EC 387: Pharmaceuticals

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1 References

The references for this lecture are:

1. Lakdawalla, Darius N. (2018) “Economics of the Pharmaceutical Industry." Journal of Economic Literature, 56 (2): 397-449.
2. Boller, Lysle, and Fiona Scott Morton (2017) “Enabling Competition in US Pharmaceutical Markets.” Brookings Institution, Hutchins Center Paper #30.

2 Background

While technically a healthcare provider industry, pharmaceuticals are very unique.

More than any other providers, pharmaceuticals are characterized by innovation.

- One of the highest R&D expenditures of any industry in US.

This means that any economic policy or regulation has to be contrasted with effects on R&D.

- For example, a policy that reduces drug prices now also reduces flow of new drugs in the future.

3 Pharmaceutical product life cycle

1. R&D (drug discovery): The first step is investing in R&D to discover a drug, then patenting the molecule and conducting tests for efficacy and safety.
    - After drug discovery, files patent to protect Intellectual Property (IP).
    - Trade-off between speed of development + testing and the probability of market acceptance. E.g. surrogate end points and uncertainty of outcome.

- On average, takes 8 years to move from start of clinical trials to market launch.
- Among largest drug companies, roughly 20-30 percent of drugs that began in phase I end up being approved for use.

2. Marketing of branded drug: Once approved, the patent + other market exclusivities mean the branded drug has a monopoly.
    - It only competes with other similar drugs.
    - If no other drug close to it in the product space, can charge very high prices and make large profits.
    - It is the possibility of getting these high profits that incentivizes the costly R&D in the first stage.
    - It is easy for a drug to be copied and produced by other firms; however the market exclusivity regulations stop these copycat drugs from flooding the market and bringing down price.
3. Generic competition: After patent expiration, bioequivalent products called generic drugs enter the market.
    - Generic manufacturers have to prove to FDA that they can create bioequivalent versions of the branded drug.
    - Mean approval time: 32$\sim$ months.
    - Costly but driven by motive to capture the profits of the monopoly branded drug.
    - More and more generics enter the market, intense price competition results.
    - Main driver of low pharmaceutical prices. Branded drug loses most sales after generic entry.

The branded drug's market exclusivity can be over before patent expiration through patent lawsuits by generic manufacturers.

- The lawsuit can try and show that the branded drug's patents are invalid, unenforceable, or not infringed by the generic product.
- In US these lawsuits are called Paragraph IV certifications.

4 Research and Development

To fix ideas, let's set down a simple model of R&D.

Here, a firm invests money into R&D. The R&D yields a new drug with some probability that is increasing in the amount of investment.

4.1 Simple positive theory of innovation and investment

- I: total level of investment into innovative activity
- $p(I)$: the probability of a successful discovery, where $p'(I) > 0$ and $p''(I) < 0$.
- D: the state of the world in which a discovery occurs
- N: the state in which no discovery occurs.
- $E(\pi \mid D)$: the innovator's expected profit, conditional on discovery, and similarly for $E(\pi \mid N)$. Innovation investments will be undertaken if and only if $E(\pi \mid D) > E(\pi \mid N)$.
- To allow for possibility that the firm may not have to bear all the cost of innovation -e.g., if some portion of research is publicly funded - define $\phi(I) \leq I$ as the firm's private cost of investment, I.
- r: the cost of capital.

The resources that the firm expects in the event of discovery equal

$$E(\pi \mid D) - (1 + r)\phi(I)$$

and in the event of no discovery,

$$E(\pi \mid N) - (1 + r)\phi(I)$$

Therefore, the privately optimal level of innovation is given by the solution to:

$$\begin{aligned} \max p(I)E(\pi \mid D) + (1 - p(I))E(\pi \mid N) \\ -(1 + r)\phi(I). \end{aligned}$$

This has the first-order condition:

$$p'(I)[E(\pi \mid D) - E(\pi \mid N)] = (1 + r)\phi'(I)$$

This condition implies that the marginal private cost of capital (RHS) equals the marginal private return of innovation investment (LHS).

Implications:

1. All else equal, innovation investment rises with the expected gain from discovery, which is the term in square brackets.
2. Investment also rises with increases in the marginal productivity of investment, $p(I)$.
3. Increases in the marginal cost of capital depress innovation investments.

5 Effect of consumer demand and price regulation

Expansions in market size boost pharmaceutical profits and stimulate innovation.

Price ceilings and related regulations constrain profits and reduce innovation.

5.1 Effect of market exclusivities

There are 3 types of market exclusivity protections:

1. Patent exclusivity: Remains in force for 20 years, and Hatch-Waxman Act extends this by 5 years to mitigate time lost in FDA approval process.

   However, these patents can be challenged in court and invalidated (happens somewhat frequently).

2. Regulatory exclusivity: Eliminates possibility of judicial challenges, but shortens period of protection. Some examples are:

   - Orphan Drug Act (ODA): Orphan drug is one that treats a disorder affecting fewer than 200,000 people in US.

     ODA grants an innovator an exclusive license to market an orphan drug for a specific indication for 7 years after its approval.

     Cannot be challenged in court, and no competitor can gain approval for a drug treating the relevant orphan indication.

   - Data exclusivity: Stops generics from using the safety and efficacy data generated by a pioneer firm for some period of time.

     Generics need to conduct their own costly trials to generate safety and efficacy data.

3. Natural barriers to entry in large-molecule drug markets: For large-molecule biologic products, very difficult to reverse-engineer the drug, so a non-regulatory barrier.

   Drug creation procedure can be protected through corporate secrecy.

All these market exclusivities serve to boost $E(\pi|D)$ and stimulate innovation.

6 Detour on Hatch-Waxman Act

The Hatch-Waxman Act, passed in 1984, made the following changes to US pharmaceutical regulations:

1. Patent life is extended by a portion of the time the drug is under regulatory review by the FDA.

2. A new five-year period of data exclusivity is awarded when the FDA approves marketing of a new drug.

3. Incentivizes generics firms to file Paragraph IV certifications by rewarding the first-filer with 180 days of administrative exclusivity if their ANDA is approved. During that period the FDA cannot approve another generic.

7 Endogeneity of patent length

Branded drug manufacturers often make a payment to the first-filer of Paragraph IV to delay entry (pay-for-delay or reverse payments).

- Other generics cannot enter until first-filer enters, so this holds up generic entry.
- Profitable for branded drugs because they get additional periods of market exclusivity.

  Profitable for first-filer since they get a share of the branded drugs' profits.

  Loss for consumers who continue paying high prices.
- Highly controversial practice, strongly opposed by FTC but not illegal. A 2013 Supreme Court decision made pay-for-delays easier to prosecute.

7.1 Drug formulary

Insurers create a drug formulary for their customers:

- A drug formulary is a schedule of Out-of-Pocket (OOP) costs that a consumer has to pay for each drug.
- OOP varies across drugs, and even varies across very similar drugs.
- Example: For drugs treating the same condition, the formulary can set OOP cost of \$5 for generics, \$30 for drugs in a "preferred" tier, and 20% of list price for "non-preferred tier".

How does this help?

- This tiering cost structure can steer consumers to certain drugs by charging them lower OOP costs for those.
- Can be used to steer patients towards cheap generics away from expensive brands.
- Insurers can also use the tiered structure to leverage lower drug prices from drug manufacturers.
- An insurer can even leave a drug out of the formulary, so that consumers would have to pay full list price.
- The way it works in reality: a drug manufacturer gives the insurer a discount over the list price (via a cash *rebate*) to stay in the formulary, or move up a tier compared to rival drugs.

In US, many intermediaries between the manufacturer producing the drug and the consumer using the drug.

- Drug manufacturers: Discover and/or manufacture the drug
- Pharmacy Benefit Managers (PBMs): Bargains reimbursement price with manufacturer on behalf of insurer, sets up formulary.
- Wholesalers: Delivers drug from manufacturer to pharmacy.
- Pharmacies/retailers: Dispenses drug to consumer.
- Insurers: Subsidises prescription drug for consumer, gets premium.
- Consumers: Uses the drug.

In reality, there is a multi-way bargaining game going on between all these agents.
All these agents are trying to get a bigger slice of the monetary pie.

Exhibit 1. Role of a Pharmacy Benefit Manager in Providing Services and Flow of Funds for Prescription Drugs

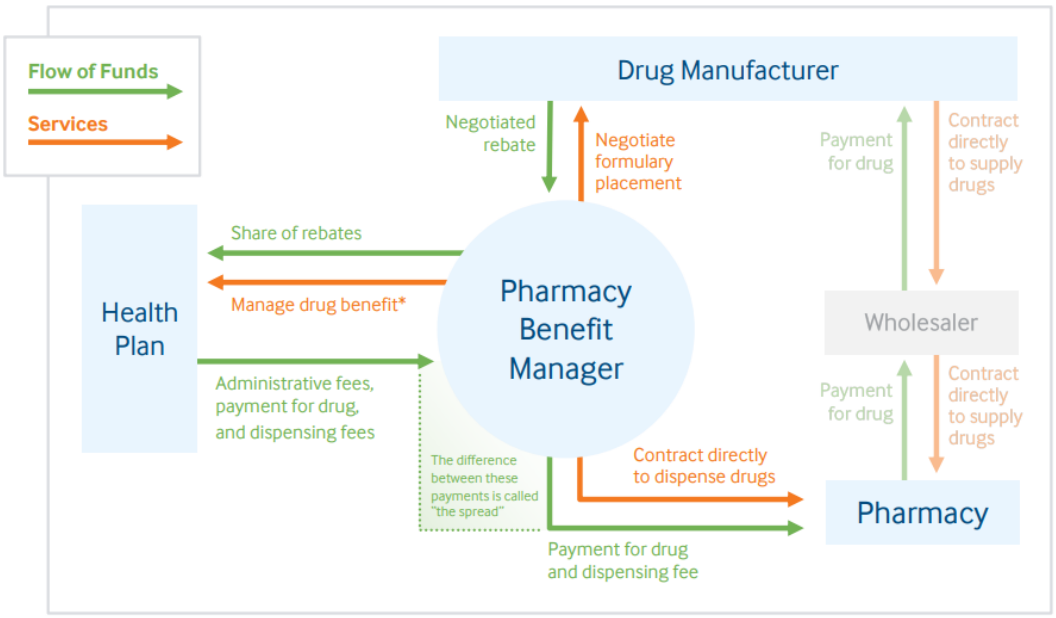

Figure 1: From Starc and Swanson (2021), "Preferred Pharmacy Networks and Drug Costs"

8 Pharmacy Benefit Managers

Pharmacy Benefit Managers (PBMs) bargain with all agents on behalf of the insurers.

How does the bargaining between PBM and drug manufacturer work?

- Each PBM has multiple insurer plans in its customer base.
- It thus controls the flow of a large amount of demand, which it can steer towards or away from a drug.
- This gives it a lot of leverage during bargaining to lower drug price. Disagreeing with a PBM over price could cause a manufacturer to lose a substantial amount of business.

How does the PBM gain? For simplicity, let's forget about the wholesalers and pharmacies.

- The PBM gets to keep a fraction of the discounts (i.e. cash rebates) that the drug manufacturer gives up to get on the insurer's formulary.

  That is, the bigger the discount they extract from the drug manufacturer, the more the insurer pays the PBM.

- How do consumers gain? The discounts get passed on by the insurer to the consumer through lower premiums.

Hopefully you can start linking this with the Nash-in-Nash bargaining model we looked at between insurers, providers and employers.

In a simplified model, the insurer bargains with the PBM over how much to pay the PBM, and the PBM bargains with the drug manufacturer over how much to pay for the drug.

- The price that the drug manufacturer can charge (i.e. list price minus rebates) depends on gains-from-trade of the PBM + insurer and the drug manufacturer.
- If there are lots of drugs in the market that can treat the disease well, or if generics are already present, then offering a high price would result in the drug being left out of the formulary/demoted to a non-preferred tier.
- If there is little competition in the drug's product space, the opposite happens. The insurer fears losing consumers if the drug is left out of the formulary, and so is willing to pay more for the drug.

Notice that the PBM has an extra tool that we didn't look at before, in the tiering structure of the formulary.

- Before, the only threat was being left out-of-network.
- In this case, there are two threats: i) being left out-of- formulary, ii) kept in-formulary but charged higher OOP through a non-preferred tier placement.
- So insurer reduces the fear of losing consumers through leaving a drug out by making them cost-share more from purchasing the drug.
- In the insurer-provider setting, you can think of coinsurance rates.

Formularies and PBMs serve another useful purpose, which is to bring back price sensitivity.

- In normal markets for goods, price sensitivity of consumers forces down prices.
- In US healthcare markets, insured consumers pay very little OOP, so drug manufacturers can get away with charging exorbitantly high prices without losing any consumer demand.
- This would result in high drug prices and high premiums, as insurers pass on the high cost to the consumers.

With PBMs and formularies:

- Formularies force consumers to internalize price differences and move away from high-priced drugs. This creates some price elasticity for the consumer.
- PBMs, by being sensitive to discounts and representing multiple insurers at once, make disagreement very costly for the drug manufacturers. This also creates some price elasticity, this time through the preference of insurers to lower costs.

This brings us to the problem of PBM competition.
In US, the PBM market is very concentrated.

- 3 PBMs cover nearly 80% of the market (Express Scripts, CVS Health, OptumRX).

Is this good or bad? Think using Nash-in-Nash bargaining:

- Few PBMs mean each control a large volume of patients, and so can extract greater discounts from the drug manufacturer (since disagreement is so costly).
- Few PBMs mean insurers have few rival PBMs to go to, and so have to pay PBMs a much larger share of the discounts. So premiums wouldn't fall as much.

There are increasing concerns about whether PBMs are facing misaligned incentives.

- Ideally, PBMs would want to lower the price insurer pays for a drug as much as possible.
- In this ideal setting, a PBM should be indifferent between i) getting a low list price, ii) getting a high list price and high discount that averages out to the same low list price.
- However, the contract structure is such that the PBM gets paid a share of the *discount*.
- This means a PBM prefers a high list price and high discount, over a low list price.

Why is this a problem?

- If low list price, then we have lower cost for insurers and lower premium for consumers.
- If high list price and high discount, the high concentration in PBM market means only a fraction of the discount is passed on to the insurer.
- Thus, insurer's cost doesn't fall as much, and consumer's premium doesn't fall as much.
- The insurer isn't realizing that the drug manufacturer was willing to offer a low list price instead of the high price + discount, and so rewards the PBM too much.

9 Pricing by Medicare

Medicare Part D is an optional prescription drug benefit program.

- Recall that Medicare enrollees buy private plans from the Part D market, and Medicare subsidises their premiums.
- Medicare prohibited by law from interfering with price negotiations between insurers and drug manufacturers.

10 Pricing by Medicaid

Medicaid is govt-funded insurance coverage for certain low-income subpopulations.

- Medicaid sets prices as a fraction of private market prices.
- Then requires that the manufacturers issue rebates if those prices end up higher than the lowest observed private market price.
- Drug manufacturers thus have incentive to raise prices in the private market to avoid paying large rebates to Medicaid.
- Duggan and Scott Morton (2006): 10 percentage point increase in Medicaid market share leads to 7-10 percent increases in the price of a prescription.

11 Pricing in non-US countries

11.1 Reference pricing

European countries often use reference pricing, both to bargain with drug manufacturers and to help with consumer cost-sharing.

Reference pricing groups similar drugs together and calculates a reference price for this group (median/min).

There are two types of reference pricing:

1. Internal reference pricing: The reference basket consists of the similar drugs being sold in the home country.
2. External reference pricing: The reference basket consists of the same/similar drug being sold in a set of predetermined countries.

What is this reference price used for?

1. Bargaining: The insurer uses the reference price to negotiate down the reimbursement price for drugs.
2. Cost-sharing: Consumers purchasing drugs in this class would pay out-of-pocket the price of the chosen drug less the reference price (OOP > 0).

In most European countries, the government (single-payer systems) or an association of insurers (Bismarck systems like Germany) negotiate directly with drug manufacturers.

- Key reason why drug prices in EU are so low.
- Using our bargaining framework, disagreement means losing sales from an entire country.
- Usually marginal cost of creating a drug once it has been discovered is very low, so prices can be driven down a lot.

The extent to which IRP and ERP are used varies across European countries.

- Germany, UK, France make little use of ERP for bargaining.
- Italy, Spain, Bulgaria make heavy use of ERP for bargaining.

ERP means that entry decisions across countries can be linked, and leads to strategic entry delays.

- Suppose Italy and Lithuania reference each other in ERP.
- Currently the drug only sells in Italy, gets very high prices.
- If it enters Lithuania, it might have to charge lower prices because Lithuania is economically worse off.
- But because of ERP, this causes drug's price in Italy to fall.
- Profitable to delay entry to Lithuania, enjoy high price in Italy for longer.
- Maini and Pammoli (2020), "Reference pricing as a deterrent to entry" find extensive evidence of such delays.

Recently, there have been discussions for US to adopt ERP for drug price negotiation.
Dubois, Gandhi and Vasserman (2019), "Bargaining and International Reference Pricing in the Pharmaceutical Industry" run a policy simulation where US uses Canadian prices to set a cap on drug prices.

- Find that such a policy results in a slight decrease in US prices and a substantial increase in Canadian prices.
- Overall, modest consumer welfare gains in the US but substantial consumer welfare losses in Canada.

Intuitively this makes sense:

- Canada's healthcare system and demand conditions mean that in general they pay far less for drugs than US.
- Under the new setup, drug manufacturers bargain up prices in Canada more - their bargaining now internalize that a lower price in Canada corresponds to a lower price in US as well.
- In fact, welfare loss for Canada possibly even worse - the simulation does not allow for strategic entry delay.

12 Pharmaceutical spending and innovation

We have seen that non-US countries engage in strict price controls to force down pharmaceutical spending.

Is this good or bad?

From our simple model of R&D investment, we know that R&D investment is increasing in expected profits from discovery.

This means that price controls in European countries are resulting in lower R&D than otherwise.

- Intuitively, European countries are spending on pharmaceuticals far less than their true economic value.
- It could be argued that the world is missing out on crucial pharmaceuticals because the R&D expenditure is too low.
- However, it allows them to lower healthcare expenses substantially.

In fact, there is a strong incentive to free-ride.

- No country fully internalizes the global benefit from pharmaceutical innovation.
- Therefore, each country would like to bring their drug prices down to marginal cost while other countries keep paying large markups and fund innovation.
- Problem of coordination.

Right now, US is chiefly responsible for funding the world's pharmaceutical R&D.

- US currently account for half the pharmaceutical revenues earned in the world.
- Pharmaceutical companies chiefly look at US to see if investing in drug discovery is worth it.
- After discovery, the marginal cost of production is low, so they take whatever price they can from other countries.

So comparing drug prices in US with EU is misleading:

- Many of these drugs came into existence *because* US is willing to pay such high prices for them.
- Most other countries are free-riding.

Should the US also adopt price controls to bring down pharmaceutical spending?

- If US were to cut down on spending, the knock-on effect on global innovation would be huge.
- However, contrast with skyrocketing healthcare costs - Medicare and Medicaid would bankrupt US if things progress at this rate.

No clear answer, and there are no painless options.

The takeaway should be that any policy discussion on slashing US pharmaceutical spending has to account for the reduced future flow of drugs.