FOUR REASONS DRUGS ARE EXPENSIVE, OF WHICH TWO ARE FALSE

AN OPINION

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This is not a research paper
Innogen has been publishing Working Papers since 2003. The majority are research papers. This one is not. It is an opinion piece, from a former sell-side equity analyst. From 2005 to 2012 it was my job to look at the drug industry from a financial perspective, to value the stocks of drug companies, and to decide whether they were “buys” or “sells”. The financial returns on private sector R&D investment are, at an industry level, more sensitive to drug pricing, than almost anything else1. Therefore, investors tend to think a lot about long term prospects for drug pricing, particularly pricing in the US.

Acknowledgements
I thank Daniel Klein and Freke Vuijst, who I met at the 2015 Goldlab Symposium, for encouraging me to try to write something “popular” and “accessible” on drug pricing, although I may have failed on both counts. I thank Larry Gold and Marc Feldmann for inviting me to the Goldlab Symposium.


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Four Reasons Drugs are Expensive

If I offered to buy your shoes you would think I was strange, but we could probably haggle a price. If I offered to buy your children, we would not get to the haggling stage. The difference between trading shoes and children is not merely legal. It is also moral. People find it unpalatable, even taboo, to put prices on things that we treat as absolutes; life, liberty, or health. People have moral qualms about the cost of medicines for the sick or dying, but not about the cost of Botox or liposuction.

Yet life-saving medicines do not exist in a parallel moral universe, free from economics. Taxes are paid, as are health insurance premiums; healthcare budgets are set; doctors earn money, often in direct proportion to the quantity of treatment they provide; professors seek riches as biotech entrepreneurs; venture capitalists gamble other people’s money on the professors’ ideas; drug companies pay wages to employees and dividends to shareholders; and former hedge fund managers set up firms to play pharmaceutical arbitrage, buying drugs low then selling them high.

A recent uptick in commercial drug discovery in diseases such as cancer, hepatitis C, and multiple sclerosis means that the price of drugs is firmly a First World Problem; not merely something that troubles poor people in faraway countries. This article focuses on the economics of the problem. The aim is to explain why many drugs are so expensive that even First World health systems struggle to pay for them.

After all, to the uninitiated, drug pricing does not make obvious sense. For around the price of a cappuccino, UNICEF can buy vaccine to immunize a child against polio. In contrast, in the 4 years before her death from metastatic breast cancer, over 5 courses of treatment, an American woman might consume drugs that cost more than $200,000 yet offer zero prospect of cure. The English National Health Service (NHS) might spend “only” $75,000 on similar drugs for a similar patient; not because the drugs are much cheaper in the UK, but because the drugs tend to stop when further treatment is unlikely to be cost effective.

Some antibiotics that kill bacteria are so cheap that they are manufactured by the ton and added to animal feed, so pigs get fat and sausages are cheaper. Yet the American health system will pay $150,000 to $700,000 per patient per year for various drugs that mitigate rare conditions such as Gaucher Disease, Hunter Syndrome, or paroxysmal nocturnal hemoglobinuria. The English NHS pays about the same but, in contrast to the breast cancer example, rarely limits access on the grounds of cost effectiveness. Life-saving insulin, for diabetic patients, is between 100 and 1000 times cheaper, costing between $1 and $20 per day, depending on the dosing regimen, the country, and the brand.

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Five years ago, drugs priced at $50,000 in the US cured just over 1 out of 3 patients with a hepatitis C infection, at a cost per cure near $140,000. Two years ago, a new drug, Sovaldi, was launched at a price around $85,000. It cured 95% of patients, at a cost per cure near $90,000. The price of Sovaldi has caused intercontinental apoplexy, but the cost per cure has fallen, and Sovaldi is cheaper than many drugs that never cure anyone.

It is not only prices that are a puzzle. The drug industry has higher profit margins and higher R&D intensity than any other industry. But some stock market analysts (me, for example) spent the last decade believing that much drug R&D was a waste of shareholders’ money, and if drug companies put their shareholders first, they would be shutting labs, firing scientists, and paying bigger dividends. A few drug companies, Valeant for example, overtly agreed. “Downsizing” elsewhere shows other companies covertly agreed. The 11 biggest drug companies employed around 140,000 fewer people in 2013 versus 2008.

So what is going on?

“Cost”, “value”, “power” and “prizes” are four ways that people think, talk or write about the mechanism by which drugs are priced. “Cost” refers to cost-based pricing; the idea that the price of goods is based on how much it costs to produce them. “Value” refers to value-based pricing; the idea that the price of goods reflects their value to the buyer. “Power” is the exercise of intellectual property rights, to create scarcity and to find the maximum price that the market will bear. “Prizes” are the incentives provided by profit tomorrow, made credible by profit today, for investors gambling on the R&D that might create tomorrow’s drugs.

In what follows, I start with more familiar but less truthful explanations of drug pricing, cost and value, before moving to more truthful but less palatable ones; power and prizes.

**Reason 1: Cost (False)**

- “Honestly, we are **not** taking advantage of you just because we have a monopoly on the only drug that can save you from an early and painful death. We would like to charge you less, but sadly we can’t. You see, this drug took a huge amount of time and money to discover and it is really hard to manufacture. If we didn’t charge you a high price, we would never recoup what we spent on it, which would be a disaster for everyone.”

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5 By R&D intensity, I mean R&D spending as a % of sales. Several companies have higher absolute R&D spending than the major drug companies, but very few, such as the technology giants Intel, Microsoft, and Google, have similar absolute spending and similar R&D intensity. For data, see European Commission (2014) *The 2014 EU Industrial R&D Investment Scoreboard*. [http://iri.jrc.ec.europa.eu/scoreboard14.html](http://iri.jrc.ec.europa.eu/scoreboard14.html)

North Korea and the drug industry are the last bastions of Marxism. I heard this from Professor Martin Michel, formerly an academic pharmacologist and now working in the drug industry at Boehringer Ingelheim.

I won’t push the idea too far. After all, it was Martin Michel’s joke. Most of us are familiar with Marx and communism, but few of us know Marx’s work on value and pricing. It is as a pricing economist, not as a communist, that Marx would feel at home in the drug industry. He believed that the economic value of something, such as a new medicine, is determined by the amount of “socially necessary” labor required to produce it. If a new drug takes twice as many working days to discover and manufacture as the old drug it supersedes, it will be twice as expensive; a kind of input-based pricing. It is a short jump from here to “covering our costs”.

Cost covering is a palatable spiel to make if one is trying to sell an expensive drug. In fact, the cost of production story has been repeated so many times for so long, that it has become plausible to lots of people who should know better. I still read in health policy papers that drug companies need to recoup their costs. This is nonsense. Sunk costs are sunk. If companies are going to spend on R&D they need to believe there are decent odds that they will make a good return on investment, but this is a different thing to recouping anyone’s historic R&D costs. This is why firms have continued to invest in Alzheimer’s when in the decade from 2002, 99.6% of the 413 clinical trials testing 244 experimental drugs were failures. Conversely, shareholders would revolt if a company voluntarily dropped its prices and cut its profits just because some arbitrary proportion of R&D costs had been recouped.

Drugs do not become cheap to buy just because they are cheap to manufacture. It seems common knowledge among European payers that certain drugs, known as monoclonal antibodies, are difficult to produce. Therefore, payers tend to be more sympathetic to antibodies’ high prices. However, the “knowledge” is now false. Monoclonal antibodies were hard to manufacture 20 years ago, but there have been huge improvements in yield since then. Production costs today are often only 5% of the selling price. Cheap monoclonal antibodies are still few and far between.

Stale spiel

Despite its public relations appeal, the cost-based pricing story is becoming less fashionable. There are awkward questions about the costs that purportedly justify the price. For example, three members of the US Congress, Henry Waxman, Frank Pallone, and Diana DeGette wrote to Gilead in March 2014, concerned about the price of Sovaldi, the ~$95,000 per cure hepatitis C drug. Drugs like Sovaldi are causing budgetary problems for health systems because they are much more convenient and tolerable for patients than the older treatments, and much more effective. The new drugs are pulling

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10 Henry Waxman, Frank Pallone, Jr, & Diana DeGette (2014) Letter to Dr John C, Martin, Chief Executive Officer, Gilead Sciences Inc. [http://hepatitisresearchandnewsupdates.blogspot.co.uk/2014/03/democratic-leaders-request-briefing-by.html](http://hepatitisresearchandnewsupdates.blogspot.co.uk/2014/03/democratic-leaders-request-briefing-by.html)
in a huge pool of previously untreated hepatitis C patients. Even for the well-funded and price insensitive US health system, treating ~3 million people at $50,000 a go (assuming discounts) is a brutal $150 billion headache.

So, Waxman, Pallone, and DeGette, after telling Gilead, with grim obviousness, that Sovaldi *will not cure patients if they cannot afford it,* asked the company how activities by the US drug regulator, the FDA, to streamline approval and reduce R&D costs, had been “factored into pricing decisions for the drug.” And then, a few months later, Senators Ron Wyden and Chuck Grassley asked for itemized accounts of the drug’s initial discovery and development costs.

Of course, neither the FDA’s streamlining nor its expediting nor any itemized R&D expenditures had ever been factored into any pricing decisions. Neither Gilead nor anyone else actually applies cost-based pricing.

Nor, as we discuss later, is it necessarily good policy to attack the economics of the winners. This is because the majority of R&D projects fail. The failures cost investors and the industry a great deal of money, but because they fail, they are never scrutinized by suspicious members of Congress. If you just look at the winners, drug R&D will look wildly profitable. The same is true of all lotteries. People buy a ticket for a dollar and win a million. However, the economics of the winners is not representative of the wider game. This is why, for example, the UK’s National Lottery is often called the tax on stupidity.

**Reason 2: Value (False)**

- *"This drug is great. Let's share the benefit. We are partners. We know the drug is expensive, but just think how much it is worth to you and your family if you recover from your illness and go back to work. You might even earn enough to pay us back what we charged you."*

As the cost-based pricing stories have gone stale, value-based pricing has become fashionable.

It is easy to understand why the drug industry is keen to talk about value-based pricing. First, most of us like being neither dead nor disabled, so value-based prices can be very high. Second, value-based stories may avoid the unpicking that cost-based stories now provoke. US politicians can ask nasty questions about the cost of the R&D required to discover and develop Sovaldi (or about its budget impact, or about the public health consequences of a high price), but they have a harder time arguing about its value versus older hepatitis C treatments or versus a great many useless things that US health systems buy without complaint.

Value-based pricing also has an appealing "logic”\(^\text{12}\). The English National Health Service (NHS), for example, does a bunch of clever health economic analyses, and believes that


\(^{12}\) See, for example, Claxton et al. (2008) *Value Based Pricing for NHS Drugs: An Opportunity Not to Be Missed?* [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2223028/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2223028/)
it provides the English population with an extra Quality Adjusted Life Year (or “QALY”) for every £20,000 to £30,000 (roughly $40,000) that it spends. To put it another way, for each $40,000 spent, someone in England gets to enjoy one year of high quality life that they would have otherwise missed.

If a new drug gave each patient an extra year of high quality life (one QALY), the NHS could pay up to $40,000 per patient, without reducing its average cost efficiency. For a drug that yielded two extra years of high quality life (two QALYs), the break-even point would be $80,000 per patient. Of course, the NHS might like to pay less, and split the economic benefits with the drug manufacturer. Nonetheless, if drugs’ prices were benchmarked against the QALYs they delivered, the NHS could be confident that it was getting decent value for money. At the same time, pricing decisions would provide an incentive for the drug industry to invent drugs that had a big health impact.

So the theory goes. The theory has spawned a whole new industry for health economists, particularly in Europe. However, from the perspective of health systems and the people who pay for them, value-based pricing struggles for several reasons, of which I highlight three.

**Theory meets reality**

The first problem for payers is that value-based pricing evolved as a way of charging customers more. Some goods or services are priced on the basis of inputs (such as labor cost) plus a mark-up. Retail stores, for example, often have standard mark-ups on certain kinds of goods. Some professionals still charge by the hour. The spot prices of oil or wholesale electricity are largely set by the marginal production cost of the most costly producer required to satisfy current demand.

In other businesses, however, sellers have learnt that they can charge higher prices, often much higher, by understanding the value of the product to the buyer. Luxury goods provide an example. No one imagines that a Chanel suit or a Louis Vuitton bag is quite so expensive because it costs a lot to make. The suit and the bag are expensive because Chanel and Louis Vuitton understand, manage, and then exploit, desire in the minds of consumers.

If I am buying something that is likely to be expensive, I specifically don’t want the seller to know the value of the product to me, because that value defines the maximum price that I would be prepared to pay. The job of professional sales people is to find and then extract that maximum. The drug industry has a lot of professional sales people.

The second flaw stems from national differences in the value that is assigned to a new drug. When presented with identical evidence on the safety and efficacy of a new drug, the English, Scots, and Swedes end up with different value estimates. Some of the difference reflects differences in disease prevalence and in medical practice. However, much reflects arbitrary differences in the way health systems account for costs and benefits. Should the value of a new drug include the tax revenue on earnings that are

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lost as a result of illness? Doesn't a dead patient cost less than a live one? How much money is a life worth in Ireland, Holland, or Slovakia? Should all lives in Holland be worth the same amount? In the absence of Sarah Palin’s imaginary “death panels”, who even decides how much a life is worth in the US?

While health systems benefit greatly from consistent internal cost-effectiveness standards against which to prioritize what they do, it is an error to confuse internal estimates of value with the price that a commercial drug company will accept.

**Value-based income tax**

Consider the idea of value-based income tax. I live in the UK. Suppose I told Her Majesty’s Revenue and Customs (HMRC, the UK tax authority; equivalent to the IRS in the US), that I shall home school my daughter, that I am a pacifist who opposed the wars in Iraq and Afghanistan, that I will am happy to take my chances if I get ill, and on that basis, my “value-based” income tax rate should be 15.7% and not the 20% to 45% that HMRC expects, depending on my level of income. No matter how precise my measure of the value of government services to me, the approach won’t save me money. This is because HMRC is more powerful than I am.

The situation with drugs is similar. An individual country’s cost-benefit analysis may not matter very much because national drug prices have global implications. The details of national pricing policies are horribly complex, but in practice, most countries try to keep a close eye on the price of drugs in other countries, and then behave like 5 year old children at a party. If they see that someone got a great price, the others cry; “It’s not fair. I want one.” Therefore, companies sometimes walk away from the most obvious low-end value estimates of small and idiosyncratic European health systems (and all European health systems are small and idiosyncratic when compared with the US). Drug company shareholders applaud this behavior, albeit quietly so that they avoid the political opprobrium that loud applause would attract.

Thus value-based pricing can drift into value-based rationing. Something along these lines occurs with expensive cancer drugs assessed by the UK’s health economic watchdog, the National Institute for Health and Clinical Excellence, or NICE\(^\text{14,15}\). A company presents its new drug. NICE calculates that the drug is poor value for money at the price at which it is offered. The company maintains a high price, fearing knock-on effects in other countries. The drug enters a British limbo; theoretically “on sale”, but at a price at which the NHS doesn’t really buy it. The high UK price is successfully signalled to other countries. British politicians and drug company public relations folks are interviewed on TV and say how amazed, disappointed, horrified, they are that such a thing ever happened. The process then repeats periodically when the next expensive cancer drugs come along, or when the annual cancer drug budget is blown.

\(^\text{14}\) See for example, Celgene’s Abraxane, Astellas’ Xtandi, and AstraZeneca’s Lynparza in 2015, and Roche’s Kadcyla and Gazyvaro in 2014.

Nobody knows anything

One of the best books about the drug industry is about the movie industry; William Goldman’s Adventures in the Screen Trade. Goldman wrote that: “Nobody knows anything...... Not one person in the entire motion picture field knows for a certainty what’s going to work. Every time out it’s a guess and, if you’re lucky, an educated one.”

Nobody knows for sure at the point of launch which drugs will transform medicine, which will turn out to be duds, and which will poison people. Drug companies and Wall Street analysts are hopeless at forecasting drug sales, even when most of the clinical trial data have been collected. I would be surprised if national health economic agencies have clairvoyant powers that the companies and the analyst lack. Therefore, rushing to do technical health economic analyses to come up with what will often be the wrong value-based price, which may be ignored by the drug company if it is lower than other countries’ wrong numbers, seems somewhat futile.

I recently heard an eminent Professor of Medicine at Oxford University, say: “… we seem to have finally worked out how to use statins.” Statins, commercially successful drugs that lower cholesterol and reduce the risk of heart attack and stroke, have been used in tens of millions of patients in the real world for nearly 30 years, yet even the statement that we “seem” to have them worked out is controversial. Respectable medical opinion remains divided on precisely who benefits and by how much.

Guessing the value of many other drugs is even harder, particularly those that are used for a variety of different things, each of which will have a different value. A drug called Rituximab, launched as an excellent treatment for one particular variety of lymphoma, is now actively marketed for 7 different uses (in non-Hodgkin’s lymphoma of various different kinds and in various different drug cocktails, in chronic lymphocytic leukemia, in rheumatoid arthritis, in Wegener’s granulomatosis and in microscopic granulomatosis). Rituximab is also used off-label in multiple sclerosis, systemic lupus erythematosus, chronic inflammatory demyelinating polyneuropathy, auto-immune anemias, idiopathic thrombocytopenic purpura, pemphigus, pemphigoid, Graves’ disease, etc., etc.

I am not sure which, if any, of these reasons explain the UK government’s 2014 decision to quietly drop its long standing plans to move the UK to value-based pricing. Other enthusiasts might reflect on the UK’s retreat.

Reason 3: Power (True)

- Abraham Lincoln: “I have already intimated my opinion that in the world’s history, certain inventions and discoveries occurred, of peculiar value, on account of their great efficiency in facilitating all other inventions and discoveries. Of these

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were the arts of writing and of printing, the discovery of America, and the introduction of Patent Laws.”

I was dismissive of cost and value. Power, on the other hand, matters; the power that follows from the rights to a legal monopoly. Most new drugs are launched with patent protection that gives the inventor the option to keep other peoples’ copies off the market for 12 or so years. Many drugs then extend their monopoly status for several years beyond the original patent term.

Power is exercised in various other industries where intellectual property matters. Books are similar. If you copy a new book without permission, you infringe copyright. If you copy and sell a new drug without permission, you infringe patents. While books can be hard to write and new drugs are hard to discover, each extra copy or dose is cheap to manufacture. If you want an English-French dictionary, you won’t be tempted by a Korean-Italian dictionary. If you are a woman with acne, you won’t be tempted by a cure for male pattern baldness. Thus direct price competition often makes little sense for producers.

Copyright-protected books and patent protected drugs that sell well are “blockbusters.” Some books for small and specialist markets (academia, law, medicine) can be very expensive. New drugs for small and specialist markets can be very expensive. On the other hand, books which are out of copyright are often available in cheap editions. Drugs whose patents have expired, which are available from several suppliers, are also often very cheap.

There are, however, two important differences. The first is the complexity of the drug buying process, which disconnects the chooser from the user from the payer. The second stems from the fact that reading the same book over and over again is even more boring than prescribing or swallowing the same pill every day.

**Power to the seller**

The US, the world’s most important drug market, illustrates the first difference. Most books are bought by someone using their own money. In contrast, most drugs are prescribed by a doctor for a patient, with much of the cost covered by an insurance company. Thus the decision to make a specific drug purchase (made mainly by the doctor and patient) is disconnected from payment (made mainly by third parties such as health insurance companies, health maintenance organizations, and pharmacy benefit managers) and disconnected from the initial choice of health cover (generally made at a different time, and often made by someone who isn’t the patient).

When I look across from Edinburgh, Americans with health cover appear to be technological optimists who like a lot of choice but who sue if things go wrong. Compared with Europeans, they tend to be more interested in progress and novelty and

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20 Market exclusivity can be extended beyond the standard patent terms to compensate for time taken during the regulatory approval process, if a company invests in paediatric trials, if there are new approved uses for a drug, or if a drug is approved for an orphan indication.
less interested social solidarity. It is difficult to sell health cover that strictly limits patients’ drug choice. It is particularly difficult to restrict coverage of new drugs that treat serious diseases and for which there are few obvious substitutes. This is because it is the fear of serious illness that provides the motivation for insuring in the first place. People don’t insure (either voluntarily, or because they now have to) because they are worried they will get a cold. They insure because they are worried about getting run over by a truck or getting cancer. Furthermore, rare diseases are individually, if not collectively, rare, and total medical costs are dominated by things other than drugs. Americans have expensive doctors; self-employed entrepreneurs who make more money the more different things they do to the patient. Therefore, covering yet one more expensive drug for yet one more rare cancer does not make much difference to the premiums that a health plan charges the employer or the individual. Not covering that one drug, on the other hand, can cause reputational damage and make health cover hard to sell. What if the spouse or child of the CEO of the corporate client ever needs that one drug? The net result is that most insurance plans in the US, by commercial necessity, are forced to cover nearly all drugs, even if in a fairly grudging manner that pushes some of the cost onto the patient.

The drug sellers’ resolve in commercial negotiations is reinforced by the fact that huge US government programmes, who often buy much more than any commercial payer, base their prices on the prices in commercial market. Medicaid, for example, is not allowed to negotiate prices itself, but can demand the best price that has been achieved by any insurance company.

Drug companies know all this and so exploit their temporary monopolies with the steely ruthlessness that their shareholders demand. And boy, are they ruthless!

**The drug formerly known as Campath**

One recent example is the case of a drug formerly known as Campath-1H (also known as alemtuzumab and Lemtrada). The drug was created in the Cambridge University Pathology Department (hence “Campath”) in the UK in the early 1980s. Campath kills white blood cells in the patient to whom it is administered. This may sound an unlikely therapeutic strategy, but it can be a good thing in certain diseases; if the patient has leukemia (which is a white blood cell cancer), or if the white blood cells are attacking the patient’s own body, as happens in auto-immune diseases. One such auto-immune disease is multiple sclerosis, where the patient’s immune system attacks nerve fibers in brain and other parts of the central nervous system, and where, over time, accumulated nerve damage can cause disability and even death.

Campath’s commercial launch in the US was for leukemia in 2001\(^2^1\). This proved a small market. However, in 1994\(^2^2\), long before the US leukemia launch, the first reports emerged that Campath was useful in multiple sclerosis. Other studies followed and Campath became a respectable treatment for a minority of patients with the disease. Campath had an unusual clinical profile. It appeared ferociously effective, but often with serious side effects. Doctors prescribing Campath in multiple sclerosis were using it “off


label”; basing the use on their judgement of the scientific literature, on the needs of the patient, but not on any formal regulatory nod. Doctors are allowed, more or less, to prescribe any drug in any way they see fit. Much more tightly regulated is the way that drug companies may promote a drug. Companies may only promote uses that have been approved by a regulator such as the FDA in the US or the EMA in Europe.

Genzyme, later acquired by Sanofi, decided to run the costly clinical trials to obtain regulatory approval to promote Campath in the lucrative multiple sclerosis market (knowing, of course, that the trials were likely to succeed given existing evidence that the drug worked). However, there was a commercial problem. When Campath was launched as a cancer drug, cancer drugs were much cheaper than they are now. Over the years, multiple sclerosis drugs have also become much more expensive. From the company’s perspective, the drug was much too cheap. Had Sanofi applied the cancer price to the multiple sclerosis dose, it would have been charging around $6,000 per year when multiple sclerosis drugs had annual prices closer to $60,00023. So Sanofi withdrew Campath from commercial sale in late 2012 and re-launched it in 2013 in Europe and in 2014 in the US with a new name, Lemtrada, a new multiple sclerosis indication, and a list price rise of over one thousand – yes, one thousand – percent24. The temporary withdrawal outraged neurologists who had been using Campath off-label for years, but who could not get the drug for their patients until the re-launch.

However, the overall picture is complicated, and the ethics of Sanofi’s steely ruthlessness could keep high school debating societies busy for a semester or two. Throughout the withdrawal, Sanofi continued to provide Campath to leukemia patients, who now generally get it for free, but with strict controls so it does not leak into the valuable multiple sclerosis market and compete with Lemtrada. Multiple sclerosis patients, who lost a treatment option during the withdrawal, have probably gained after the re-launch. Lemtrada has a unique and powerful profile. It is possible, though not yet proven, that it is unusually effective in halting the progress of multiple sclerosis. More patients now get it, because doctors and health systems were often reluctant to use Campath off-label, even if thought it was cheap. The additional cost to health systems is offset by the fact that many of the patients who get Lemtrada would have consumed another expensive multiple sclerosis drug had Lemtrada never been approved.

Even the UK’s cost conscious NHS calculates that Lemtrada provides good value for money. You may recall here that I said that value-based pricing first evolved as a way of charging customers more.

**Power games**

Pricing power is exercised ruthlessly but ruthlessness can be subtle and strategic; a scalpel rather than a bludgeon.

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23 Tracey Staton (2012) *Sanofi pulls Campath to clear way for higher-priced Lemtrada.*  
http://www.fiercepharma.com/story/sanofi-pulls-campath-clear-way-higher-priced-lemtrada/2012-08-21

24 Tracy Staton (2014) *Sanofi tags newly OK’d MS drug Lemtrada at $158K, ready to tout head-to-head Rebif data.*  

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Power and prices are very sensitive to competition. Their simultaneous collapse is most obvious when patents and regulatory exclusivities expire. At that point, chemically and biologically equivalent generic copies enter the market and health insurers can switch patients without physicians getting in the way. This is called “generic substitution” and is an automatic and incredibly effective process in some major health systems. Lipitor, a cholesterol treatment and formerly the World’s best-selling drug, cost around $1,500 per patient per year in the US before its patent expired. You can now buy versions of the generic for $100 per year. Around 86% of all US prescriptions are now for generic drugs.25

“Therapeutic substitution” occurs when two or more drugs are medically similar, though not chemically identical, and it is reasonable for a health system to encourage, cajole, or force patients to use one drug rather than the others. This is trickier than generic substitution. Since the drugs are not identical, there may be medical reasons why one person might prefer drug a over drug b, but someone else would prefer drug b to drug a. This is common in psychiatry or cancer where patients may have strong preferences, often based on side effects. However, when drugs are similar and highly effective (so someone rarely needs drug b after having taken drug a), therapeutic substitution can boost health systems’ power in price negotiations.

Returning to the hepatitis C market, there is a wonderful illustration that I heard discussed by Geoff Porges, the biotechnology analyst at Sanford Bernstein, a Wall Street investment firm, and Professor Barry Nalebuf, an economist and game theory expert from Yale. The discussion concerned a tactical dance involving Gilead and its competitor AbbVie, which may be joined in 2016 by Merck and in 2018 by Johnson & Johnson.

Gilead’s hepatitis C drug Sovaldi now has a younger Gilead sibling, Harvoni, and since late 2014, Gilead has faced a competitor; AbbVie’s Viekira Pak. Porges and Nalebuf argued that the challenge that Gilead, AbbVie, Merck, and Johnson & Johnson face is reminiscent of what has become a standard item on the business school curriculum, the case of Holland Sweetener, NutraSweet, Coke, and Pepsi26.

**Holland Sweetener**

NutraSweet once had a lucrative patent-protected monopoly on a chemical called aspartame, used by both Coke and Pepsi to make their low calorie drinks less disgusting. Holland Sweetener was set up to challenge NutraSweet’s monopoly when the European and American patents expired in 1987 and 1992. Holland Sweetener invested several tens of millions of dollars building aspartame manufacturing facilities. However, its attempt to enter the market did little more than force NutraSweet into a price war. NutraSweet agreed cheap long-term contracts with both Coke and Pepsi, leaving Holland Sweetener with a tiny share of the market at the miserably low price that its market entry had triggered. Coke and Pepsi gained around $200 million per year from

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26 With thanks to Geoff Porges of Sanford Bernstein for this example.
lower aspartame prices and NutraSweet lost a symmetric sum. Holland Sweetener was a great disappointment for its investors, but a great bonus for Coke and Pepsi, even though neither ever bought any of its aspartame.

A mild parallel has already occurred in the US hepatitis C market. Viekira Pak is slightly less convenient and less widely useful than the Gilead drugs, although still extremely effective. AbbVie did an exclusive deal with one US payer, Express Scripts, at a price much lower than Gilead. In response, Gilead agreed exclusive contracts with a range of payers at a large discount to its former price. Before Viekira Pak, the average Gilead discount was around 20%. After Viekira Pak, the average Gilead discount may approach 45%. In a manner reminiscent of Holland Sweetener, Viekira Pak gained only 5% of the market, yet pushed down prices across the board. It is proving more valuable to US consumers than to AbbVie, the company that brought it to market.

Competition is likely to ramp up again in 2016 and 2018, with new drugs from Merck and Johnson & Johnson. The challenge for these newcomers will be to sell their drugs without firing large torpedoes into the market they are trying to enter. The challenge for Gilead and AbbVie is to somehow contract with the payers soon so as to render themselves torpedo proof, while at the same time deterring Merck and Johnson & Johnson from trying anything too explosive. Meanwhile, some payers will act as agents provocateurs, hoping that Gilead, AbbVie, Merck, and Johnson & Johnson behave like the German High Seas Fleet in Scapa Flow in 1919, and scuttle themselves.

**Elastic bands and deadweight losses**

Commercial shenanigans occur in the US health system, an environment in which used car salesmen and game theorists would flourish. Most other drug buying systems, particularly those in Europe, appear to have been designed by civil servants and public sector health economists who imagine there is a “correct” cost-based or value-based price for a drug (although this may be changing. Sovaldi has given several European countries a crash course in competitive procurement). European governments tend to be price setters who can in principle exert strong control over the drug consumption of the people who use their health systems. But their freedom to operate is constrained by the value-based rationing problem from the previous section. As one global healthcare investor told me last year, “Drug companies fear a political backlash in the US unless they narrow the US – Europe price differential. This does not necessarily mean US prices go down.” This fear acts like economic elastic which prevents developed world drug prices from straying too far from the US.

Before we Europeans complain about American elastic dragging up our drug prices, we should remember that profits from individual European countries are too puny to motivate serious commercial R&D investment. As Simon Baker, an investment analyst at Exane BNP Paribas, told me last year, “drug R&D is like NATO from 1949 to 1989; something from which Europeans derive huge benefit, but largely paid for by Americans.” And before Americans complain that their high prices are subsidizing Europeans, they should remember that their drugs are mainly expensive because they have a buying process that gives power to the industry. If European’s paid a lot more, American’s would not pay much less (although Americans might get a few more new drugs).
The economic elastic protects US profits, and profits in other price insensitive countries. However, the tighter the elastic, the more countries and more patients, who would have paid something for the drug, end up consuming and paying nothing. The loss of benefit to consumers is called a “deadweight loss” by economists. When it comes to medicine, most of us regard the deadweight loss as morally offensive, particularly now it applies to rich people like us, rather than HIV patients in Africa.

Companies have a way of loosening the elastic, reducing the deadweight loss, and making more money at the same time. Economists call the loosening process “price discrimination.”

Elastic loosens when pricing is opaque rather than transparent; when one health system cannot easily eavesdrop on another, and complain that “it’s not fair”. Thus there is a lot of deliberate obfuscation of the real prices, net of rebates, discounts, clawbacks, budget caps, etc., that health systems actually pay. Elastic also loosens when there are barriers to trade. The European Union is a free trade zone. Therefore, if one sells pills into Greece, where prices are low, it is more profitable overall to make sure they are in Greek language-only packaging, in Greek language-only blister packs, with something obvious and Greek printed on the pills, and — if possible — in a dose that is subtly different from any dose that can be legally sold in the UK or Germany. This makes it tedious to repackage the pills, before shipping them to parts of the European Union where they compete with similar pills that the manufacturer is selling a higher price: Tedium but not impossible, as German friends taking re-exported Greek drugs recently told me.

The elastic becomes extremely loose when companies are confident they can control leakage. Original Campath is now available for free in leukemia, but Campath rebranded as Lemtrada costs around $140,000 for a course in multiple sclerosis. Sovaldi has an $85,000 US list price (offset by opaque discounts in the range of 30% to 45%). Most Western Europeans are stuck with prices that are more than half the US figure. However, India and Egypt get the same drug for less than $1,000 per patient; extremely expensive for Indians and Egyptians; highly problematic for national health provision; but less than 2% of the discounted US price.

This raises dreams of pharmaceutical tourism: “Enjoy a 12 week Grand Tour, where you can gaze at the awesome pyramids and the inscrutable Sphinx of Giza, explore the treasures of Tutankhamen, gasp at the wonders of Luxor, while basking in the sustained virologic response you can only dream of buying in the US.” Some may dream, but Gilead got there already and put its corporate towels on the sun loungers. Egyptians must prove residency to get Sovaldi. Tourists need not apply27.

The power of the old

At the start of the Power section, we compared drugs with books, but said there were some important differences. Here we return to the second; novelty.

Only people who are very young or very religious like looking at the exact same book over and over again. In contrast, doctors do not get bored of prescribing the same drug, 

day after day. Many drugs become more valuable over time, as their risks are managed and their benefits explored. Drugs also get much cheaper at the point at which their patents expire and generic versions enter the market. The drug industry is creating an ever-improving back catalogue of virtually free and highly effective medicines, against which new inventions compete.

I have called this “The Better than the Beatles Problem”\(^28\). It would be hard to sell new songs if every new song was compared for quality against the Beatles’ discography, if everyone already owned the Beatles’ records, and – importantly – if no one ever got bored of listening to Strawberry Fields or Hey Jude. This is the situation in the drug industry; an intellectual property business, where patents expire yet the classics become neither boring nor unfashionable.

The Better than the Beatles Problem is a huge economic drag on the industry. It is the main reason why R&D has been pushed towards rarer and generally serious diseases where regulators are more risk tolerant and where payers have the least ability to resist the companies’ pricing power.

- **The Better than the Beatles Problem**: “Stop griping you ingrates. While you were moaning about our greed, we have built you a fantastic collection of almost free generic medicine. All that old stuff that actually works is making it near impossible to find anything that makes us money. You think you have got problems with drug prices! We are cutting our throats here!”

Drug companies have a point. Patents come and go but generics are forever (for non-infectious diseases, at least). The generic pharmacopoeia has become a medical wonder. I don’t know for sure, but I would guess that one can buy today, at rock bottom generic prices, a set of small molecule drugs that has greater medical utility than the entire set available to anyone, anywhere, at any price in 1995.

Nearly all the generic medicine chest was created by firms who invested in R&D to win future profits that they tried pretty hard to maximize: Short-term financial gain building a long-term common good. This strikes me as the strongest defence of the current system. But unfortunately for the drug industry, it is a tough defence to sell to the jury, no matter what Abraham Lincoln thought about patents and progress.

**Reason 4: Prizes (True)**

- **George Orwell**: “The Lottery, with its weekly pay-out of enormous prizes, was the one public event to which the proles paid serious attention.”\(^29\)

Drug R&D has economics that resemble a lottery; albeit a peculiar one where the prize is the right to exercise a legal monopoly.

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\(^29\) George Orwell (1948) *1984*
Only someone lacking ambition would play the lottery hoping to “recoup” their costs. Private sector investors, the “proles” in the Orwell quote, do not lack ambition. Furthermore, the R&D lottery is expensive to play, most games are a bust, and the rare wins take a long time to pay out. Investors and drug companies choose their games (cancer, Alzheimer’s, obesity, etc.) by guessing at the value of the monopoly, the cost of the R&D, and the odds of success.

**Expensive tickets**

That commercial drug R&D is often an expensive game is, to use British vernacular, both “bleedin’ obvious” and controversial at the same time. It is bleedin’ obvious because drug companies’ average costs per win can be estimated by dividing one unambiguous and publicly available number (the amount spent by the drug industry on R&D every year, which is over $100 billion) by another unambiguous and publicly available number (the number of new drugs approved each year by the FDA and EMA, which in recent years has been in the range of 20 to 40). This gives average costs in the range of $2.5 to $5 billion per new drug that emerges. Health economists at Tufts University routinely get to similar numbers in a much cleverer way, and routinely attract flak from industry critics for their bleedin’ obvious result.

Some Tufts’ critics argue that drugs can be discovered and brought to market for a sum that is much closer to the cost of a McDonald’s Happy Meal than it is to $2.5 billion. I think the bleedin’ obvious commercial average is criticized for two reasons. One of the reasons is very bad, but the other is worth thinking about.

The bad reason is that people have given too much credence to the industry’s spiel on the cost of production. They imagine that prices will fall if they can somehow prove that the industry is lying about the cost of producing new drugs. They are mistaken, because prices depend on market power, and not on R&D costs.

The other objection is interesting, but does not invalidate the bleedin’ obvious commercial average. Per-drug R&D spending is hugely variable. Some cancer drugs emerge after trials in only a couple of hundred patients. Trials for drugs that change the risk of heart attacks and stroke, on the other hand, sometimes need 20,000 or 30,000 patients. Some therapy areas have consumed huge resources but have so far yielded very little (e.g., the 99.6% failure rate of the 413 Alzheimer’s disease trials between 2002 and 2012). Commercial R&D is also – well – commercial. Companies absolutely require expensive clinical trial data to convince the regulator to allow them to promote a drug for any particular use, to convince health systems to pay for the drug, and to persuade physicians to prescribe drug a rather than similar drug b (and vice versa). Even Rituximab, a therapeutic triumph, required different clinical trials to support each one of its seven approved indications. If one were to focus on the costs of R&D for

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orphan drugs for rare diseases, or for neglected diseases in the poorer parts of the world, which is what some of the industry’s well informed critics do, R&D costs per drug would probably be far lower than the $2.5 billion commercial average; maybe ten times lower or less\textsuperscript{33}.

However, if we return to the bleedin’ obvious commercial figure, we can dissect it as follows. First, investors believe that money has a cost. If they had not put money into drug R&D, they could have put it to work in alcohol, fast food, or tobacco. Drug R&D is a slow process, and a lot of money is spent early on things that don’t work. Therefore, around half of the $2.5 billion is the time cost of money; investors’ interest on the cash that was tied up for years. Some people find the inclusion of the time cost of money objectionable\textsuperscript{34}. If any readers share this objection, they may want to lend me $1.25 billion dollars at zero percent interest. I will try to pay it back in 20 years; roughly the time it takes to get paid back on R&D spending. Ladies and gentlemen, form an orderly line please.

Of the $1.25 billion of “out of pocket” costs, the direct spending on each approved drug, although wildly variable, averages around 30% of the total. Direct spending on things that failed averages around 70%\textsuperscript{36}.

It takes luck. It’s not fair. Roughly nine out of ten drug candidates that enter clinical trials in man are never launched. Even for the few drugs that are ultimately approved, the winnings are skewed. The most successful 10% of approved drugs, only 1% of those that entered clinical trials, maybe 3 new drugs each year, generate half of the profits of the entire drug industry\textsuperscript{36}.

\textbf{Because that’s where the money is}

As is typical for lotteries, games get more or less popular as players’ guesses of the odds, costs, and prizes change. The cancer R&D lottery is popular right now, with companies raising money from venture capitalists, from flotations on stock markets, and by selling themselves to big drug companies. Better diagnoses and new treatment approaches have improved the odds of success and have made smaller and cheaper clinical trials practical. Pricing power is high, and investors seem to be making a big bet that, despite noisy complaints, US health systems’ inability to say “no” to expensive cancer drugs will last another decade at least.

Some games, such as the antibiotic R&D lottery, fall out of fashion. Buyers for newly discovered antibiotics are generally hospitals and, by historical accident, hospitals struggle to pass the cost of in-patient antibiotics through to insurance companies. Hospitals, which may be getting a fixed $10,000 fee for the surgical patient who acquired an infection, would hate to spend $4,000 on an antibiotic, when – as per the Better than

\textsuperscript{33} See, for example, DNDi (2013) Ten Years of Experience & Lessons Learned by DNDi. \url{http://www.dndi.org/about-us/business-model/dndis-model.html}
\textsuperscript{35} Paul et al. (2010). How to improve R&D productivity: the pharmaceutical industry’s grand challenge. \url{http://www.nature.com/nrd/journal/v9/n3/full/nrd3078.html}
the Beatles Problem – there is a large back catalogue of virtually free generics, one or more of which are likely to work. It is therefore much easier to sell a barely-effective cancer drug for $70,000 per treatment than it is to sell a life-saving antibiotic for $4,000.

And other lotteries never really get off the ground. How many investors would gamble to win monopoly pricing power over poor people with tropical diseases even if the R&D tickets were dirt cheap? When such games are played (e.g., GlaxoSmithKline’s striking persistence and modest clinical success with a malaria vaccine, or 600 million anti-malarial treatments from Novartis, they tend to be philanthropic not commercial.

Futile Reforms versus Implausible Reforms

It is normal to finish this kind of article with a few firm recommendations. Why explain a problem if you don’t pretend you know how to fix it? And anyway, recommendations make it easier to get speaking engagements and lucrative consulting work. However, I am going to go against fashion. I will explain why the problem of high drug prices is hard to fix, before making a few vague suggestions that experts should regard as implausible.

A mistake that many critics of the drug industry make is to imagine that because new drugs are very expensive, the industry is systematically cheating, there must be a lot of slack in the system, and if only the slack were removed, we would have a flow of good cheap new drugs. I think that the truth is much worse: The industry is trying hard to discover and develop things to sell; it is charging as much as the market will bear; even First World health systems are baulking; access to the newest drugs is problematic; but outside of a select few disease areas the financial returns on R&D investment are poor; and without the private sector investors there would be vanishingly few new drugs.

It is true that investors are happier now than they were 4 or 5 years ago when pipelines seemed very bare, but the recent increase in new drug approvals is linked to therapy areas where pricing power is highest and where, as direct consequence, prices attract the most political scrutiny. Therefore, this feels like a potentially fragile recovery.

Remember, it is not unusual to have industries where customers and investors both believe they are getting a bad deal, so customers and capital simultaneously retreat: The US steel industry between 1960 and 1980; the British ship building industry between 1950 and 1980; the sperm whale oil industry between 1840 and 1880; etc. The situation, when it arises, is characteristic of industries in decline.

There is a class of policy problem where common-sense has been applied for several decades but nothing much seems to change and we are still unhappy with the result. When faced with such a problem, options include: (a) Rational futility (i.e., keep repeating common sense “solutions” which experience shows either can’t be implemented or else don’t work); or (b), hopeful implausibility (i.e., try new things that are

probable rather than sure-fire failures). This is the policy equivalent of Sherlock Holmes’ line: “How often have I said to you that when you have eliminated the impossible, whatever remains, however improbable, must be the truth?” But it is worse. There was always a “truth” for Holmes, but there may be no ideal policy.

High drug prices look to me like one of these problems. Reforming health systems is very difficult. The creation of the National Health Service in the UK in 1948 required the Great Depression and the Second World War to build collectivist consensus. Looking across from Edinburgh, the most surprising thing about Obamacare is how much political and legal fuss it caused while making little change to the structures that make US healthcare expensive. The US government kept its nose out of drug pricing. Affluent Americans remain technological optimists who like choice. The buying power of health plans remains low.

If, as still seems likely, the US escapes major drug price reforms, then invisible economic elastic will hold up prices in other developed countries. And anyway, if the US took effective action to reduce drug prices, it would trigger some withdrawal of capital from drug R&D. Aggressive price reform could be a Pyrrhic victory: lower prices but on fewer new drugs in the long run.

Therefore, a likely outcome is that things grind slowly along their current trajectories. The economic structures within which drugs are bought will be largely unreformed. The temporary monopolies that give inventors pricing power will remain in place. The existing power relationships will persist. New drugs will generally remain expensive. US healthcare expenditures will creep higher as a percentage of GDP. A few more countries may follow the likes of the England, Scotland, Ireland, and the Netherlands and set firm cost-effectiveness thresholds. Perhaps European countries will club together more frequently to increase their power in price negotiations. The industry and buyers may get better at price discrimination. Therapeutic substitution will provide occasional price relief when several similar drugs emerge at roughly the same time. The industry may get better at making drugs like Sovaldi easy to buy without blowing this year’s health budget (e.g., “Don’t wait, cure today, with the cost spread over 10 easy and convenient annual payments”). This seems to be what most drug and biotech investors expect. They may be wrong, but they have less reason to be biased than most other people involved in the drug business.

**Hopeful implausibility**

So much for rational futility. What about hopeful implausibility?

Prices will fall if buyers increase their power versus sellers. European countries should buy as a block. The block should pay to keep more me-too drugs in the game, fund trials to prove therapeutic equivalence, and then run competitive tenders to find the cheapest supplier for pan European demand. Some Democrats in the US want the publicly funded Medicare and Medicaid programmes to use their huge untapped buying power to negotiate prices. Most US Republicans hate this idea, but some might conceive of libertarian alternatives. Insurance companies could price and sell policies on the basis of

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the cost effectiveness of any treatment they cover. Optimists with limited cash might choose to insure themselves and their families for all treatments that cost up to $30,000 per QALY. They can expect to be picked up if they are run over by a truck, but too bad if one of their kids is born with an expensive disease. Wealthy hypochondriacs, on the other hand, could buy cover up to $2,000,000 per QALY; all the useless and expensive drugs they want and their dog gets free Botox. This arrangement would establish a market-based link between treatment price and volume, and drive down prices.

Pricing power can also shift with a change in intellectual property laws, or in their enforcement. At present, the intellectual property tail is firmly wagging the therapeutic dog. Intellectual property laws are not laws of nature, but are there to promote the common good41. It should, therefore, be possible to put the dog back in charge of its tail.

Patents have only ever given carefully bounded rights to the holder. The boundaries change over time. Some boundaries could be retracted to increase affordability. For example, very long periods of market exclusivity are costly to health systems, yet do little to incentivize the initial R&D investment. This is because the initial R&D investors, with their time cost of money, largely ignore earnings in the distant future, long after the drug has been brought to market.

Other boundaries may be extended. Evolution is lazy. Biological machinery that does one thing (e.g., signal pain) is recycled to do others (e.g., make blood clot) so drugs that do one thing tend to do other things too. Aspirin is a painkiller, an anti-inflammatory, and protects people from heart attacks. However, once patents expire, it is hard to incentivize work to exploit new uses, even when the work is cheap. At present, the drug industry is forced to focus on robustly patentable novel molecules rather than therapeutic utility per se. Novel molecules are risky and unpredictable, which raises the cost of R&D, reduces competition, and raises the industry’s pricing power. There should be stronger incentives to commercialize new uses of old drugs42.

De-linkage

I asked several experts to read drafts of this article. The few who got this far said that I should finish with something about R&D costs and how to reduce them. After all, if power shifts from sellers to buyers, prices fall and prizes shrink, so you need cheaper R&D to keep the private sector interested in the game. I should, they advised, consider “adaptive licensing,” “open innovation,” “precision medicine,” “phenotypic screening” and various other things.

I am sympathetic to such ideas, so I thought hard about the advice before ignoring it. I don’t see it is practical to write usefully about the problem of R&D costs without writing a different article or a much longer article. Therefore, I am going to conclude with something simpler, which does not depend on cheaper R&D; a big prize that comes without pricing power.

As I said in the previous section, the R&D lottery for antibiotics was a lousy game for the last 20 years. The science is hard, the trials were expensive, the buyers are peculiarly price sensitive, and the best new drugs may be held in reserve. What capitalist would risk money on R&D for cheap drugs that hardly anyone will use? Unfortunately, drug resistant bacteria don’t care about the economics of R&D. They will happily evolve while the capitalists invest in something else. Thus there is market failure: The rise of drug resistant bacteria fifty years after we got used to the idea that rich people like us don’t get horrible bacterial infections anymore.

There is a big idea at the heart of some proposals to deliver new antibiotics. The idea is to weaken, or even eliminate, the connection between pricing power and the size of the prize that companies receive for successful R&D. The idea is called “de-linkage”\(^\text{43}\). In its most extreme form, an international consortium would offer large prospective prizes to drug companies for each new class of antibiotics; prizes up to $3.5 billion. On receipt of the prize, the company hands over all intellectual property rights to the consortium which then arranges cheap manufacture and controls distribution.

De-linkage has entered the mainstream for antibiotics because the conventional prize for successful R&D, rights to exercise a monopoly, fails for two reasons. First, the value of the monopoly is too small to excite enough investors. Second, high prices, even if they could be achieved, might create the wrong incentives. There would be the temptation to maximize profits by selling lots of the new pills, encouraging the evolution of drug resistance among bacteria, and achieving precisely the wrong policy outcome.

If de-linkage stimulates antibiotic R&D and supports equitable and responsible use of new antibiotics, at reasonable cost to governments who put up the prize money, then de-linkage variants could apply to drug classes where First World health systems think the market is failing in different ways. With antibiotics the problem is insufficient market power. In some other therapy areas, the problem is too much.

I am not sure if de-linkage will work for antibiotics. It looks fiercely complex in practice. It requires international cooperation and agencies that don’t yet exist. It may prove less cost effective than price-based incentives. It may appeal to collectivist Europeans but founder on the shoals of US healthcare exceptionalism. We should know in around 15 years.

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