Understanding the Drug Development Process

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Drug Discovery/Development is an expensive and risky process
Risks include developmental, clinical, regulatory and marketing
Many are developing novel biology that is unproven in man
Companies’ drugs may fail in the clinic
Companies may fail to file additional INDs
Companies may face future litigation to defend patents
Companies may invest more than projected to develop drugs
Many diseases are competitive with several companies attempting to develop drugs
Companies may not enter into new collaborations/partnerships
Companies may need to access markets for additional cash
The Good News…

Dramatic advances in target and drug discovery techniques that are revolutionizing the field.

- Sequencing of human genome in 2000
- Functional genomics tools: microarrays, RNAi and transgenics
- Pathway elucidation and Systems biology
- Combinatorial, computational and medicinal chemistry
- High-throughput screening and predictive toxicology
- Antibodies and next-gen drugs such as antisense and RNAi
- Gene and Cell Therapy are making real progress
More Good News…

Strengthened Venture Capital and Financial Markets.

• Access to capital for early ideas and rare diseases
• More biotech companies than any other point in history
• Big companies are taking an interest in orphan & rare diseases

Genzyme Corporation and PTC Therapeutics Announce Collaboration on Small Molecule for Genetic Diseases

- Potential New Treatment Paradigm, PTC124 -

CAMBRIDGE, MA and SOUTH PLAINFIELD, NJ - July 17, 2008 - Genzyme Corporation (Nasdaq: GENZ) and PTC Therapeutics, Inc. (PTC) today announced an exclusive global collaboration to develop and commercialize PTC124, PTC's novel oral therapy in late-stage development for the treatment of genetic disorders due to nonsense mutations.
The News…

Drugs Approval Statistics…Not Very Encouraging

• Only 1 in 5 drugs that enter the clinic are ever approved!!
  • 71% chance of entering Phase II studies
  • 31.4% chance of advancing into Phase III studies
  • From Phase III, an estimated 68.5% of drugs reach the market

• Takes on average 11 years to develop a new drug!!
  • 5 years (60.4 months) from discovery to IND
  • 6 years (72.1 months) in the clinic

• Total costs to get a drug approved are >$800 million!!

• High pricing for new life-saving drugs creates market incentive

Target Identification & Validation:

- Genetics
- Genomics
- Proteomics
- Pathway Research
- Systems Biology
- RNAi and Transgenic Models
Drug Discovery:
- Protein Synthesis
- Antibody generation and optimization
  - High-throughput Screening
    - Medicinal Chemistry
    - Antisense or RNAi
- Gene or Cell Therapy
- Formulation and Delivery
Preclinical Studies:

- Animal Models
  - ADME
    - GLP Toxicology
    - Manufacturing Scale-up
  - Investigational New Drug (IND)

Other Phases:

- Target Identification & Validation
- Clinical Trials
- Regulatory Approval and Market Launch
Target Identification & Validation

Clinical Trials:
- Phase I: Safety in Man
- Phase II: Dosing and Efficacy
- Phase III: Registrational Trials

Regulatory Approval and Market Launch
Regulatory Approval and Market:

- NDA or BLA Submission to FDA
  - Orphan Drug Status
    - Sub Part H: Fast-Track Review
    - Panel Meeting
  - Labeling
  - Post-Market Testing
- Reimbursement
- Overseas Regulatory Filings
• Subpart H: Humanitarian Use Devices

• FDA Allows for Accelerated Approval
  • Under Subpart H, approval may be based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity ("Surrogate") [21 CFR 314.510]
  • a product may be approved with restrictions to assure safe use ("Restricted") [21 CFR 314.520]

• Typically reviewed w/in 6 mos vs. standard 10 mos

• Require additional Post-marketing studies
• "Rare Disease or Condition" that affects <200,000 Americans

1) there are many diseases and conditions, such as Huntington's disease, myoclonus, ALS, Tourettes, and muscular dystrophy which affect such small numbers of individuals in the U.S. that the diseases and conditions are considered rare
2) adequate drugs for many of such diseases and conditions have not been developed
3) drugs for these diseases and conditions are referred to as "orphan drugs"
4) because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss
5) there is reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs
6) it is in the public interest to provide such changes and incentives for the development of orphan drugs. Under Subpart H, approval may be based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity ("Surrogate") [21 CFR 314.510], or a product may be approved with restrictions to assure safe use ("Restricted") [21 CFR 314.520].

• Eligible for certain grants or contracts
• Receive 7-years of market exclusivity
<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>COMPANY</th>
<th>TYPE OF DRUG</th>
<th>TARGET or MECHANISM</th>
<th>STATUS</th>
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<td>PTC124</td>
<td>PTC Therapeutics</td>
<td>Small Molecule</td>
<td>Nonsense Mutations</td>
<td>Phase IIb</td>
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<td>Idebenone (SNT-MC17)</td>
<td>Santhera</td>
<td>Small Molecule</td>
<td>Electron transport in mitochondria</td>
<td>Phase IIb</td>
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<td>Protein</td>
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<td>Mirus</td>
<td>Gene Therapy</td>
<td>Dystrophin</td>
<td>Phase I/II</td>
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<td>Prosensa</td>
<td>Antisense</td>
<td>Dystrophin exon skipping</td>
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<td>Phase I</td>
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<td>Small Molecule</td>
<td>Cyclophilin D Inhibitor</td>
<td>Preclinical</td>
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<td>Summit Corporation</td>
<td>Small Molecule</td>
<td>Utrophin</td>
<td>Preclinical</td>
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</table>

**NOVEL TARGETS**

- Alpha-7 integrin
- Utrophin
- Myostatin
- Muscle-specific insulin-like growth factor
- SERCA2a
- PGC-1 alpha
- Phospholamban

*Source: Company reports and Piper Jaffray analysis.*
• Defer to the experts; physicians and clinical researchers
• Sound biological rationale or mechanism of action
• Activity in multiple, appropriate animal models
• Clean safety profile or tox package
• Feasible manufacturing process
• Safety and efficacy in combination with steroids
• Clear end-point / path to regulatory approval
• Experienced management, clinical development & regulatory teams & Strong scientific advisors
• Sufficient capital to reach “Go / No-Go” decisions
• Ability to terminate failed programs
Analyst Certification—Analyst Name

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