Advancing Healthcare™

Improving Pharmaceutical Innovation By Building A More Comprehensive Database On Drug Development and Use

Jonathan S Leff
March 13, 2015
Available Metrics Point to Long-Term Decline in BioPharma R&D Productivity

Source: Health Affairs, February 3, 2015

Policy Makers Are Looking For Solutions

Public Law 112–144
112th Congress
An Act
To amend the Federal Food, Drug, and Cosmetic Act to revise and extend the
user-fee programs for prescription drugs and medical devices, to establish user-
fee programs for generic drugs and biosimilars, and for other purposes.

Be it enacted by the Senate and House of Representatives of
the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.
This Act may be cited as the “Food and Drug Administration
Safety and Innovation Act”,

July 9, 2012
[S. 3187]
Food and Drug Administration
Safety and
Innovation Act.
21 USC 301 note.

REPORT TO THE PRESIDENT ON
PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT,
AND EVALUATION

Executive Office of the President
President’s Council of Advisors on
Science and Technology
SEPTEMBER 2012

21st Century Cures: A Call to Action

Overview

For decades, our nation’s commitment to the discovery, development, and
delivery of new treatments and cures has made the U.S. the biomedical innovation
capital of the world, bringing life-saving drugs and devices to patients and well over a
million high-paying jobs to local communities. This success has not gone unnoticed
in the rest of the world, and other nations are now actively working to gain a
competitive edge in various elements, whether through a focus on basic research or a
streamlined approval process to bring new treatments to market more quickly.

It is clear that the discovery, development, and delivery process is a cycle,
meaning that even data captured and analyzed at one stage can lead to
the “next” phase of the process. The delivery phase is the focus of this report.

As part of the 21st Century Cures initiative, the committee will issue a series of
white papers seeking input and soliciting ideas on how Congress can help accelerate
the discovery, development, and delivery of promising new treatments to patients.
To accomplish our objectives, we must ensure that this cycle is robust—and
embraces—by the regulatory policies we have in place.

We know our goal is shared by the National Institutes of Health (NIH), Food
and Drug Administration (FDA), and other agencies, as well as by our nation’s
payers and scientific partners in academia and industry. We also recognize that
much work remains to be done. According to the President’s Council of Advisors on
Science and Technology (PCAST), “the pace of new therapeutic development has not
kept up with the explosion of scientific knowledge.”

[1] See Miller Institute, Accelerating Innovation in the Biomedical Research Sector: Report from the
# How Can We Fix It If We Can’t Measure It?

## Commonly Cited Metrics
- NME approvals per year
- R&D spending
- Venture capital investment
- New company formation
- FDA performance metrics
- Cost of drug development
- Success rates in development

## Limitations
- Incomplete picture of innovation process
- Inconsistent or incomplete data sources
- Survey-based as opposed to comprehensive
- Metrics not routinely collected and updated
- Lack of broad access to underlying data
Primary objective: develop, populate, maintain and make publicly available a comprehensive repository containing key metrics of new drug development, utilization and impact.
# Proposed Research Categories and Initial Data Elements

<table>
<thead>
<tr>
<th>Research category</th>
<th>Example questions</th>
<th>Data sets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measuring characteristics of approved drugs</td>
<td>What is the impact of X policy on successfully marketed drugs? How are trends in development timelines and costs different by therapeutic area?</td>
<td>[Public data on approved NMEs]</td>
</tr>
<tr>
<td>Measuring impact of new drugs on health outcomes</td>
<td>How does the postmarket/clinical use environment change the way we view innovation? How can we better define innovative by including more patient-centric parameters?</td>
<td>[Public data on approved NMEs] + [Clinical outcomes data]</td>
</tr>
<tr>
<td>Measuring drivers of development success</td>
<td>What are the drivers of success overall and at each stage of development? What are the commonalities between drugs that are not approved, and how do these trends differ from those drugs that complete regulatory review?</td>
<td>[Public data on approved NMEs] + [Data on non-approved products]</td>
</tr>
<tr>
<td>Measuring “macro” influences on innovation</td>
<td>What are the broader underlying characteristics of therapeutic areas that enable innovative drug development? How does the number or output of PPPs dedicated to a specific therapeutic area affect downstream innovation?</td>
<td>[Data on therapeutic area-wide characteristics] + [Public data on approved NMEs] + [Clinical outcomes data]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>EXHIBIT 4</strong></th>
<th>Initial Data Elements for the Proposed First Phase of a Database on Approved New Molecular Entities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category of Information</strong></td>
<td><strong>Data elements</strong></td>
</tr>
<tr>
<td>Background</td>
<td>Unique drug identification number, Trade name, Active ingredient, Drug class, Therapeutic area, Innovation category, Sponsor company size</td>
</tr>
<tr>
<td>Patent and early-stage development</td>
<td>Inventor name, Country of origin, Initial patent approval date, Patent sponsor, Country of origin for mechanism of action, Companies that played a role in development, Funding sources</td>
</tr>
<tr>
<td>Clinical trial</td>
<td>Date first used in humans, Number of healthy trial volunteers, Number of enrolled patients, Number of trials sites in the US, EU, Japan, and rest of world, Number of centers enrolling patients</td>
</tr>
<tr>
<td>Regulatory review</td>
<td>Company filing in the US or EU, Primary filing day, FDA review tools used (such as Priority Review), EMA priority review status, Primary indication in US or EU, Additional indications in US or EU</td>
</tr>
<tr>
<td>Academic publication</td>
<td>Number of articles, Average impact factor, First appearance in literature</td>
</tr>
<tr>
<td>Price and uptake</td>
<td>Type of uptake curve, Initial price, Current price, Peak year for sales, Blockbuster status</td>
</tr>
<tr>
<td>Competitors and generic products</td>
<td>Date of market entry, Pricing, Uptake, Development characteristics</td>
</tr>
</tbody>
</table>
Path To Success

- **Commitment**: Brookings and Deerfield have developed the database concept with input from a variety of stakeholders, and are now committing substantial resources to support database development and data collection.

- **Collaboration**: create a consortium of healthcare stakeholders who share the vision of providing broad access to new drug innovation metrics.

- **Expertise**: Build consensus around key metrics and methodology.

- **Accuracy**: Efficient sourcing of the data is a top priority.
Next Steps

- Engage with key stakeholders who can contribute thought-leadership and data sources
- Develop expert groups to build consensus on research questions of interest, database design and definitions of data elements
Thank you
Tracking Innovation: Recent Research

Brookings Institution
March 13, 2015
Decline In Economic Returns From New Drugs Raises Questions About Sustaining Innovations

Ernst R. Berndt, Louis E. Seley Professor in Applied Economics, Alfred P. Sloan School of Management, MIT
Deanna Nass, Michael Kleinrock, Murray Aitken, IMS Institute for Healthcare Informatics

Research supported in part by the Pharmaceutical Research and Manufacturers of America, who provided funding for the data analysis undertaken by the IMS Institute for Healthcare Informatics.
Average Present Value Of Lifetime Global Net Sales Of Novel Active Substances (NASs) By Launch Cohort

<table>
<thead>
<tr>
<th>Launch Cohort</th>
<th>Small Molecules</th>
<th>Biologics</th>
<th>All NASs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991-94</td>
<td>$3.3</td>
<td>$4.2</td>
<td>$3.4</td>
</tr>
<tr>
<td>1995-99</td>
<td>$4.2</td>
<td>$7.7</td>
<td>$4.6</td>
</tr>
<tr>
<td>2000-04</td>
<td>$4.8</td>
<td>$5.8</td>
<td>$5.1</td>
</tr>
<tr>
<td>2005-09</td>
<td>$2.9</td>
<td>$2.7</td>
<td>$2.9</td>
</tr>
</tbody>
</table>

SOURCE: Authors’ analysis of 1991-2012 data from IMS Health Inc.’s MIDAS database. NOTE: Average present value is the value discounted for the cost of capital, reflecting the time value of money.
Average Lifetime After-tax Net Economic Returns Of Novel Active Substances (NASs), By Launch Cohort

SOURCE: Authors’ analysis of 1991-2012 data from IMS Health Inc.’s MIDAS database.
PRECLINICAL PIPELINE BY ATC LEVEL

Source: IMS R&D Focus; IMS Institute analysis
### Average and Time for R&D Projects to Progress to Next Phase of Research

<table>
<thead>
<tr>
<th></th>
<th>Phase I to II</th>
<th>Phase II to III</th>
<th>Phase III to Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010-14</td>
<td>25</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>2005-09</td>
<td>22</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>2000-04</td>
<td>18</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td><strong>Traditional</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010-14</td>
<td>23</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>2005-09</td>
<td>21</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>2000-04</td>
<td>18</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td><strong>Specialty</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010-14</td>
<td>28</td>
<td>35</td>
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Source: IMS R&D Focus; IMS Institute analysis
State of Biomedical Innovation CER

Presentation at Brookings

March 13, 2015
Peter J. Neumann, Sc.D.
Tufts Medical Center
Measuring innovation

1. Tufts Cost-Effectiveness Analysis Registry

2. QALY gains

3. Predicting coverage/reimbursement
1. Tufts Cost-Effectiveness Analysis Registry

www.cearegistry.org
Cost/QALY Ratios

\[
\frac{\text{COSTS}}{\text{QUALITY-ADJUSTED LIFE YEARS}}
\]
Cost Effectiveness of Selected Interventions

- Cost-saving
- $20k/QALY
- $50k/QALY
- $150k/QALY
- $500k/QALY

1. Vaccination of infants against chickenpox
2. Gene assay guiding chemotherapy in breast cancer patients
3. Sofosbuvir treatment of HCV
4. Screening 65 year-old men for osteoporosis
5. CT screening for lung cancer
6. Lung volume reduction surgery in non-high-risk patients
2. QALY GAINS
Despite High Costs, Specialty Drugs May Offer Value For Money Comparable To That Of Traditional Drugs

ABSTRACT Specialty drugs are often many times more expensive than traditional drugs, which raises questions of affordability and value. We compared the value of specialty and traditional drugs approved by the Food and Drug Administration (FDA) in the period 1999–2011. To do this, we identified published estimates of additional health gains (measured in quality-adjusted life-years, or QALYs) and increased costs of drug and health care resource use that were associated with fifty-eight specialty drugs and forty-four traditional drugs, compared to preexisting care. We found that specialty drugs offered greater QALY gains (0.183 versus 0.002 QALYs) but were associated with greater additional costs ($12,238 versus $784), compared to traditional drugs. The two types of drugs had comparable cost-effectiveness. However, the distributions across the two
# QALY gains by FDA designation

<table>
<thead>
<tr>
<th>FDA designation</th>
<th>Mean QALY Gains of Drugs</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rapid review</td>
<td>Regular review</td>
<td></td>
</tr>
<tr>
<td>Fast-track (24 of 102 drugs)</td>
<td>0.34</td>
<td>0.12**</td>
<td></td>
</tr>
<tr>
<td>Accelerated approval (15 of 102 drugs)</td>
<td>0.43</td>
<td>0.13**</td>
<td></td>
</tr>
<tr>
<td>Priority reviewer (54 of 102 drugs)</td>
<td>0.35</td>
<td>-0.02**</td>
<td></td>
</tr>
</tbody>
</table>

** p < 0.05  
Chambers et al., 2015. Preliminary data. ** > 0.05
3. Predicting coverage

Perspective

Medicare’s Enduring Struggle to Define “Reasonable and Necessary” Care

Peter J. Neumann, Sc.D., and James D. Chambers, Ph.D.
Policy implications

- Focus on value not cost
- Quantify innovation/value
- The information can inform decisions
- But combine with changed incentives
Therapeutic Context and the Cost of Drug Development

Marta E. Wosińska, PhD
Director, Economics Staff
Office of Program and Strategic Analysis (OPSA)
Center for Drug Evaluation and Research (CDER)

March 13, 2015
Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.
Q: How much does it cost to develop a drug? A: It varies greatly.

Three-Year Rolling Average Cash Costs to Develop an Asset from Discovery to Launch

Therapeutic context helps explain variation in R&D costs

- Therapeutic context reflects:
  - Characteristics of the disease (the What)
  - Level of scientific knowledge (the Why)
  - Existing treatment options (the How)

- Relevant because it is the context for the regulator’s determination whether benefits outweigh the risks

- Therapeutic context has implications for R&D cost through:
  - Its impact on study design
  - Its impact on the timing of trials
Characteristics of the disease: the *What* of therapeutic context

- **Examples of impact on trial design:**
  - In general, chronic/episodic conditions require long studies if no surrogate endpoints are available.
  - Does the drug try to prevent an infrequent event?

- **Examples of impact on trial timing:**
  - Phase 1 might be combined with Phase 2 if drug is expected to have toxicity unacceptable for healthy volunteers.
  - After establishing efficacy, regulator may accept a greater risk for severe diseases with few or no treatment options.
Scientific knowledge: the *Why* of therapeutic context

- Understanding disease pathophysiology, biochemical and genetic underpinnings of disease helps:
  - Lower cash costs if firms do not have to do such research
  - Lower failure cost by pointing out dead ends
  - Identify which people are likely not to respond or likely to experience side effects
  - Cut trial length if surrogate endpoints are established

- Examples:
  - Disappointments in Alzheimer’s
  - Success stories in HIV and cancer
Existing therapeutic options: the *How* of therapeutic context

- Therapeutic options determine the extent of unmet medical need for a given indication

- Impact on trial design
  - Active control may be used for ethical reasons
  - Generally, establishing superiority or non-inferiority may require a large sample size

- Impact on trial timing
  - Regulator may less willing to accept more uncertainty around a drug’s safety profile if safe and efficacious therapies abound
Visualizing therapeutic context in the clinical development process...

Example (example drug)

Pivotal Trial Marker

Phase 1

Phase 2

Phase 3

Phase 4

NDA Submitted

NDA Approved

Years since NDA Approval

-8 -6 -4 -2 0 2 4
Brilinta (ticagrelor)

Note: Trial data from clinicaltrials.gov; not all trials may be in the database.
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Sovaldi (sofosbuvir)

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Summary of Enrollment in Pivotal Trials
NME Approvals 2011-2014, by Review Division

Patients Enrolled in Pivotal Trials, per Approval

- Cardiovascular
- Metabolism and Endocrinology
- Reproductive and Urologic
- Pulmonary, Allergy, and Rheumatology
- Antiviral
- Psychiatry
- Anti-Infective
- Neurology
- Transplant and Ophthalmology
- Dermatology
- Gastroenterology
- Oncology
- Medical Imaging

Marta Wosinska, PhD
CDER Economics

Mean
Min Median Max
Therapeutic context is an important driver of drug development cost

- **Implications for researchers:**
  - When studying R&D costs and/or drug development timelines, account for the what, why, and how of therapeutic context

- **Implications for policymakers:**
  - The “What” of therapeutic context is a given
  - The “How” or how we treat is a measure of our past success
  - But the “Why” can be affected with investments in scientific infrastructure
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Source: Measuring the Return from Pharmaceutical Innovation, Deloitte (2014)
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Min, Median, Mean, Max

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