How Should We Be Developing Drugs In The 21st Century?

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Lesson 1

• The traditional clinical development model must and will change because drug development is becoming an unsustainable proposition for the industry

Source: PAREXEL’s Pharmaceutical R&D Statistical Sourcebook 2004/2005, pages 1 and 188
*2003 Pharmaceutical R&D spending estimate; Number of NDAs pending is not available
Drug Development Is Getting More Expensive

- Tufts Center for the study of Drug Development (CSDD)
  - Estimate of cost to develop a new drug (2003 study) – 897 million in 2000 dollars
    - Included in the cost are expenses of drug failures and the impact that long development times have on investment costs
  - Estimates in prior studies was $802 million in 2001 and $231 million ($318 million in 2000 dollars) in 1987
  - Driver for increasing costs thought to be clinical trials costs

<table>
<thead>
<tr>
<th></th>
<th>Out-of-Pocket Expenses</th>
<th>Including Cost of Capital</th>
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</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>$121</td>
<td>$336</td>
</tr>
<tr>
<td>Clinical</td>
<td>$282</td>
<td>$466</td>
</tr>
<tr>
<td>Total</td>
<td>$403</td>
<td>$802</td>
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</table>
Declining R&D Success Rates: A 2003 Assessment

NUMBER OF COMPOUNDS ENTERING PHASE

<table>
<thead>
<tr>
<th></th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III/ File</th>
<th>Launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical (1996-2000)</td>
<td>8</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Current (2000-2002)</td>
<td>13</td>
<td>9</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Cumulative Success Rate

- Historical: 14%
- Current: 8%

Lesson 2

Surrogate markers can add enormous value when validated, but…

Be Careful: You Don’t Know What You Don’t Know
Integration of Surrogate Endpoints in Clinical Drug Development: Addressing The Challenges of Clinical Development

- **Proof of Target**
  - Does drug hit target in patients
- **Proof of Activity/Mechanism**
  - Measure biological response in patients
  - Understand molecular mechanism in patients
- **Proof of Efficacy**
  - Surrogate biomarker correlated with approvable clinical endpoint
  - Approvable Clinical Endpoint
Biomarkers have the potential to:

- **Improve the probability that the drugs which enter phase 2 are successful by**
  - Designing phase 1 and 2 studies to include PD Biomarkers (making sure the drug hits the target)
    - Example 1: Saturation of CD11a receptor for efalizumab in Psoriasis

- **Improve the probability that the drugs which enter phase 3 are successful by**
  - Designing phase 2 studies which use biomarkers to identify the appropriate dose for phase 3
    - Example 2: TIMI Flow in AMI: A Biomarker used Dose Selection of TNK
  - Designing Phase 2 studies using biomarkers which are correlated with clinical outcome
    - Example 3: Response Rate: A Biomarker for Avastin in Colorectal Metastatic Cancer
    - Example 4: DCE-MRI with Gadolinium: A Biomarker study for PTK787 in Colorectal Cancer Patients
  - Designing phase 2 and 3 studies which enroll higher-risk patients (identified by prognostic biomarkers) likely to have a greater treatment respond (predictive biomarkers)
    - Example 5: Her 2 Over-expression predicts worse outcome and identifies patients most likely to respond to Herceptin
  - **Reduce the resources/time required for current drug development efforts (surrogate biomarkers)**

- **Improve our ability to identify toxicity signals (biomarkers which are correlated with SAEs)**
- Environmental factors
  (Hypoxia, pH)
- Growth factors
  (EGF, bFGF, PDGF, IGF-1, IL-1α, IL-6)
- Genes involved
  in tumorigenesis
  (p53, p73, src, ras, vHL, Bcr-Abl)

VEGF: The Central Mediator of Angiogenesis

VEGF receptor activation

Endothelial cell activation

Endothelial cell survival, proliferation, migration
Using Biomarkers/Surrogates which are correlated with clinical outcome

- IFL/Placebo (n=412)
  RR=34.8%

- IFL/Avastin (n=403)
  RR=44.8%, p=0.004

HR=0.65, p=0.00003
Median Survival: 15.6 vs 20.3 mos

Hurwitz et al. NEJM. 350:2335-2342.
Phase III MBC Trial With Avastin: Progression-free Survival

Cap/Placebo (n=230)
RR=19.1%

Cap/Avastin (n=232)
RR=30.2% p=0.006

RR is not always a good biomarker though!

Miller et al. JCO 23:792-99
PTK787 dose-dependently reduced tumor perfusion/permeability, as measured by Ki.

Significant correlation between reduction in perfusion/permeability and clinical outcome.

**Graphs:**
- **Left Graph:** Percentage of baseline MRI-Ki vs. dose (mg) for progressive disease.
- **Right Graph:** Percentage of baseline MRI-Ki for stable and progressive disease with statistical significance indicated by $P = .006$. 

*Morgan et al. JCO. 21:3955-64*
Surrogate End Points In Cardiology: Arrhythmia Suppression

Numerous studies have shown that PVCs are a risk factor for sudden and nonsudden cardiac death post-MI.
Surrogate End Points In Cardiology: The Cardiac Arrhythmia Pilot Study

• In the 1980’s and early 90’s antiarrhythmic drugs were often used to suppress PVCs despite the fact that no study ever documented that antiarrhythmic therapy reduced sudden cardiac death
• The Cardiac Arrhythmia Pilot Study (CAPS) - sponsored by the NHLBI to determine whether postinfarction ventricular arrhythmias can be reduced.
• Patients with > 10 VPC or at least 5 runs of 3 to 9 consecutive PVCs in 24 hours
• Results:
  – 1. Flecaininde, Encaininde and Moricizine were shown to suppress PVCs
  – 2. The FDA approved their use.
  – 3. >200,000 persons per year eventually took these drugs in the US

*American Journal of Cardiology. 57(1):91-5, 1986 Jan 1.*
Surrogate End Points In Cardiology: Arrhythmia Suppression

- Placebo (n = 743)
- Encainide or Flecaïnide (n = 755)

P = 0.0004
How Should We Be Developing Drugs In The 21\textsuperscript{st} Century?

\textbf{ANSWER: Develop Targeted Therapy}
What Is Targeted Therapy Anyway?

• At its simplest, targeted therapy implies a therapy with a specific molecular target

DRUG + MOLECULAR TARGET = TARGETED THERAPY

• However, any therapy that works must have a molecular target. (Encainide is targeted!)
• Is it in the specificity for a target?
  – Probably not because Imatinib, which inhibits numerous TKs, is held as an example of one of the classic targeted agents
There's targeted therapies and then there's Targeted Therapies

DRUG Acting On A MOLECULAR TARGET
(necessary but not sufficient)

Additional Requirements:

1. The MOLECULAR TARGET should be important in causing the pathophysiology of the disease
2. The MOLECULAR TARGET should be measurable in the clinic
3. Measurement of the MOLECULAR TARGET should have a predictive impact on the therapy

Targeted Therapy and The Role Of Diagnostics

Drug \rightarrow Target \rightarrow Biological Response \rightarrow Clinical Surrogate \rightarrow Clinical Endpoint

DIAGNOSTICS

DIAGNOSTICS
Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2

Dennis J. Slamon, M.D., Ph.D., Brian Leyland-Jones, M.D., Steven Shak, M.D., Hank Fuchs, M.D., Virginia Paton, Pharm.D., Alex Bajamonde, Ph.D., Thomas Fleming, Ph.D., Wolfgang Eiermann, M.D., Janet Wolter, M.D., Mark Pegram, M.D., Jose Baselga, M.D., and Larry Norton, M.D.*

RR = 0.76  
p = .025

Survival (%)  
Months after Enrollment

Chemotherapy alone  
20.3 mo

Chemotherapy plus trastuzumab  
25.4 mo (25%↑)

**Her 2 Over-expression and The Development of Herceptin: The Importance of a Predictive Biomarker**

<table>
<thead>
<tr>
<th>Expected Benefit</th>
<th>Target Prevalence</th>
<th>Actual Benefit (All Patients)</th>
<th>Required Sample Size And Study Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ 5 months (22.7%)</td>
<td>100%</td>
<td>↑ 5 mos (22.7%)</td>
<td>1250 → 52 mos</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>↑ 2.5 mos (11.4%)</td>
<td>3500 → 108 mos</td>
</tr>
<tr>
<td></td>
<td>25%</td>
<td>↑ 1.25 mos (5.7%)</td>
<td>11000 → 349 mos</td>
</tr>
</tbody>
</table>

*Easy to miss a potentially active new therapy as target prevalence decreases*
Patient Selection – Without selection, a potentially active new therapy could be missed

A Phase III in which 50% of patients show a treatment effect.

Unspecified date and program
Source: Biostatistics (pangc1). pgm/immuno/hs2/h0648gfcurrent/biostat/kp_simulate)
Patient Selection – Without selection, a potentially active new therapy could be missed

A Phase III in which 25% of patients show a treatment effect.
Is Targeted Therapy Just For Oncology?
Immunological Mechanisms Involved in Allergic Disease

Sensitization

Allergen

Environment

Submucosa

Antigen-Presenting Cell

MHC Class II Protein and Epitope

Th2-Cell + B-Cell

Production of Antigen-Specific IgE

Mast Cell Degranulation

Clinical Effects

Asthma, Rhinitis, Urticaria

Re-Exposure

Mediators
IgE and Asthma Relationship in Adults

N = 2657

Stable Steroid Phase: Patients With ≥ 1 Significant Asthma Exacerbations

Distribution of AEEs per patient

- **US (008)**
  - Omalizumab: 14.6%
  - Placebo: 25.7%
  - **P = .009**

- **International (009)**
  - Omalizumab: 12.8%
  - Placebo: 27.2%
  - **P < .001**

- **Pediatric (010)**
  - Omalizumab: 22.5%
  - Placebo: 10.9%
  - **P = .095**

**Significant asthma exacerbation** = episode requiring course of oral CS or doubling dose of ICS
What Is Targeted Therapy?

1. The MOLECULAR TARGET should be important in causing the pathophysiology of the disease
2. The MOLECULAR TARGET should be measurable in the clinic
3. Measurement of the MOLECULAR TARGET should have a predictive impact on the therapy

- GH for GH Deficiency
- Herceptin for Her2 positive Metastatic Breast Cancer
- Xolair for Allergic Asthma
- Thrombolytics for AMI
  - The ECG (ST segment elevation) identifies patients with a fibrin rich clot
- Rituxan for NHL
  - Almost all NHL patients have CD20 expressed on lymphocytes
- Tarceva for 2nd Line Lung Cancer?
  - EGFR IHC+, Non-smokers, Patients with activating mutations
- Avastin Breast/Lung/Colon Cancer
- Raptiva Psoriasis
- Pulmozyme for CF
Lesson 3

Drugs Are NOT Safe…They Offer *Benefit for Risk*
On 1st October 2004:

- More than 2 million Vioxx scripts were written in the US - 60,000 every week. 19% of all scripts for arthritis pain were for Vioxx

On 1st October 2004:

- Vioxx was withdrawn from the market on concerns that long term use may lead to increased risk of heart attacks and stroke
Suppose There Is A New Therapeutic At The FDA For Review

• PROS:
  – This therapy will result in a substantial improvement in the quality of life (by all validated instruments)
  – It results in remarkably fewer days missed from work
  – The therapy is relatively cost-effective

• CONS
  – The therapy clearly does not improve survival. In fact, there appears to be a rare safety signal which requires hospitalization leading to death (estimated risk is 1 / 7500)
  – The unmet need can be addressed by other therapies which are less toxic, but much less effective
The “Therapy” Is Approved

- Predictors of this rare safety signal were identified, but largely ignored
- Currently this “therapy” results in about 40,000 deaths per year, as well as many hospital admissions and ER visits
The “Therapy” Remains on the Market

<table>
<thead>
<tr>
<th>VEHICLE WEIGHT</th>
<th>CARS</th>
<th>SUVS</th>
<th>PICKUP TRUCKS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>overall</td>
<td>mv / sv / roll</td>
<td>overall</td>
</tr>
<tr>
<td>2,500 lbs. or less</td>
<td>115</td>
<td>71 42 20</td>
<td>—</td>
</tr>
<tr>
<td>2,501-3,000 lbs.</td>
<td>102</td>
<td>54 46 25</td>
<td>128</td>
</tr>
<tr>
<td>3,001-3,500 lbs.</td>
<td>84</td>
<td>44 39 19</td>
<td>98</td>
</tr>
<tr>
<td>3,501-4,000 lbs.</td>
<td>56</td>
<td>33 23 10</td>
<td>98</td>
</tr>
<tr>
<td>4,001-4,500 lbs.</td>
<td>47</td>
<td>27 20 7</td>
<td>73</td>
</tr>
<tr>
<td>4,501-5,000 lbs.</td>
<td>—</td>
<td>—</td>
<td>66</td>
</tr>
<tr>
<td>More than 5,000 lbs.</td>
<td>—</td>
<td>—</td>
<td>55</td>
</tr>
</tbody>
</table>

*overall* driver death rate per million registered vehicle years
*mv* driver death rate in multiple-vehicle crashes
*sv* driver death rate in single-vehicle crashes
*roll* driver death rate in single-vehicle rollover crashes
*—* no exposure or insufficient exposure
How Should We Be Developing Drugs In The 21st Century?

ANSWER: Develop Targeted Therapy, but realize it isn’t easy

WHY?
It’s the right thing for patients: matching drugs with patients that will benefit and not treating those that will not
Conclusions

• The traditional clinical development model must and will change because drug development is becoming an unsustainable proposition for the industry

• Developing Targeted Therapies Offers Significant Advantages, but

  ➢ You Don’t Know What You Don’t Know

• The Only Safe Drug Is A Placebo:
  – Drugs Are NOT Safe…They Offer Benefit for Risk