The Cost of Innovation in the Pharmaceutical Industry – A Review

Prof. Dr. Alexander Schuhmacher, Reutlingen University, March 2014

Conflict of interest: nothing to disclose
Executive Summary

• Despite scientific, technical and process-related advances in the past years and an escalating demand for medicine and a growing global healthcare market, the pharmaceutical industry is still facing huge challenges.

• These are related to the nature of the pharmaceutical industry as its main driver of growth is innovation.

• In the past years, the R&D costs per new drug increased and the R&D efficiency of pharmaceutical companies reduced.

• Today, discovering and developing a new drug costs more than 1.8 billion USD.

Key Facts on Pharmaceutical R&D

A detailed analysis of the situation
**FDA approved 1,346 NMEs since 1950**

![Chart showing new drugs approved from 1993 to 2013 with peak years in 2001 and 2002 with 53 and 39 new drugs respectively. There is a trend of decreasing new drugs approved each year with 25-30 new drugs approved per annum.](chart)


**Only some pharmacos have been successful over a longer period of time**

Approx. 4,300 pharmaceutical companies

Since 1950, 261 pharmacos have registered at least 1 NME

593 NMEs from 137 pharmacos that disappeared by M&A

21 companies have produced 50% of all NMEs since 1950

360 NMEs by 9 big pharmacos that exist since 1950

Most productive pharmacos since 1950: Merck & Co. (56), Eli Lilly (51), Roche (51)

76% of pharmacos with active R&D come from Europe and US and top pharmacos invest more than USD 5 billion p.a. in R&D

<table>
<thead>
<tr>
<th>Pharmaco</th>
<th>AstraZeneca</th>
<th>Eli Lilly</th>
<th>GSK</th>
<th>Merck &amp;Co.</th>
<th>Novartis</th>
<th>Pfizer</th>
<th>Roche</th>
<th>Sanofi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of total employees:</td>
<td>57.200</td>
<td>38.080</td>
<td>97.389</td>
<td>86.000</td>
<td>123.686</td>
<td>103.700</td>
<td>80.129</td>
<td>113.719</td>
</tr>
<tr>
<td>R&amp;D rate (%):</td>
<td>16.4</td>
<td>20.7</td>
<td>14.2</td>
<td>16.1</td>
<td>20.8</td>
<td>15.8</td>
<td>19.0</td>
<td>20.1</td>
</tr>
<tr>
<td>Number of R&amp;D employees:</td>
<td>11.300</td>
<td>7.400</td>
<td>12.687</td>
<td>11.000</td>
<td>23.000</td>
<td>14.000</td>
<td>18.000</td>
<td>18.000</td>
</tr>
<tr>
<td>Number of main R&amp;D sites:</td>
<td>14</td>
<td>9</td>
<td>14</td>
<td>n.a.</td>
<td>11</td>
<td>10</td>
<td>18</td>
<td>25</td>
</tr>
</tbody>
</table>

Source: Evaluate Pharma®, Annual Company Reports 2011 and 2012

Pharmacos are among the top investors in R&D WW

1. Toyota Motors
2. Roche
3. Microsoft
4. Volkswagen
5. Pfizer
6. Novartis
7. Nokia
8. Johnson & Johnson
9. Sanofi Aventis
10. Samsung

The Pharma Innovation Process and the R&D Value Levers

From Cost to Efficiency

The pharmaceutical R&D process is highly regulated, lengthy, and risky

- **Drug Discovery**: 5,000-10,000 compounds, 3-6 years
- **Preclinical**: 250
- **Clinical Development**:
  - Phase I: 5-10
  - Phase II: 6-8 years
  - Phase III: 6-8 years
- **FDA Review**: 6-8 years
- **Launch**: 0.5-2 years
- **Number of volunteers**:
  - Phase I: 20-100
  - Phase II: 100-500
  - Phase III: 1,000-5,000

IND (Investigational New Drug), NDA (New Drug Application), FDA (Food and Drug Administration)

Figure adapted from PhRMA (2011) Pharmaceutical Industry 2011 Profile
Pharmaceutical R&D has a low probability of success

- Cumulated phase transition rate from Phase I to submission\(^1\): 16%
- Only 8% of drug candidates successfully make it to the market\(^2\)
  - Probability of success (PoS) for SMOLs: 7%
  - PoS biologics: 11%
- Most failures in Phase II and III resulted from lack of efficacy\(^3,4\)
- PoS that a company is generating 2 or 3 NMEs p.a. is 0.06% and 0.003%, respectively\(^5\)


Possible reasons for high attrition rates in R&D despite scientific and technical advances in the last years

- Shift towards developing drugs for chronic diseases correlate with reduced PoS\(^1\)
  - Average PoS for chronic diseases: 6.88%
  - Average PoS for acute diseases 8.77%
- Target-based drug discovery contributes to the high attrition rates in pharmaceutical R&D\(^2\)

Drug R&D last for decades

- Average time of clinical development phases ranges from 6-8 years\(^1,2\)
- The total time for drug R&D increased in the past years to 14 years (2013)\(^2,3\)
  - Not including time for basic research, target identification and validation or Phase IV trials

New drug approvals today are associated with R&D expenditures that were invested many years ago


The costs of pharmaceutical R&D increased significantly (1950s – 1987)

<table>
<thead>
<tr>
<th>Period</th>
<th>R&amp;D Costs</th>
<th>Literature</th>
<th>Commentary</th>
</tr>
</thead>
</table>

\(\rightarrow\) Since mid 1980s, out-of-the-pocket costs and capitalized costs per NME increased by 7.6% and 7.4% p.a. (above general price inflation), respectively

Substantially higher costs of clinical development have resulted in higher R&D costs

Development costs of biologics are higher

- Capitalized costs per biologic: USD 1,318 million¹
- The capitalized costs of drug development per new asset increased from USD 1,019 million (2010) to USD 1,219 million (2013)²
- Calculations do not include Phase IV (post-approval) costs, costs for regulatory approval in non-US markets or new indications

Today, capitalized costs per launch are USD 1.8 billion and clinical development accounts for 63% of total costs.

<table>
<thead>
<tr>
<th></th>
<th>Target-to-hit</th>
<th>Hit-to-lead</th>
<th>Lead optimization</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Sub-mission to launch</th>
<th>Launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>p(TS)</td>
<td>80%</td>
<td>75%</td>
<td>85%</td>
<td>69%</td>
<td>54%</td>
<td>34%</td>
<td>70%</td>
<td>91%</td>
<td>80%</td>
</tr>
<tr>
<td>WIP needed for 1 launch</td>
<td>24,3</td>
<td>19,4</td>
<td>14,6</td>
<td>12,4</td>
<td>8,6</td>
<td>4,6</td>
<td>1,6</td>
<td>1,1</td>
<td>1</td>
</tr>
<tr>
<td>Cycle times (years)</td>
<td>1,0</td>
<td>1,5</td>
<td>2,0</td>
<td>1,0</td>
<td>1,5</td>
<td>2,5</td>
<td>2,5</td>
<td>1,5</td>
<td>1</td>
</tr>
<tr>
<td>Cost per launch (million USD)</td>
<td>24</td>
<td>49</td>
<td>146</td>
<td>62</td>
<td>128</td>
<td>185</td>
<td>235</td>
<td>44</td>
<td>873</td>
</tr>
<tr>
<td>Capitalized costs per launch (million USD)</td>
<td>94</td>
<td>166</td>
<td>414</td>
<td>150</td>
<td>273</td>
<td>319</td>
<td>314</td>
<td>48</td>
<td>1.778</td>
</tr>
</tbody>
</table>


Total pharma R&D expenditures increased

Source: PhRMA (2011) Pharmaceutical Industry 2011 Profile; PhRMA (Pharmaceutical Research and Manufacturers of America); substantial proportions of R&D expenditures are missing: (1) expenditure of in-licensed drugs and (2) not every pharmaceutical company is PhRMA member.
R&D costs increased by 8.6% p.a. since 1950

- Annual increase in capitalized R&D costs since 1950: 12.3%¹
- Inflation since 1950: 3.7% p.a.
- Remaining 8.6% p.a. may result from
  - Advanced complexity of drug targets
  - Greater complexity of clinical trials
  - Higher demands of regulatory authorities
  - More R&D personnel² → Clinical development functions account for more than 50% of all R&D expenditures


The dimensions of R&D efficiency are cost per launch

Productivity = Value per cost

Inputs → Output → Outcome

R&D efficiency: Cost per launch
R&D effectiveness: Value per launch

What are the costs per launch?

Number of approved drugs | Median (USD million) | Mean (USD million)
--- | --- | ---
8-13 | 5,459 | 5,998
4-6 | 5,151 | 5,052
2-3 | 1,803 | 2,303
1 | 351 | 953

10 years R&D spending (USD million) | Median (USD million) | Mean (USD million)
--- | --- | ---
>20,000 | 6,348 | 6,623
>5,000 | 2,883 | 2,961
>2,000 | 1,917 | 2,480
>1,000 | 1,459 | 741

Source: PWC (2012) From vision to decision Pharma 2020 (www.pwc.com/pharma2020)

What are the costs per launch?

<table>
<thead>
<tr>
<th>Rank</th>
<th>Company</th>
<th>NMEs</th>
<th>10 years R&amp;D spending (USD million)</th>
<th>R&amp;D costs per drug (USD million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abbott/Abbvie</td>
<td>1</td>
<td>13,183</td>
<td>13,183</td>
</tr>
<tr>
<td>2</td>
<td>Sanofi</td>
<td>6</td>
<td>60,768</td>
<td>10,128</td>
</tr>
<tr>
<td>3</td>
<td>AstraZeneca</td>
<td>4</td>
<td>38,245</td>
<td>9,561</td>
</tr>
<tr>
<td>4</td>
<td>Roche</td>
<td>8</td>
<td>70,928</td>
<td>8,866</td>
</tr>
<tr>
<td>5</td>
<td>Pfizer</td>
<td>10</td>
<td>77,786</td>
<td>7,779</td>
</tr>
<tr>
<td>6</td>
<td>Wyeth</td>
<td>3</td>
<td>22,702</td>
<td>7,567</td>
</tr>
<tr>
<td>7</td>
<td>Eli Lilly</td>
<td>4</td>
<td>26,710</td>
<td>6,678</td>
</tr>
<tr>
<td>8</td>
<td>Bayer</td>
<td>5</td>
<td>33,118</td>
<td>6,624</td>
</tr>
<tr>
<td>9</td>
<td>Schering-Plough</td>
<td>3</td>
<td>18,845</td>
<td>6,282</td>
</tr>
<tr>
<td>9</td>
<td>Novartis</td>
<td>10</td>
<td>60,727</td>
<td>6,073</td>
</tr>
<tr>
<td>10</td>
<td>Takeda</td>
<td>4</td>
<td>24,132</td>
<td>6,033</td>
</tr>
</tbody>
</table>


Number of NMEs per billion USD of R&D spending has nearly halved every 9 years since 1950

Possible reasons for the reduced R&D efficiency

- Insufficient number of projects in preclinical and early clinical phases\(^1\)
- Increasing number of approved drugs raise the hurdle for approval and reimbursement of new drugs\(^2\)
- A lower risk tolerance of drug regulators increases both the challenges for launching new drugs and the development-associated costs\(^2\)
- Target-based screening in drug discovery replaced an older and perhaps more productive method of drug research (phenotypic screening)\(^2\)
- Increasing number of mergers might have influenced pharmaceutical R&D negatively\(^3\)


How did the pharmaceutical industry react?

\[ P = \text{WIP} \times \text{PTRS} \times \text{V} \]

\[ \text{P} = \text{CT} \times \text{C} \]

- Optimize Work in progress
- Increase Probability of Success
- Increase Value of Pipeline
- Decrease Cycle Times
- Reduce Costs per clinical candidate

The global R&D pipeline is growing ...

... as pharmacos have increased the number of R&D projects in their pipelines

<table>
<thead>
<tr>
<th>Position in 2014</th>
<th>Company</th>
<th>Number of R&amp;D pipeline drugs (2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GlaxoSmithKline</td>
<td>261</td>
</tr>
<tr>
<td>2</td>
<td>Roche</td>
<td>248</td>
</tr>
<tr>
<td>3</td>
<td>Novartis</td>
<td>223</td>
</tr>
<tr>
<td>4</td>
<td>Pfizer</td>
<td>205</td>
</tr>
<tr>
<td>5</td>
<td>AstraZeneca</td>
<td>197</td>
</tr>
<tr>
<td>6</td>
<td>Merck &amp; Co.</td>
<td>186</td>
</tr>
<tr>
<td>7</td>
<td>Sanofi</td>
<td>180</td>
</tr>
<tr>
<td>8</td>
<td>Johnson &amp; Johnson</td>
<td>164</td>
</tr>
<tr>
<td>9</td>
<td>BMS</td>
<td>133</td>
</tr>
<tr>
<td>10</td>
<td>Takeda</td>
<td>132</td>
</tr>
</tbody>
</table>

Pharmacos have reduced their R&D costs …

• Pharmacos have reduced their personnel in R&D
• Outsourcing to provide lean and flexible R&D organizations
• Some pharmacos reduced their R&D rates under the historical benchmark of 20%
  – AstraZeneca (2011): 15.6%
  – Sanofi (2011): 15.1%
  – Pfizer (2011): 14.8%
  – GlaxoSmithKline (2011): 14.5%

Source: Germann PG et al. (2013) Human Genomics 7: 5

…and focused on licensing and acquiring drug candidates from external sources


Did these measures effect an increased R&D efficiency?

• “...the drug industry produces no more NMEs today than 60 years ago.”1

• Average of 25-30 NMEs p.a. “... may reflect the innovative capacity of the established R&D model.”1


How many NMEs are required for large pharma?

“...large pharmaceutical companies ... need to produce an average of 2-3 NMEs per year to meet their growth objectives, the fact that none of them has ever approached this level of output is concerning.”1

“Pfizer with pharmaceutical revenues in 2003 of approximately USD 45 billion, will need to generate approximately nine high-quality NCEs per annum.”2

As the R&D efficiency is reduced, could the pharmaceutical industry increase the value resulting from drug R&D?

- Projected revenues of NMEs launched between 2012 and 2016 (USD 58 billion\(^1\)) will not compensate the revenue losses by patent expirations between 2010 and 2014 (USD 89.5 billion)

- Average peak sales per NME is expected to decline from 900 million USD (2012) to 600 million USD (2015), showing the increasing difficulty of offering benefits over existing treatments in light of the increasing price pressure\(^1\)

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Are there any alternatives in view of these challenges?

There is a rapidly increasing demand for medicines in emerging countries

Source: PWC (2012) From vision to decision Pharma 2020 (www.pwc.com/pharma2020)
Consequently, four big pharmacos already earn a third of their revenues outside the main markets

![Chart showing prescription sales (2011) (USD billion)](source)

Patients in the growth markets can’t afford costly new drugs, such as biologics

<table>
<thead>
<tr>
<th></th>
<th>Private share of healthcare expenditures (%)</th>
<th>Per capita health spending, 2010 (USD)</th>
<th>Population with net assets of USD 10,000 or less (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>53,0</td>
<td>990</td>
<td>62,1</td>
</tr>
<tr>
<td>China</td>
<td>46,4</td>
<td>221</td>
<td>66,4</td>
</tr>
<tr>
<td>India</td>
<td>70,8</td>
<td>54</td>
<td>92,8</td>
</tr>
<tr>
<td>Russia</td>
<td>37,9</td>
<td>525</td>
<td>75,4</td>
</tr>
</tbody>
</table>

• Growing countries currently lack the financial power to reward innovation
• Increase in pharma sales is expected to come from generics

Source: PWC (2012) From vision to decision Pharma 2020 (www.pwc.com/pharma2020)
What else could be done to increase efficiency of pharmaceutical R&D and the value of pharmaceutical innovation?

Research & Development

• Focus on therapeutic areas and compounds with the greatest probability of success
• R&D focused on patients' needs
• Personalized medicine
• Opening R&D towards external innovation (e.g. crowdsourcing, licensing)
• Further reducing R&D costs (e.g. outsourcing, virtual R&D)

Marketing & Sales

• Specialty products
• Oncology as a key revenue generator
• Higher value of biologics

Thank you for your attention

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Defining Innovation

• “Innovation encompasses both the development and application of a new product, process or service. It assumes novelty in the device, the application, or both. Thus, innovation can include the use of an existing type of product in a new application or the development of a new device in an existing application.”

• “Incremental [sequential or follow-on] innovations ... are improvements ... on existing innovations.” Examples: Reformulations or me-too drugs

• “Radical [major, stand-alone discontinuous] innovations ... [are] innovations that represent something completely new and different.” Example: First-in-class drugs

• “NME is a new drug product that contain active moieties that have not been approved by FDA previously, either as a single ingredient drug or as part of a combination product” [http://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/default.htm]

Rewardable Innovation

- An innovation must be novel and useful
- Usefulness can come from:
  - Benefit in a condition with no existing effective treatment
  - Improvement in the treatment of a condition that does not have consistently satisfactory treatment
  - Safer treatment
  - More cost-effective treatment
  - More convenient treatment
- Rewardable innovation is defined as “a medical product that provides … something novel, with the potential or proven ability to yield … a treatment not previously available or clinically significant improvement in treatment … at an acceptable cost.”


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Rewardable Innovation

- A highly innovative product may result from a new target or a mechanism-of-action, from improved identification of patients who are likely to benefit or from a novel application of an existing drug
- A moderately innovative product may result from a new class of compound, fewer adverse reactions or drug-drug interactions, or a novel method of synthesis
- A slightly innovative product may result from improved pharmacokinetics or improved formulations
- A non-health-related innovation may result from a improved production method

Impact of Incremental Innovations

• Simply counting NMEs may underestimate the innovation potential of pharmaceutical R&D
  • Not all NMEs provide blockbuster potential
  • Incremental innovations are an important source of revenues and profits as they provide fewer technical risks at reduced costs
  • Between 1990-2003 FDA approved 1,174 NDAs (New Drug Applications), of which 34% were NMEs (New Molecular Entities) and 66% were non-NMEs (new formulations, dosages, indications)¹
  • Incremental innovation generate significant economic and health benefits²
    • Improved patient compliance
    • Improved pharmacokinetics
    • Reduced adverse effects
    • Ability to effectively treat a new patient population


Impact of Incremental Innovations

• First-in-class or best-in-class drugs are important for the success of pharmacos
  • Many pharmacos are pursuing the same disease areas, working with the same targets, following the same rationals and providing similar innovations, which is not suitable in today's payers' climate
  • The development of blockbuster drugs is becoming increasingly complex, as the development of a superior product in an area where a previous highly efficacious blockbuster went off patent is very difficult

76% of pharmacos with active R&D come from Europe and US

Global distribution of pharmacos with active R&D


Lack of efficacy is still the main reason for compound failure

- Between 2007-2010, 83 compounds failed in Phase III or during the submission process
  - 66% insufficient efficacy
  - 32% not better than placebo
  - 5% not better than active control
  - 29% no real benefits as add-on therapies
- Between 2011-2012, 56% of total failures in Phase II and III resulted from lack of efficacy

Mean clinical phase and approval time from 60 to 80 months

Data derived from: Reichert JM (2003) Nature Reviews Drug Discovery 2: 695-702; 504 NDAs, 50 BLAs

FDA Drug Approval Times

Source: Kaitin KI and DiMasi JA (2011) Clinical Pharmacology and Therapeutics 89(2): 183-188
Trends in attrition rates in 2011-2012

Phase II failures:
- Efficacy: 29%
- Safety: 51%
- Strategic: 19%
- Operational: 1%

Phase III and submission failures:
- Efficacy: 21%
- Safety: 7%
- Strategic: 6%
- Financial: 66.0%
- Other: 1%


Costs of Innovation (1987)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Mean Duration [months]</th>
<th>Mean Phase Costs [USD millions]</th>
<th>Capitalized Costs [USD millions]*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>42.6</td>
<td>65.5</td>
<td>155.6</td>
</tr>
<tr>
<td>Phase I</td>
<td>15.5</td>
<td>9.3</td>
<td>17.8</td>
</tr>
<tr>
<td>Phase II</td>
<td>24.3</td>
<td>12.9</td>
<td>21.4</td>
</tr>
<tr>
<td>Phase III</td>
<td>36.0</td>
<td>20.2</td>
<td>27.1</td>
</tr>
<tr>
<td>Long-term animal studies</td>
<td>33.6</td>
<td>5.3</td>
<td>8.2</td>
</tr>
<tr>
<td>Other animal studies</td>
<td>33.6</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>113.6</td>
<td>230.8</td>
</tr>
</tbody>
</table>


*23% success rate in clinical phases, 9% discount rate
New drug approvals today are associated with R&D expenditure that were invested many years ago ...


Total Size of R&D Pipeline by Development Phase (2014)

26% of all drug targets are in the field of oncology


How many NMEs are required for large pharma?

<table>
<thead>
<tr>
<th>2002 sales</th>
<th>Anticipated sales from current products in 2012</th>
<th>Annual real growth rate</th>
<th>Sales gap for new products to fill in 2012</th>
<th>Estimated number of NCEs required to fill the gap (over ten years)</th>
<th>Year 2012 required NCE output</th>
</tr>
</thead>
<tbody>
<tr>
<td>USD 45 billion</td>
<td>USD 30 billion</td>
<td>5%</td>
<td>USD 43.5 billion</td>
<td>75-90</td>
<td>9.5-11</td>
</tr>
<tr>
<td>USD 30 billion</td>
<td>USD 20 billion</td>
<td>5%</td>
<td>USD 29 billion</td>
<td>50-60</td>
<td>6.5-7.5</td>
</tr>
<tr>
<td>USD 20 billion</td>
<td>USD 13.3 billion</td>
<td>5%</td>
<td>USD 19.3 billion</td>
<td>33-40</td>
<td>4.3-5</td>
</tr>
<tr>
<td>USD 15 billion</td>
<td>USD 10 billion</td>
<td>5%</td>
<td>USD 14.5 billion</td>
<td>25-30</td>
<td>3.25-3.75</td>
</tr>
<tr>
<td>USD 10 billion</td>
<td>USD 6.67 billion</td>
<td>5%</td>
<td>USD 9.67 billion</td>
<td>16.5-20</td>
<td>2.15-2.25</td>
</tr>
</tbody>
</table>

Pharmacos have reduced their R&D personnel

<table>
<thead>
<tr>
<th>Company</th>
<th>Date</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novartis</td>
<td>Jan. 2012</td>
<td>2,000 US sales jobs</td>
</tr>
<tr>
<td>Sanofi</td>
<td>Imminent</td>
<td>Up to 2,000 French jobs</td>
</tr>
<tr>
<td>Pfizer</td>
<td>2005</td>
<td>Still another 12,100 of planned 60,000 jobs to be cut</td>
</tr>
<tr>
<td>Roche</td>
<td>June 2012</td>
<td>Nutley site closed, 1,000 R&amp;D jobs cut</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>n.a.</td>
<td>Ongoing restructuring, no specific job target announced</td>
</tr>
<tr>
<td>Merck &amp; Co.</td>
<td>July 2011</td>
<td>12-13% workforce reduction in addition to earlier cuts following the Schering-Plough merger</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>Nov. 2009</td>
<td>7,000 – 8,200 jobs</td>
</tr>
<tr>
<td>Abbott</td>
<td>Jan. 2012</td>
<td>700 manufacturing jobs</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>n.a.</td>
<td>Ongoing, 295 jobs cut in 2012</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Feb. 2012</td>
<td>7,300 jobs (incl. 2,200 in R&amp;D)</td>
</tr>
</tbody>
</table>

Source: Germann PG et al. (2013) Human Genomics 7: 5