The Future for Drug Development in an Increasingly Evidence-based Environment

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SEMINAR SERIES
Pharmaceutical Safety, Value and Innovation
Educational Objectives

• Identify some key elements of recent changes in US healthcare that will impact the drug development environment
• Better understand some of the key dynamics impacting the bio-pharmaceutical industry
• Project the likely impact of the new healthcare context on the bio-pharmaceutical industry and drug development
Presentation Outline

• Environmental factors driving healthcare changes
• Key changes in structure of US healthcare
• Pharmaceutical industry response
• Implications for drug development
The global push towards universal access to healthcare

- High/rising expectations for health care
- Unsustainable cost increases
- Politicization of health policy and health reform

\(\rightarrow\)

- Fundamentally conflicting goals involving:
  - Large populations
  - Large sums of money
- Need to make difficult or controversial decisions
Why do we need health reform?
Figure 1. Life Expectancy at Birth in Selected OECD Countries, 1960–2009.

Data for all Organization for Economic Co-operation and Development (OECD) countries appear in the Supplementary Appendix.

Source: Fineberg, 2012
Figure 2. Health Expenditures as a Percentage of Gross Domestic Product (GDP) in Selected OECD Countries, 1960–2009.
Data for all OECD countries appear in the Supplementary Appendix.
Sources of Inefficiency in US Health Care

- Payment for wrong outputs (units of service rather than episode of illness, health outcomes, or covered lives)
- Financial incentives that reward inefficiency (complications or readmissions)
- Lack of price information and incentives for patients
- Indifference of providers to induced costs
- Dysfunctional competition rather than performance-based competition
- Lack of personal or professional ethos to care about societal costs of health care
- Failure to take full advantage of professional skills of nurses
- Lack of uniform systems and processes to ensure safe and high-quality care
- Uneven patient flows, resulting in overcrowding, suboptimal care, and waste
- Insufficient involvement of patients in decision making (as in end-of-life care)
- Insufficient attention to prevention, disparities, primary care, health literacy, population health, and long-term results
- Fragmented and uncoordinated delivery, without continuity of care
- Lack of information on resource costs, performance, comparative effectiveness, quality of care, and health outcomes
- Scientific uncertainty about effectiveness and cost, especially of newer tests and treatments
- Cultural predisposition to believe that more care is better
- Administrative complexity of coping with multiple forms, regimens, and requirements of different insurers
- Rewarding of inventors and entrepreneurs for possible performance advantage more than for significant savings in overall system cost
- Regulatory regime that can only retard and not accelerate innovation
- Insufficient reliance on competitive bidding for drugs and devices
- Distortions resulting from fraud, conflict of interest, and a dysfunctional malpractice system

Source: Fineberg, 2012
Figure 14. Medicine’s Triangle of Conflicting Expectations

**Consumer view**
*What is right for me?*
- Priorities
  - Prevention and care
  - Information and unbiased guidance
  - Perceived value

**Professional view**
*What is best for medicine?*
- Priorities
  - Professionalism
  - Autonomy
  - Science and technology

**Societal view**
*What is best for society?*
- Priorities
  - Measured effectiveness
  - Access
  - Cost
US Healthcare reform is occurring within the global and local political context, but it is not new

- Eisenhower: Good health care should be accessible to all.
- Nixon: Good health care should be available to all citizens.
- Reagan: Health care costs are climbing so fast [that] they may soon threaten the quality of care and access to care which Americans enjoy.
- Bush 41: We must reform our healthcare system
- Bush 43: The first goal: all should be able to choose a health care plan that meets their needs at affordable prices. . . . Many of the poor and uninsured, including legal immigrants, are outside our system of health care entirely.
A range of potential health reform were possible

- Co-operative plans
- Voluntary, subsidized access for <20mn uninsured
- Partial filling of the donut hole
- Continuation of annual budget and reimbursement actions
- Greater scrutiny of insurance company actions

Incremental change

Substantial change

- Public plan
- Mandatory/full coverage of uninsured
- Closing the donut hole
- Price controls/direct negotiation
- Powerful IMAC independent of Congress
- Mandated insurance company practices

Wholesale restructuring

- Single payer
- Universal coverage
- Full coverage with patient incentives to make proper health choices
- Health care funded by taxes and run as public good
- Innovation driven by government-funded research and private-sector incentives
HC reform debate around the ACA was actually limited by the insurance and pharmaceutical industries

- The health insurance industry was the main target of health reform: the “three legs of the stool”
  - Insurance companies may not deny coverage
  - Everyone must carry health insurance (the “mandate”)
  - Financial assistance will be provided to those who cannot afford health insurance
- An early deal with the administration and PhRMA limited discussion of:
  - Direct price negotiation
  - Re-importation
  - Wide-spread use of Medicaid pricing approach
- Medicare Part D was a large net positive to the pharmaceutical industry
- There was little reason to PhRMA to resist Obamacare
Insurance companies agreed to two key elements of the ACA

• A step toward universal health care coverage, if supported by a mandate to buy health insurance
  – That way, the pool of participants will be large enough to offer lower, more affordable premiums per customer through a balance of high-risk and low-risk clients. The mandate will also help to eliminate the provision on denying coverage due to pre-existing conditions.

• No “public option”
  – If allowed, the government could always offer lower premiums than the for-profit companies. Small businesses or individuals might feel compelled to drop their coverage to save money and opt out of private health care coverage.
PhRMA’s contribution to the ACA was substantial – and not without something in return

- PhRMA proposed to cut $80 billion in projected costs to taxpayers and senior citizens over 10 years. This would include:
  - Increasing the Medicaid rebate from 15 to 23 percent, cutting medication costs for low-income individuals
  - Allowing medication to be sold to Medicare patients at a 50 percent discount
  - Help defray government’s costs of administering the programs, but not to exceed the $80 billion limit
- In exchange, the Obama administration agreed to:
  - Oppose any congressional effort to demand additional savings from the pharmaceutical industry beyond the $80 billion allotted in the deal
  - Prohibit the importation of less costly foreign drugs or generic drugs identical to the drugs sold by the pharmaceutical industry in America
  - Reject any legislation that would give the government the authority to negotiate lower prices for drugs
  - Oppose moving more expensive Medicare Part B medications to Medicare Part D, which offers lower prices for patients
Where the $80B went

Standard Medicare Prescription Drug Benefit, 2013

**CATASTROPHIC COVERAGE**
- Enrollee pays 5%
- Plan pays 15%; Medicare pays 80%
- Catastrophic Coverage Limit = $6,955 in Estimated Total Drug Costs

**COVERAGE GAP**
- Brand-name drugs
  - Enrollee pays 47.5%
  - Plan pays 2.5%
  - 50% manufacturer discount
- Generic drugs
  - Enrollee pays 79%
  - Plan pays 21%
- Initial Coverage Limit = $2,970 in Total Drug Costs

**INITIAL COVERAGE PERIOD**
- Enrollee pays 25%
- Plan pays 75%

**DEDUCTIBLE**
- Deductible = $325

**NOTE:** *Amount corresponds to the estimated catastrophic coverage limit for non-low-income subsidy enrollees ($6,734 for LIS enrollees), which corresponds to True Out-of-Pocket (TrOOP) spending of $4,750 (the amount used to determine when an enrollee reaches the catastrophic coverage threshold. SOURCE: Kaiser Family Foundation illustration of standard Medicare drug benefit for 2013 (standard benefit parameter update from Centers for Medicare & Medicaid Services, 2012). Amounts rounded to nearest dollar.*
Bio-pharmaceutical industry has rebounded from the “great recession”

• The market has expanded
• The pipeline and the number of approvals has returned to robust levels of the late 1990s and early 2000s
• The FDA has been keeping pace with submissions
New drug approvals have rebounded from 2010 low
New therapies are increasingly orphan and specialty.

New molecular entities launched in the U.S. 2004-2013

- **2004**: 5 New Mechanism, 6 Orphan, 3 Existing Mechanism
- **2005**: 4 New Mechanism, 6 Orphan, 5 Existing Mechanism
- **2006**: 9 New Mechanism, 9 Orphan, 5 Existing Mechanism
- **2007**: 7 New Mechanism, 6 Orphan, 5 Existing Mechanism
- **2008**: 7 New Mechanism, 7 Orphan, 5 Existing Mechanism
- **2009**: 8 New Mechanism, 8 Orphan, 6 Existing Mechanism
- **2010**: 10 New Mechanism, 10 Orphan, 6 Existing Mechanism
- **2011**: 13 New Mechanism, 12 Orphan, 7 Existing Mechanism
- **2012**: 10 New Mechanism, 11 Orphan, 8 Existing Mechanism
- **2013**: 12 New Mechanism, 17 Orphan, 7 Existing Mechanism

Source: IMS Institute for Healthcare Informatics, Feb 2014
Recent changes have allowed faster approvals by FDA

- **Expedited approval (percent in 2013)**
  - Fast Track – 37% - drugs with the potential to address unmet medical needs
  - Breakthrough (11) – drugs with preliminary clinical evidence that demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy
  - Priority Review (37) – CDER determines the drug to potentially provide a significant advance in medical care (approval target changes to 6 months instead of the standard 10)
  - Accelerated Approval (7) – early approval of a drug for serious or life-threatening illness that offers a benefit over current treatments.

- **Under the Prescription Drug User Fee Act (PDUFA), sponsors are assessed user fees that provide FDA with the additional resources needed to meet performance goals.**
  - Throughout the year, CDER was able to meet or exceed PDUFA goal dates for application review, agreed to with the pharmaceutical industry and approved by Congress. In CY 2013, CDER met its PDUFA goal dates for 100% of the NMEs approved in CY 2013.
2013 approvals reflect the trend toward orphan & specialty

Source: FDA, Novel new drugs, Summary, 2013, Jan 2014
But, there are concerns about the demand side for drugs

- Less employer-offered coverage
- Higher health care costs for patients, even as more are covered under the ACA
- Patients bear a greater share of insurance costs
- Patients pay a higher proportion of drug costs
Employer-supplied health insurance continues to decline

Percentage of All Firms Offering Health Benefits, 1999-2014

Smaller firms only $\frac{1}{2}$ as likely to offer health benefits

Percentage of Firms Offering Health Benefits to At Least Some of their Workers, by Firm Size, 2014

HDHPs have continued to increase

Percentage of Covered Workers Enrolled in Either a HDHP/HRA or HSA-Qualified HDHP, 2006-2014

Employees in smaller firms have higher risk

Percentage of Covered Workers Enrolled in a Plan with a General Annual Deductible of $2,000 or More for Single Coverage, By Firm Size, 2006-2014

Retiree health benefits continue to wane

Among All Large Firms (200 or More Workers) Offering Health Benefits to Active Workers, Percentage of Firms Offering Retiree Health Benefits, 1988-2014

Wellness benefits are an interesting counter trend.

Among Firms Offering Health Benefits, Percentage Offering a Particular Wellness Program to Their Employees, by Firm Size, 2014

- Offer at Least One Specified Wellness Program*: 98%
- Class in Nutrition/Healthy Living*: 47%
- Flu Shot*: 87%
- Employee Assistance Program*: 79%
- Weight Loss Programs*: 48%
- Biometric Screening*: 51%
- Lifestyle or Behavioral Coaching*: 58%
- Wellness Newsletter*: 60%
- Web-based Resources for Healthy Living*: 77%
- Smoking Cessation Program*: 64%
- Gym Membership Discounts or On-Site Exercise Facilities*: 64%
- Other Wellness Program*: 15%

Covered workers are exposed to higher drug copayments

### Distribution of Covered Workers Facing Different Cost-Sharing Formulas for Prescription Drug Benefits, 2000-2012

<table>
<thead>
<tr>
<th>Year</th>
<th>Four or More Tiers</th>
<th>Three Tiers</th>
<th>Two Tiers</th>
<th>Payment is the same regardless of type of drug</th>
<th>No cost sharing after deductible is met</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>2%</td>
<td>27%</td>
<td>41%</td>
<td>15%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>2001*</td>
<td>1%</td>
<td>41%</td>
<td>55%</td>
<td>15%</td>
<td>2%</td>
<td>2%</td>
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<tr>
<td>2002*</td>
<td>1%</td>
<td>63%</td>
<td>55%</td>
<td>15%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>2003*</td>
<td>1%</td>
<td>63%</td>
<td>55%</td>
<td>15%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>2004‡</td>
<td>1%</td>
<td>65%</td>
<td>63%</td>
<td>15%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>2005</td>
<td>2%</td>
<td>69%</td>
<td>63%</td>
<td>15%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>2006</td>
<td>2%</td>
<td>69%</td>
<td>63%</td>
<td>15%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>2007‡</td>
<td>1%</td>
<td>68%</td>
<td>63%</td>
<td>15%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>2008</td>
<td>1%</td>
<td>70%</td>
<td>63%</td>
<td>15%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>2009</td>
<td>3%</td>
<td>67%</td>
<td>63%</td>
<td>15%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>2010</td>
<td>4%</td>
<td>65%</td>
<td>63%</td>
<td>15%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>2011</td>
<td>3%</td>
<td>63%</td>
<td>63%</td>
<td>15%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>2012</td>
<td>5%</td>
<td>63%</td>
<td>63%</td>
<td>15%</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

* Distribution is statistically different from distribution for the previous year shown (p<.05).
‡ No statistical tests are conducted between 2003 and 2004 or between 2006 and 2007 due to the addition of a new category.

NOTE: Fourth-tier drug cost-sharing information was not obtained prior to 2004.

Coinsurance is becoming the norm for the most costly drugs

Type of Cost-Sharing for Prescription Drug Benefits, Employer-Sponsored Plans, 2014

<table>
<thead>
<tr>
<th></th>
<th>Copayment</th>
<th>Coinsurance</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-Tier Drugs (Generic)</td>
<td>85%</td>
<td>11%</td>
</tr>
<tr>
<td>Second-Tier Drugs (Preferred)</td>
<td>77%</td>
<td>22%</td>
</tr>
<tr>
<td>Third-Tier Drugs (Nonpreferred)</td>
<td>73%</td>
<td>25%</td>
</tr>
<tr>
<td>Fourth-Tier Drugs</td>
<td>39%</td>
<td>49%</td>
</tr>
</tbody>
</table>

Source: Pembroke Consulting analysis of 2014 Kaiser/HRET Employer Health Benefits Survey. Data presented for covered workers with three, four, or more tiers of prescription cost sharing. Percentages do not sum to 100% because other plan designs are excluded for the purposes of presentation.

Published on Drug Channels (www.DrugChannels.net) on September 16, 2014.
4-tier plans are growing rapidly (7-fold increase in 10 years)

**Distribution of Cost-Sharing Formulas for Prescription Drug Benefits in Employer-Sponsored Plans, 2004 vs. 2014**

<table>
<thead>
<tr>
<th>Plan Level</th>
<th>2014</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Three tiers</strong></td>
<td>60%</td>
<td>65%</td>
</tr>
<tr>
<td><strong>Four or more tiers</strong></td>
<td>3%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Two tiers</strong></td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Payment is the same regardless of drug type</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>No cost sharing after deductible is met/Other</td>
<td>4%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Total does not sum to 100% due to rounding and omission of “Other” category.
Fourth-tier drug cost-sharing information was not obtained prior to 2004.

Published on Drug Channels ([www.DrugChannels.net](http://www.DrugChannels.net)) on September 16, 2014
Patient cost shares have escalated, especially in higher tiers.

**Average Copayments by Prescription Drug Tier, 2002 vs. 2014**

- **First-Tier Drugs (Generic)**: $9 (2002) vs. $11 (2014)
- **Second-Tier Drugs (Preferred)**: $18 (2002) vs. $31 (2014)
- **Third-Tier Drugs (Nonpreferred)**: $32 (2002) vs. $53 (2014)
- **Fourth-Tier Drugs**: $83 (2014)

Source: Pembroke Consulting analysis of 2014 Kaiser/HRET Employer Health Benefits Survey. Data presented for covered workers with three, four, or more tiers of prescription cost sharing. Fourth-tier copayment information was not collected prior to 2004.

Published on Drug Channels (www.DrugChannels.net) on September 16, 2014.
Generic use is approaching 80% in employer-sponsored plans.
Medicare Part D premiums appear to be moderating

Weighted Average Monthly Premiums for Medicare Part D Stand-Alone Prescription Drug Plans, 2006-2013

2006-2013: 49% increase

2012-2013: 2% increase

NOTE: Average premiums are weighted by enrollment in each year (March for 2013). Excludes Part D plans in the territories. SOURCE: Georgetown/NORC analysis of data from CMS for the Kaiser Family Foundation.
Generic utilization approaches 80% in Part D

GDR Trends - All Part D
FDA vs. Medi-Span/FDB

- 2009: FDA defined (72.1%), Medi-Span/FDB derived (72.1%)
- 2010: FDA defined (74.9%), Medi-Span/FDB derived (74.9%)
- 2011: FDA defined (77.4%), Medi-Span/FDB derived (77.4%)

Source: cms.gov
Poverty and lack of health insurance directly impact utilization

Nonreceipt of needed prescription drugs due to cost: Adults aged 18-64

NOTE: In the past 12 months.

SOURCE: CDC/NCHS, Health, United States, 2013, Figure 23. Data from the National Health Interview Survey.
There will be several impacts from demand-side developments

- Increased cost-shifting to patients will lead to a more cost-sensitive environment
- Use of generics will continue to increase
- Governments may need to shoulder more of the cost burden for patients who cannot
- Payers will continue to implement/offer policies to hold down cost increases or shift the costs to patients
Bio-pharmaceutical industry in global context

- Global view - necessary for full understanding
- Key market trends
The global bio-pharmaceutical industry is approaching $1T.

Total global spending on medicines will reach about $1.2Tn in 2017, an increase of $205-235Bn from 2012.

Global Spending and Growth, 2008-2017

Source: IMS Market Prognosis, September 2013
But, generics will be an increasing share of the market

Generics will represent a larger share of the market in volume and value terms

**Global Spending, 2012 and 2017**

<table>
<thead>
<tr>
<th>Region</th>
<th>2012</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brand</td>
<td>72%</td>
<td>67%</td>
</tr>
<tr>
<td>Generic</td>
<td>16%</td>
<td>21%</td>
</tr>
<tr>
<td>Other</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Total</td>
<td>$622Bn</td>
<td>$650-680Bn</td>
</tr>
<tr>
<td>Pharmerging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brand</td>
<td>31%</td>
<td>26%</td>
</tr>
<tr>
<td>Generic</td>
<td>58%</td>
<td>63%</td>
</tr>
<tr>
<td>Other</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Total</td>
<td>$224Bn</td>
<td>$370-400Bn</td>
</tr>
<tr>
<td>Rest of the World</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brand</td>
<td>57%</td>
<td>52%</td>
</tr>
<tr>
<td>Generic</td>
<td>27%</td>
<td>31%</td>
</tr>
<tr>
<td>Other</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td>Total</td>
<td>$120Bn</td>
<td>$125-155Bn</td>
</tr>
<tr>
<td>World</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brand</td>
<td>61%</td>
<td>52%</td>
</tr>
<tr>
<td>Generic</td>
<td>27%</td>
<td>36%</td>
</tr>
<tr>
<td>Other</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Total</td>
<td>$965Bn</td>
<td>$1,170-1,200Bn</td>
</tr>
</tbody>
</table>

Source: IMS Health Thought Leadership, September 2013
Patent expiries will continue to erode bio-pharma revenues, but the worst is over.

Patent expiries on small molecule products will reduce brand spending in developed markets by $113Bn through 2017.

Developed Markets Patent Expiry Exposure and Impact

Source: IMS Institute for Healthcare Informatics, September 2013
The bio-pharmaceutical industry reaction to market conditions

• Change in product mix
  – More orphan diseases
  – More biologics
  – More specialty pharmaceuticals

• Mergers and acquisitions
  – And cost-cutting measures

• The growth of global generic giants
As in US, global launches are increasing with similar focus on orphan diseases. . .

Increasing numbers of innovative new medicines and orphan drugs are expected to be launched

Global Launches of New Molecular Entities

Source: IMS Institute for Healthcare Informatics, October 2013
A growing share of all medicines are biologic, with biosimilars and non-original biologic (NOB) products now taking a small share of the total market.
And increased growth of specialty bio-pharmaceuticals across all markets

Spending on specialty pharmaceuticals will increase rapidly in both developed and pharmerging markets

Specialty Spending between 2012 and 2017

Source: IMS Health Thought Leadership, September 2013
Global bio-pharma growth expected to improve, with increasing growth rates in emerging economies

Annual spending growth will reach a low point in 2013, followed by increased growth particularly in developed markets

Global Growth, 2008-2017

Source: IMS Health Market Prognosis, September 2013
Developed and emerging economics will differ on disease and specialty/traditional mix.

Spending levels in 2017 on medicine for specific disease areas will differ significantly between developed and pharmerging markets.

**Spending by Therapy Area in 2017**

<table>
<thead>
<tr>
<th>Top 20 Classes 71%</th>
<th>Others 29%</th>
<th>Top 20 Classes 45%</th>
<th>Others 55%</th>
</tr>
</thead>
</table>

### Developed Markets

- **Oncology**
- **Diabetes**
- **Anti-TNFs**
- **Pain**
- **Asthma/COPD**
- **Other CNS Drugs**
- **Hypertension**
- **Immunostimulants**
- **HIV Antivirals**
- **Dermatology**
- **Antibiotics**
- **Cholesterol**
- **Anti-Epileptics**
- **Immunosuppressants**
- **Antipsychotics**
- **Antilcerants**
- **Antidepressants**
- **Antivirals excluding HIV**
- **ADHD**
- **Interferons**

### Sales in 2017 (LCS)

- **Oncology**: $74-84Bn
- **Diabetes**: $34-39Bn
- **Anti-TNFs**: $32-37Bn
- **Pain**: $31-36Bn
- **Asthma/COPD**: $31-36Bn
- **Other CNS Drugs**: $26-31Bn
- **Hypertension**: $23-26Bn
- **Immunostimulants**: $22-25Bn
- **HIV Antivirals**: $22-25Bn
- **Dermatology**: $22-25Bn
- **Antibiotics**: $18-21Bn
- **Cholesterol**: $16-19Bn
- **Anti-Epileptics**: $15-18Bn
- **Immunosuppressants**: $15-18Bn
- **Antipsychotics**: $13-16Bn
- **Antilcerants**: $12-14Bn
- **Antidepressants**: $10-12Bn
- **Antivirals excluding HIV**: $8-10Bn
- **ADHD**: $7-9Bn
- **Interferons**: $6-8Bn

### Pharringering Markets

- **Pain**: $22-25Bn
- **Other CNS Drugs**: $20-23Bn
- **Antibiotics**: $18-21Bn
- **Oncology**: $17-20Bn
- **Hypertension**: $14-17Bn
- **Diabetes**: $10-12Bn
- **Dermatology**: $10-12Bn
- **Antilcerants**: $9-11Bn
- **Cholesterol**: $6-8Bn
- **Asthma/COPD**: $3-5Bn
- **Anti-Epileptics**: $3-5Bn
- **Antivirals excluding HIV**: $3-5Bn
- **Immunosuppressants**: $3-5Bn
- **Allergy**: $3-5Bn
- **Antidepressants**: $3-5Bn
- **Antiplatelet**: $3-5Bn
- **Antipsychotics**: $2-3Bn
- **Heparins**: $1-2Bn
- **Erectile Dysfunction**: $1-2Bn
- **Immunostimulants**: $1-2Bn

**Source:** IMS Health Thought Leadership, September 2013
M&A in the bio-pharmaceutical industry are on the upswing

Pharma and biotech M&A transactions announced each quarter

Analysis excludes mega-merger takeovers of Genentech, Wyeth, Schering-Plough and Alcon

Source: EvaluatePharma
“Mega mergers” have shaken up the industry

<table>
<thead>
<tr>
<th>Year Announced</th>
<th>Acquirer/Resultant Company</th>
<th>Target / Merging Companies</th>
<th>Deal Type</th>
<th>Announced Total Value ($bn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>Pfizer</td>
<td>Warner-Lambert</td>
<td>Acquisition</td>
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<td>Acquisition</td>
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<td>2000</td>
<td>GlaxoSmithKline</td>
<td>Smithkline Beecham + Glaxo Wellcome</td>
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<td>2002</td>
<td>Pfizer</td>
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<td>Wyeth</td>
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<td>Acquisition</td>
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<td>Acquisition</td>
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<tr>
<td>1998</td>
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<td>Astra + Zeneca</td>
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<td>30.4</td>
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<tr>
<td>1996</td>
<td>Novartis</td>
<td>Ciba-Geigy + Sandoz</td>
<td>Merger</td>
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<tr>
<td>1999</td>
<td>Pharmacia</td>
<td>Pharmacia &amp; Upjohn + Monsanto</td>
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<tr>
<td>2014</td>
<td>Actavis</td>
<td>Forest Laboratories</td>
<td>Acquisition</td>
<td>20.7</td>
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<tr>
<td>2010</td>
<td>Sanofi</td>
<td>Genzyme</td>
<td>Acquisition</td>
<td>19.6</td>
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<td>2006</td>
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<td>Schering AG</td>
<td>Acquisition</td>
<td>18.4</td>
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<td>2001</td>
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<td>Immunex</td>
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<td>2006</td>
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<td>Pfizer consumer health</td>
<td>Business unit</td>
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<td>2007</td>
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<td>Business unit</td>
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<tr>
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<td>Business unit</td>
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<tr>
<td>1995</td>
<td>Glaxo Wellcome</td>
<td>Wellcome</td>
<td>Acquisition</td>
<td>14.2</td>
</tr>
<tr>
<td>2014</td>
<td>Bayer</td>
<td>Merck &amp; Co. consumer health</td>
<td>Business unit</td>
<td>14.2</td>
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Source: Bloomberg
### Table I: Top global pharmaceutical companies, 1990

<table>
<thead>
<tr>
<th>Rank</th>
<th>Company</th>
<th>Global sales ($ Billion)*</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Merck &amp; Co.</td>
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<tr>
<td>2</td>
<td>Bristol-Myers Squibb</td>
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<td>Glaxo</td>
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<td>5</td>
<td>Ciba-Geigey</td>
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<td>6</td>
<td>American Home Products</td>
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<td>Hoechst</td>
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<td>Johnson &amp; Johnson</td>
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<td>Roche</td>
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<td>Sandoz</td>
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<tr>
<td>15</td>
<td>Schering-Plough</td>
<td>2.205</td>
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</tbody>
</table>

*Sales of human prescription drugs reported in constant US dollars.

Source: IMS Institute of Healthcare Informatics

### Table II: Top global pharmaceutical companies, 2000

<table>
<thead>
<tr>
<th>Rank</th>
<th>Company</th>
<th>Global sales ($ Billion)*</th>
</tr>
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<td>1</td>
<td>Pfizer</td>
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<td>Bristol-Myers Squibb</td>
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<td>6</td>
<td>Novartis</td>
<td>12.414</td>
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<td>7</td>
<td>Johnson &amp; Johnson</td>
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<td>8</td>
<td>Aventis</td>
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<td>9</td>
<td>Pharmacia</td>
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<td>15</td>
<td>Bayer</td>
<td>6.155</td>
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</table>

*Sales of human prescription drugs reported in constant US dollars.

Source: IMS Institute of Healthcare Informatics

### Table III: Top global pharmaceutical companies, 2011

<table>
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<tr>
<th>Rank</th>
<th>Company</th>
<th>Global sales ($ Billion)*</th>
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<td>Novartis</td>
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<td>6</td>
<td>Roche</td>
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<td>7</td>
<td>GlaxoSmithKline</td>
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<td>8</td>
<td>Johnson &amp; Johnson</td>
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<td>9</td>
<td>Abbott</td>
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<td>Teva</td>
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<td>Eli Lilly</td>
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<td>12</td>
<td>Takeda</td>
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<td>13</td>
<td>Bristol-Myers Squibb</td>
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<tr>
<td>14</td>
<td>Bayer</td>
<td>16.4</td>
</tr>
<tr>
<td>15</td>
<td>Amgen</td>
<td>16.3</td>
</tr>
</tbody>
</table>

*Sales of human prescription drugs reported in constant US dollars.

Source: IMS Institute of Healthcare Informatics
Similar M&A activity has characterized the generic industry.

**FIGURE 1: Total Spend on M&A in the Generic Drug Industry Between 2000 and 2009**

M&A strategies have been successful for the most part
Some changes in the US that are leading to increased scrutiny of benefits, risks and relative value of healthcare technologies
A new post-launch scrutiny of benefits, risks and relative value

**Examples**

- HTA
- CER
- Sentinel
- REMS & PMCs

These are in play now, but they may be subject modification by the political process
Centers for Health Technology Assessment (HTA) have existed for a long time, but their global reach now pervasive
HTA exists in the US, but it is pluralistic and applied unevenly

- Medicare (local and national coverage policies) and Medicaid (locally-determined at state level)
- Drug Effectiveness Review Project (DERP, 2001 – present), contracts with 14 Medicaid programs
- Agency for Healthcare Research and Quality (AHRQ)
  - Evidence-based Practice Centers (EPCs)
  - Centers for Education and Research on Therapeutics (CERT)
  - Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Program
- Other government programs
  - Veterans Affairs (VA): Pharmacy Benefits Management Strategic Healthcare Group (PBMSHG)
  - Military Health System: Department of Defence PharmacoEconomic Center (PEC)
- National Institutes of Health (NIH’s evidence reviews)
- Food and Drug Administration (FDA, safety and efficacy only)
- Private bodies
  - BCBS Tech Assessment Committee -> WellPoint HTA Guidelines
  - Health Plans: United Healthcare, Aetna, Cigna, Kaiser Permanente
  - PBMs: Caremark, Medco, Express Scripts
Comparative Effectiveness Research

• CER has been on the table before
  – Clinton Health Reform (1993)
• But CER has not survived the political process
Advantages of a government CER initiative

• For many, government involvement should improve the credibility, objectivity, and balance of the information studied and the methods used

• Information on comparative effectiveness meets part of economists’ classic definition of a “public good”

• Once the information is available, its use by one person doesn’t diminish availability for others, and it’s hard—although technically possible—to exclude users other than whoever paid for it

*Excerpted from Wilensky GR. Developing a center for comparative effectiveness information. Health Aff (Millwood) 2006;25:w572-w585.
Under PCORI, CER data will be available for all health policy makers and stakeholders, with a focus on patients

• “Patient Centered Outcomes Research Institute”, PCORI (ACA, 2010)
  – To help “people make informed healthcare decisions, and improves healthcare delivery and outcomes, by producing and promoting high-integrity, evidence-based information that comes from research guided by patients, caregivers, and the broader healthcare community.”
PCORI has been extremely active

- PCORI is an “innovative funder of research living up to our commitment to “research done differently.”
  - PCORI has about $1.5B for CER research grants
- Central to that vision is supporting CER that will be useful to patients and other clinical decision makers by ensuring that their questions and concerns are the focus of our work.” (Selby, 2013)
- Three PCORI goals:
  - Increase substantially the quantity, quality, and timeliness of useful, trustworthy information available to support health decisions.
  - Second, we will speed the implementation and use of patient centered outcomes research (PCOR) evidence.
  - Finally, we will seek to influence clinical and healthcare research funded by others to be more patient-centered.
Nearly ½ of research budget allocated. . .

Our Research Portfolio: First Four Years

360 funded research projects

$671 M in funded research projects

Our research portfolio is guided by our five broad National Priorities for Research and input received from across the healthcare community through our advisory panels, review panels, and other channels.

- Assessment of Prevention, Diagnosis, and Treatment Options
- Improving Healthcare Systems
- Addressing Disparities
- Communication and Dissemination Research
- Accelerating Patient-Centered Outcomes Research and Methodologic Research

We build our portfolio based on the research community’s best ideas and suggestions from a broad range of stakeholders for studies of specific, high-impact health topics. We are also developing PCORnet, a large patient-centered “network of networks” that will allow clinical research to be conducted faster and more effectively. In addition to our research awards, we fund opportunities to advance engagement in research by patients, clinicians, and others.

39 states where PCORI is funding research
(plus the District of Columbia and Quebec)
Across key disease areas and populations

**Selected Conditions Studied**

- Mental/Behavioral Health: 45 studies funded
- Cardiovascular Diseases: 44 studies funded
- Cancer: 36 studies funded
- Endocrine System Disorders: 23 studies funded
- Nervous System Disorders: 21 studies funded
- Musculoskeletal Disorders: 14 studies funded

**Selected Populations Studied**

- Racial/Ethnic Minorities: 130 studies funded
- Older Adults: 90 studies funded
- Socioeconomic Status: 87 studies funded
- Rural: 64 studies funded
- Urban: 46 studies funded
- Children: 45 studies funded

*Through September 30, 2014*
But, will PCORI survive?

• There is an ongoing concern by some that CER information will be used for reimbursement policy
  – Current Food and Drug Administration (FDA) determinations of safety and efficacy seem both sufficient and appropriate for making coverage decisions
    • Although NEJM article (Aug 25, 2009) suggests adding CER information to label
  – Payers could and should decide for themselves how best to use such information – but likely there will be a leader-follower (or snowball) effect
• Some political commentators suggest that PCORI could be defunded in next congress
The SENTINEL Initiative is changing post-marketing surveillance from reactive to proactive

- A national electronic system that will transform FDA’s ability to track the safety of drugs, biologics, medical devices
- “The Sentinel Initiative aims to develop and implement a proactive system that will complement existing systems that the Agency has in place to track reports of adverse events linked to the use of its regulated products.”
- About contracts to date have covered:
  - Governance
  - Methods
  - Data sources
  - IT infrastructure
  - Mini-SENTINEL pilot

Source: fda.gov
Surveillance under SENTINEL will impact post-marketing environment

- This public-private partnership model will allow post-marketing analysis of areas of FDA concern
- Queries are available via the Mini-Sentinel web site
  - exposures to medical products*
  - occurrences of particular diagnoses and medical procedures
  - health outcomes** among individuals exposed to medical products
  - impact of FDA’s regulatory actions and interventions
- Data is de-identified and disseminated
- Signal detection methods have been examined and improved through OMOP (Observational Medical Outcomes Partnership) and the Mini-Sentinel Methods Core (committee)
The Mini-sentinel data base is enormous

- 150 million individuals
  - 356 million person-years of observation time
  - 49 million individuals currently enrolled, accumulating new data
  - 35 million individuals have over 3 years of data
- 3.9 billion dispensings
- Accumulating over 45 million dispensings per month
- 4.0 billion unique encounters, including 41 million acute inpatient stays
- Accumulating over 51 million encounters per month
- 24.7 million individuals with at least 1 laboratory result**
Post-marketing FDA surveillance has increased

- More adverse event reports are triggering more scrutiny
- Manufactures are drawn into post-marketing monitoring and management
  - Risk Evaluation and Mitigation Strategies (REMS)
  - Post market requirements (PMRs) and commitments (PMCs)
The number of potential or possible AE reports continues to increase
FDA approvals increasingly carry obligations

- Risk Evaluation and Mitigation Strategies are
- Label revisions, including black box warnings

![Diagram showing label revisions from 2003 to 2008 with categories like medication guide/patient insert, adverse reactions, precautions, warnings, contraindications, and black box warnings]
Postmarket requirements/commitments continues to increase

Number of Postmarket Requirements (PMRs) and Postmarket Commitments (PMCs) established by quarter (2010 – 2014)

Source: FDA
The post-health reform world will be more transparent and more risky for the bio-pharmaceutical industry

- From Phase III development through post-marketing surveillance medical drug and other medical technologies will be under a new level of scrutiny
- This scrutiny will be driven government-funded programs governed on a public-private partnership model, and with manufacturers assistance
- CER, the FDA’s drug approval process, the SENTINEL Initiative, echoed by similar initiatives in EMEA, will all generate data on medical technologies that will be:
  - Determined by broadly representative steering committees, not solely or primarily by private commercial interests
  - Available typically via websites, including payers, providers, patients
  - Will require significant investments in early commercial risk planning for down-stream (1) clinical effectiveness and comparisons to alternative technologies and approaches as well as (2) safety concerns
FDA heightened safety focus, SENTINEL and CER will raise the bar for evidence generation

• Safety concerns may begin to power studies in development (larger, more risky)
• Post-marketing surveillance will be transformed into a more proactive search for earlier signals
  – There may be “false positives” that will need to be defended
  – At the same time, companies are involved in post-marketing management and scrutiny themselves
• CER will incentivize companies to consider relative value as a condition of go/no go development decisions
  – “Me too drugs” will represent greater risk for the reward
  – Post-marketed CER studies (e.g., ENHANCE) will loom for any product making it to market
This will put more pressure on the traditional pharma model

\[ \text{Portfolio Productivity} = \frac{\sum P_i V_i}{\sum C_i} \]

- \( V_i \) = Expected Commercial Value Given a Product for Asset \( i \)
- \( C_i \) = Expected Development Cost to Completion for Asset \( i \)
- \( P_i \) = Probability of a Commercial Product from Asset \( i \)

Need more shots on goal

Tougher safety hurdles

Harder to differentiate

Smaller, nichier products

More challenges

Larger studies

Longer development times

Need more shots on goal
Health care reform can provide a positive challenge for pharma...

- For *in-market* products, some will benefit and some will lose from CER and SENTINEL
- For *late-stage products*, we need to find clear differentiation and thoroughly understand where the TA class is in terms of competitive dynamics
  - With a greater premium on acceptance and adoption we must focus on these as success measures rather than registration alone
  - We need to address pricing and stratification (all the way to “targeted therapies”) with appropriate trial design
  - We need to make sure incentives are aligned with market success
- For *early-stage products*, we must try to simulate their effects as early as possible and drive them to failure as early as possible, if they are going to fail
“As this is your proposal, Cosgrove, its failure could mean the end of your career. I think, however, that is an acceptable risk.”