Note to teachers:

This case study is about market failures. We cover this after units that cover supply, demand, surplus, elasticity, and price discrimination. We start with the basics of “excludable” and “depletable” as use that as the basis for this case study. The case study looks separately at the actual pill and the “recipe”, as the two have different properties.

The case study is heavy on reading and light on math—note the number of articles attached after the questions. You might find some of them unnecessary.

This case study explores the causes of the market failure as well as potential solutions. Patents are a nice solution to make a good excludable by other manufacturers, so that it may be in the realm of a private good. But there are some issues, such as creating a monopoly. Parts of the case study encourage the students to consider other solutions to the market failure, such as a bounty system (government payments to drugmakers for the “recipe” to new medicines) and a government takeover of the industry. The recent success of the mRNA coronavirus vaccine compared to Sinovac reveals some advantages of the US system over the Chinese one.

In this case study, I encourage students to think about other aspects of market failure in this industry, and thus other places the government needs to be involved—such as testing new medicines. It also has questions involving price discrimination and “orphan” drugs.

I have used this for years and find that it gets students thinking carefully about many interesting and challenging real-world applications of the economics we study.

Market Failure Case Study

The pharmaceutical business is a very large industry, both in the US and overseas. Some of the largest companies include Pfizer, Roche, Lilly, Merck, Bristol Meyers, and Sanofi. Their business basically involves extensive research to create drugs that treat diseases and improve the quality of peoples' lives. The material below outlines the basics of the industry, though it is certainly an over-simplification.

Creating New Drugs

It can take many years (often decades) between starting research on a new medicine and being able to sell it. It also can cost hundreds of millions of dollars, even billions some times (when opportunity cost is included in the calculations). Once a drug appears effective—after a large investment in research—there are clinical trials that governments require (the FDA, in the US) to test the effectiveness of the drug and check for side-effects. These trials are expensive and can take years. Many drugs fail to get FDA approval because of side-effects or because the studies do not "prove" (beyond a statistical "reasonable doubt") that the drug is effective. Then the time and money invested to date are usually wasted. Some estimates are that only 20% of drugs that begin testing are eventually approved for sale. Thus, for the pharmaceutical company to stay in business, the drugs that can be sold need to pay for all of the costs of the failures as well as the cost of their own development.

Pricing a New Drug

While it can be very expensive to develop a new drug, once it has been developed, tested, and approved, it is typical very **in**expensive to produce each dose. Some estimates are as low as a few pennies per dose. But that obviously does not include the considerable cost of producing new drugs. Whalen referred to this in chapter 3 of Naked Economics.

Note: we may later look at the economics of fixed- versus variable costs. Drugs are high fixed cost in that to produce the first dose is very expensive (since it includes all of the research) but subsequent doses are very inexpensive. The variable cost is essentially the marginal cost of producing additional units—which is very low here. Other businesses have very low fixed costs and all of the costs are variable. For example, think of knitting sweaters. Making two will be about twice as expensive as making one—it is only the cost of the knitting needles that makes the first more expensive than the second.

The first two stories attached stories are on drug pricing.

Copying a Drug

Once a drug is invented, it can be fairly easy for other companies to determine its chemical composition and copy it. In a totally free market, this would occur all of the time. Copies tend to not require extensive tests from the FDA. Copies are often called "generics". In the US, there are some companies that specialize in generics. Overseas this is quite common as well. India is known to be a very large producer of generic drugs.

Patents

In the US (and many countries recognizing each other's patents), a drug company get s a patent for a new medicine early in the testing process. A patent makes it illegal for a competitor to copy it, typically for 20 years. This twenty years includes the time during testing ("clinical trials") so typically drugs have 8-12 years of patent protection once they are approved.

Selling Globally

By dollar value, most prescription drugs sales occur in developed Western countries. Annual costs of individual drugs can run into many thousands of dollars per person. Most of the costs are paid by insurance companies, including the government's Medicare and Medicaid programs. Many people feel that, since most poor people in developing countries cannot afford the US prices for drugs and they are so inexpensive to manufacture, that drug companies should sell them very cheaply in poorer developing countries.

In addition to the articles attached, you should at least skim over Chapter 5 in Naked Economics; it covers the economics of information. You may NOT do research on-line (or in the library) about the issues addressed here.

Questions

1. Many economists feel that the government should only get involved in the economy when there are market failures. Patents are one form of government involvement. Without patents, would the markets fail? Would the private markets under- or over-produce the socially optimal level of (new) drugs? Discuss.

2. Discuss how prescription drugs may be thought of in terms of "rivals in consumption" and "excludable". Think separately of an actual pill versus the "recipe" for how to product the pill. You may assume that, once a pill is sold, a buyer with a laboratory could analyze the pill and determine the recipe at not too great an expense (sometimes this is called "reverse-engineering" a product.) ***Assume there are no patents*** for this question. Based on your answers, are drug recipes a common resource, a club good, a public good, or something the private market should be able to handle optimally on its own?

3. Based on your answer to the last part of prior question, what role, if any, would it be appropriate for the government to take in pharmaceutical research (this still assumes a world without patents)? Now, how do patents change the nature of the good and the possible role of the government? Assume the patents are enforced rigorously. Note: the role of government can involve setting laws, not just providing goods (such as public goods)

4. Once the government has granted a patent on a drug, they are essentially giving its producer a monopoly on the product for a period of time. Describe how the monopolist is likely to act. Address the issue of price elasticity of demand in your analysis.

5. Most national governments are involved in testing and licensing drugs, only approving drugs where there is strong evidence that they help people without significant side effects. Some critics of government have stated that the government does not need to be involved. They argue, for instance, that if Snapper makes bad lawn mowers then people won't buy them, so it is in Snapper's interest to make good products.

Do you find this argument compelling? They could also argue that a private company (like Consumer Reports) could also test medicine for effectiveness and safety, rather than having it be a government function. Would it make sense for such a "third-party" (neither the consumer nor the manufacturer) to do the testing? Who would pay for the testing—the drug manufacturer or the consumer? What would likely happen if private companies were to do this (imagine you were the head of a private company doing this…. Is this a good business to be in)? What are some potential disadvantages of having this done in the private sector?

6. Some people feel that it is unreasonable and even unethical for pharmaceutical companies to sell something that costs pennies to make for thousands of dollars per year. Do you agree with these critics of the industry? Is there a price that is unfairly high? How can one determine what is reasonable and what is not? Much has been written in the last year or two about how Martin Shkreli and Valeant Pharmaceuticals (and others) bought the rights to patented medicines and immediately raised the prices by a very large amount.

7. Imagine you are the CEO of a pharmaceutical company. It costs you 3 cents per dose to produce your new medicine. You sell it for $20 per dose in the US. One person on your staff has suggested selling it in Africa for 30 cents per dose. You currently sell none in Africa. Assume shipping costs are low enough that you could still profit at this price. Would this price discrimination be a good idea? Discuss.

8. There are some diseases in the US that afflict relatively few people but affect them in ways that are very damaging. Assume that it is no easier to develop drugs for these diseases. In the free market, what would you expect in terms of drugs for these diseases compared to more widespread diseases? Drugs to treat these are often called "orphan drugs". What can and should the government do about this? To what extent is it a problem that less work is being done to try rare diseases? Might one say that this is the invisible hand of the market at work, encouraging researchers to develop drugs that will most benefit society?

A similar issue arises with drugs to treat diseases rare or non-existent in developed countries but common in poorer countries. What, if anything, should be done by governments? And which governments, the rich or the poor?

9. Many in the medical community are concerned about bacteria that are resistant to antibiotics. Given the life span of bacteria, they can evolve resistance very quickly. In the course of a year, a reasonably high portion of Americans take at least some antibiotics—typically for a week at a time in the case of an infection. (in addition, farm animals consume huge amounts of antibiotics to help them survive in crowded and somewhat unsanitary conditions). Antibiotics are fairly inexpensive—maybe $100 or so for a week's treatment. The last article attached is about antibiotics.

a. To what extent are there externalities in deciding to take antibiotics? Consider both positive and negative.

b. Despite the need for newer antibiotics, most major pharmaceutical companies are not developing them. Why not? Has market failed, even with patents? Many have called upon the government to subsidize drug companies to do so. Why might they not develop them on their own? On what grounds might a subsidy be justified?

10. It seems that the government needs to be quite involved with this market, and the pure free market does not work particularly well. Should the government just take over the industry and hire people to develop and produce drugs, instead of letting the private market do so under fairly tightly managed policies. What about some sort of system where the government has private companies do research but it buys the patent once a useful drug is developed (this is sometimes called a "bounty system". Discuss the advantages and disadvantages of these two systems compared to the current system with patents in the US.

Runaway Drug Prices

By THE EDITORIAL BOARD (NY Times) MAY 5, 2015

A drug to treat abnormal heart rhythms can cost about $200 on one day and more than $1,300 the next. A diagnosis of multiple sclerosis can lead to a drug bill of at least $50,000 a year. How companies set prices of specialty drugs for these and other complex diseases, like cancer and AIDS, has been a mystery to the patients who need them. Now the Obama administration and some states are tackling that lack of transparency and the rising costs.

Mr. Obama has asked Congress to let Medicare officials negotiate prices with drug manufacturers, a practice forbidden by current law that may be hard to change with the antiregulatory mood among Republicans. And several states are considering bills that would require drug companies to justify their prices to public agencies. It is the least the states can do to bring costs to levels that patients, hospitals and government programs can afford.

Spending on all prescription drugs, including commonly used medicines like antibiotics, accounts for a tenth of the nation's total health spending. Prices have been rising slowly in recent years mainly because many brand-name drugs lost protection and lower-cost generics were prescribed. But there are fewer patent expirations ahead. Specialized medicines already on the market carry huge price tags, as The Times reported recently, and strain the budgets of Medicare, Medicaid and consumers. The list price for a one-year's supply of Kalydeco to treat cystic fibrosis is $311,000. A standard course of treatment with Blincyto, a leukemia drug, is about $178,000.

Drugs used to treat multiple sclerosis are of particular concern. A recent study by researchers in Oregon found that first-generation drugs that came on the market in the 1990s ranged in price from $8,000 to $11,000 a year. Prices for those drugs rose even though new drugs entered the market, theoretically providing competition. One drug that first cost $8,700 now costs $62,400 a year.

There are no multiple sclerosis drugs available in the United States with a list price below $50,000 a year, the researchers say, which is two to three times more than the list prices in Canada, Australia or Britain.

The drug and biotech companies contend that high prices are justified to cover the large costs of bringing a drug to market and to compensate for the large number of drugs that fail in late stages of costly clinical trials. But it appears that many companies raise prices arbitrarily and charge what public and private insurers will pay.

A recent report in The Wall Street Journal described how Valeant Pharmaceuticals International, based in Canada, bought the rights to two lifesaving heart drugs on Feb. 10 and raised their prices the same day. The list price for a one-milliliter vial of Isuprel, used to treat abnormal heart rhythms, rose to $1,347 from $215. The price for a two-milliliter vial of Nitropress, for dangerously high blood pressure and acute heart failure, increased from to $806 from $258. The Journal cites similar increases for Ofirmev pain injections and Vimovo pain tablets after new companies acquired the rights.

Bills have been introduced in several states requiring drug makers to report profits and expenses for costly drugs or sometimes for all drugs, according to The Journal's pharmaceutical blog. Such disclosures might shame companies into restraining their price increases and provide state officials with information to determine what action to take.

The industry helped defeat such a bill in Oregon and is fighting to head off a bill in California that would impose new reporting requirements on makers of any prescription drug whose wholesale costs are $10,000 or more annually or per course of treatment. They would have to disclose the research, development, marketing and manufacturing costs, as well as the profits, attributable to the drug. The companies complain that some of these costs are hard to quantify and that compiling the data would be burdensome. But surely the public would benefit from increased transparency that might deter the worst abuses.

I Am Paying for Your Expensive Medicine

NY TIMES NOV. 7, 2015 Ezekiel J. Emanuel

YOU may not know it, but you could be on the hook to pay at least $124 this year for a drug you probably don't take.

The drug is a new class of cholesterol-lowering agents called PCSK9 inhibitors. Its cost and how we are paying for it illustrate why we all need to care about not only our own health care bills but also those of our neighbors. And it helps focus the debate about drug prices on two questions: What is the value delivered by the drug, and can that be linked to its price? And how should such value-based prices be implemented?

In July, the Food and Drug Administration approved the first of two new PCSK9 inhibitors that lower the bad type of cholesterol, LDL. Studies suggest that they can reduce it by up to 60 percent, compared with a placebo, and reduce it up to 36 percent more than statins and a drug called ezetimibe. However, there are no definitive data on how much these drugs actually reduce heart attacks, strokes and deaths from heart disease. Researchers suggest they might decrease the likelihood of such bad outcomes. For example, one preliminary study found that taking the drug lowered the overall chances that a patient would experience a heart attack or stroke, or hospitalization or death from heart disease, to 1.7 percent from 3.3 percent. The definitive studies will be out in 2017.

Drugs like these can help us lead longer, more productive lives. The problem is that the companies producing these drugs — Amgen, Sanofi and Regeneron — announced that the retail price for a prescription would be more than $14,000 per patient per year. The price is particularly steep given that these drugs may need to be taken for the rest of the patients' lives. How much patients pay directly would depend on their insurance plan.

But the high prices insurers will have to pay will eventually be reflected in higher premiums for all of us. According to a recent article in The New England Journal of Medicine by Kevin A. Schulman and his colleagues at Duke, even if the price came down to about $11,000 per patient per year, and only 1.1 million of the roughly 23 million middle-age Americans with high cholesterol actually took these drugs, the bill would be so high that for a typical insurance plan, "annual insurance premiums would increase by $124 for every person" in the insurance plan. The authors point out that "taxpayers will have the additional burden of paying for similar increases in" the costs for Medicare to cover such drugs. The same is true for Medicaid and the Veterans Affairs department.

To protect patients, many policy makers and academics are proposing various changes in drug benefit arrangements such as separating out deductible limits for drugs from deductibles for other health benefits and limiting co-pays for these drugs to $100 to $250.

These proposals are a good start and necessary, especially for low-income Americans who struggle the most to pay out-of-pocket medical costs. But they will not solve the systemic problem of super-high drug costs. Someone — even if it's a less than sympathetic insurance company — still has to pay the full bill. A growing chorus is arguing that we should start paying for value in health care. Paying for value is the common-sense idea that prices should be linked to benefits; high prices would have to be justified by high health benefits.

What would paying for value look like in the case of PCSK9 inhibitors? We have estimates of the benefits in terms of lowering risks from cardiovascular disease. At what price would those benefits be a good value?

In the rest of the economy we let individuals determine value. They decide whether a new gadget is worth the expense when they spend their own money on a television, a car or a smartphone. And in health care many want only patients to determine value.

But as these PCSK9 inhibitors make clear, it is not just patients' perspectives we need to take into account. Patients get the benefits, but all of us are paying the bill. As Dr. Schulman and his colleagues show, the nature of the way we pay for health care — through private and public health insurance pools, which spread financial risk and costs among large populations — means we all pay for an exorbitantly priced high cholesterol drug even if we don't have high cholesterol and we don't take the drug. The high costs are hidden in our ever-increasing insurance premiums and taxes. Because we all pay, all Americans have to have a voice in determining value.

As the PCSK9 story is making clear, the drug cost debate is now beginning to focus on two questions that are currently unresolved: First, how do we determine value so the perspectives of all Americans are considered? Second, how do we implement and enforce that determination of value?

The traditional answer to the first question is to determine the cost-effectiveness of the new drugs by assessing how much they improve the lives of patients measured by quality-adjusted life years (QALY). This is certainly an important measure for patients. The controversy centers on how much we should pay for each additional year of life. Is it $50,000? $100,000? More? In England they have a flexible target, wherein above $45,000 per QALY drugs require an increasingly stronger case for coverage. But even if we use a much higher target in the United States — say, $150,000, which is about three times the median household income — it turns out these PCSK9 inhibitors still fail the value test. The drugs would cost patients as much as $300,000 for every quality-adjusted life year they add. Their price would have to shrink by more than half, to roughly $5,000 per patient per year, to make the $150,000 level.

The answer to the second question is just as unsettled. Many people hope that the drug industry will self-regulate, using value-based pricing of its new drugs. But if past experience is any indication of future behavior, self-regulation may be a pipe dream. Recent price increases for generic drugs long off patent and patented drugs in which there is no additional research aren't encouraging signs.

In the United States, government regulation is usually a solution of last resort when industry self-regulation fails. But if insurance premiums keep going up $124 per person because of a single drug, Americans may find it more appealing.

Ezekiel J. Emanuel is an oncologist and a vice provost at the University of Pennsylvania.

Trump's F.D.A. Pick Could Undo Decades of Drug Safeguards

By KATIE THOMAS FEB. 5, 2017

President Trump's vow to overhaul the Food and Drug Administration could bring major changes in policy, including steps to accelerate the process of approving new prescription drugs, setting up a clash with critics who say his push for deregulation might put consumers at risk.

Mr. Trump has been vetting candidates to run the agency, which regulates the safety of everything from drugs and medical devices to food and cosmetics. Among them is Jim O'Neill, a former official at the Health and Human Services Department who is an associate of the Silicon Valley billionaire and Trump supporter Peter Thiel. Mr. O'Neill has argued that companies should not have to prove that their drugs work in clinical trials before selling them to consumers.

Other candidates also have called for reducing regulatory hurdles.

If the most significant proposals are adopted — and many would require an act of Congress — they will reverse decades of policy and consumer protections dating to the 1960s. Congress toughened the drug approval process in the wake of the worldwide crisis over thalidomide, which caused severe birth defects in babies whose mothers had taken the drug in pregnancy. Since then, the F.D.A. has come to be viewed as the world's leading watchdog for protecting the safety of food and drugs, a gold standard whose lead other countries often follow.

Mr. Trump's most recent statements, made at a White House round-table discussion last week with leaders of the nation's top drug companies, have reverberated throughout the medical and pharmaceutical industries. Supporters of deregulation have long wanted to reduce bureaucracy and lessen oversight of drugs and devices, while critics say the market for drugs could be destabilized and the door opened to unproven products based on junk science.

"Everyone depends on the agency, from the drugs in our medicine cabinet to the food on our dinner table, to our blood supplies," said Dr. David Kessler, who was commissioner of the F.D.A. during the presidencies of the elder George Bush and Bill Clinton. "We are the envy of the world because our honey is our honey. Our foods are not laced with pesticides. Our drugs work."

Mr. Trump said at the meeting that he was close to naming a "fantastic" person to lead the agency. In addition to Mr. O'Neill, candidates whose names have recently surfaced include Dr. Scott Gottlieb, a former F.D.A. official with longstanding ties to pharmaceutical and biotech companies, and Dr. Joseph Gulfo, a former biotech and medical device executive.

All three have called for streamlining the drug approval process, but Mr. O'Neill's stance has drawn the most attention. He is a managing director of Mithril Capital Management, an investment firm Mr. Thiel co-founded, and previously led the Thiel Foundation, Mr. Thiel's philanthropic organization. During the George W. Bush administration, Mr. O'Neill held a series of roles in the Health and Human Services Department, including as principal associate deputy secretary, where he worked on policy, including for the F.D.A., according to his LinkedIn profile.

Mr. O'Neill is a libertarian who is on the board of the SENS Research Foundation, a charity that funds anti-aging research, and until recently served on the board of the Seasteading Institute, an effort to create new societies at sea.

At an anti-aging conference in 2014, Mr. O'Neill advocated something he called "progressive" approval, in which drugs that were proved safe, but not yet proven effective, could be allowed on the market. "Let people start using them, at their own risk," Mr. O'Neill said. "Let's prove efficacy after they've been legalized."

Companies have been required to prove that their drugs work since 1962, when Congress passed legislation requiring that licensing for sale be based not just on safety but also on "substantial evidence" of a drug's efficacy. That law, and others passed since, forced companies to rigorously test their products, running them through a gantlet of clinical trials whose results are then vetted by the F.D.A. before any sales to consumers. Ninety percent of drugs that enter clinical development fail these trials. (The F.D.A. also regulates medical devices, but they undergo a separate approval process.)

As a result, newly discovered drugs can take years to reach the market, a period that Mr. Trump said last week was too lengthy.

"When you have a drug, you can actually get it approved if it works, instead of waiting for many, many years," he told the pharmaceutical executives. "We're going to be cutting regulations at a level that nobody's ever seen before, and we're going to have tremendous protection for the people."

Some have suggested that a commissioner determined to weaken the efficacy standard need not seek congressional action, but could interpret existing regulations loosely so that requirements for certain clinical trials — particularly the costly, large-scale ones that can take years and involve thousands of patients — can be rolled back.

That could have serious implications for patients. Last month, the F.D.A. released a study of 22 drugs that appeared promising in early studies but failed in final, large-scale trials. Drug safety watchdogs point to examples like the painkiller Vioxx, which was withdrawn from the market in 2004 over safety concerns, as proof of the high stakes involved in drug approval.

While Mr. Trump's call to cut regulations has been warmly received by other industries, some biotech executives have reacted to his remarks with alarm. Those affiliated with some smaller companies have privately described the choice of Mr. O'Neill as a worst-case scenario that could send the drug industry into chaos. The F.D.A., they say, is not perfect, but its standards provide a level playing field on which both big and small companies can compete.

"We're not selling Coca-Cola and Pepsi, where patients can taste the Coca-Cola and decide if they like it," said John M. Maraganore, the chief executive of Alnylam Pharmaceuticals, a Massachusetts biotech firm. "Our products are lifesaving medicines."

Industry executives said big changes to the agency would also be bad for business, making it difficult for companies with breakthrough treatments to distinguish their products from those that are shams. If standards at the F.D.A. are rolled back, "then we might as well be advertising in the middle of the night on how terrifically we can cure all your illnesses," said Dr. Leonard S. Schleifer, the chief

executive of Regeneron, a pharmaceutical company in Tarrytown, N.Y. “That’s not the business that I think most of us want to be in.”

Daniel Carpenter, a professor at Harvard University who studies the F.D.A., said its role is not just to ensure the safety of a drug. “The underpinnings of belief among patients, payers, even investors, is that somebody out there has tested these things and has shown, with some evidence, that they work,” he said. Mr. O’Neill did not respond to emails and a phone call requesting comment, and Dr. Gottlieb declined to comment.

Dr. Gulfo, the former biotech executive, said he had spoken with several people on the president’s transition team about the F.D.A. job. He said he was in favor of keeping the efficacy requirement. But he said he believed the agency’s standards were too rigid and burdensome to companies with innovative ideas. He called on the agency to approve more drugs based on what are known as “surrogate endpoints” — showing that a diabetes drug lowers blood sugar, for example — rather than forcing companies to prove that the product improves long-term outcomes like survival rates or lowering the chance for heart attacks.

“Let’s bring the F.D.A. back to what its mission is, and its mission is to make sure that drugs can be labeled for safe use, and that they’re not snake oil,” said Dr. Gulfo, the former chief executive of MELA Sciences, who wrote a book about his company’s failed efforts to get its skin cancer detection device approved. (The agency eventually cleared it for use in 2011.)

Several drug company executives said the F.D.A., while not perfect, had sped up the approval process in recent years and had been responsive to requests to approve drugs based on interim measurements, particularly for life-threatening diseases that have no other treatments. The agency sets a 10-month goal for approving standard drugs, and a six-month period for those that have qualified for expedited approval; one recent study showed it decides on drugs more quickly than its counterparts in Europe and Canada.

A majority of recent new drugs were approved through expedited approvals, another recent study found. In December, Congress passed a law that further speeds approvals for certain drugs and medical devices.

Drug industry leaders say that they want the F.D.A. to be more open to allowing new kinds of clinical trials, and that it needs to become more nimble in keeping up with the breathtaking pace of medical advances. They have also been prodding the agency to fill an estimated 1,000 staff vacancies so that decisions can be made on more quickly. But that is apparently delayed because the president ordered an across-the-board hiring freeze.

“The only way you would make it shorter is you staff up,” said Michael Gilman, an entrepreneur who has founded several biotech companies. “You certainly don’t do it by slashing staff. So the logic of the whole thing doesn’t compute for me.”

THE ECONOMICS OF ANTIBIOTIC RESISTANCE

UPDATED: JUN 14, 2017 ORIGINAL: JUN 15, 2016

The business model for developing new antibiotics is broken, researchers say. The question is, can we make a new one that works?

By Nathan Collins

Drug discovery is big business with oftentimes questionable ethics. Nowhere is that more true than in the world of antibiotics. Older drugs are fast losing their ability to fight disease, and we're in dire need of new antibiotic treatments—but a strange brew of evolutionary and economic forces makes it unlikely that companies will pursue new drugs to fight back.

The solution, according to an essay published this week in *PLoS Medicine*, is to decouple antibiotic sales from research and development—basically, to find a new way to fund drug research while, at least to some extent, discouraging sales. But sorting out the details is going to take some hard work, even if drug companies get on board with the basic idea.

"The current business model for antibiotics is plagued by market failures and perverse incentives that both work against [efforts to maintain drugs' effectiveness] and provide insufficient rewards to drive the development of much-needed new treatments for resistant infection," writes a team led by Boston University law professor Kevin Outterson, who specializes in health law and intellectual property.

Fundamentally, the public-health problem is that we overuse antibiotics, which—in a perverse evolutionary twist—fosters the creation of drug-resistant bacteria. The economics are odd too: Understandably, drug companies want to profit from the drugs they develop, which means selling more of them. This, in turn, compounds the resistance problem. But in discouraging overprescribing (and overusing), public-health officials indirectly discourage the development of new antibiotics.

Unless, of course, someone comes up with a new business model. The most promising alternative, Outterson and his colleagues write, is to pay for R&D in a different way—to "delink" drug development from sales. But who should pay for the R&D?

Early on in the R&D process, the answer is the government, the researchers argue, in the form of publicly funded university research. Tax credits, prizes, grants, and extra support through the clinical trial process could help through the next phase of development.

Most crucial—and tricky—is what happens once a new antibiotic gets approved. At that stage, Outterson and his colleagues argue, the government needs to pay drug developers based not on sales, but on development costs and the potential benefits to public health. Doing so, the team writes, more directly rewards innovation itself, rather than whomever sells the most pills. Even then, there will be issues to deal with, such as intellectual property rights and their effects on the global distribution of a new antibiotic drug.

"[W]e see the need for a global conversation that applies delinkage principles to address access, conservation, and innovation of antibiotics in concert and not in isolation," the authors write. "Global political commitment is needed now to transform antibiotic delinkage from a promising idea into reality."

https://psmag.com/news/the-economics-of-antibiotic-resistance

How economics killed the antibiotic dream

By Tim HarfordBBC World Service, 50 Things That Made the Modern Economy

On a ramshackle pig farm near Wuxi, in Jiangsu province, China, a foreigner gets out of a taxi.

The family are surprised. Their little farm is at the end of a bumpy track through rice paddies, and they do not get many foreigners asking to use the toilet.

The stranger's name is Philip Lymbery, and he runs a campaigning group called Compassion in World Farming.

As he explains in his book about intensive farming, he is not there to berate the farmers about their pigs' living conditions, although sows are crammed uncomfortably into crates.

Mr Lymbery is there to investigate whether pig manure is polluting the local waterways.

He has tried unsuccessfully to visit local large, commercial farms, so has turned up on spec at a family farm instead.

The farmer is happy to talk.

Yes, they dump waste in the river. No, they are not supposed to. But they just bribe the local official.

Then, Mr Lymbery notices a pile of needles for antibiotics. Have they been prescribed by a vet? No, the farmer explains. You don't need a prescription to buy antibiotics.

And anyway, vets are expensive. Antibiotics are cheap. The farmer has very little money, so she injects her pigs with them routinely, hoping it will stop them getting sick.

She is far from alone. Cramped and dirty conditions on intensive farms are breeding grounds for disease. Routine, low antibiotic doses can help to stop it spreading.

Antibiotics also fatten animals, which means more money for farmers. Scientists are studying gut microbes to understand why.

No wonder more antibiotics are injected into healthy animals than sick humans.

In the big emerging economies - where demand for meat grows as incomes rise - use of agricultural antibiotics is set to double in 20 years.

Widespread unnecessary use of antibiotics is not restricted to agriculture.

Many doctors are guilty, too.

They should know better - as should regulators who let people buy antibiotics over the counter.

Serendipity

Meanwhile, bacteria are busily evolving resistance to drugs, and public health experts fear we are entering a post-antibiotic age.

One recent review estimated drug-resistant bugs could kill 10 million people a year by 2050 - more than currently die from cancer.

It is hard to put a monetary cost on antibiotics becoming useless, but the review tried: $1tn (£790bn).

The story of antibiotics starts with a healthy dose of serendipity.

A young man named Alexander Fleming had a boring job in shipping when his uncle died, leaving him enough money to resign and enrol at St Mary's Hospital Medical School in London instead.

There, he became a valued member of the rifle club.

The captain of the shooting team wanted to keep Fleming when his studies finished, so found him a job.

That is how Fleming became a bacteriologist.

One day in 1928, Fleming failed to tidy up his petri dishes before going back home to Scotland on holiday.

On his return, he noticed one dish had become mouldy in his absence, and the mould was killing the bacteria he had used the dish to cultivate.

Fleming tried to investigate further by making more mould, but he was not a chemist and could not work out how to make enough.

He published his observations, but nobody paid attention.

A decade passed, then more serendipity.

In Oxford, Ernst Chain was flicking through back copies of medical journals when he chanced upon Fleming's old article.

And Chain, a Jew who had fled Nazi Germany, was a chemist - a brilliant one.

Chain and his colleague Howard Florey set about isolating and purifying enough penicillin for further experiments.

This required hundreds of litres of mouldy fluid.

Their colleague Norman Heatley rigged up a crazy-looking Heath Robinson system involving milk churns, baths, ceramic bedpans commissioned from a local pottery company, rubber tubes, drinks bottles and a doorbell.

They employed six women to operate it - the "penicillin girls".

The first patient given an experimental dose was a 43-year-old policeman who had scratched his cheek pruning roses and developed septicaemia.

Heatley's makeshift system could not produce penicillin quickly enough, and the policeman died.

But, by 1945, penicillin - the first mass-produced antibiotic - was rolling off production lines.

Chain, Florey and Fleming shared a Nobel Prize.

And Fleming took the opportunity to issue a warning.

The tragedy of the commons

"It is not difficult," Fleming said, "to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them."

Fleming worried an "ignorant man" might under-dose himself, allowing drug-resistant bacteria to evolve.

But ignorance hasn't been the problem.

We know the risks, but face incentives to take them anyway.

Suppose I feel ill.

Perhaps it is viral, meaning antibiotics are useless. Even if it is bacterial, I will probably fight it off.

But if there is any chance that antibiotics might speed my recovery, my incentive is to take them.

Or suppose I run a pig farm.

Giving routine low doses of antibiotics to my pigs is the perfect way to breed antibiotic-resistant bacteria.

But that is not my problem.

My only incentive is to care about whether dosing my pigs seems to increase my revenues by more than the cost of the drugs.

This is a classic example of the tragedy of the commons, where individuals rationally pursuing their own interests ultimately create a collective disaster.

Until the 1970s, scientists kept discovering new antibiotics: when bacteria evolved resistance to one type, we could introduce another.

But then the development pipeline dried up.

It is possible new antibiotics will start coming through again.

Some researchers have come up with a promising new technique to find antimicrobial compounds in soil.

Again, though, this is all about incentives.

What the world really needs is new antibiotics we put on the shelf and use only in the direst emergencies.

But a product that does not get used is not much of a money spinner for drug companies.

We need to devise better incentives to encourage more research.

One attempt to do just that is called an "advanced market commitment", where donors promise to pay for doses of a medicine that does not yet exist.

We will also need smarter regulations as to how new antibiotics are used, by doctors and farmers alike.

Denmark shows it can be done - world-famous for its bacon, it strictly controls antibiotic use in pigs.

One key appears to be improving other regulations to make farm animals' living conditions less cramped and unhygienic.

That makes disease less likely to spread.

And recent studies suggest that when animals are kept in better conditions, routine low doses of antibiotics have very little impact on their growth.

The pig farmer in Wuxi meant well.

She clearly did not understand the implications of overusing antibiotics.

But even if she had, she would have faced the same economic incentives to overuse them.

Ultimately, that is what needs to change.

https://www.bbc.com/news/business-38828079

Crisis Looms in Antibiotics as Drug Makers Go Bankrupt

First Big Pharma fled the field, and now start-ups are going belly up, threatening to stifle the development of new drugs.

By Andrew Jacobs Published Dec. 25, 2019; Updated Dec. 26, 2019

At a time when germs are growing more resistant to common antibiotics, many companies that are developing new versions of the drugs are hemorrhaging money and going out of business, gravely undermining efforts to contain the spread of deadly, drug-resistant bacteria.

Antibiotic start-ups like Achaogen and Aradigm have gone belly up in recent months, pharmaceutical behemoths like Novartis and Allergan have abandoned the sector and many of the remaining American antibiotic companies are teetering toward insolvency. One of the biggest developers of antibiotics, Melinta Therapeutics, recently warned regulators it was running out of cash.

Experts say the grim financial outlook for the few companies still committed to antibiotic research is driving away investors and threatening to strangle the development of new lifesaving drugs at a time when they are urgently needed.

“This is a crisis that should alarm everyone,” said Dr. Helen Boucher, an infectious disease specialist at Tufts Medical Center and a member of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria.

The problem is straightforward: The companies that have invested billions to develop the drugs have not found a way to make money selling them. Most antibiotics are prescribed for just days or weeks — unlike medicines for chronic conditions like diabetes or rheumatoid arthritis that have been blockbusters — and many hospitals have been unwilling to pay high prices for the new therapies. Political gridlock in Congress has thwarted legislative efforts to address the problem.

The challenges facing antibiotic makers come at time when many of the drugs designed to vanquish infections are becoming ineffective against bacteria and fungi, as overuse of the decades-old drugs has spurred them to develop defenses against the medicines.

Drug-resistant infections now kill 35,000 people in the United States each year and sicken 2.8 million, according a report from the Centers for Disease Control and Prevention released last month. Without new therapies, the United Nations says the global death toll could soar to 10 million by 2050.

The newest antibiotics have proved effective at tackling some of the most stubborn and deadly germs, including anthrax, bacterial pneumonia, E. coli and multi-drug-resistant skin infections.

The experience of the biotech company Achaogen is a case in point. It spent 15 years and a billion dollars to win Food and Drug Administration approval for Zemdri, a drug for hard-to-treat urinary tract infections. In July, the World Health Organization added Zemdri to its list of essential new medicines.

By then, however, there was no one left at Achaogen to celebrate.

This past spring, with its stock price hovering near zero and executives unable to raise the hundreds of millions of dollars needed to market the drug and do additional clinical studies, the company sold off lab equipment and fired its remaining scientists. In April, the company declared bankruptcy.

Public health experts say the crisis calls for government intervention. Among the ideas that have wide backing are increased reimbursements for new antibiotics, federal funding to stockpile drugs effective against resistant germs and financial incentives that would offer much needed aid to start-ups and lure back the pharmaceutical giants. Despite bipartisan support, legislation aimed at addressing the problem has languished in Congress.

“If this doesn’t get fixed in the next six to 12 months, the last of the Mohicans will go broke and investors won’t return to the market for another decade or two,” said Chen Yu, a health care venture capitalist who has invested in the field.

The industry faces another challenge: After years of being bombarded with warnings against profligate use of antibiotics, doctors have become reluctant to prescribe the newest medications, limiting the ability of companies to recoup the investment spent to discover the compounds and win regulatory approval. And in their drive to save money, many hospital pharmacies will dispense cheaper generics even when a newer drug is far superior.

“You’d never tell a cancer patient, ‘Why don’t you try a 1950s drug first and if doesn’t work, we’ll move on to one from the 1980s,’” said Kevin Outterson, the executive director of CARB-X, a government-funded nonprofit that provides grants to companies working on antimicrobial resistance. “We do this with antibiotics and it’s really having an adverse effect on patients and the marketplace.”

Many of the new drugs are not cheap, at least when compared to older generics that can cost a few dollars a pill. A typical course of Xerava, a newly approved antibiotic that targets multi-drug-resistant infections, can cost as much as $2,000.

“Unlike expensive new cancer drugs that extend survival by three-to-six months, antibiotics like ours truly save a patient’s life,” said Larry Edwards, chief executive of the company that makes Xerava, Tetraphase Pharmaceuticals. “It’s frustrating.”

Tetraphase, based in Watertown, Mass., has struggled to get hospitals to embrace Xerava, which took more than a decade to discover and bring to market, even though the drug can vanquish resistant germs like MRSA and CRE, a group of resistant bacteria that kills 13,000 people a year.

Tetraphase’s stock price has been hovering around $2, down from nearly $40 a year ago. To trim costs, Mr. Edwards recently shuttered the company’s labs, laid off some 40 scientists and scuttled plans to move forward on three other promising antibiotics.

For Melinta Therapeutics based in Morristown, N.J., the future is even grimmer. Last month, the company’s stock price dropped 45 percent after executives issued a warning about the company’s long-term prospects. Melinta makes four antibiotics, including Baxdela, which recently received F.D.A. approval to treat the kind of drug-resistant pneumonia that often kills hospitalized patients. Jennifer Sanfilippo, Melinta’s interim chief executive, said she was hoping a sale or merger would buy the company more time to raise awareness about the antibiotics’ value among hospital pharmacists and increase sales.

“These drugs are my babies, and they are so urgently needed,” she said.

Coming up with new compounds is no easy feat. Only two new classes of antibiotics have been introduced in the last 20 years — most new drugs are variations on existing ones — and the diminishing financial returns have driven most companies from the market. In the 1980s, there were 18 major pharmaceutical companies developing new antibiotics; today there are three.

“The science is hard, really hard,” said Dr. David Shlaes, a former vice president at Wyeth Pharmaceuticals and a board member of the Global Antibiotic Research and Development Partnership, a nonprofit advocacy organization. “And reducing the number of people who work on it by abandoning antibiotic R & D is not going to get us anywhere.”

A new antibiotic can cost $2.6 billion to develop, he said, and the biggest part of that cost is the failures along the way.

Some of the sector’s biggest players have coalesced around a raft of interventions and incentives that would treat antibiotics as a global good. They include extending the exclusivity for new antibiotics to give companies more time to earn back their investments and creating a program to buy and store critical antibiotics much the way the federal government stockpiles emergency medication for possible pandemics or bioterror threats like anthrax and smallpox.

The DISARM Act, a bill introduced in Congress this year, would direct Medicare to reimburse hospitals for new and critically important antibiotics. The bill has bipartisan support but has yet to advance.

One of its sponsors, Senator Bob Casey, Democrat of Pennsylvania, said some of the reluctance to push it forward stemmed from the political sensitivity over soaring prescription drug prices. “There is some institutional resistance to any legislation that provides financial incentives to drug companies,” he said.

Washington has not entirely been sitting on its hands. Over the past decade, the Biomedical Advanced Research and Development Authority, or BARDA, a federal effort to counter chemical, nuclear and other public health threats, has invested a billion dollars in companies developing promising antimicrobial drugs and diagnostics that can help address antibiotic resistance.

“If we don’t have drugs to combat these multi-drug-resistant organisms, then we’re not doing our job to keep Americans safe,” Rick A. Bright, the director of the agency, said.

Dr. Bright has had a firsthand experience with the problem. Two years ago, his thumb became infected after he nicked it while gardening in his backyard. The antibiotic he was prescribed had no effect, nor did six others he was given at the hospital. It turned out he had MRSA.

The infection spread, and doctors scheduled surgery to amputate the thumb. His doctor prescribed one last antibiotic but only after complaining about its cost and warning that Dr. Bright’s insurance might not cover it. Within hours, the infection began to improve and the amputation was canceled.

“If I had gotten the right drug on Day 1, I would have never had to go to the emergency room,” he said.

Achaogen and its 300 employees had held out hope for government intervention, especially given that the company had received $124 million from BARDA to develop Zemdri.

As recently as two years ago, the company had a market capitalization of more than $1 billion and Zemdri was so promising that it became the first antibiotic the F.D.A. designated as a breakthrough therapy, expediting the approval process.

Dr. Ryan Cirz, one of Achaogen's founders and the vice president for research, recalled the days when venture capitalists took a shine to the company and investors snapped up its stock. "It wasn't hype," Dr. Cirz, a microbiologist, said. "This was about saving lives."

In June, investors at the bankruptcy sale bought out the company's lab equipment and the rights to Zemdri for a pittance: $16 million. (The buyer, the generic-drug maker Cipla USA, has continued to manufacture the drug.) Many of Achaogen's scientists have since found research jobs in more lucrative fields like oncology.

Dr. Cirz lost his life savings, but he said he had bigger concerns. Without effective antibiotics, many common medical procedures could one day become life-threatening.

"This is a problem that can be solved, it's not that complicated," he said. "We can deal with the problem now, or we can just sit here and wait until greater numbers of people start dying. That would be a tragedy."

https://www.nytimes.com/2019/12/25/health/antibiotics-new-resistance.html