH) | 300 patients |
| Heterozygous Familial Hypercholesterolemia (HeFH) | 600,000 patients |
| Apheresis Candidates | 30,000 – 60,000 patients |

BioCentury, January 14, 2008
Why not a partner with an extant large cardiovascular franchise?
- Genzyme has significant experience in targeting physician specialists; Familial hypercholesterolemia is typically treated by lipidologist.
- Genzyme is currently marketing Cholestagel in Europe, which falls into the same therapeutic space as mipomersen and will use the same sales force.

Terms of the deal:
- Genzyme is paying Isis $325M up front.
- Isis could receive $1.575B in milestones including:
  - $50M in regulatory and development milestones for HoFH
  - $150M in regulatory and development milestones for HeFH
  - Three commercial milestones worth $250M each (sales in two consecutive years of $3B, $4B, and $5B).
  - $375M in additional milestones if Mipomersen gains approval for non-familial hypercholesterolemia.
  - $250M if a follow-on product is developed. (Isis is currently developing an oral formulation of mipomersen).
- Profit-sharing: 30% initially, increasing to 50% when WW revenues reach $2B.
Isis Pharmaceuticals

This Orphan’s Family Grows

• Genzyme is hoping for approved use of mipomersen in all familial hypercholesterolemia patients, not just for apheresis candidates.

• Genzyme believes the greatest potential for mipomersen is in treating non-familial hypercholesterolemia patients.

• Target population – High risk patients:
  – Unable to reduce LDL to 100mg/dl target
  – Currently on optimal therapy
  – Fully compliant with current therapy
  – Have secondary risk factors: stent, diabetes, prior cardiac event
  – Tend to be treated by lipidologist, which aligns with Genzyme’s Cholestagel sales force.

• Phase III testing is expected to commence in 2009.

• Pricing will be adjusted as the label expands.

By The Numbers (US)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estimated Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Familial Hypercholesterolemia</td>
<td>30 million</td>
</tr>
<tr>
<td>Non-Familial Hypercholesterolemia (unable to achieve target LDL)</td>
<td>16 million</td>
</tr>
<tr>
<td>High Risk Non-Familial Hypercholesterolemia</td>
<td>1.6 million</td>
</tr>
</tbody>
</table>

BioCentury, January 14, 2008
Paroxysmal Nocturnal Hemoglobinuria (PNH)

- A chronic disease occurring as a consequence of nonmalignant clonal expansion of one or several hematopoietic stem cells that are deficient in GPI-anchor protein (GPI-AP), resulting in a lack of complement-regulating surface proteins in their hematopoietic cells.
- PNH affects an estimated 8,000-10,000 individuals in the U.S. and Western Europe.
- Patients are typically diagnosed between 20 and 40 years of age and studies indicate that median survival is approximately 10 years. The main causes of death being venous thrombosis, followed by complications of bone marrow failure.
- Prior to approval of Soliris treatment was limited to palliative care.

Soliris (Eculizumab)

- Soliris is a monoclonal antibody directed against the C5 complement protein, which effectively blocks complement mediated cell destruction.
- Soliris received a broad approval for PNH by the FDA and EMEA in March and June of 2007, respectively.
- Soliris’s TRIUMPH trial showed a significant reduction in transfusion rates (0 units/pt on Soliris vs. 10 units/pt on placebo) and hemoglobin stabilization (49% of Soliris vs. 0% on placebo). Adverse events were similar to placebo.

Source: Alexion Pharmaceuticals; Ferris, Baker Watts; Cowen and Company; http://www.emedicine.com, Defined Health primary research and analysis.
Alexion Pharmaceuticals

Expanding The Label

- Alexion intends to gain maximal benefit from Soliris by pursing indications for myasthenia gravis, multifocal motor neuropathy, organ transplantation, asthma, and AMD.

- Development of eculizumab is currently in phase II clinical trials for asthma in North America. The asthma market represents a significant opportunity with combined sales of Advair (GSK), Singulair (Merck), and Xolair (Genentech) exceeding $8B in 2006. However, development of an effective nebulized formulation of eculizumab may face significant hurdles. An IV formulation of eculizumab could be used as a second-line therapy.

- Alexion is also developing eculizumab for use in organ transplant patients that are at high-risk for rejection, due to antigen exposure during a pregnancy, blood transfusion, or previous transplantation. Use of eculizumab in these patients could potentially block complement-mediated organ rejection.

![Product Indications Table]

*Source: Alexion Pharmaceuticals; Ferris, Baker Watts; Cowen and Company; http://www.emedicine.com, Defined Health primary research and analysis.*

© Defined Health, 2008
Estimates suggest that worldwide sales of Soliris for PNH alone could reach approximately $900 million by 2012.
Monday, April 23, 2007

Number of Orphan Drugs Increases, but Costs High for Consumers

The Hartford Courant on Sunday examined orphan drugs -- those that treat disorders affecting fewer than 200,000 people -- which are "one of the fastest-growing areas in pharmaceuticals" and can be "extraordinarily costly" for consumers. The drugs often are extremely expensive because they are developed for a small pool of patients and "because developing any new medication is a long, risky and costly undertaking," the Courant reports. The pharmaceutical industry estimates that the cost of developing a drug costs $800 million from inception to human clinical trials, and only 30% of experimental drugs ever receive FDA approval. As a result, "when it comes time to affix a price to an orphan drug, companies are eager to recoup their investment quickly," the Courant reports. The increase in orphan drug development activity can be attributed to a 1983 federal law that offers tax breaks and market exclusivity for such products, as well as the "realization by smaller pharmaceutical companies that the drugs represent a lucrative entrepreneurial niche," according to the Courant.

Orphan Drug Profiled

The Courant profiled the orphan drug Soliris, made by Alexion Pharmaceuticals. Soliris is designed to treat paroxysmal nocturnal hemoglobinuria, a life-threatening blood disorder that affects 10,000 people worldwide. The wholesale price for a year's treatment of Soliris is $389,000. Many people with the disorder are expected to receive their first dose of the medication this month, and health insurers are "in the early stages of evaluating their policy" on the drug, leading many patients to worry whether they will be able to afford it, the Courant reports. Bill Sidford, a participant in clinical trials for Soliris, said, "There's a lot of concern. Do you have to become indigent to afford it? Is it being priced so we can't receive it? Who has accessibility? Do you have to give up everything else to afford it? At this point, it's all conjecture." David Araten, an assistant professor of hematology at the New York University School of Medicine who has treated patients with PHN, said, "For patients who do well on this drug, it's like night and day. For them, it's going to be worth every penny, ... and I am certainly hoping the insurance company will fully cover the cost of this drug." Lindsay Shearer, a spokesperson for CIGNA HealthCare, in an e-mail wrote, "Whether or not a medication is categorized as an orphan drug does not determine our coverage policy. CIGNA covers FDA-approved medications consistent with their FDA labeling, according to the terms of the member's employer-sponsored health plan." Many health insurers have a $1 million lifetime expenditure cap, meaning a patient receiving Soliris at a cost of more than $300,000 a year likely would lose coverage after two years, according to Abbey Meyers, president of the National Organization for Rare Disorders (Podsada, Hartford Courant, 4/22).

http://www.kaisernetwork.org

Defined Health Insight Series
January, 2008 – page 64

© Defined Health, 2008
What Does the Future Hold?
Environment

• Political Environment:
  – What should we expect from a Democratic administration (White House and Congress)?

• Regulatory Challenges:
  – Biosimilars.
  – Will heightened safety standards affect Orphan Drugs?

• Payers - the end of the exception?
  – If 10 million patients hit the PMPM.
What Does the Future Hold? Industry

• Will more pharmaceutical companies embrace these opportunities?
  – If so, how will they source innovation? (in-house, in-license, acquire).

• Will Biotech go it alone?
  – Unique opportunity to build a FIBCo.
  – Perfect chance to go global?