## Pharmaceutical and Device Advances Have Significantly Impacted Health and Survival

<table>
<thead>
<tr>
<th>Disease</th>
<th>Disease Before Treatment</th>
<th>Pharmaceutical/Device Advances</th>
<th>Positive Impact</th>
<th>Risks – Negative Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Heart Disease</td>
<td>1979 345 deaths/100,000 pop. ¹</td>
<td>1980s – 1990s</td>
<td>2002 171 deaths/100,000 pop. ¹</td>
<td>Thrombolytics 1% risk of intracranial hemorrhage ⁶</td>
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<td></td>
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<td>ACE inhibitors</td>
<td></td>
<td>Angioplasty with or without stents 0.4% MI 0.5%-1.4% mortality ⁷</td>
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<td>Beta blockers</td>
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<td>Thrombolytics/Stents</td>
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<td>Anti-platelet Tx</td>
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<td>ICDs</td>
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<td>Stroke</td>
<td>1960 178 deaths/100,000 pop. ¹</td>
<td>Treatment of hypertension</td>
<td>2002 56 deaths/100,000 pop. ¹</td>
<td>ACE Inhibitors &lt;10% Hypokalemia, hypotension, &lt;1% serious allergic responses ¹⁴</td>
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<td>Diuretics</td>
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<td>ACE inhibitors</td>
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<td>Hypertension, acute renal failure, hyperkalemia ¹⁵</td>
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<td>Calcium channel blockers</td>
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<tr>
<td>HIV/AIDS</td>
<td>1997 6,647 deaths / 100,000 HIV/AIDS patients. ²</td>
<td>Mid-1990s</td>
<td>2003 1,620 deaths / 100,000 HIV/AIDS patients. ²</td>
<td>GI symptoms, metabolic abnormalities, malaise ⁵</td>
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<td>Nucleoside Reverse Transcriptase Inhibitors</td>
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<td>Non-Nucleoside Reverse Transcriptase Inhibitors</td>
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<td>Protease Inhibitors</td>
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<tr>
<td>Measles</td>
<td>1963 3-4 million U.S. cases (~500,000 reported) ³</td>
<td>1963 Measles vaccine</td>
<td>2000 86 confirmed cases in the U.S. ³</td>
<td>2/1 million doses Pneumonia, 1/1 million doses Encephalitis, 5/1 million doses Anaphalaxis (none fatal) ⁸</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>1997 50% survival post-diagnosis at 18 months⁴</td>
<td>2001 Kinase inhibitors</td>
<td>2004 3 year survival rate estimated at ~94%⁴</td>
<td>GI symptoms, myalgia ⁹</td>
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Abbott
A Promise for Life
Declining Research Productivity of PhRMA
R&D expenditures increasing with incremental change of NDAs / NMEs

Source: GAO, Jan 2006
Modest Improvements in R&D Productivity Yield Double-Digit Pharma Growth Rates

Steady State Growth Model at Industry Average R&D Productivity

- R&D Productivity Model Targets
  - Increase launch success rate from 1 in 10 to 2 in 10
  - Reduce development cycle times from 8.9 years to 6.5 (acute) and 8 years (chronic)
  - Terminate marginal compounds to increase sales per launched compound of >$500MM

Source: Decision Support Group, Integral, CMRI; Tufts Center For Drug Development
Pharma Industry Dilemma

ESCALATING COSTS OF INDUSTRY DRUG DISCOVERY AND DEVELOPMENT

• Industrywide Averages
  – 1 in 10 compounds succeed
  – >$1 Billion per approved compound
  – 8.9 years spent in development
  – > 50% don’t provide adequate return on investment

Cost Lies in Generating Information

- Molecules can be created for low costs at small scale
- Molecules can be copied for low costs (generics)
- Cost of all testing required for any new drug is very high
  - Regulatory standards are increasing
  - Payor standards are increasing

Value lies in identifying the molecule with all of the desired characteristics and then proving it is safe and effective for its intended medical use (FDA standard for Approval)
Abbott Discovery and Development Approach

INVENT AND SELECT SUPERIOR DRUG CANDIDATES

- **Strategies**
  - Focus on key therapeutic areas
  - Increase investment
  - Apply advanced technology

- **Expected Results**
  - Increased quantity and quality of compounds
  - Shifted attrition from development to discovery
  - Harnessed state-of-the-art science
Making new medicine can be broken into steps with corresponding technologies and disciplines.

<table>
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<tr>
<th>Stage</th>
<th>Goal</th>
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<tr>
<td>Target Identification</td>
<td>What will make a difference?</td>
</tr>
<tr>
<td>Lead Identification</td>
<td>How to make a difference?</td>
</tr>
<tr>
<td>Candidate Selection</td>
<td>Our best guess</td>
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<td>Pre-clinical Testing</td>
<td>Hedging bets</td>
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<tr>
<td>Produce the Candidate</td>
<td>Preparing for the test</td>
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<tr>
<td>Clinical Testing</td>
<td>The test</td>
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<td>Population Surveillance</td>
<td>Continuing Education</td>
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Key Stages of Drug Discovery

**ENABLING TECHNOLOGIES**

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<td>MicroARCS Affinity Selection Screening SAR by NMR</td>
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<td>Pharmaco-dynamic Modeling Toxico-genomics Selection Criteria</td>
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Market
Sometimes the targets are relatively clear

HIV Protease
But often there are many potential drug Targets
Target Validation Technologies are Key to Selecting a Program

• Look for clues in humans
  – Replacement therapies
  – Epidemiological associations
  – Genetic clues
  – Other drugs

• Create non-human alternatives
  – Simple Animal models
  – Transgenic animals
  – RNAi

* RISC = RNA-Induced Silencing Complex
Target Validation is Essential to Making Good Choices
## Key Stages of Drug Discovery

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- **Market**
Lead Identification: The starting point

Library Diversity Essential

Select Modality
- Small molecule
- Peptide
- Antibody
- Nucleic acid
- other

>100,000
drug compounds
Screened to find a few leads
per approved molecule
Leads enable candidate generation

Leads may generate 10,000 candidates
Drug Discovery Searches for Molecules That Satisfy Many Criteria

10,000 Drug Candidates from initial leads

10 Clinical Candidates

- non-teratogenic
- non-mutagenic
- manufacturable
- patentable
- physically stable
- durable
- reversible
- non-inducing
- metabolically stable
- permeable
- soluble
- selective
- potent
- targeted

Valid Biomedical Hypothesis?
### Key Stages of Drug Discovery

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**ENABLING TECHNOLOGIES**

- Pathway Elucidation
- Functional Genomics
  - RNAi
  - Literature Analysis
  - Affinity Selection
  - Screening
  - SAR by NMR
- HTS
  - Literature
- Automated Synthesis
- Molecular Modeling
- Yeast Display
- Structural Biology
- Pharmacodynamic Modeling
- Toxico-genomics
- Selection Criteria
- Biomarkers
- Market
Structural Biology
Abbott Made an Early Investment to Address Drug Discovery from a Rational Perspective

• Protein purification and crystallization
• NMR
• X-ray crystallography
• Virtual ligand screening

Results:
SAR by NMR proprietary technology:
6 NMR machines dedicated to structural biology
Automated x-ray crystallography lab
1996: 25 structures identified
2004: 525 structures identified
Revolutionizing Structure-Based Design

- **Crystallize target**
  - Weeks to Months
- **Determine protein-ligand complexes**
  - Days to Weeks

### Number of Target Proteins
- **1996**: 6
- **2005**: >50

### Number of Crystal Structures
- **1996**: 25
- **2005**: >525
ABT-834 Identified With Molecular Modeling

NOVEL $H_3$ RECEPTOR ANTAGONIST IN PHASE I FOR COGNITION

ABT-834 binds $H_3$ Receptor

ABT-834 repels HERG Channel (White Bars)
Advanced candidates are extremely expensive to test

Discovery:
10,000 candidates

Development:
10 molecules

100,000 drug compounds
Drug Development Searches for Molecules That Satisfy Many Criteria

All discovery criteria met:
- Regulatory filing
- Competitive profile
- Cost-effective manufacturing
- Carcinogenicity studies
- Long-term safety
- Efficacy
- Side effect profile
- Trial sites and investigators
- Patient recruitment
- Dosing ranges
- Stability
- Formulation
- Safe and active in lab and animal models
- All discovery criteria met
It Takes about 9 – 12 Years to Bring a New Drug to Patients

- **Discovery**
  - Drug candidate selection
- **Early Development**
  - Phase I & II
  - Proof of Pharmacology
  - Human testing begins
  - Phase III
  - Proof of Concept
- **Late Development**
  - Phase III
  - New Drug Approval
- **Continued Learning**
  - Patients
  - 10’s
  - 100’s
  - 1000’s
  - >100k-millions
Clinical Development - Overarching Challenges

• Cost
  – Approaching $1B, need to decrease

• Time
  – 10+ years, need to bring down time to answer

• Success
  – Major cost comes late, need to decrease the chance for Ph III (and II) failure, identify safety issues not detected in preclinical testing
Phase I Goals

• Establish Time course of Drug levels in blood (PK), Tolerability and Safety in Healthy Volunteers

• Gather evidence that the drug interacts with its molecular target (Proof of Target)
  – Example: Dosing of statin blocks the enzymatic production of circulating mevalonate (cholesterol precursor) by HMG CoA Reductase

• Validate methods that might be used to prove pharmacology in Ph II (surrogate biomarkers of pharmacology and efficacy)

• Explore potential issues affecting use in broader populations
  – Examples: Potential for interactions with other drugs, food effects
Phase II Goals

• Gather evidence that the drug has the intended pharmacology (Proof of Pharmacology)
  – Example: Dosing of statin drug in lowers LDL-C in patients with high cholesterol
  – Note: Most sponsors are now seeking to establish some aspects of Proof-of-Pharmacology in Ph I

• Explore the pharmacology and safety of the drug in patient populations with different characteristics
  – Example: Study statins in patients with high cholesterol with and without previous history of heart disease

• Gather more evidence regarding safety

• Establish the dose(s) and patients to be used in large Ph III pivotal studies
Ph III Goals

• Establish the safety and efficacy in populations reflecting the population to be treated
  – Often requires outcome data (eg, morbidity and mortality)
  – High cost and time consuming (complex)
  – Develop more complete picture of risk and benefits
Improving the overall odds of success is the single most important goal of R and D.
A Conceptual Representation of Pharmaceutical R and D
Maintain Diversity, Select Winners
A Risk/Benefit Balance Is Determined at Approval

Male-Pattern Baldness

- Efficacy
- Safety
- Unmet Medical Need

Lung Cancer

- Efficacy
- Safety
- Unmet Medical Need
A Risk/Benefit Analysis Is Never Finished

>20 Million Exposed Patients

Database at approval
(1/4000th of final U.S. patient exposure)

5,000 Patients