Feeding the Pipeline VIII: Over the Gap and Beyond?

Ed Saltzman
Defined Health

LES 2007 Annual Meeting
October 14-18, 2007
Vancouver, BC, Canada
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 report, are subject to change.
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• Ginny Llobell
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Some Perspective on Attrition
Phillies lose 10,000th game

Dan Gelston, The Associated Press

Through the last-place finishes, September collapses and every agonizing failure over the past 125 years, no team has lost quite like the Philadelphia Phillies.

Futility has followed them since the day they were born, and Sunday night was no different. Loss No. 10,000 came when Albert Pujols hit two of the St. Louis Cardinals' six homers in a 10-2 rout.

Not surprisingly, this defeat resembled the thousands that came before. Bad starting pitching, brutal relief and hardly any hitting. And, of course, lots of booing.

By the ninth inning, with the outcome inevitable, the boos turned to cheers. Fans in the sellout crowd of 44,872 thumbed their noses at the dubious mark, standing and applauding. One held up a sign that read: "10,000 N Proud" as NL MVP Ryan Howard struck out to end the game.

"I don't know too much about 10,000 losses," Phillies manager Charlie Manuel said. "I try and concentrate on the wins."

From the Baker Bowl to Connie Mack Stadium to the Vet and Citizens Bank Park, and at ballparks all over, the Phillies have cemented their place as the losingest team in professional sports. The franchise, born in 1883 ...

They haven't lost 100 games since 1961, and they won the NL East three straight years from 1976-78 behind Mike Schmidt, Steve Carlton and Larry Bowa. Philadelphia lost the World Series in 1983 and 1993, though it hasn't returned to the playoffs since.

"I think they need to forget about it and move forward," said Greg Luzinski, the starting left fielder for the 1980 team.

After combining for 23 runs and 37 hits in the first two games of the series, the Phillies were held in check by Adam Wainwright (8-7). He threw seven shutout innings against the highest-scoring team in the National League...
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This just in:
Today the American Medical Association issued an advisory that the Universal Choking Sign has been revised.

Old Symbol

New Symbol
Some Perspective on My Perspective
Once Upon a Time…

- Big Pharma: a self-contained “Innovation Loop”
- It was a beautiful thing!
Once Upon a Time…

• Big Pharma: a closed “Innovation Loop”
• It was a beautiful thing!
• Until the innovation went away…
The Path Away from Self-Reliance

% Sales from Organic Top 10 Pharmaceutical Companies in 2006

% Sales from Internally Discovered Drugs Top 10 Pharmaceutical Companies in 2006

EvaluatePharma; Companies include GlaxoSmithKline, Roche, Sanofi-Aventis, Novartis, Pfizer, Merck & Co, J&J, AstraZeneca, Abbott, Eli Lilly.
Filling the Gap: “AEIH” = *Almost* Everything Invented Here, Though Not Consistently
In-Licensing 1992-95: The “Gap Filler”

A Bigger, Later and Scarier Gap!

BP-600
BP-102
BP-306
BP-456
BP-226
BP-145
BP-807
BP-814
BP-973
BP-980

Bigger Gap
In-Licensing 1995 - Present: Struggling With a Growing Gap!

Spiraling R&D Expense and Decreasing Output


Feeding the Pipeline VIII
October, 2007 - Pg. 22

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The Gap Will Soon Become a Chasm for Every Big Pharma

Sales to be Lost to Generics and Number of Companies Losing $3bn or More in Sales

Lehman Brothers PharmaPipeline (Sept 2007), DH Analysis.
August 8, 2007

More Generics Slow the Surge In Drug Prices

By Stephanie Saul

A quiet coup is taking place in American medicine cabinets. Prescription bottles bearing catchy brand names like Zoloft and Flonase are being pushed aside by tongue-twisting generics like sertraline and fluticasone propionate.

"There's a tidal wave of generic drugs, and we are just in the beginning of the tidal wave," said Laizer Kornwasser, an executive for Medco Health Solutions, which manages prescription drug plans.

The rise of generics has helped slow spending increases for prescription medications overall, even though an aging population is consuming more drugs and even as new medicines enter the market -- including cancer drugs costing tens of thousands of dollars.

Several experts predict that generic drugs will keep drug price inflation in the single digits for the next several years.

And now, as nearly every big drug maker watches its best sellers fade away, there are fewer potential blockbuster drugs waiting to take their place.

"At the end of the day, it's basically a failure of innovation," said Richard T. Evans, a consultant with the firm Avos Life Sciences, a research and consulting firm for the drug industry. Mr. Evans said it was hard to know whether the drug industry was merely in a cyclical lull or whether it suffered from a systemic decline in productivity.

But the Pharmaceutical Research and Manufacturers of America, the trade group for brand-name companies, said that company …
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Tomorrow’s Innovation Gap Will be Too Large for Traditional Licensing to Fill!
Why Was Anyone Surprised?

In 1996 Jurgen Drews Brings an Unwelcome Warning...
Why Was Anyone Surprised?

“Continued 10 – 15% annual growth requires 1 – 2 blockbuster introductions each year…”
- Jurgen Drews, 1996

(P.S. It Didn’t Happen!)
It was Clear to This Once Young Man

Ed: Circa 1985

Ed: Circa 1995

Ed: Present Day
It was Clear to This Once Young Man


Ed: Circa 2000
Ed Saltzman Seen Here in 2000 Late-Stage Opportunity Hunting
Feeding the Pipeline: Alternatives to the Late Stage Product Stampede

Ed Saltzman
President
Defined Health

LES 2000 Annual Meeting
Toronto
“Let’s In-License A Late-Stage Blockbuster.”
A Recent Gathering of Pharma Industry Licensing Executives Looking for Late Stage Compounds with Sales Potential >$500 million
Why the Stampede (For Late-Stage Products)?

• Pushing the Supertanker
  – Sustaining enormous blockbuster and merger-driven growth rates depends on more blockbusters (or at least a lot more multi-hundred million dollar products)
• “A nice problem to have” is now a real, serious problem

<table>
<thead>
<tr>
<th>Blockbuster</th>
<th>Launch Date</th>
<th>1999 WW Sales $B</th>
<th>% Total Pharma Sales</th>
<th>Patent Expiration</th>
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</thead>
<tbody>
<tr>
<td>Prilosec</td>
<td>1988</td>
<td>$5.9</td>
<td>40%</td>
<td>2001</td>
</tr>
<tr>
<td>Zocor</td>
<td>1991</td>
<td>$4.5</td>
<td>25%</td>
<td>2005</td>
</tr>
<tr>
<td>Norvasc</td>
<td>1992</td>
<td>$3.0</td>
<td>14%</td>
<td>2007</td>
</tr>
<tr>
<td>Claritin</td>
<td>1993</td>
<td>$2.7</td>
<td>33%</td>
<td>2002</td>
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<tr>
<td>Prozac</td>
<td>1987</td>
<td>$2.6</td>
<td>28%</td>
<td>2001</td>
</tr>
</tbody>
</table>

EvaluatePharma.
“Let’s In-License a Late-Stage Blockbuster”

THE PROBLEM IS LACK OF INVENTORY!!!

• Defined Health Analysis: Phase III and above compounds in US development (Adis R&D Insight)

• 7 Top Therapeutic Classes
“Let’s In-License a Late-Stage Blockbuster”

At Least 20 Companies Are Chasing 26 Compounds!

<table>
<thead>
<tr>
<th>Category</th>
<th>Phase III Compounds</th>
<th>Already Licensed</th>
<th>Internal Priorities</th>
<th>Dogs</th>
<th>Realistic Opportunities</th>
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<tbody>
<tr>
<td>CV</td>
<td>48</td>
<td>-14</td>
<td>-17</td>
<td>-12</td>
<td>5</td>
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<tr>
<td>Alimentary/ Metabolism</td>
<td>34</td>
<td>-7</td>
<td>-12</td>
<td>-13</td>
<td>2</td>
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<tr>
<td>CNS</td>
<td>58</td>
<td>-22</td>
<td>-20</td>
<td>-12</td>
<td>4</td>
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<tr>
<td>Anti-Infectives</td>
<td>38</td>
<td>-18</td>
<td>-12</td>
<td>-5</td>
<td>3</td>
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<tr>
<td>Respiratory</td>
<td>19</td>
<td>-3</td>
<td>-13</td>
<td>-2</td>
<td>1</td>
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<tr>
<td>Oncology</td>
<td>78</td>
<td>-29</td>
<td>-15</td>
<td>-27</td>
<td>7</td>
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<tr>
<td>Anti-Inflammatory/ Immune</td>
<td>36</td>
<td>-8</td>
<td>-10</td>
<td>-14</td>
<td>4</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>301</strong></td>
<td><strong>99</strong></td>
<td></td>
<td></td>
<td><strong>26</strong></td>
</tr>
</tbody>
</table>

Some co-promotion opps?
Licensing Late-Stage Blockbusters: Gone with the Century!

• Late-stage licensing fed the 1990s Pharma launches
• Since then no blockbuster has been licensed

EvaluatePharma, DH Analysis.
# In-Licensed Late-Stage Blockbusters: Gone with the Century!

<table>
<thead>
<tr>
<th>Year</th>
<th>Company</th>
<th>Product</th>
<th>2006</th>
<th>Status on Deal Date</th>
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<tbody>
<tr>
<td>1987</td>
<td>GlaxoSmithKline</td>
<td>Coreg IR/Kredex</td>
<td>$1,436</td>
<td>Phase II</td>
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<tr>
<td>1989</td>
<td>Merck &amp; Co</td>
<td>Cozaar</td>
<td>3,163</td>
<td>Phase II</td>
</tr>
<tr>
<td>1993</td>
<td>BMS</td>
<td>Avapro</td>
<td>1,097</td>
<td>Phase II</td>
</tr>
<tr>
<td>1993</td>
<td>BMS</td>
<td>Plavix</td>
<td>3,257</td>
<td>Phase III</td>
</tr>
<tr>
<td>1994</td>
<td>AstraZeneca</td>
<td>Atacand</td>
<td>1,110</td>
<td>Phase III</td>
</tr>
<tr>
<td>1994</td>
<td>BI</td>
<td>Flomax/Alna</td>
<td>1,158</td>
<td>Phase III</td>
</tr>
<tr>
<td>1994</td>
<td>Sanofi-Aventis</td>
<td>Eloxatin</td>
<td>2,127</td>
<td>Phase III</td>
</tr>
<tr>
<td>1995</td>
<td>Sanofi-Aventis</td>
<td>Copaxone</td>
<td>1,343</td>
<td>Phase III</td>
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<tr>
<td>1995</td>
<td>Genentech</td>
<td>Rituxan</td>
<td>2,071</td>
<td>Phase II</td>
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<tr>
<td>1996</td>
<td>Wyeth</td>
<td>Protonix</td>
<td>1,795</td>
<td>Phase II</td>
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<td>1997</td>
<td>Abbott</td>
<td>TriCor</td>
<td>1,048</td>
<td>Filed</td>
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<tr>
<td>1997</td>
<td>J&amp;J</td>
<td>Aciphex/Pariet</td>
<td>1,239</td>
<td>Filed</td>
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<tr>
<td>1997</td>
<td>Pfizer</td>
<td>Lipitor</td>
<td>11,239</td>
<td>Approved</td>
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<tr>
<td>1998</td>
<td>Schering-Plough</td>
<td>Remicade-ex US</td>
<td>1,240</td>
<td>Phase III</td>
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<tr>
<td>1998</td>
<td>AstraZeneca</td>
<td>Crestor</td>
<td>2,028</td>
<td>Phase II</td>
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</table>

**EvaluatePharma, DH Analysis.**
The Urge to Merge
### The Urge to Merge: Major Pharma M&A 1994-1995

<table>
<thead>
<tr>
<th>Date</th>
<th>Acquirer</th>
<th>Acquiree</th>
<th>Deal Value ($millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>Hoechst</td>
<td>Marion Merrill Dow</td>
<td>$7,160</td>
</tr>
<tr>
<td>1995</td>
<td>Glaxo</td>
<td>Wellcome</td>
<td>$14,151</td>
</tr>
<tr>
<td>1995</td>
<td>Upjohn</td>
<td>Pharmacia</td>
<td>$6,500</td>
</tr>
<tr>
<td>1994</td>
<td>AHP</td>
<td>Cyanamid</td>
<td>$9,700</td>
</tr>
<tr>
<td>1994</td>
<td>Sanofi</td>
<td>Sterling</td>
<td>$1,825</td>
</tr>
<tr>
<td>1994</td>
<td>Ciba-Geigy</td>
<td>Chiron</td>
<td>$2,065</td>
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<tr>
<td>1994</td>
<td>BASF</td>
<td>Boots</td>
<td>$1,360</td>
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<td>1994</td>
<td>SmithKline</td>
<td>Sterling Winthrop</td>
<td>$2,925</td>
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</tbody>
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Windhover Information.
## The Urge to Merge: Major Pharma M&A 1996-2002

<table>
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<th>Acquiree</th>
<th>Deal Value ($millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>Pfizer</td>
<td>Pharmacia</td>
<td>$58,966</td>
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<td>2001</td>
<td>BMS</td>
<td>DuPont Pharma</td>
<td>$7,800</td>
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<td>2000</td>
<td>Glaxo</td>
<td>SmithKline</td>
<td>$78,000</td>
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<tr>
<td>2000</td>
<td>Abbott</td>
<td>Knoll</td>
<td>$6,900</td>
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<tr>
<td>1999</td>
<td>Pfizer</td>
<td>Warner Lambert</td>
<td>$84,083</td>
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<tr>
<td>1999</td>
<td>Monsanto</td>
<td>Pharmacia &amp; Upjohn</td>
<td>$26,355</td>
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<tr>
<td>1998</td>
<td>Zeneca</td>
<td>Astra</td>
<td>$31,155</td>
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<tr>
<td>1998</td>
<td>Sanofi</td>
<td>Synthelabo</td>
<td>$12,000</td>
</tr>
<tr>
<td>1997</td>
<td>Roche</td>
<td>Boehringer Mannheim</td>
<td>$11,000</td>
</tr>
<tr>
<td>1996</td>
<td>Ciba-Geigy</td>
<td>Sandoz</td>
<td>$27,000</td>
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Windhover Information.
GlaxoSmithKline to be formed in £114bn "merger of equals"

Dr Jean-Pierre Garnier (chief operating officer, Smithkline Beecham, and chief executive designate, GSK) said: "This is a merger of strong with strong, in contrast to some other mergers in this industry." He said that the merger would produce five key competitive advantages for the new company:

- **Enhanced R&D productivity** "Money and scale are important, but you also need quality." The two companies have 13 compounds and 10 vaccines currently in phase III development. Both companies were leaders in genomics and bioinformatics.

- **Superior marketing power** Over 40,000 employees in sales and marketing, including 8,000 representatives in the US, making the company the marketing partner of choice.

- **Superior consumer marketing skills** "These will be much more important than ever before." The market was being changed by direct-to-consumer advertising and e-marketing via the internet. Many of the company's products would be switched to over-the-counter status in the future.

- **Operational excellence** Efficiency savings of over £750m would be achieved over three years, on top of savings of £570m already achieved. Savings of £250m would be made by streamlining research and development. This money would be reinvested.

- **A talented management team** Both sides had previous experience of integrating companies after mergers.
The Bigger the Merger, The Greater the Value Destruction

Company values prior to merger announcement.

PFE
- 221B
- $51B
- $74B
- 91B

Big Pharma Index

Big Pharma Index

-31%
-4%
-28%
-14%

GSK

- $188B
- $118B

SEC filings, YahooFinance, DH Analysis.
Enhanced Productivity?

Glaxo Wellcome + SmithKline Beecham

26 NMEs Filed and approved

6 year total Pre-merger

GSK

15 NMEs Filed and approved

6 year total Post-merger

Drugs@FDA, CDER, DH Analysis; Filing to approval time estimated to 24 months when specific dates not available.
Mega Pharma’s Problem at a Glance!

American Medical Association; 2007/2008 Parexel R&D Statistical Factbook; Verispan; EvaluatePharma.

*: Cash, Cash equivalent and liquid assets.
The Mega-Merged Pharma Has Turned Out to be an Innovation-Challenged Environment
...so in summary, we will obtain 30% of our product candidates from our internal discovery and 50% from external partnerships. Any questions?
Where will you get the remaining 20%?
There Must be a Better Answer!
There Must Be a Better Answer!

- Pharma Industry Strategies to Deal with the Innovation Deficit Resulting from the End of Late Stage Licensing:
  - Buying revenue-stage biotechs (1999-present)
  - Getting smaller, headcount speaking (2006-present)
  - Getting larger, molecularly speaking (2005-present)
  - Sharpening disease area focus (2004-present)
  - Increasing early-stage dealmaking/M&A (2005-present)
Big Pharma/Big Biotech M&A: A Better Answer?

- Historically, few revenue stage biotechs with attractive pipelines limits realistic opportunities.
- Though a small $n$, benefit of hindsight suggests most of these deals were unsuccessful.
- AZ/MedImmune – the jury is still a long way out, but by historical standards it does not look unreasonable.
Cheap at any price?

When MedImmune, a Maryland biotechnology company, announced on 12 April that it was looking for a buyer, market watchers ...

Even so, the markets’ verdict was that MedImmune’s price was too high: after the announcement, the biotechnology company’s stock rose by 18%, but AstraZeneca’s fell by 5%. Some shareholders at the latter’s annual meeting in London on 26 April spoke out against the purchase — one called it “an act of desperation”.

MedImmune has several interesting, but preliminary, assets including three anti-cancer therapies and three candidate drugs to fight inflammatory disorders, none of which has yet made it beyond stage II trials. “There aren’t that many companies out there with that level of a biologic programme in their pipeline,” says Philip Nadeau, an analyst at Cowen and Company, another New York investment bank.

AstraZeneca will benefit from the cash flow that MedImmune’s current products provide, particularly because they hold fresher patents and therefore will not be challenged by generics in the near future. As well as providing biotechnology expertise, MedImmune will provide AstraZeneca with an entry into the vaccine market. AstraZeneca may also have been drawn to MedImmune’s manufacturing capacity, according to Yang.

But the biggest factor of all in setting such a high price may have been competition from other suitors. The bidding for MedImmune is said to have been fierce, with pharmaceutical companies such as Eli Lilly and Merck reportedly entering the fray. Such companies are clamouring for new acquisitions, and there are few setups of MedImmune’s stature to feed that appetite. The past year had already seen a spate of smaller purchases, such as Merck’s purchase of Sirna for $1.1 billion — twice the market value of the....
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Some analysts agreed. “It is difficult to rationalize today’s price,” said an analyst report from CIBC World Markets in Toronto, Canada. But others saw the deal as a smart move in the long term. Analysts at Bear Stearns said: “In our view, the MedImmune acquisition makes sense, financially and strategically.”

….. on the market, including Synagis, the first monoclonal antibody approved to fight infectious disease and used to treat a respiratory virus in children. But revenue from Flu-Mist, an inhalable flu vaccine that was widely regarded as MedImmune’s most promising product, peaked in 2004 at only $53.5 million. Beyond that, MedImmune has several interesting, but preliminary, assets including three anti-cancer therapies and three candidate drugs to fight inflammatory disorders, none of which has yet made it beyond stage II trials. “There aren’t that many companies out there with that level of a biologic programme in their pipeline,” says Philip Nadeau, an analyst at Cowen and Company, another New York investment bank.

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By Historical Standards, AZ/MedImmune is Clearly Expensive, but Not Outrageous

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<tr>
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<tr>
<td>2001</td>
<td>J&amp;J</td>
<td>ALZA</td>
<td>$10,800</td>
<td>$988</td>
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<td>1999</td>
<td>J&amp;J</td>
<td>Centocor</td>
<td>$4,900</td>
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<td>1999</td>
<td>WL</td>
<td>Agouron</td>
<td>$2,100</td>
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<td>AHP</td>
<td>Genetics Institute</td>
<td>$1,250</td>
<td>$172</td>
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Windhover Information.
Ultimately, Value Will be Determined by the Pipeline

<table>
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<tr>
<th>Infectious Diseases</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Market</th>
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<tbody>
<tr>
<td>Synagis®</td>
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<tr>
<td>FluMist®</td>
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<td></td>
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<td>CAIV-T</td>
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<td></td>
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<td>Mavizumab</td>
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<tr>
<td>Epstein Barr Virus vaccine</td>
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</tr>
<tr>
<td>RSV/PIV-3 vaccine</td>
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<tr>
<td>Pneumococcal vaccine</td>
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<tr>
<td>H5N1 vaccine</td>
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<td></td>
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<tr>
<td>hMPV/PIV-3 vaccine</td>
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<td>hMPV MAb &amp; vaccine</td>
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<tr>
<td>Anti-RSV drug</td>
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<td>Anti-staph HP MAb</td>
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<table>
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<th>Phase 3</th>
<th>Market</th>
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<tbody>
<tr>
<td>Ethylol®</td>
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<td></td>
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<tr>
<td>HPV cervical cancer vaccine</td>
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<td></td>
<td></td>
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<tr>
<td>Hsp90 inhibitor</td>
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<tr>
<td>Anti-CD19 BiTE® (MT103)</td>
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<tr>
<td>Anti-EphA2 BiTE &amp; conjugate</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hedgehog pathway inhibitor</td>
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<tr>
<td>Listeria-EphA2 vaccine</td>
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<tr>
<td>Anti-EphA4 MAb</td>
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<tr>
<td>Anti-CD19/20/22 MAb</td>
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<tr>
<td>Anti-ALK MAb</td>
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<tr>
<td>Anti-cMet Avimer™</td>
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<tr>
<td>Anti-IL-9 MAb</td>
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</tr>
<tr>
<td>Anti-IFNα MAb</td>
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</tr>
<tr>
<td>Anti-IL-6R MAb</td>
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<tr>
<td>Anti-IFNαR MAb</td>
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<tr>
<td>Anti-HMGB-1 MAb</td>
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<tr>
<td>Anti-ICOS MAb</td>
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<tr>
<td>Anti-CD19, CD20 &amp; CD22 MAb</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Anti-Chitinase MAb</td>
<td>✓</td>
<td></td>
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"J&J believes that it can push sales of Concerta, Ditropan XL and Doxil not merely beyond what Alza could do but what anybody really expects from these drugs. Putting **Concerta** into a WW launch and **Ditropan XL** into J&J's primary care sales force will, they figure, add hundreds of millions of extra growth." (INVIVO, April 2001, Windhover)

"J&J can probably afford to pay more for Alza than other drug companies since it will now no longer have to pay transfer fees and royalties on the Alza-developed fentanyl patch (**Duragesic**) or the Duragesic line-extension Alza is working on...." (INVIVO, April 2001, Windhover)
Products Acquired - What Happened to Them?

<table>
<thead>
<tr>
<th>Pipeline @ Time of Acq</th>
<th>5+ years Later</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionsys</td>
<td>$8M Sales</td>
<td>$430M Sales</td>
</tr>
<tr>
<td>OrthoEva</td>
<td>$450M Sales</td>
<td>0</td>
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<tr>
<td>Duragesic Line Extension</td>
<td>Discontinued</td>
<td>N/A</td>
</tr>
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*: Value of retired royalty paid by J&J to ALZA *. Windhover; Recap; ** Assuming 30% net profit margin and 15% discount rate.
J&J Could Have Maximized the “Upside”

Alza Corp. leaving city after 17 years by Daniel DeBolt
Mountain View Voice Staff

Last October, Mountain View officials and community members gathered in Alza Corporation's lobby to celebrate a groundbreaking partnership with the city. Harnessing methane gas from the landfill under Shoreline Park, Alza planned to generate power for its corporate office, bringing in revenue for the city and helping the environment for years to come.

But no one guessed the longtime local company would be leaving town within a year.

Johnson and Johnson, the company's owner, announced late last month that Alza, one of Mountain View's largest employers and philanthropic donors, will be leaving Mountain View along with sister company Scios, laying off 600 employees in the process.

The company's Science at Shoreline program was of particular interest to Noe. "I'm hopeful that another company will pick that up and keep that going," she said.

Many wonder what will happen to Alza's building at 1900 Charleston Road, and its methane gas generation plant, when the company leaves. The generators were lauded as an environmental "win-win" by taking the landfill's methane gas and turning it into electricity, resulting in a reduction in greenhouse gases equivalent to taking 1,500 cars off the road annually.
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The company’s headquarters next to Google on Charleston Road will be up for sale by the end of the year. "It’s a drag," said city finance director Bob Locke, "they’ve been here a…"

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Centocor/J&J - 1999

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<td>N/A</td>
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DH Valuation $2.7B**

J&J paid: $5.0B

Windhover; Recap; ** Assuming 30% net profit margin and 15% discount rate.
"Scios also brings an advanced research program on kinase inhibitors, which is an exciting new area of research." Christine Poon. (Windhover, Press Release)

"Scios strengthens our growing cardiovascular franchise and broadens our pipeline with several potential new chemical entities, said Christine Poon, WW Chairman, Pharmaceuticals Group, J&J, "NATRECOR® is a truly unique product for a largely underserved and growing market." (Windhover, Press Release)

**Acquired Products- What Happened to Them?**

<table>
<thead>
<tr>
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<th>At Time of Acquisition</th>
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<tr>
<td>Natrecor</td>
<td>190</td>
<td>76</td>
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DH Valuation $240m**

J&J paid: $2.3B

Windhover; Recap; ** Assuming 30% net profit margin and 15% discount rate.
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<th>5+ Years Later</th>
<th>2012</th>
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<tr>
<td>Axitinib (AG-13,736)</td>
<td>Phase III</td>
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<td>$512M Sales</td>
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<tr>
<td>AG3340 (Phase III @ Acq)</td>
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<td>Remune (Phase II/III @ Acq)</td>
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<td>AG2037</td>
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<td>AG-24322</td>
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<td>CMV protease inhibitor</td>
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<td>GnRh antagonist</td>
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<td>Hepatitis C protease inhibitor</td>
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Windhover; Recap; **Assuming 30% net profit margin and 15% discount rate.
AZ/MedImmune: Why Does Everyone Seem to Have Sticker Shock?

• J&J/Alza -- 2001, $10 bln
  – Mature products and mature drug delivery platform
• Schering-Plough/Organon 2007, $14 bln
  – Ph III shots on goal but no sure bets
  – What else to leverage?
• Centocor cost $5 bln in 1999
### By Historical Standards, AZN/MedImmune Was Not That Expensive

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<td>$10,500</td>
<td>$988</td>
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<tr>
<td>1999</td>
<td>J&amp;J</td>
<td>Centocor</td>
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<td>Genentech</td>
<td>$3,684</td>
<td>$1,151</td>
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<td>WL</td>
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<td>$467</td>
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<td>1996</td>
<td>AHP</td>
<td>Genetics Institute</td>
<td>$1,250</td>
<td>$172</td>
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Windhover Information; DH analysis.
AZ/MedImmune: Buying Promise

• Though early, a significant number of pipeline compounds, including several vaccines
• A critical mass in biotech projects
  – Increased total AZ large molecule projects from 7% to 27% of portfolio
• A critical infrastructure in protein therapeutics
  – MedImmune personnel will manage AZ’s aspirations in this area
AZ/MedImmune: Buying Scarcity

Few New Biotechs Reaching Commercial Scale

- Genentech 2000
- Gilead 2003
- MedImmune 2006
- Amgen 1994
- Genzyme 2001
- Biogen Idec 2003
- Celgene 2007
- Actelion 2007
- Vertex 2011

EvaluatePharma.
Biogen Idec Inc. (BIIB) has put itself up for sale, but said little else.

Biogen's market capitalization means any suitor would need to be huge, something the company acknowledges.

It expressed confidence in its strategy and value, but notes that interest from "major pharmaceutical companies" might result in superior value in the current environment.

Biogen says it received expressions of interest in a sale of the company, including one from billionaire investor Carl Icahn, and has hired Goldman Sachs & Co. (GS) and Merrill Lynch & Co. (MER) as financial advisors. Icahn wasn't immediately available to comment on the news.

In late August, Icahn received clearance from the Federal Trade Commission to add to his stake in Biogen Idec. Icahn reported beneficially owning 2.74 million shares of Biogen, a biopharmaceutical company, as of June 30.

Brozak dismissed any notion that Icahn would want to buy the company and noted that Icahn is simply interesting in attaining the best return possible on his investment....
Pharma’s Embrace of Genomics: A Better Answer?
Pharma’s Embrace of Genomics: A Better Answer?

In a December 2001 interview with Technology Review, Levin was candid about his lofty plans for Millennium: "Over the next five to 10 years, our goal is to become a company that's leading the world in personalized medicines, a company that is leading the world in productivity, a company with a value of over $100 billion, a company that has five to 10 products on the market that are making a big difference in people's lives, a company with the strongest pipeline in the entire industry."

No Shortage of Takers

Committed Funding in Deals w/Millennium – 1993 – 2001

- Roche $70 MM +
- Eli Lilly $50 MM + 70 MM
- Astra $60 MM
- Bayer $465 MM
- Bristol-Myers Squibb $32 MM
- Becton, Dickinson $70 MM
- Aventis $450 MM
- Abbott $250 MM
Millennium

- $2 billion in partnership funding since 1994
  - Hundreds of targets delivered to partners
- But just one compound completed phase I
  - Abbott dropped it—eventually dropped whole Millennium alliance
  - No other clinical-stage compound from Millennium discovery around which it can claim either IP rights or pending financial obligation
- Own pipeline acquired and in-licensed
  - Applying discovery mentality & technologies to compounds of others
    - E.g., PARIS database and set of computational pathway analysis tools used in in-licensing/identification of MLN944 from Xenova
- **Velcade**
  - Significant part of Millennium’s valuation depends on this drug…acquired with Leukosite…who acquired it from Proscript when it was PS-341
    - As PS-341, originally an anti-inflammatory

*InVivo, March 2003.*
Only 3 compounds are reportedly in active development (1 in Phase II and 2 in Phase I, at s-a). All others are noted as “Discontinued” (6) or “No development reported” (9) or “Preclinical” (3)
Reducing Headcount: A Better Answer?
Scale is not an asset. In today's environment, extreme scale, scale that companies haven't learned to deal with, is something of a handicap. It's a skill-based industry, and our focus is on trying to develop our skills. Being No. 1 in the industry in size just doesn't really matter.

Robert Essner, CEO of Wyeth, January, 2007

Wyeth's CEO on changing sales tactics, TV ads, finding new drugs and consumer resentment; Monday, January 22, 2007; By Scott Hensley, The Wall Street Journal.
Lots of Pink Slips Handed Out in 2007

LLY 700
ABT 700
SGP 1,100
AMGN 2,400
JNJ 4,800
Bayer 6,100
MRK 7,000
AZN 7,600
PFE 10,000

InVivo, Pharma Layoffs, Sept 2007: Data since Jan 2007. Does not reflect announced but unspecified restructuring at BMS.
Downsizing Might Not Result in Greater Accountability

“The weird thing is we can’t find anyone qualified to replace him.”

What Will Be Different This Time Around?

I’ll be happy to give you innovative thinking. What are the guidelines?

Despite striking advances in the biomedical sciences, the flow of new drugs has slowed to a trickle, impairing therapeutic advances as well as the commercial success of drug companies. Reduced productivity in the drug industry is caused mainly by corporate policies that discourage innovation. This is compounded by various consequences of mega-mergers, the obsession for blockbuster drugs, the shift of control of research from scientists to marketers, the need for fast sales growth, and the discontinuation of development compounds for nontechnical reasons.

Prior to 1980, most drug companies functioned differently. They were smaller than today’s companies, and the nontechnical executives knew and were proud of their scientists and were more likely to allow R&D staff to pursue objectives with little interference. Informal systems dominated behavior. Each company had its unique ways, history, character, and culture.

Most appreciated that their existence and fortunes were based on a combination of need and economic benefit, such that profitability was balanced with public responsibility. …

In the 1970s things began to change. Modern managers entered as chief executive officers (CEOs) and other high-level executives, mostly with little or no technical experience. Many had legal or business school training or came from non-drug industries that functioned with greater organizational discipline. Those promoted internally were often from legal or finance departments, with little or no experience in research, manufacturing, or engineering. Most were unacquainted with research and were uncomfortable with seemingly “unfocused” research organizations that they perceived to operate in a freewheeling, independent style. These executives found comfort in outside management consulting firms that were called upon to suggest structural reshapings and behavioral changes. Corporate management had an instrument by which to introduce order into the research establishments.
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Lessons from the past indicate that these problems can be overcome, and herein, new and improved directions for drug discovery are suggested.

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Drug Discovery in Jeopardy
Pedro Cuatrecasas

Departments of Pharmacology and Medicine, University of California San Diego, San Diego, California, USA.

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Unfortunately, while consulting firms had experience in advising non–technology-based corporations, few were familiar with drug companies or complex professional-based matrix organizations. Their recommendations to change organizational structures, procedures, and even program and project portfolios were patterned after companies with which they were familiar, such as General Electric and other so-called well-managed companies.

Use of these consulting firms became so fashionable that virtually every Pharma underwent similar externally driven reshaping in an effort to manage and control its scientific enterprise. Further, by popularizing “benchmarking,” a process in which companies review their activities against what others are doing, rather than exploiting their own unique skills and experiences, drug companies began to all look alike. Conformism.

With such restructuring, drug companies now felt more confident that they could manage and mandate results with discipline, order, formality, and efficiency. Unfortunately, many of these qualities are ones that suffocate creativity and innovation. Freedom, spontaneity, flexibility, nimbleness, tolerance, compassion, humor, and diversity were replaced by bulky and inflexible organizational structures characterized by regimentation, control,… and there was no evidence of improved long-term profitability. Ironically, great-sounding slogans were used to achieve conformity while proclaiming the importance of innovation, empowerment, diversity, and compassion.
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Why Pharma Must Go Hollywood

An even more stifling trend has been the recent importation of the "six sigma" business improvement methodology into aspects of pharma R&D. Six sigma was designed to improve manufacturing processes, but has been well documented to quench innovation. The intellectual bankruptcy typical of many current pharma leaders is well illustrated by the typical pharma response to faltering productivity and the resultant fall in earnings. Take, for example, Pfizer's acquisitions since 2000 of Warner-Lambert and Pharmacia. Rather than investigating and addressing the fundamental etiologies of the problem and contrary to the readily available data in the business literature, the leadership plunges into the short-term fix and ego-satisfying drama of a merger, which is almost guaranteed to stifle innovation even further.

LOOKING TO HOLLYWOOD

To address mismanagement in pharma, what might be learned from the lessons of other industries? Hollywood is dependent on creativity and innovation, so its evolving business model can provide useful insights.

The Hollywood business model is more evolved than the model currently followed across pharma. Until the 1950s Hollywood studios employed everyone, from actors, writers, and directors to producers and marketers. Then the "talent" — actors, writers, and directors — realized that their expertise was undervalued, and their personal interests were much better served if they functioned autonomously. Hollywood studios are now mainly responsible only for financing and marketing movies. The creativity resides outside the studios, with independent producers, such as the Weinstein brothers at Miramax. They have created and followed a simple formula that has led …

But Big Pharma continues to follow the old studio model, though there are signs that this may be changing. A similar and necessary evolution to what Hollywood underwent in the 1950s may be beginning, with increasingly more drugs being discovered outside Big Pharma, presumably because the R&D process elsewhere is more conducive to creativity. Biotechs or small pharma settings tend …

There is a precedent for pharma emulating Hollywood: Pharma's main preoccupation, the creation of blockbusters, was directly copied from Hollywood. The blockbuster model is really defined by broad and aggressive marketing, though the term is less accurately, if more commonly, …. 
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## Top 30 Companies

<table>
<thead>
<tr>
<th>Rank</th>
<th>Company Name and Global HQ</th>
<th>Type</th>
<th>Total No. of Employees Worldwide</th>
<th>Most Highly Ranked Factors</th>
<th>Least Highly Ranked Factors</th>
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<tbody>
<tr>
<td>1.</td>
<td>Tocris Laboratories and BioTechnology</td>
<td>Pharmaceutical</td>
<td>100 or less</td>
<td>Management</td>
<td>Research Environment</td>
</tr>
<tr>
<td>2</td>
<td>Novartis Cambridge, MA</td>
<td>Pharmaceutical</td>
<td>20,000+</td>
<td>Policies and Practices</td>
<td>Remuneration and Benefits</td>
</tr>
<tr>
<td>3.</td>
<td>Transform Pharmaceuticals Cambridge, MA</td>
<td>Pharmaceutical</td>
<td>150-500</td>
<td>Remuneration and Benefits</td>
<td>Training and Development</td>
</tr>
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<td>4.</td>
<td>Tocris Pharmaceuticals Chester, MA</td>
<td>Pharmaceutical</td>
<td>100 or less</td>
<td>Policies and Practices</td>
<td>Management</td>
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<tr>
<td>5.</td>
<td>Biogen Idec Cambridge, MA</td>
<td>Pharmaceutical</td>
<td>5,000-10,000</td>
<td>Training and Development</td>
<td>Job Satisfaction</td>
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<tr>
<td>6.</td>
<td>Thermo Fisher, Inc.</td>
<td>Biotechnology</td>
<td>50,000+</td>
<td>Research Environment</td>
<td>Remuneration and Benefits</td>
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<td>7.</td>
<td>Infinity Pharmaceuticals Cambridge, MA</td>
<td>Pharmaceutical</td>
<td>200 or less</td>
<td>Management</td>
<td>Research Environment</td>
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<td>8.</td>
<td>Cookson Biosciences Rockland, PA</td>
<td>Biotechnology</td>
<td>20,000+</td>
<td>Research Environment</td>
<td>Remuneration and Benefits</td>
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<tr>
<td>9.</td>
<td>Amgen Pharmaceuticals San Francisco, CA</td>
<td>Pharmaceutical</td>
<td>1,000-2,000</td>
<td>Policies and Practices</td>
<td>Research Environment</td>
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<td>10.</td>
<td>Takeda Pharmaceuticals RTP, NC</td>
<td>Pharmaceutical</td>
<td>1,000-2,000</td>
<td>Research Environment</td>
<td>Remuneration and Benefits</td>
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<td>11.</td>
<td>Lundbeck Research USA Plainsboro, NJ</td>
<td>Pharmaceutical</td>
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<td>Policies and Practices</td>
<td>Research Environment</td>
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<td>12.</td>
<td>QIAGEN Venlo, The Netherlands</td>
<td>Biotechnology</td>
<td>1,000-2,000</td>
<td>Research Environment</td>
<td>Remuneration and Benefits</td>
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<td>13.</td>
<td>H. Lundbeck Corporation, New York, NY</td>
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<td>Policies and Practices</td>
<td>Research Environment</td>
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<td>14.</td>
<td>Merck &amp; Co Whitehouse Station, NJ</td>
<td>Pharmaceutical</td>
<td>1,000-2,000</td>
<td>Research Environment</td>
<td>Remuneration and Benefits</td>
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<td>Schering-Plough, Kenilworth, NJ</td>
<td>Pharmaceutical</td>
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<td>Policies and Practices</td>
<td>Research Environment</td>
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<td>Boehringer Ingelheim Pharmaceuticals, Inc.</td>
<td>Pharmaceutical</td>
<td>1,000-2,000</td>
<td>Research Environment</td>
<td>Remuneration and Benefits</td>
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<td>17.</td>
<td>Wyeth Pharmaceuticals, Philadelphia, PA</td>
<td>Pharmaceutical</td>
<td>1,000-2,000</td>
<td>Policies and Practices</td>
<td>Research Environment</td>
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<tr>
<td>18.</td>
<td>Alexion Pharmaceuticals, Cheshire, CT</td>
<td>Pharmaceutical</td>
<td>1,000-2,000</td>
<td>Policies and Practices</td>
<td>Research Environment</td>
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<td>19.</td>
<td>AstraZeneca London, UK</td>
<td>Pharmaceutical</td>
<td>1,000-2,000</td>
<td>Policies and Practices</td>
<td>Research Environment</td>
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<tr>
<td>20.</td>
<td>GlaxoSmithKline, Research Triangle Park, NC</td>
<td>Pharmaceutical</td>
<td>1,000-2,000</td>
<td>Policies and Practices</td>
<td>Research Environment</td>
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<td>22.</td>
<td>Biogen-Idec, Cambridge, MA</td>
<td>Pharmaceutical</td>
<td>1,000-2,000</td>
<td>Policies and Practices</td>
<td>Research Environment</td>
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<tr>
<td>23.</td>
<td>Merck Research Laboratories, Kenilworth, NJ</td>
<td>Pharmaceutical</td>
<td>1,000-2,000</td>
<td>Policies and Practices</td>
<td>Research Environment</td>
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<tr>
<td>24.</td>
<td>Abbott Laboratories Abbott Park, IL</td>
<td>Pharmaceutical</td>
<td>1,000-2,000</td>
<td>Policies and Practices</td>
<td>Research Environment</td>
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<tr>
<td>25.</td>
<td>EndoPharma, Inc., New York, NY</td>
<td>Pharmaceutical</td>
<td>1,000-2,000</td>
<td>Policies and Practices</td>
<td>Research Environment</td>
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<tr>
<td>26.</td>
<td>ImClone Systems, New York, NY</td>
<td>Pharmaceutical</td>
<td>1,000-2,000</td>
<td>Policies and Practices</td>
<td>Research Environment</td>
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<td>27.</td>
<td>Protein Design Labs, Cambridge, MA</td>
<td>Pharmaceutical</td>
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<td>Policies and Practices</td>
<td>Research Environment</td>
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<td>29.</td>
<td>Merck-Serono, Inc., Kenilworth, NJ</td>
<td>Pharmaceutical</td>
<td>1,000-2,000</td>
<td>Policies and Practices</td>
<td>Research Environment</td>
</tr>
</tbody>
</table>
Why Are These Companies the Best?

- Novartis
- Amgen
- Merck
- AstraZeneca
- Pfizer
- sanofi-aventis
- J&J
- Abbott
- Eli Lilly
Remuneration & Benefits
Why Are These Companies the Best?

Infinity Pharmaceuticals
Targacept
Exelixis
Lexicon Genetics
BMS
Embracing Large Molecules: A Better Answer?
Getting Larger - Moleculary Speaking

• All Big Pharmacos are enthusiastic about this, but evidence that Big Pharma can innovate in large molecules is lacking.

• Cynical observation, but embrace of large molecules is driven by perceived lack of generic exposure, (as opposed to science) which may be another short-sighted move.
Pfizer will aggressively advance the 25 pre-clinical and clinical programs already in its development pipeline, as well as a range of external opportunities, including those developed by the new biotherapeutics and bioinnovation center. Within PGRD, as well as in the new independent center, Pfizer will continue to make investments to substantially expand biotherapeutics capabilities.

Pfizer press release 4 Oct. 2007
Big Pharma blurring the lines with Big Biotech

**Biotech drugs**, which are made out of living cell cultures, instead of the simple molecules used to create traditional pharmaceuticals, are an attractive investment for Big Pharma for two reasons: the industry is fast-growing, and generic competitors can't touch it.

Biotech drugs are also appealing because they're not vulnerable to patent expirations and generic competition, which are the chief concerns of the pharma industry.
<table>
<thead>
<tr>
<th>BRAND</th>
<th>ACTIVE SUBSTANCES</th>
<th>MARKETER</th>
<th>YEAR OF APPROVAL</th>
<th>2005 SALES ($M)</th>
<th>GENERICS UNDER DEVELOPMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neupogen</td>
<td>Filgrastim</td>
<td>Amgen</td>
<td>1991</td>
<td>$3,500</td>
<td>Yes</td>
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<tr>
<td>Procrit</td>
<td>Epoetin alpha</td>
<td>Ortho Biotech</td>
<td>1990</td>
<td>$3,000</td>
<td>Yes</td>
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<tr>
<td>Epogen</td>
<td>Epoetin alpha</td>
<td>Amgen</td>
<td>1989</td>
<td>$3,000</td>
<td>Yes</td>
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<tr>
<td>Enbrel</td>
<td>Etanercept</td>
<td>Immunex</td>
<td>1998</td>
<td>$2,700</td>
<td>No</td>
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<tr>
<td>Remicade</td>
<td>TNF alpha</td>
<td>JNJ (Centocor)</td>
<td>1998</td>
<td>$2,200</td>
<td>Yes</td>
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<tr>
<td>Rituxan</td>
<td>Anti-CD20 Mab</td>
<td>Genentech</td>
<td>1997</td>
<td>$1,500</td>
<td>No</td>
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<tr>
<td>Avonex</td>
<td>Interferon beta-1a</td>
<td>Biogen</td>
<td>1996</td>
<td>$1,500</td>
<td>Yes</td>
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<tr>
<td>Intron A</td>
<td>Interferon alpha-2b</td>
<td>Schering Plough</td>
<td>1995</td>
<td>$900</td>
<td>Yes</td>
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<tr>
<td>Betaferon</td>
<td>Interferon beta-1a</td>
<td>Schering AG</td>
<td>1995</td>
<td>$682</td>
<td>Yes</td>
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<tr>
<td>Humulin</td>
<td>75% human insulin isophane suspension, 25% human rec. insulin</td>
<td>Eli Lilly</td>
<td>1992</td>
<td>$630</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Source: IMS Healthcare, Burrill & Company
Increasing Disease Area Focus: A Better Answer?
Increasing Disease Area Focus: A Better Answer?

- Disease Area Rationalization for all Big Pharmas predicted at Defined Health’s Therapeutic Insight Conference in 2001

Save the Date!
Therapeutic Insight 2008
April 28-30
The Westin New York at Times Square
Increasing Disease Area Focus: A Better Answer?

*Industrialization of drug discovery will reduce the role of serendipity at the same time that company scientists must deal with an increasingly unwieldy glut of information.*

*As a result, executives will be forced to make binding decisions as to which therapeutic franchises their companies should exit, enter or expand within.*

Ed Saltzman, 2001
Increasing Disease Area Focus: A Better Answer?

The serendipitous nature of drug discovery and comparatively low barriers to entry in many therapeutic classes have allowed companies to seesaw in and out of different therapeutic areas. This will not be the case in the future.

ibid
Evolution of the Pharma Business Model & Therapeutic Franchise Strategy

Therapeutic Franchise Strategy

1970’s

None

1980’s

Healthcare Business

1990’s

Evolving Therapeutic Focus

00’s
New pharma model: Disease Biology Areas (DBAs)

Alignment and focus

Disease Biology Areas (DBAs)

- Initial focus on five DBAs
- Decisions made by Disease Biology Leadership Teams (DBLTs) against measurable metrics
- **Up to Proof of Concept:** DBLTs manage compound progression within respective DBA
- **After Proof of Concept:** DBLTs responsible for conducting scientific/medical reviews and providing options to Pharma Leadership Team

- **Clear focus**
- **More independent and flexible disease areas**
- **Faster and simpler decision processes**
GSK CEDD Set-up in 2000; CEEDD added later
Disease area strategy

**Build**
- Diabetes/Obesity
- Analgesia
- Infection
- Inhalation
- Translational Science Oncology

**Maintain**
- Alzheimer's
- Arrhythmias
- Asthma
- Atherosclerosis
- Bipolar Disorder
- Chronic Obstructive Pulmonary Disease
- Depression/Anxiety
- Oncology
- Osteoarthritis
- Schizophrenia
- Thrombosis
- GERD
- Rheumatoid Arthritis

**Exit**
- Hypertension
- Inflammatory Bowel Diseases
- Functional GI Disorders
- Parkinson's
- Multiple Sclerosis
- Addiction
- Insomnia
- Neuroprotection in Stroke
Early Stage Dealmaking: A Better Answer?
Early Stage Dealmaking: A Better Answer?

• Pharma’s Historic Aversion to Early Stage Deals is Now a Love Fest

• Dreaming of a “Shots on Goal” Solution to the Innovation Famine?
Buying Shots on Goal: Pharma’s New “Early Bird” Strategy

Number of Preclinical/Phase I Deals with Upfront Payments Greater than $20 M

Windhover’s Strategic Transactions Database.
But Pharma is Now Buying Early-Stage Programs at Yesterday’s Late-Stage Prices

2001-2007 Biotech & Pharma
Early Stage Deals…
Upfront Payments

...Milestones

...Total Deal Value

MedTRACK; Defined Health analysis.
### Pharma/Biotech M&A: More “Shots per Deal”

#### Selected Pharma/Biotech M&A – Early-Stage Pipelines (2006-Sept 2007)

<table>
<thead>
<tr>
<th>Company Acquired</th>
<th>Founded</th>
<th>Acquirer</th>
<th>Value</th>
<th>Date Signed</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambridge Antibody</td>
<td>1990</td>
<td>AstraZeneca</td>
<td>$1,100 M</td>
<td>08/06</td>
<td>Cash</td>
</tr>
<tr>
<td>Sirna</td>
<td>1993</td>
<td>Merck</td>
<td>$1,100 M</td>
<td>12/06</td>
<td>Cash</td>
</tr>
<tr>
<td>AnorMED</td>
<td>1996</td>
<td>Genzyme</td>
<td>$580 M</td>
<td>11/06</td>
<td>Cash</td>
</tr>
<tr>
<td>Domantis</td>
<td>2000</td>
<td>GSK</td>
<td>$450 M</td>
<td>01/07E</td>
<td>Cash</td>
</tr>
<tr>
<td>GlycoFi</td>
<td>2000</td>
<td>Merck</td>
<td>$400 M</td>
<td>06/06</td>
<td>Cash</td>
</tr>
<tr>
<td>Avidia</td>
<td>2003</td>
<td>Amgen</td>
<td>$380 M</td>
<td>10/06</td>
<td>$290+ $90*</td>
</tr>
<tr>
<td>KuDOS</td>
<td>1997</td>
<td>AstraZeneca</td>
<td>$210 M</td>
<td>1Q06</td>
<td>Cash</td>
</tr>
<tr>
<td>Praecis</td>
<td>1993</td>
<td>GSK</td>
<td>$55 M</td>
<td>1Q07E</td>
<td>Cash</td>
</tr>
<tr>
<td>Arrow Therapeutics</td>
<td>1998</td>
<td>AstraZeneca</td>
<td>$150 M</td>
<td>02/07</td>
<td>Cash</td>
</tr>
<tr>
<td>Hypnion</td>
<td>2000</td>
<td>Lilly</td>
<td>$315 M</td>
<td>03/07</td>
<td>Cash</td>
</tr>
<tr>
<td>Morphotek</td>
<td>2000</td>
<td>Eisai</td>
<td>$325 M</td>
<td>03/07</td>
<td>Cash</td>
</tr>
<tr>
<td>THP</td>
<td>2002</td>
<td>Roche</td>
<td>$54 M</td>
<td>04/07</td>
<td>Cash</td>
</tr>
<tr>
<td>Adnexus</td>
<td>2002</td>
<td>BMS</td>
<td>$490 M</td>
<td>09/07</td>
<td>Cash</td>
</tr>
</tbody>
</table>

*Note: Values and terms are approximate and subject to change.*

Cowen & Company, MedTRACK, Recombinant Capital, Signals Magazine; Defined Health analysis.
Can A Small Number of “Goals” Close the Gap?

But Early Stage Licensing and M&A Still Lacks “Proof of Concept”

- Few drugs licensed or acquired pre-Ph II have yet made it to market.
- Ph II attrition rate now 80%! (though contribution from internal vs. externally sourced compounds remains unknown).
- Prices rising as fast as attrition.
Phase II Deal Prices Are Rising Faster Than Phase III Deal Prices

Average Upfront Payments From Major Pharmaceutical Companies

- **Phase II Deals**
- **Phase III Deals**

InVivo.
Scary Increase in Ph II Attrition

Parexel (Industry estimates) in 1991 - 2000
Robert Ruffolo (Wyeth) in 2005
Steve Paul, (Lilly) in 2006

Back to the Future: A Renewed Urge to Merge?

"STOCKS REMAINED STEADY, DUE TO WEAK PRODUCTION IN THE RUMOR MILLS TODAY..."
Rumours of Pfizer, Sanofi mega-merger emerge

Bayer stock jumps on Novartis buyout speculation

Report of possible merger lifts Bristol-Myers
Why not Buy More Shots on Goal from Other Pharmas?

- Past generations of Pharma mergers driven by hopes of maintaining EPS growth via “synergies.” Pipelines considered but mostly as “upside.”
- Pharma is now the Emperor wearing no clothes, so the next round of mergers could be driven through coveting other companies’ pipelines, especially in the “shots on goal” era.
- A back of envelope analysis suggests it may be cheaper to buy shots on goal from Pharma/Pharma M&A than Pharma/Biotech M&A.
- Eager bankers will need address emerging “Dangerfieldization” problem before this will happen.
What Would it Cost to Buy BMS’s Pipeline?

BMS’s clinical pipeline is comprised of 13 late preclinical or early clinical projects, and 4 unpartnered projects in late clinical development.

Source: company website; DH analysis

<table>
<thead>
<tr>
<th>Exploratory Development</th>
<th>Full Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Oral Taxane</td>
<td>• Ixabepilone</td>
</tr>
<tr>
<td>• VEGFR/FGFR Kinase Inhibitor</td>
<td>• Vinflunine</td>
</tr>
<tr>
<td>• Pan Her/VEGFR2 Inhibitor</td>
<td>• Ipilimumab</td>
</tr>
<tr>
<td>• Anti CD137</td>
<td>• Belatacept</td>
</tr>
<tr>
<td>• AR Antagonist</td>
<td>• Saxagliptin</td>
</tr>
<tr>
<td>• p38 Kinase Inhibitor</td>
<td>• Apixaban</td>
</tr>
<tr>
<td>• p38 Kinase Inhibitor Follow On</td>
<td></td>
</tr>
<tr>
<td>• HIV Attachment Inhibitor</td>
<td></td>
</tr>
<tr>
<td>• HIV Integrase Inhibitor</td>
<td></td>
</tr>
<tr>
<td>• CRF Antagonist</td>
<td></td>
</tr>
<tr>
<td>• CB1 Antagonist</td>
<td></td>
</tr>
<tr>
<td>• Dapagliflozin</td>
<td></td>
</tr>
<tr>
<td>• GLP-1 Receptor Agonist</td>
<td></td>
</tr>
</tbody>
</table>

Yahoo!finance (Enterprise Value), Lehman Brothers (% of value derived from pipeline), Company website; DH analysis (pipeline analysis).
According to a Lehman Brothers’ analysis, 14% ($9B) of BMS enterprise value is derived from its 17-program pipeline.

The average per project value of the pipeline would be $530M.
What Would it Cost to Buy SNY’s Pipeline?

<table>
<thead>
<tr>
<th>Category</th>
<th>Phase I</th>
<th>Phase IIa</th>
<th>Phase IIb</th>
<th>Phase III</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic Disorders</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>5</td>
<td></td>
<td>4</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>2</td>
<td></td>
<td>3</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>CNS</td>
<td>8</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Oncology</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Vaccines</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>32</strong></td>
<td><strong>12</strong></td>
<td><strong>20</strong></td>
<td><strong>28</strong></td>
<td><strong>92</strong></td>
</tr>
</tbody>
</table>

Of 92 clinical development programs, SNY pipeline consists of about 74 unique non marketed molecules.

Yahoo!finance (Enterprise Value), Lehman Brothers (% of value derived from pipeline), DH analysis (pipeline analysis).
What Would it Cost to Buy SNY’s Pipeline?

According to a Lehman Brothers’ Analysis, 13% ($17B) of SNY enterprise value is derived from its 74-program pipeline*. The average per project value of the pipeline would be: $221M.

SNY Enterprise Value

Yahoo!Finance, Lehman Brothers, DH analysis. (*): excluding follow-on programs.
How Does That Compare With Recent Acquisitions?

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Cost</th>
<th>Cost per Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idun (Immunology: Apoptosis Platform)</td>
<td>One Phase II product</td>
<td>$298M</td>
<td>$298M</td>
</tr>
<tr>
<td>AnorMED</td>
<td>One Phase III product</td>
<td>$580M</td>
<td>$589M</td>
</tr>
<tr>
<td>Hypnion</td>
<td>One Phase II product</td>
<td>$315M</td>
<td>$315M</td>
</tr>
</tbody>
</table>
The Dangerfieldization of Pharma’s Innovation Quality

• Is our competitor’s pipeline really better than ours?

• Biotech pipelines may be better, and at least for now, are cheaper!
Sellers of “Innovation” to Pharma, Beware

Pharma is the second largest and most consistent “buyer” of innovation
Pre-Exit: Pharma “Buys” Nearly Half of all Innovation via Partnering Deals

US Biotech Industry Fundraising ($ in Millions)

<table>
<thead>
<tr>
<th>Year</th>
<th>Public</th>
<th>Private</th>
<th>Other</th>
<th>Total Financing</th>
<th>Partnering</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>$670</td>
<td>$1,084</td>
<td>$237</td>
<td>$10,749</td>
<td>$5,844</td>
<td>$16,593</td>
</tr>
<tr>
<td>2000</td>
<td>$6,490</td>
<td>$2,872</td>
<td>$203</td>
<td>$32,005</td>
<td>$5,805</td>
<td>$38,906</td>
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<tr>
<td>2001</td>
<td>$440</td>
<td>$2,397</td>
<td>$9</td>
<td>$11,976</td>
<td>$1,433</td>
<td>$19,462</td>
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<tr>
<td>2002</td>
<td>$445</td>
<td>$2,688</td>
<td>$178</td>
<td>$10,548</td>
<td>$1,741</td>
<td>$18,044</td>
</tr>
<tr>
<td>2003</td>
<td>$456</td>
<td>$2,841</td>
<td>$178</td>
<td>$16,348</td>
<td>$2,051</td>
<td>$25,281</td>
</tr>
<tr>
<td>2004</td>
<td>$1,701</td>
<td>$3,733</td>
<td>$294</td>
<td>$19,927</td>
<td>$2,417</td>
<td>$30,860</td>
</tr>
<tr>
<td>2005</td>
<td>$819</td>
<td>$3,518</td>
<td>$269</td>
<td>$17,586</td>
<td>$2,376</td>
<td>$34,854</td>
</tr>
<tr>
<td>2006</td>
<td>$920</td>
<td>$4,236</td>
<td>$1,114</td>
<td>$27,352</td>
<td>$20,000</td>
<td>$47,352</td>
</tr>
</tbody>
</table>

Source: Burrill & Company
And Pharma Still Buys When the Public Gets Fickle

US Biotech Industry Fundraising
($ in Millions)

<table>
<thead>
<tr>
<th>Year</th>
<th>Public</th>
<th>Private</th>
<th>Partnering</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2000</td>
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</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Public Financing Windows

Burrill & Company.
Pharma is the Most Consistent Buyer

- Percent Investment through partnering has been at a steady 35 -36% for the past several years (2001-2004); jumped to 50% in 2005.

![Biotech Capital Raised 1980-2005](chart)

Burrill & Company.
Many of Pharma’s Purchases Have Not Yet Provided a Better Answer (And in Some Cases, A Worse One!)

• Mega mergers failed for many reasons but mostly due to no payoff from pipeline.
  • Pfizer/Pharmacia
• Buying >$ bln biotechs was not a success the first time around and the scarcity of opportunities now and for foreseeable future will accelerate sticker shock and decrease the likelihood of an accretive “win” for Pharma buyers.
• Genomics deals look embarrassing 7 years later.
Elephant in the Backseat: No Better Answer So Far…

• Will Pharma Continue to “Buy” Early?
• Early stage licensing should have its own “proof of concept” moment within 2-3 years. Advance indicators suggest attrition from products in-licensed early is greater than for those discovered internally. Staggering increase in the cost of early-stage deals thus increases overall risk.

• For now, Pharma’s fascination with early-stage pipelines is driven more by a “grass is greener” view of biotech innovation vs. its homegrown kind than by actual data.

• Lilly’s Chorus experiment, if widely adopted by other cos could result in profound change in the way Pharma deals with internal discovery and may reduce interest in buying “shots on goal” externally.
For Now: Pharma and VCs are Tight

• Increasing competition for late-stage clinical assets is forcing the pharmaceutical industry to reach out to the venture capital community as a source of deals, sending a clear message that the market is open for earlier-stage technology and compounds.

• Earlier this month, Astra-Zeneca plc and Pfizer Inc. were the latest pharma giants to try to establish more open communication with VCs by hosting orientation days in London. Each company invited about 60 leading European life science venture and private equity groups to join senior executives in exploring how they might be able to interact symbiotically.

Is Pharma Buying the Same Level of Innovation Today?

Robert Swanson and Herbert Boyer: Giving Birth To Biotech

A venture capitalist and a scientist changed how drugs are made

In 1976, Robert Swanson and Herbert Boyer created the biotechnology industry over a couple of beers at a San Francisco bar called Churchill's. Swanson, at just 29, was an ambitious venture capitalist who wanted to commercialize a new way of engineering drugs based on splicing DNA from one organism into the genome of another. Boyer, a 40-year-old biochemistry and biophysics professor at the University of California at San Francisco, had co-developed an ingenious technique for doing exactly that. So Swanson cold-called Boyer, stopped by his lab, and the two retreated to the bar to sketch out a business plan. They were about to change the drug industry forever.

Pharma May Need More Boyers and Swansons

• In 1990, Herbert Boyer and his wife gave the single largest donation bestowed on the Yale School of Medicine by an individual. The Boyer Center for Molecular Medicine was named after the Boyer family in 1991.

• Robert Swanson is regarded as an instrumental figure in launching the biotechnology revolution. On 6 December, 1999, Robert Swanson succumbed to brain cancer, at the age of 52.

Wikipedia.com.
Once Upon a Time, All Biotech VC was Early-Stage, but Percent has Steadily Withered

Percentage of $$ Raised by Round

2000’s Partnering Wasteland Has Become 2007’s Hottest Space!!

“Promised Land”

Pre-Clinical  Phase I  Phase II  Phase III  NDA

Security

Valley of Death

Security

© Defined Health 2007
Today’s VCs are Not Your Father’s VCs!

Novartis opts in

Novartis has launched a new venture fund, the $200 million Novartis Option Fund, which will give the pharmaceutical company a first option to license a very early stage program at portfolio companies.

"As I started doing collaborations, I noticed that there had been a sea change in the way that venture investors were willing to participate in risk," Jeremy Levin, global head of strategic alliances for the Novartis Institutes for BioMedical Research, told Ebb & Flow. "An increasing number of VCs were focused on late-stage compounds or late-stage assets because the public markets were valuing them far more. New novel compounds were not being discovered."

Even among venture firms associated with pharmaceutical companies, "very few of them start up companies," noted Levin. With the options fund, he's hoping new companies and novel compounds will result.

"An increasing number of VCs were focused on late-stage compounds or late-stage assets because the public markets were valuing them far more. New novel compounds were not being discovered."

Potential portfolio companies must have "three or four programs simultaneously - that's a really important consideration for us. We don't want to limit the company in its upside potential - if we license one program, all the others need to be free for development," he said. Ambros expects some initial investments will be as little as $100,000 and range up to $3-$6 million. He anticipates that companies will move from the seed to the lead optimization stage within 18 months to two years and hit the clinic after four years. During that time, Novartis (NVS; SWX:NOVN) will have three chances to option a single program from any given portfolio company: at lead optimization, pre-IND, and when a compound first goes into humans. The company must then honor pre-negotiated terms to exercise the option associated with that point in development. NVS will pay an additional fee, beyond its investment, to exercise the option.

Whether or not the option is exercised, the Novartis Option Fund will continue to be invested in the company as long as it is "operationally sound," said Ambros.

"The option fund is more strategic than the current fund," noted Ambros, who also oversees the Novartis Venture Fund, a $300 million evergreen fund that invests in early stage companies.

"Many times a pharmaceutical company only works on validated targets, I want to discover new targets," he said. "We will have a much bigger reach and impact."

Selling “De-Risked” Ph II Programs to Pharma is Today’s Flavour du Jour

• 71% of the venture capitalists surveyed believe the purchase of portfolio companies by private equity firms will become a more attractive option in 2007.

• Private equity players once believed to shun biotech due to risk and timelines are now excited about much shorter term and less risky “bioarbitrage” opportunities.

• But does Pharma really want to buy de-risked opportunities from risk-adverse PE firms?

• Even if they do, will they ever be able to sell them?

Elephant in the Backseat: What Happens if Pharma Stops Buying?

Venture Exits – IPOs to M&As

With regard to the public markets as a viable exit strategy, VCs are sharply divided with 47 percent of respondents predicting that the US IPO market will remain sluggish and 50 percent expecting to see signs of recovery in 2007. Only 3 percent expect a strong IPO recovery next year. Mergers and acquisitions are predicted to deliver returns in 2007 with more than three-quarters of respondents (78 percent) saying M&A deals will be the exit of choice and only 22 percent forecasting a decrease from 2006 levels.


But what happens if what they bought does not provide an answer to their innovation dilemma?
Corporate venture capitalists invested $1.3 billion into 390 deals in the first half of 2007, representing the highest percentage of corporate venture deals and dollars since 2001 according to the MoneyTree Report by PriceWaterHouse Coopers and the National Venture Capital Association (NVCA) based on Thomson Financial data.

In the first half of 2007, investment was heaviest in the Software, Biotechnology and Medical Devices and Equipment sectors.

• Biotechnology and Medical Devices and Equipment account for 19% and 15%, respectively.

“Despite uncertainty in the US economy, those corporations engaging in venture capital activity are stepping up to the highest levels post-bubble,” said Mark Heesen, president of the NVCA. “In doing so, they are supporting some of the most exciting start-ups in their respective industries while providing themselves access to cutting edge innovations. If corporate venture investment continues at this pace, we could see all-time record levels in the near future.”
What Happens if Pharma Starts Doing More Funding Than “Buying?”

“We are also today launching a new biotherapeutics and bioinnovation center with a unique structure to discover, license and acquire more new product candidates that we can put into development,” said Mr. Kindler. “With this strategy, we are leveraging Pfizer’s excellence in drug discovery and development by complementing it with a distinct, California-based enterprise led by world-class scientists charged with discovering and bringing in new compounds,” he added.

Pfizer press release 4 Oct. 2007