Potential Consequences of Comparative Effectiveness Research for Biopharmaceutical Innovation

Professor John Vernon
University of North Carolina at Chapel Hill
National Bureau of Economic Research

Third Annual National CER Summit
Washington, DC
October 13-14, 2011

This presentation is based on (1) research ongoing with Robert Dubois and Jennifer Graff of the National Pharmaceutical Council; and (2) research with Robert Goldberg and Peter Pitts of CMPI
Agenda

- Why should we care so much about biopharmaceutical research and development (R&D) and innovation? Don’t we have too many marginal innovations and “me-too” products?
  - New economic research and evidence on the socio-economic value of medical and biopharmaceutical research: orders of magnitude > cost
- It is unclear how CER will evolve in the U.S. and therefore if and by how much R&D and innovation will be affected
- Economic theory of investment and the determinants of biopharmaceutical R&D: principal ways CER could impact R&D
- Policy and legislative considerations: balancing the benefits and costs
Perspectives on biopharmaceutical productivity and the value of innovation

“The failure of the pharmaceutical industry to produce drugs for common chronic diseases, emerging diseases, and the potential threats of bioterrorism or the spread of tropical diseases contrasts sharply with the industry’s output of lifestyle and "me-too" drugs”

--Health Affairs [article abstract]

“The number of new products in the development pipeline is not where we’d like it to be. Timelines are long, costs are high, and failure rates are distressingly high…Federal regulators need to be a gateway not a barrier”

--FDA Commissioner Hamburg

“Critics decry the lack of 'truly innovative' new medicines and question the role of the pharmaceutical industry in creating the few that are developed. Is this an accurate portrayal of the state of pharmaceutical innovation? Does major pharma still innovate?”

--Nature Reviews Drug Discovery [article abstract]

“Pharma’s R&D Future is Questioned”

--News Story Headline, The PharmaTimes
A broader economic perspective on R&D and innovation: new evidence and its implications

- A growing body of empirical economic research offers an alternative perspective (Lichtenberg, 2004, 2006; 2010; Murphy and Topel, 2003, 2006; Nordhaus, 2005)

- **Retrospective Findings:** the economic value associated with more and better healthcare treatment options and outcomes has roughly equaled the sum total of all other economic production in the past half century--in 2010 alone the U.S. economy produced $14.6 trillion in output
  - A 2006 study estimated that over the period from 1960 to 2001 for ever $926 invested in pharmaceutical R&D the U.S. gained a single life year
  - If a life year is conservatively valued at $50,000 this is a 5,300% ROI for society

- **Prospective Estimates:** a single percent (1%) reduction in cancer mortality would have a value to society of $800 billion
  - This $800 billion value could alternatively be achieved by reducing age-specific death rates in either breast cancer or digestive cancer by 10%
  - Implication: an investment of $80 billion would be worth while if it had at least a 1 in 10 chance of reducing cancer mortality by 1 %
  - An investment program of $800 million would be worth while if it had at least a 1 in 1,000 chance of reducing cancer mortality by 1 % (a NME has been estimated to cost $802 million)
Which perspective is correct? Does it depend on the point of reference?

- For the sake of argument accept as given the following two priors about a hypothetical investment game or gamble:
  - Any investment (gamble) with a 1 in 1,000 chance of reducing cancer mortality by a single percent is a good investment (bet) for society
  - Societal returns (winnings or payout) from this investment (gamble) are vastly underestimated or obfuscated in some way, both prospectively and retrospectively, even after an investment or bet pays off

- Then observing repeated investments being made, or gambles being placed, might look like a very inefficient and wasteful way to allocate one's resources.

- Similarly, repeated investments (bets) of $800 million to develop a new drug with a 1 in 1,000 chance of reducing cancer mortality might look very inefficient.

- **Conclusion:** someone who believes these economists, who are among the world’s most preeminent, have only a 1 in 100 chance of being correct (assume there is a 99 in 100 chance value is nil, to be very conservative), then expected R&D productivity and the value of innovation are still of a very large order of magnitude and we should be quite concerned with how new policies and regulations might affect R&D investment levels and the social value it produces.
The form CER will ultimately take in the U.S. is uncertain: this will determine how innovation incentives are affected.

---

**CER Creates Incentives**

Does Comparative-Effectiveness Research Threaten Personalized Medicine?

Alan M. Garber, M.D., Ph.D., and Sean R. Tunis, M.D.

As CER guides individual patient care, it will also guide and promote innovation. In some cases, federal support of the research will reduce the development costs of new medical technologies. Emerging CER methods promise to be more rapid, relevant, and efficient.

---

**CER Decreases Incentives**

CER Could Lead to $10 Billion per Year Drop In R&D – Think Tank Analysis

August 08, 2011

Investments in drug and medical device research and development will decrease as comparative effectiveness research conducted under the Patient-Centered Outcomes..

---

Garber AM, Tunis SR. NEJM 2009; 360;19; Peterson NEJM 2009; Murray Arch Intern Medicine 2010; .; The Pink Sheet August 8, 2011
Research methods and modeling perspectives: recent studies and ongoing work

- Because of the uncertainty around CER policy we model a range of scenarios and consider how innovation incentives and R&D investment are affected under each
  - **Micro-case perspective**: Case applications and the phase III go-no-go development decision: under which CER scenarios and economic assumptions would the case study drug have been terminated due to unfavorable financial prospects
    - TNF-α Inhibitors
    - Lucentis for AMD
  - **Industry-level perspective**: Simulation models calibrated using industry-average data and parameter estimates from econometric analyses of the determinants of biopharmaceutical R&D investment
    - A CER-induced 50 percent increase in average phase III clinical trial size → a 15 percent increase in average total drug development costs → 2.5 percentage point decline in average industry profit margins → 10 percent decline R&D spending or $6B (off a base of $60B)
      → Long run implications are greater because the policy-induced shift to a lower equilibrium investment level carries forward into future years: using a social discount rate of 8 percent present value forgone R&D is $75B (over 10 years it is about $40B)

- **Starting point**: Economic theory of investment and the firm R&D budgeting decision
Conceptual Model and the Firm Perspective

Determinants of R&D Investment Demand

Expected market size
Product attributes
Drug development cost
Probability of technical success
Effective patent life

CER Policy Scenario

R&D Project Expected Cash Flows

Financial risk (cost of capital)
May not be exogenous to CER

E(NPV₀) = \sum_{t=0}^{T} \frac{E(C_t)}{(1 + r)^t} = E(C₀) + \frac{E(C_1)}{(1 + r)} + \frac{E(C_2)}{(1 + r)^2} + \frac{E(C_3)}{(1 + r)^3} + \ldots + \frac{E(C_T)}{(1 + r)^T}

Improved Health = Social Value

Innovation

R&D Investment
Hypothetical life-cycle cash flow profile for a biopharmaceutical R&D project

How might CER change the shape of a project’s expected cash flow profile?

\[
E(\text{NPV}_0) = \sum_{t=0}^{T} \frac{E(C_t)}{(1 + r)^t} = E(C_0) + \frac{E(C_1)}{(1 + r)^1} + \frac{E(C_2)}{(1 + r)^2} + \frac{E(C_3)}{(1 + r)^3} + \ldots + \frac{E(C_T)}{(1 + r)^T}
\]
Three hypothetical CER policy scenarios and their impact on expected life-cycle cash flows

![Graph showing net revenues over years for different scenarios: FDA App. A, FDA App. B and C, E(CF) Scenario A, E(CF) Scenario B, E(CF) Scenario C. The graph illustrates the financial impacts in clinical trials and post-launch phases.]
A closer look at $C_t(\cdot)$ and factors that affect expected future cash flows and thus expected investment returns to biopharmaceutical R&D

- **Demand for R&D Investment**
  - Product market demand (expected profitability)
    - Target population; disease prevalence
    - Product attributes
    - Effective patent life
    - Competition
    - Reimbursement and formulary placement
    - Government regulations and health policies
  - Product market supply
    - Clinical development time and cost
    - Clinical trial sizes
    - Number of clinical trials
    - Clinical trial length and complexity
    - Probabilities of technical success and attrition
    - Production, marketing, and distribution costs

- **Supply price of (R&D) capital**
  - Financial or systematic risk; beta
2 Case Examples

Case 1: TNF-Inhibitor
- Approval based upon ACR20 scores at 24 weeks vs. methotrexate and placebo
- Request for long-term data, joint progression
- Sequencing

Case 2: Lucentis for AMD
- FDA approval based upon 1300 patients for visual acuity vs. placebo
- NIH sponsored CATT study compared to off-label Avastin is a 4 year study
  - Interim data generated controversy in approval and Medicare Coverage questions

AMD: Age-related Macular Degeneration; CATT: Comparison of Age-related macular degeneration Treatments Trial
TNF-α inhibitors CER case study and possible CER effects on key model variables (R&D determinants)

<table>
<thead>
<tr>
<th>Investment Demand for R&amp;D</th>
<th>TNF Joint Progression</th>
<th>TNF Sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product Market Demand Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Market Size Disease Prevalence</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Pricing, Market Access, Formulary Placement</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Effective Patent Life</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Competition and Barriers to Entry</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>Regulatory Stringency</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td><strong>Product Market Supply Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical-Drug Development Times</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Clinical Trial Size and Length</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Number and Complexity of Trials</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Probabilities of Technical Success by Stage</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Probability of FDA Approval/Priority Review</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td><strong>Supply Cost of R&amp;D Capital</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Net Impact on R&amp;D Investment</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lucentis for AMD CER case study and possible CER effects on key model variables (R&D determinants)

<table>
<thead>
<tr>
<th>Investment Demand for R&amp;D</th>
<th>CATT for Approval</th>
<th>CATT for Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product Demand</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Market Size Disease Prevalence</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Pricing, Market Access. Formulary Placement</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Effective Patent Life</td>
<td>↓↓↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Competition and Barriers to Entry</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Regulatory Stringency</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td><strong>Product Supply</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical-Drug Development Times</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Clinical Trial Size and Length</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Number and Complexity of Trials</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Probabilities of Technical Success by Stage</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Probability of FDA Approval/Priority Review</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td><strong>NET IMPACT</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Policy Considerations in the News

- CMS use of CER in Coverage and Decision-Making
- Coverage with Evidence Requirements
- Product Labeling includes CER
- Market Approval Contingent Upon CER

Impact on Innovation?

Tradeoffs for Innovation Incentives

**Incentives**
- Personalized medicine ($ and savings in R&D)
- New trial designs
- Broader Outcomes
- ↑ adoption of effective treatments

**Disincentives**
- Active comparisons
- Precision/Cost of Perfect Information
- Long-Term endpoints
- Trial Subgroups
Policy Considerations Commiserate with A Net Incentive for Innovation

Regulatory Considerations
- Regulatory reform incentives to reduce cost/time to approval
- Broader and aligned endpoints and trial designs
- Patient extension or other incentives for products with comparative data
- Awareness of communication needs for patient-centered outcomes

Market Considerations
- Increased and earlier agreement on endpoints to decrease development uncertainties
- Increased collaborations with public/private data to allow for real-time evidence development
- Increased certainty of evidence thresholds for adoption
- Increased value thresholds for CER evidence
Diminishing returns and the implications for the cost-benefit calculus of net benefit on the margin
A balanced assessment of any new policy or regulation must consider explicit tradeoffs.

**Type II Costs**: reduced access to innovations and their benefits because of longer drug development times and diminished R&D investment incentives.

**Type I Costs**: poor clinical outcomes and effects due to treatment imprecision—perhaps resulting from the use of surrogate endpoints.
Improved treatment precision and outcomes using CER will come at a cost: less innovation and access to future drugs.
CER and Innovation: Two Elements Frequently Forgotten

Subsequent Indications

Incentives for Developing Future Products

- Product A
- Product A’
- Product B
- Product C
Awareness of the Potential Implications of CER on Innovation

- PCORI Statute\(^1\)

“(iv) Not less frequently than every 5 years….Such review shall include an analysis of the extent to which research findings are used by health care decision-makers, the effect of the dissemination of such findings on reducing practice variation and disparities in health care, and the effect of the research conducted and disseminated on innovation and the health care economy of the United States”
CER and innovation: considering the policy and legislative options on an empty stomach because there is no “free lunch!”

- **There are unavoidable tradeoffs**
  - Making these tradeoffs without due consideration to the long-run consequences (costs and benefits) is unwise

- **Potential tradeoffs between CER and innovation**
  - CER can lead to significant expansions in our understanding of the absolute and relative treatment efficacies of different pharmaceutical therapies
  - CER can be therefore be used to develop more efficient treatments guidelines and protocols and can improve the quality of healthcare delivery
    - A good thing all else held constant (like safer FDA-approved drugs)
  - Surrogate endpoints versus clinical endpoints
    - Degrees of predictability
    - Better information about clinical efficacy
    - The cost of obtaining the better (perfect) information
    - Striking a balance or going to extremes
Conclusions

- A new and growing body of economic research suggests that the socio-economic value of biopharmaceutical R&D and innovation may be far greater than we realize
  - Careful attention to policies affecting private-sector R&D investment levels is warranted
- Biopharmaceutical investment has been shown to be highly sensitive to policies and regulations
- CER is a policy with identifiable causal links into important and well-studied determinants of pharmaceutical R&D investment.
- Uncertainty around how CER will evolve and take shape makes predicting the impact on R&D difficult
- Tradeoffs are unavoidable and there are no “free lunches” unfortunately
- As CER develops, consideration of net impact on innovation is needed or a systematic re-balance may be needed