Acknowledgements and disclaimer

• The basis of this presentation is work done in collaboration with Peter Bach, Ernst Berndt, Melinda Buntin, Stacie Dusetzina, David Howard, Sayeh Nikpay, Blasé Polite, Meredith Rosenthal, Josh Sharfstein, Jeff Ward.

• I am grateful for the support of the NIH NCI, National Institute on Aging, The Commonwealth Fund, the American Cancer Society and the National Bureau of Economic Research.

• I have benefited from extraordinary data support from IQVIA/QuintilesIMS, and from discussion of regulatory and legal issues with Karl R. Karst of Hyman, Phelps and McNamara PC.

• I am undergoing the last stages of vetting to be an economist at the FDA.

• Opinions expressed are mine alone and publicly available in a series of peer reviewed publications.
We stand in the midst of incredible scientific breakthroughs.
Unprecedented wave of new drugs: >7,000 in development

Alzheimer’s  
PREVALENCE  5.4 million  
ANNUAL COST  $35,000

Cancer  
PREVALENCE  14 million  
ANNUAL COST  >$100,000

High Cholesterol  
PREVALENCE  71 million  
ANNUAL COST  >$14,000

Source: 2015 Profile Biopharmaceutical Research Industry, PhRMA
Patients’ access to some effective treatments is limited.
Medicines are increasingly salient to national spending.

### Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>Personal Health Care (PHEC)</th>
<th>Retail Prescription Drugs</th>
<th>Non-Retail Prescription Drugs</th>
<th>Total Prescription Drugs</th>
<th>Percent of all PHEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>2,118</td>
<td>255</td>
<td>99</td>
<td>354</td>
<td>16.7</td>
</tr>
<tr>
<td>2010</td>
<td>2,196</td>
<td>256</td>
<td>100</td>
<td>356</td>
<td>16.2</td>
</tr>
<tr>
<td>2011</td>
<td>2,282</td>
<td>263</td>
<td>103</td>
<td>366</td>
<td>16.0</td>
</tr>
<tr>
<td>2012</td>
<td>2,379</td>
<td>264</td>
<td>103</td>
<td>367</td>
<td>15.4</td>
</tr>
<tr>
<td>2013</td>
<td>2,469</td>
<td>271</td>
<td>106</td>
<td>377</td>
<td>15.3</td>
</tr>
<tr>
<td>2014*</td>
<td>2,596</td>
<td>305</td>
<td>119</td>
<td>424</td>
<td>16.3</td>
</tr>
<tr>
<td>2015*</td>
<td>2,729</td>
<td>328</td>
<td>128</td>
<td>457</td>
<td>16.7</td>
</tr>
<tr>
<td>2016*</td>
<td>2,862</td>
<td>343</td>
<td>134</td>
<td>477</td>
<td>16.7</td>
</tr>
<tr>
<td>2017*</td>
<td>3,016</td>
<td>364</td>
<td>142</td>
<td>506</td>
<td>16.8</td>
</tr>
<tr>
<td>2018*</td>
<td>3,184</td>
<td>385</td>
<td>150</td>
<td>535</td>
<td>16.8</td>
</tr>
</tbody>
</table>

* Projected.

Source: CMS, National Health Expenditure (NHE) Amounts by Type of Expenditure and Source of Funds: Calendar Years 1960-2024. The projections are based on the 2013 version of the NHE released in December 2014.

1 Estimated based on the assumption that non-retail drugs are 28 percent of all drug expenditures.
Exhibit 10: Brand Spending Growth of Specialty and Traditional Drugs 2013-2022 in the Developed Markets

Exhibit 3: Number of Next Generation Biotherapeutics Currently Marketed or in Late-Stage Pipeline

Source: IQVIA Institute, Oct 2017
Notes: Developed markets include: U.S., Japan, Germany, France, Italy, U.K., Spain, Canada, S.Korea, Australia.

Source: IQVIA Institute, IQVIA R&D Insight, Jan 2018
Notes: Reg = Registered.
Patient out of pocket spending on drugs is growing
Who is to blame for high prices? 1961 to 2016
Who is to blame?

Greedy ______________________

✓ Pharmaceutical companies
✓ Insurers
✓ PBM/Pharmacies
✓ Physicians/hospitals/patients

@contirena1
Spending growth: a mix of price and volume growth

Chart 8: Net Medicines Revenue Growth and Contribution by Type

Understanding the Drivers of Drug Expenditure in the U.S. Report by the QuintilesIMS Institute

Source: QuintilesIMS, National Sales Perspectives, Market Prognosis, QuintilesIMS Institute, Mar 2017
Overprescribing is major contributor to opioid crisis

*BMJ* 2017; 359 doi: [https://doi.org/10.1136/bmj.j4792](https://doi.org/10.1136/bmj.j4792) (Published 19 October 2017)

**Fig 1** Distribution of surgeons by number of opioid pills they prescribed after laparoscopic cholecystectomy.
Why are prescription drug prices high and growing?

A closer look at current incentives for pricing new drugs.
Manufacturers practice monopoly “by design” pricing

- Patent system fixes a “market failure” (time inconsistent preferences):
  - Encourages private flow of capital into risky, time intensive, uncertain investment in innovation.

- Manufacturers face an inelastic downward sloping demand curve.

- Where should pricing be set under these conditions?
  - Let’s draw a picture of demand for these drugs and discuss.
Does that mean that increasing prices reflect increased “value”?

• An empirical question!

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval
1965-2016

Source: Peter B. Bach, MD, Memorial Sloan Kettering Cancer Center
Data

- Anticancer drugs approved 1995-2013.
- Price = amount paid by Medicare based on typical intensity and duration of use, stated in 2013 USD.
- Survival benefit = increase in median survival time in months between treatment and control.
- Other attributes: side effects, approval basis, administration route.

Pricing formula

<table>
<thead>
<tr>
<th>Approval year</th>
<th>IV</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre-1997</td>
<td>100% of AWP</td>
<td>100% of AWP</td>
</tr>
<tr>
<td>1997-2003</td>
<td>95% of AWP</td>
<td>95% of AWP</td>
</tr>
<tr>
<td>2004</td>
<td>85% of AWP</td>
<td>85% of AWP</td>
</tr>
<tr>
<td>2005-2006</td>
<td>106% of ASP</td>
<td>106% of ASP</td>
</tr>
<tr>
<td>2006-2007</td>
<td>106% of ASP</td>
<td>Medicare price</td>
</tr>
<tr>
<td>2008-2012</td>
<td>100% of WAC</td>
<td>Medicare price</td>
</tr>
</tbody>
</table>

Source: Howard, Berndt, Bach, Conti, JEP 2015
Newer drugs are not associated with greater survival benefits compared to older drugs.

Small and insignificant coefficient:
- 0.005 years of life gained;
- 95 percent CI: -0.024 to 0.034 years of life gained.

Source: Howard, Berndt, Bach, Conti, JEP 2015
Relationship between “benefit adjusted prices” & approval year

• We focus on trends in the price per life year gained
  • equals price per treatment episode (in 2013 dollars) divided by survival benefits.
• The sample average is $150,100 per year of life gained (SD: $130,500).
  • Similar to willingness-to-pay for a quality-adjusted life year (Hirth et al. 2000).

Source: Howard, Berndt, Bach, Conti, JEP 2015
In other words, in 1995 patients and their insurers paid $54,100 for a year of life. A decade later, 2005, they paid $139,100 for the same benefit. By 2013, they paid $207,000.

The best fit line is: Price per year of life gained = $101,077 + $7,396 × Approval year.
For purposes of display, we re-coded one value from $825,000 to $500,000.
RCT: randomized controlled trial. OS: Overall survival. PFS: Progression-free survival.
Table 2: Impact of approval year and other variables on the natural logarithm of the price per life year gained in $1,000s of 2013 USD for 58 cancer drugs approved between 1995 and 2013

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval year</td>
<td>0.10 [0.06, 0.14]*</td>
<td>0.10 [0.06, 0.14]*</td>
<td>0.10 [0.06, 0.14]*</td>
<td>0.10 [0.06, 0.15]*</td>
<td>0.10 [0.06, 0.15]*</td>
<td>0.09 [0.05, 0.13]*</td>
</tr>
<tr>
<td>GI complication rate</td>
<td>1.70 [0.47, 2.94]*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia rate</td>
<td>0.26 [-0.76, 1.28]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV drug</td>
<td></td>
<td>0.26 [-0.22, 0.74]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biologic</td>
<td></td>
<td>-0.15 [-0.67, 0.36]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiproduct firm</td>
<td></td>
<td>0.38 [-0.14, 0.90]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized controlled trial</td>
<td></td>
<td></td>
<td></td>
<td>0.12 [-0.45, 0.69]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression free survival</td>
<td></td>
<td></td>
<td></td>
<td>-0.36 [-0.91, 0.20]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo comparator</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.46 [-0.02, 0.94]*</td>
</tr>
<tr>
<td>R-squared</td>
<td>0.28</td>
<td>0.37</td>
<td>0.29</td>
<td>0.31</td>
<td>0.30</td>
<td>0.32</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval year</td>
<td>0.10 [0.06, 0.14]*</td>
<td>0.10 [0.06, 0.14]*</td>
<td>0.09 [0.05, 0.15]*</td>
<td>0.11 [0.06, 0.15]*</td>
<td></td>
</tr>
<tr>
<td>Priority drug</td>
<td>0.93 [0.46, 1.30]*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orphan drug</td>
<td>-0.17 [-0.67, 0.33]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ln competitors</td>
<td>-0.64 [-0.99, -0.29]*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene test</td>
<td>-0.59 [-1.05, -0.14]*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second line therapy</td>
<td>0.15 [-0.33, 0.62]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline survival</td>
<td>-0.29 [-0.53, -0.05]*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality rate</td>
<td>0.77 [-0.38, 1.92]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-squared</td>
<td>0.44</td>
<td>0.41</td>
<td>0.36</td>
<td>0.35</td>
<td>0.30</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.10
95% Confidence intervals are in brackets.
GI: gastrointestinal, IV: intravenous.
Other “obvious” explanations don’t make sense

• **Demand:**
  • Neither increases in income nor the income elasticity of the demand for health care appear to have shifted greatly.

• **Supply:**
  • Production costs likely stable over time
  • May have decreased due to firm choices and U.S. regulatory policy.
What about R&D costs?

- R&D costs are sunk, so they shouldn’t influence price setting.
- Most economists think the relationship goes in the opposite direction:
  - High prices “pull” R&D, rather than R&D costs determine price of finished product.
  - We will come back to this later.
Manufacturers might be practicing “reference pricing”

- Demanders face no direct incentives to avoid costly drugs
  - All might balk at using drugs with prices they perceive as “unreasonable”.
- Perceptions of “unreasonableness” are malleable and influenced by the prices of previously approved drugs.
  - Not necessarily within class or disease because of limited entry (winner take all markets).
Demand curve w/ loss aversion

If the reference price is $X, manufacturers can set the price of a new drug at $X + \epsilon$ without incurring a demand penalty.
Reference pricing in action: Luxturna 😊

The Most Expensive U.S. Medicine Now Has an Official Sticker Price

This gene therapy for vision loss will initially cost $850,000

“As far as the price, and the structures to pay the price, I think it’s all pretty much in line with what we’re seeing in other innovative therapies,” said Dr. Stuart Orkin, a pediatric oncologist at the Dana-Farber Cancer Institute and Boston Children’s Hospital. He cited CAR-T therapies for cancer, which cost hundreds of thousands of dollars, and newfangled immuno-oncology treatments with similar price tags.

“I feel like we made the right middle ground decision,” Marrazzo said in an interview, balancing the company’s desire to capture the economic value of Luxturna while ensuring patients will have access to the therapy.
Let’s talk more about “demand” for prescription drugs
Inelasticity of demand appears to be reinforced by payer policies

• Insurers cover specialty drugs for FDA-approved & off-label uses; no coverage exclusions.

• Limited reliance on generics, no automatic generic substitution in specialty drug classes.

• Patients face low cost sharing at the margin.

• Physicians face very limited incentives/information to be cost conscious:
  • Specialty physicians pride themselves on an attitude of “progress at any cost”.
  • Limited comparative/cost effectiveness evidence (ICER fills this void).

@contirena1
Different prices coexist for the same drug in the US

- Full, “list” price: What manufacturers charge purchasers for their product.
- Wholesale/acquisition costs: list - rebates and discounts
- Net “paid” amount: Negotiated by payer = insurer.
- Out of pocket costs: Determined by insurer.
Middlemen make money off supply chain

The ability of intermediaries to extract rents is growing

• Insurers/Hospitals/PBM/Pharmacies/Practices are “merging” and “affiliating”.
  • Causes are likely complex.
Impact of consolidation is ripe for empirical study

• Vertical consolidation promises significant social and patient benefit in the form of lower prices/spending, improved access/quality of care (reduce double marginalization, Chicago school).
• Policymakers worry vertical consolidation may have perverse effects on consumers (foreclosure; post-Chicago school).
  • Entry, exit heavily regulated.
  • Assymmetric information, agency.

Hospital consolidation with specialty practices contributes directly to pricing perversity.
Oncology Drug Profits, 340B-Covered Entities vs. Noncovered Entities, 2013

Sources: Pembroke Consulting analysis of Part B Payments for 340B-Purchased Drugs, OIG, November 2015.
Published on Drug Channels (www.DrugChannels.com) on December 1, 2015.
Complexity of system contributes to firms’ pricing practices

• Manufacturers build rent seeking activities into launch prices, price setting over time.

• Multi-product firms face choices where to rent seek off current system:
  • A subject of ongoing empirical study
  • We find preliminary evidence to suggest price increases concentrate among drugs where:
    • product characteristics or market more generally breeds inelastic demand.
Isn’t increasing reliance on generic drugs the answer?
Generics part of a “virtuous circle”, yet worry promise is fading
Suppliers of generic drugs are increasingly concentrated

• Prices of generic drugs are observed to increase statistically significantly over time; after MMA implementation prices rise 0.101 percentage points, after ACA prices rise 0.401 percentage points, and after GDUFA implementation prices rise 0.751 percentage points (Column 1) compared to the Pre-MMA period.

• We find prices are negatively associated with larger counts of corporations (Columns 2-7) and manufacturers (Columns 8-13) – a one percent increase in corporation count results in a 0.736 percentage point fall in price and a one percent increase in manufacturer count results in a 0.720 percentage point fall in price.

WHILE MOST GENERIC FIRMS HAVE SMALL DRUG PORTFOLIOS, THERE ARE A SMALL NUMBER OF “BEHEMOTH” PORTFOLIO HOLDERS

TABLE 5: ANDA PORTFOLIO SIZE AND OWNERSHIP DISTRIBUTION
AS OF SEPTEMBER 8, 2017

<table>
<thead>
<tr>
<th>ANDA PORTFOLIO SIZE</th>
<th>NO. OF SPONSORS</th>
<th>SHARE OF SPONSORS</th>
<th>NO. OF ANDAS HELD</th>
<th>SHARE OF ANDAS HELD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5</td>
<td>306</td>
<td>71.7%</td>
<td>603</td>
<td>6.0%</td>
</tr>
<tr>
<td>6-10</td>
<td>35</td>
<td>8.2%</td>
<td>266</td>
<td>2.6%</td>
</tr>
<tr>
<td>11-50</td>
<td>52</td>
<td>12.2%</td>
<td>1181</td>
<td>11.7%</td>
</tr>
<tr>
<td>51-150</td>
<td>18</td>
<td>4.2%</td>
<td>1540</td>
<td>15.2%</td>
</tr>
<tr>
<td>151-300</td>
<td>9</td>
<td>2.1%</td>
<td>1816</td>
<td>18.0%</td>
</tr>
<tr>
<td>&gt;300</td>
<td>7</td>
<td>1.6%</td>
<td>4700</td>
<td>46.5%</td>
</tr>
<tr>
<td>TOTALS</td>
<td>427</td>
<td>100.0%</td>
<td>10106</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Berndt, Conti, Murphy, “The Generic Drug User Fee Amendments: An Economic Perspective” *Journal of Law and the Biosciences*, April 2018
### Who Are the “Behemoth” Portfolio Owners in 2017?

1. TEVA Pharmaceuticals USA 1,569 ANDAs
2. Mylan Inc. 699
3. Novartis Corporation (Sandoz) 649
4. Sun Pharma 580
5. Hikma Pharmaceuticals PLC 498
6. Endo International PLC 378
7. Aurobindo Pharma LTD 327
8. Apotex Inc 288
9. Pfizer Inc (Hospira, Greenstone) 262
10. Perrigo Company PLC 228

**Total Top 10** 5,478 (54.2% of total 10,106 ANDAs)

Some of these firms also a major suppliers of branded drugs.

---

Berndt, Conti, Murphy, “The Generic Drug User Fee Amendments: An Economic Perspective” *Journal of Law and the Biosciences*, April 2018
We hypothesize:

• Number of firms able to make “generic” drugs decreasing
  • Some product markets may be experiencing reduced “contestibility”
  • Ongoing empirical work with FDA office of generic drugs/commissioner

• Contracting practices with multi-product firms may reinforce “winner take all” markets across brands and generics
  • Ongoing empirical work with Tim Simcoe
Public concern creates an opportunity for reform.

In such a complex system, there are no “silver bullets”.

@contirena1
Best reforms will embody three principals

1) Improve patient access/affordability.
2) Improve transparency, reduce rent seeking across the value chain.
3) Identify new paradigms for financing innovation.
Improve generic supply competition

• FTC/DOJ has critical role to play:
  • Increase merger scrutiny, (Congress may need to reform Scott-Hart-Rodino thresholds).
  • Vigorously pursue pay for delay & other “evergreening” activities.

• FDA has critical role to play:
  • Lower barriers to entry through GDUFA fee revisions.
  • Preserve ability to reenter molecule markets after temporary supply disruptions/exits.
  • Identify alternative suppliers meeting quality manufacturing metrics.

• Increase coordination across FTC/DOJ/FDA/CMS to focus on specific areas that matter for patient access/affordability.

@contirena1
Reduce profit seeking in the value chain

• Policymakers should reduce intermediaries ability to profit off drugs.
  • Reimbursement should favor flat fees rather than price/revenue share arrangements.
  • Existing 340B reform, proposed Part D reform are good steps forward.
  • Transparency initiatives at state level (MD, IL)

• DOJ/FTC increasing their role:
  • Increased enforcement of anti-kickback & RICO statutes.
  • Expect great scrutiny of affiliations and proposed mergers between value chain actors.
What about high prices of new innovative drugs?

- Difficult because price/expected revenue a **major** driver of R&D investment.
- So, do we do nothing?
  - No: Not obvious current system rewards the “right” mix/quantity of drugs from society’s perspective.
- Some potential fixes already exist:
  - “Value based purchasing”, advance purchasing (price/quantity) commitments (NASEM committee rec on Hep C, CARB-X, Ran White (HIV))
  - Derisk R&D even more: difficult commitment enforcement
  - Likely need more thinking, likely pilot testing.
I’m happy to discuss, debate and provide more detail.

rconti@uchicago.edu

Thank you.
Manufacturers practice price discrimination across payers based on willingness to pay.