# Bitter Pills: Why the NHS can't swallow big pharma's profiteering

## Big Pharma prices are breaking the NHS

The strain on Britain's National Health Service is plain for all to see. Serious under-investment, under-staffing, ill-conceived part-privatisation schemes and strategic failure in related areas like social care have all played an enormous role in this crisis. But one further driver of the crisis is less reported on: the spiralling cost of new medicines.

The manufacturing costs of these medicines is actually very low, yet the NHS is being charged astronomically high prices for them by pharmaceutical companies which have often only played a relatively minor role in their development.

In this report, we document how serious this aspect of the crisis is by looking at the amount NHS England spends on the top ten most expensive drugs. **We find the service spent an eye-watering £13 billion on just these ten medicines in the ten years up to 2022.**

Total NHS medicine spending is far in excess of this, likely amounting to hundreds of billions of pounds over the same period, though exact figures are hard to ascertain. But here, we focus on just the most costly medicines in order to show that the problem of super-expensive drugs is a rapidly growing problem.

This report focuses on costs to the NHS, but takes place within a global context of enormous growth in the price of new medicines globally. In the US, estimated net prices of newly launched prescription drugs increased from an average of around $1,400 a year (£1,200; €1,300) in 2008 to over $150,000 a year in 2021.[1]

As astronomical as UK spending on drugs is, it could be even worse. Thankfully the NHS is currently able to negotiate prices to some degree, as well as claw back funds through the Voluntary Scheme for Branded Medicines Pricing and Access or VPAS, which aims to cap the total NHS drugs bill and keep the increase in spending on branded medicines to 2% a year. The agreement - struck between

[1] Aris Angelis et al, 'High drug prices are not justified by industry's spending on research and development', *British Medical Journal,* 15 February 2023. Available at: https://www.bmj.com/content/380/bmj-2022-071710

the government and industry in 2019 - means that when spending exceeds the agreed amount, industry must pay a rebate to the government.

But this vital cost saving is being challenged by the pharmaceutical industry right now. Two pharma giants, Eli Lilly and AbbVie, have already left the scheme, in apparent protest at how much of their profits they have had to repay to the NHS.[2] Meanwhile, the Association of the British Pharmaceutical Industry (ABPI) has made proposals that argue for the replacement of the current VPAS scheme with a much lower rebate.[3] The government's own estimates suggest the scheme proposed by the ABPI would cost the NHS an extra £2.5 billion per year.[4]

We find that over the last decade, the NHS has secured savings of £9 billion on the 10 drugs focused on during this study, including through collective negotiation through the National Institute for Health and Care Excellence (NICE) and with VPAS. Across all branded medicines the NHS has been able to recover £7 billion of excess pharma profits via the VPAS scheme in the past five years. But **we find that pharmaceutical companies have still extracted an estimated £11.9-12.6 billion of excess profits from the NHS through these drugs.**

We anticipate the drugs bill crisis could get even worse if the government cedes ground to the pharma industry on pricing agreements including VPAS.[5]. Following complaints by pharmaceutical companies about the UK's tax environment, as well as some threats to pull R&D investment, a recent report by Angelis et al also makes the important point that supposed links between national pricing policy and the location of industry's R&D investment are not consistent with the available evidence.[6]

It should also be noted that even the 2019 VPAS agreement does not shield patients from the consequences of the monopoly prices demanded by drug companies, with many drugs over the 10 year period rejected by the cost-effectiveness watchdog, NICE, for being overpriced. This has led to patients and families being forced to battle, sometimes for years, to win affordable access to lifesaving medicines, for conditions such as cancer, hepatitis C, and cystic fibrosis.

## Big Pharma rarely invents the drugs we use

The second part of this report examines the role the companies profiting from these medicines have played in creating them. Advocates for the existing model of pharmaceutical innovation would have us believe that, yes, medicines are expensive, but that's because they are costly for drug companies

[2] 'Leading global pharma firms exit UK drug pricing agreement', 16 January 2023. Available at: https://www.abpi.org.uk/media/news/2023/january/leading-global-pharma-firms-exit-uk-drug-pricing-agreement/

[3] 'ABPI sets out new proposals to support the NHS and economic growth', ABPI. Available at: https://www.abpi.org.uk/media/news/2023/march/abpi-sets-out-new-proposals-to-support-the-nhs-and-economic-growth/

[4] Hannah Kuchler, 'UK says drugmakers' call for fixed-rate medicines tax 'unaffordable', *Financial Times*, 1 March 2023

[5] NHS set to save £7 billion thanks to world-leading medicine pricing scheme', *UK Government*, 24 April 2023. Available at https://www.gov.uk/government/news/nhs-set-to-save-7-billion-thanks-to-world-leading-medicine-pricing-scheme

[6] Aris Angelis, James Lomas, Beth Woods and Huseyin Naci, Promoting population health through pharmaceutical policy, *London School of Economics and Political Science*, June 2023

to research and develop. They want to convince us that, unless we pay these prices, we will have no new medicines at all.

Drug companies often claim high prices are justified by the high costs of inventing new drugs. But we find that each of the 10 drugs analysed in this report benefited from work by scientists from public institutions, from public funding, from charitable funding or in some cases a mixture of all three. Very few of these drugs could reasonably be said to have been fully invented by the companies that now market them.

One of the most extreme examples is the anti-inflammatory drug adalimumab, sold exclusively under the brand name Humira, by pharma giant AbbVie, until its patent monopoly period ran out in 2018. The cost of this drug to NHS England has been £2.7 billion over the 10 years.

AbbVie has made $208 billion globally from Humira – making it the most lucrative drug in history.[7] But AbbVie didn't invent the drug. That was a lengthy process which entailed a huge amount of public money, and was grounded in Nobel Prize-winning research at Cambridge University,[8] as well as work from smaller companies. AbbVie's parent company bought out the company that owned Humira, and proceeded to charge eye-wateringly high prices for the drug. A US Congressional committee discovered in 2021, that AbbVie spent a tiny proportion of the money it made on Humira undertaking 'research and development' for the drug – indeed a large portion of the research and development that was spent was dedicated to extending the company's market monopoly and extending its patents.[9]

Then there's lenalidomide, sold under the brand name Revlimid, made by Celgene, a subsidiary of pharma giant Bristol Myers Squibb. The drug is actually a modified version of the very old and scandal-ridden thalidomide. In this modified form, the medicine has been found to be an effective treatment for certain types of cancer.

However, the science behind this drug is old and as a US government investigation found that Celgene "contributed very little to the science first establishing that drugs like Revlimid could be an effective treatment for multiple myeloma. Rather, Celgene benefited from the acquisition of a decades-old product, academic and non-profit research, and at least eight federally funded studies." The company was even forced to pay Boston Children's Hospital nearly £200 million in a legal wrangle over royalties.[10]

All of the drugs on the list are made by Big Pharma – or companies now owned by Big Pharma. All of them benefited from work by scientists from public institutions, from public funding, from charitable funding or in some cases a mixture of all three. And many of these corporations stand accused of trying to lengthen or deepen their monopolies on these medicines so they can go on charging astronomical prices for longer. While there is variance in the level of direct input that each of the companies marketing these drugs has made into their development, with some of the most extreme

---

[7] Rosalind Turkie, 'AbbVie overcharged the Dutch health care system by as much as €1.2 billion for Humira', *Pharmaceutical Accountability Foundation*, 21 February 2023

[8] John Gapper, 'The painfully high price of Humira is patently wrong', Financial Times, 24 February 2023. Available at: https://www.ft.com/content/a8685c8d-60da-4fe8-9bba-ec1ba3bf62cc

[9] Staff Report, Committee on Oversight and Reform U.S. House of Representatives 'Drug Pricing Investigation Industry Spending on Buybacks, Dividends, and Executive Compensation', July 2021

[10] Tracy Staton. Celgene, Boston Children's play tug-of-war over Revlimid royalties. FiercePharma. 2014; published online Jan 6. https://www.fiercepharma.com/legal/celgene-boston-children-s-play-tug-of-war-over-revlimid-royalties

cases of value extraction highlighted above, this research makes clear the fundamental role that the public sector plays in the development of medicines. This leads us to conclude that governments, including the UK, can and must do far more to build a pharmaceutical system that prioritises fair and reasonable access to medicines over excessive corporate profits - and secure appropriate returns on public resources and risk.

All of this is particularly important to understand because there is a growing political consensus that government spending on research and development across the economy is too low.

We agree that increasing public investment is a vital part of creating the medicines of the future. Given the public sector accounts for such a large proportion of drug research, if we want new medicines, we're going to have to fund them. But if we do not want this public funding to be syphoned off into the pockets of the shareholders of big corporations, at a huge cost to the NHS, we believe we need a very different model which guarantees public value.

## We're paying for profit

Finally, this report looks at the amount the NHS could save if measures were taken to reduce the profiteering of Big Pharma corporations.

The process by which pharmaceutical corporations set their prices is notoriously opaque. It has regularly been found that actual research, development and production costs bear no relation to the final price of a medicine.[11] Rather, thanks to the monopolies these corporations enjoy over new medicines, they can charge whatever they think they will be able to get away with.

Actual costs of developing and producing drugs to the company concerned are shrouded in secrecy, and so calculating potential NHS over-payment is far from an exact science. However, based on the information we have, and detailed studies of previous drug pricing, we estimate that the cost being paid by the NHS is *massively* inflated and that **the service could save between £11.9 billion and £12.6 billion over 10 years if it was able to pay the real cost of manufacture for these medicines.**

At the lower end of our estimates, some medicines cost as little to produce as 0.3% of what the NHS is being charged. On the most generous assumptions we can make, the production costs of one drug on the list could be as much as 28% of the price the NHS pays. But no other medicine's production costs are more than 20% of the price the NHS pays. Most are estimated to cost well below 10% of the price charged to the NHS. The excess profits described in this report represent mark-ups above the estimated cost price of the drugs *plus* a reasonable profit margin of up to 50%. In other words, under a different model where drug companies are prevented from making excessive profits, the NHS would be saving the vast bulk of the money it is currently paying for new medicines.

This extreme profiteering would certainly be consistent with the enormous amounts of money the corporations who market the drugs represented in this study return to their wealthy shareholders – returns which represent in effect an extraction of investment from the new medicines we need. This

[11] Aris Angelis et al, 'High drug prices are not justified by industry's spending on research and development', *British Medical Journal,* 15 February 2023. Available at: https://www.bmj.com/content/380/bmj-2022-071710

research is consistent with broader research which shows that profits of big pharma companies are almost twice the average for publicly listed companies,[12] with margins of up to 90%.[13]

Our figures do not account for the costs of research and development of new drugs, but, as we've already seen, these funds are to a significant extent provided from outside the big corporations who end up marketing these medicines. Globally, it is estimated that the public pays for two-thirds of all upfront drug R&D costs, with around a third of new medicines originating in public research institutions.[14] Furthermore, originator R&D costs, including the costs of failures, are likely to be recouped in the first year of global sales, while a recent report in the British Medical Journal demonstrates that high drug prices are not justified by industry spending on research and development.[15]

What's more, the current system walls off the technology and know-how which should, in a knowledge economy, be shared and diffused as widely as possible, resulting in the kinds of grotesque inequalities in access to life-saving vaccines, treatments, and diagnostics seen during the COVID pandemic, exacerbating a neo-colonial divide in public health outcomes across the world.

## Recommendations

The VPAS stand-off between industry and government and the threat it poses to our health and the NHS should present us with an opportunity to step back and reassess the scientific, economic and ethical sustainability of the status quo in pharmaceutical drug development, access, and financing. These recommendations are a set of simple steps which our government could start implementing immediately in order to achieve a more balanced and public-health driven pharmaceutical ecosystem: Such a system would create:

- Better prices for the NHS
- Better public return for the research and development costs spent by the state on medical research
- Better sharing of medical knowledge, allowing a fairer, more innovative and more collaborative model that delivers better medicines

1. **All R&D spend by the public sector must have strict conditions to safeguard global affordability and promote open-source research.** Conditions in R&D contracts from the public sector must ensure that sharing of technology, transparency and value for money is a key component of all public support, including support through tax incentives.

---

[12] Fred D. Ledley, Sarah Shonka McCoy, Gregory Vaughan, et al, 'Profitability of Large Pharmaceutical Companies Compared With Other Large Public Companies' Jama, March 3 2020

[13] '40 to 90 percent! Astronomical profit margins of Pharma companies cause skyrocketing premiums', Public Eye, 12 September 2022. Available at: https://www.publiceye.ch/en/media-corner/press-releases/detail/40-to-90-percent-astronomical-profit-margins-of-pharma-companies-cause-skyrocketing-premiums

[14] Dr Dzintars Gotham, Chris Redd, Morten Thaysen, Tabitha Ha, Heidi Chow and Katy Athersuch, STOPAIDS and Global Justice Now, October 2017. Available at: https://stopaids.org.uk/wp-content/uploads/2017/10/Pills-and-profits-report-WEB-002.pdf

[15] Aris Angelis et al, 'High drug prices are not justified by industry's spending on research and development', *British Medical Journal,* 15 February 2023. Available at: https://www.bmj.com/content/380/bmj-2022-071710

2. **Intellectual Property should be managed to maximise public good.** Exclusive intellectual property rights are an increasingly poor way of rewarding innovation, especially in an economy based on knowledge sharing. Innovation should be rewarded in alternative ways, such as prize giving to avoid monopoly control over knowledge and manufacturing. Meanwhile IP on publicly funded medicines should be held by an IP management system which aims at encouraging global access to medicines and collaboration in scientific knowledge, and a more balanced pharmaceutical sector.
3. **Where the private sector is failing, public infrastructure must be rebuilt.** The gross global inequity in accessing Covid-19 vaccines showed us the problems of being over-reliant on a small handful of companies who have the capacity to produce certain medicines. The government must intervene to prevent these 'bottlenecks', for example by establishing public manufacturing centres where needed and supporting the WHO mRNA technology Hub.
4. **Anti-monopoly powers should be used to ensure a balanced pharmaceutical sector.** The biggest players in the pharmaceutical market are protected from competition, and mergers and acquisitions have become key to the sector. This approach allows Big Pharma to set high prices whilst making it difficult for smaller innovator companies and generic manufacturers to enter the market. A more strategic application of competition law could create a more balanced sector which would incentivise innovation within smaller companies and lead to lower prices through generic competition. The Competition and Markets Authority should engage in a rigorous investigation of various IP-related practices of Big Pharma that may have a negative effect on pricing and access to medicines.
5. **The government should resist completely any attempts by the pharmaceutical industry to extract more excess profits out of the NHS**, including rejecting proposals made by the ABPI for a much lower rebate to replace the VPAS scheme.

# Analysis of top drugs by cost to NHS England: costs, development history, and estimated manufacturing costs

*Prepared by Dzintars Gotham†*

## 1. Top drugs by cost to NHS

The top 10 medicines by total cost to NHS England over 2012-22 (primary and secondary care) are shown in the table and graph below. Details on data sources and calculation are provided in the methodological appendix.

Table. Top 10 medicines by total cost to NHS England over 2012-22 (primary and secondary care).

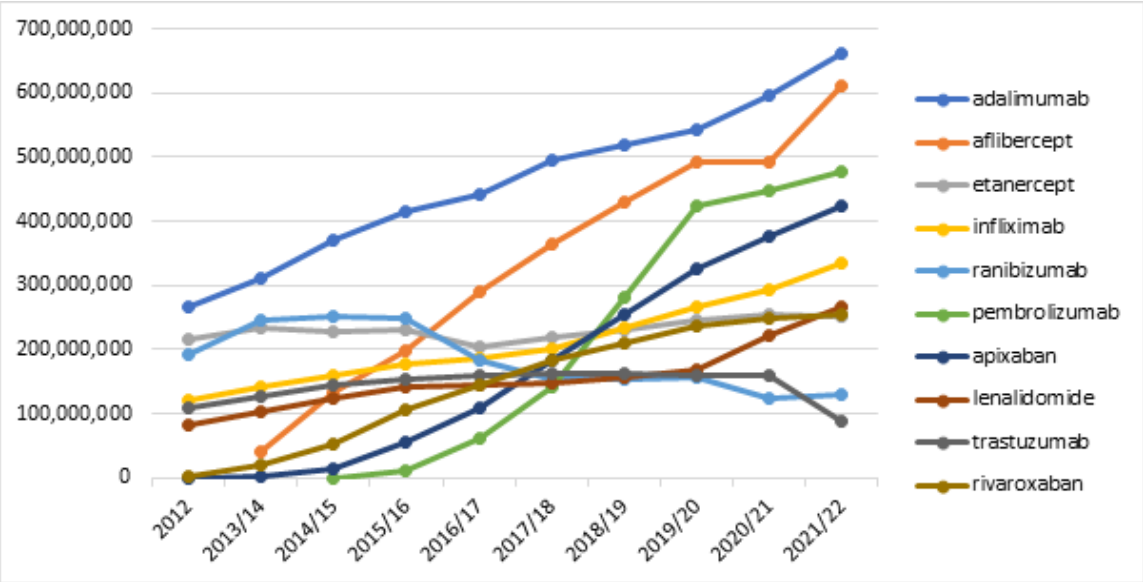
| Rank | Medicine and main use | Total at indicative price (GBP)* | Estimated cost after confidential discounts (GBP)** |
|---|---|---|---|
| 1 | adalimumab *(anti-inflammatory including for arthritis)* | 4,618,214,289 | 2,724,746,431 |
| 2 | aflibercept (colorectal cancer) | 3,053,371,007 | 1,801,488,894 |
| 3 | etanercept (arthritis) | 2,318,608,049 | 1,367,978,749 |
| 4 | infliximab (arthritis) | 2,113,813,123 | 1,247,149,742 |
| 5 | ranibizumab (age-related macular degeneration) | 1,839,452,710 | 1,085,277,099 |
| 6 | pembrolizumab (cancer) | 1,849,390,089 | 1,091,140,153 |
| 7 | apixaban (blood clots) | 1,743,241,750 | 1,028,512,632 |
| 8 | lenalidomide (cancer) | 1,562,760,029 | 922,028,417 |
| 9 | trastuzumab (cancer) | 1,428,348,262 | 842,725,474 |
| 10 | rivaroxaban (blood clots) | 1,460,916,685 | 861,940,844 |
| | **Total** | **21,988,115,991** | **12,972,988,435** |

*'Indicative prices' are reported in a number of NHS publications. No precise definition of this term is available, but it is assumed to be roughly equal to the list price.
**discounts assumed to be 38% (see appendix).

Note: These figures exclude Covid vaccines which are not included in the routine figures reported by the NHS, though the addition of the total cost of Covid-19 vaccines to the UK would hugely inflate the total spend.

† Dr Dzintars Gotham is a researcher, policy consultant, and medical doctor who works on access to medicines and biomedical R&D policy. He has served as a consultant to the World Health Organization, Médecins Sans Frontières, the Medicines Patent Pool, Treatment Action Group, STOPAIDS, and Global Justice Now. His research work focuses on the role of the public sector research in health product R&D, pharmaceutical costs of manufacture, and policy options for reducing the costs of health products.

Figure. Top 10 medicines by total cost to the NHS over 2012-22 (primary and secondary care), yearly cost at indicative price.




## 2. Drug development histories

**Aflibercept**

Aflibercept is a soluble VEGF receptor fusion protein that counteracts VEGF. Aflibercept has two main uses in medicine: the treatment of wet age-related macular degeneration (wet AMD) and the treatment of colorectal cancer.

VEGF (vascular endothelial growth factor) is a substance that occurs naturally in the human body, which promotes the growth of new blood vessels. VEGF plays a role in certain diseases. In wet AMD, VEGF promotes abnormal blood vessel growth in the retina, but the new vessels are fragile and can leak or rupture, damaging the retina and causing impaired sight or blindness. Counteracting VEGF in the eye prolongs maintenance of vision in people with wet AMD. In cancer, the formation of new blood vessels to supply tumour tissue is a requirement for tumour growth, and VEGF is a key component in promoting the growth of new (tumour) blood vessels. Counteracting VEGF can thus counteract or reverse the growth of tumours in some types of cancer.

Discovery of the role of VEGF in vascularization

Isaac Michaleson at the University of Glasgow proposed in 1948 that heightened levels of a factor promoting blood vessel growth in the eye may be contributing to abnormal blood vessel growth in certain types of eye disease.[1]

In 1971, Judah Folkman at Harvard Medical School investigated the utility of using agents that restrict the growth of blood vessels to limit tumour growth (as tumors rely on new blood vessels).[1] For a while, the key substances involved in promoting abnormal blood vessel growth – and methods of counteracting them – were not identified.

In the 1980s, Nicola Ferrara, working as a postdoctoral researcher at UCSF, began studying the question, isolated a strain of cells that appeared to produce a factor that promoted blood vessel growth. Shortly after joining Genentech in 1988, he was able to isolate the factor, naming it VEGF.[1,2]

(The VEGF protein was discovered independently and simultaneously by work at Harvard Medical School and Monsanto.[1]) Ferrara then discovered the VEGF receptor in 1992, in collaboration with Lewis Williams at UCSF.[1]

Development of anti-VEGF therapies

In 1994 Ferrara began investigating the usefulness of anti-VEGF factors to treat retinal disease. Collaborating with Lloyd Paul Aiello at Brigham and Women's Hospital and Harvard Medical School, he demonstrated that VEGF levels in the eye correlated with the overdevelopment of new blood vessels in the retina.[1,3]

The first anti-VEGF therapy developed by Ferrara was bevacizumab, as well as a derivative of bevacizumab, ranibizumab, which are high-cost medicines but not covered in this document.[2]

The concept of using VEGF 'decoy receptors' to prevent retinal neovascularization was first developed by Ferrara and colleagues at the Children's Hospital, Boston, publishing findings in 1995.[3] That work was funded by grants from the National Eye Institute, the Juvenile Diabetes Foundation International, the V. Kann Rasmussen Foundation, and the National Institutes of Health.[3] (VEGF decoy receptors had been developed by Ferrara and colleagues at Genentech earlier in the 90s, though they were being used mainly as a research tool rather than a treatment in themselves.[4]) The concept of using soluble VEGF receptor proteins to inhibit abnormal blood vessel growth was further proven in studies at Ferrara et al (working at Genentech) in 1998,[5] Ferrara with colleagues at Genentech working with the University of California in 1999,[6] and Genentech in 2000,[7] and by Kuo and colleagues at Harvard Medical School (with funding from the National Institutes of Health, Howard Hughes Medical Institute, and generous grants from The Association for the Cure of Cancer of the Prostate (CaPCURE) and Radley Family Foundations) in 2001.[8]

Identification of the aflibercept compound

The final drug compound was developed by the biotech Regeneron, by developing three optimized drug candidates that were more potent and less toxic versions of the compounds used in the earlier Ferrara/Genentech studies cited above.[9] Investigation to evaluate these three candidates were contributed to by researchers at Johns Hopkins University, confirming its efficacy (funded by US Public Health Service, the Foundation Fighting Blindness, Research to Prevent Blindness, and Dr. and Mrs. William Lake).[10,11] Regeneron, the proprietor of aflibercept, and Genentech, where much of the development of anti-VEGF therapies took place in the 90s, later engaged in a range of patent lawsuits concerning aflibercept.[12]

Clinical testing of aflibercept

After the final aflibercept compound was identified at Regeneron, further preclinical development to prove effectiveness in treating tumours was undertaken at Columbia University (collaborating with Regeneron, funded by the Pediatric Cancer Foundation, the Sorkin Fund, and the National Cancer Institute Grant),[13–16] the University of California San Francisco (collaborating with Regeneron, with funding from the NIH, Pfizer, Pfizer La Jolla Laboratories, the AngelWorks Foundation, and the Vascular Mapping Project),[17] among others.

The pivotal Phase 3 trials for the wet AMD indication (VIEW1 and VIEW2) were funded by the originator pharmaceutical companies (Regeneron and Bayer), with lead authors being clinicians at European and Japanese public hospitals, and US private healthcare institutions.[18]

The pivotal Phase 3 trial for colorectal cancer indication (VELOUS) was sponsored by Sanofi and Regeneron, with lead authors being clinicians at hospitals in Europe, the UK, Russia, South Africa, and Australia.[19]

**Note on monoclonal antibodies**

The development of all monoclonal antibody medicines – including adalimumab, infliximab, ranibizumab, pembrolizumab, and trastuzumab – benefitted from the development of the basic techniques for creating monoclonal antibodies, which took place at the Medical Research Council Laboratory of Molecular Biology (Cambridge, UK) in the 1980s.[20]

**Anti-TNF therapies**

TNF was first discovered at Memory Sloan-Kettering Centre in 1975,[21] and was shown to play a role in human disease by Beutler et al at Rockefeller University in 1985.[22]

Professors Marc Feldman, Maini, and Brennan, at Charing Cross Hospital in London, hypothesised that TNF plays a key role in autoimmune disease and, specifically, rheumatoid arthritis. Investigations of therapies blocking TNF had previously focused on treating sepsis, and the investigators later recounted how it was difficult to convince companies to provide any of the investigational anti-TNF agents to test for autoimmune indications.[23]

The following three case studies – adalimumab, infliximab, and etanercept – are all anti-TNF agents. With rheumatoid arthritis being the first approved indication for all three medicines (and still a major part of the market demand), they all benefit from the work by Feldmann and colleagues in proving the role of anti-TNF agents in treating rheumatoid arthritis (see above and in infliximab case study).

<u>Adalimumab</u>

Adalimumab was developed using Winter's phage display technology.[24,25] In 1993, a company called BASF Pharma commissioned Cambridge Antibody Technology, a spin-off led by scientists from the UK Medical Research Council Laboratory of Molecular Biology, to develop a fully humanized mab that would neutralise TNF.[26] This resulted in adalimumab, which proved highly effective in treating rheumatoid arthritis. At the end of 2000, Abbott Laboratories bought the division of BASF that owned the rights to adalimumab for $6.9 billion.[27]

<u>Infliximab</u>

The progenitor molecule to infliximab (a murine antibody version) was first created at New York University School of medicine, in a lab financially supported by the pharmaceutical company Centocor, with Centocor assisting in creating the chimeric antibody version – infliximab as it is today – in 1993.[23,28,29]

> According to Jan Vilcek, who first created the infliximab progenitor molecule at NYU: "A research and licensing agreement signed by NYU and Centocor in 1984 stipulated that my laboratory at NYU would provide Centocor with monoclonal antibodies to several cytokines, including IFN-γ, lymphotoxin and TNF. (In justifying to Centocor why it would be wise to invest in the development of antibodies to lymphotoxin and TNF, I mentioned the possibility of their therapeutic usefulness in autoimmune diseases.) In return, Centocor agreed to provide research support for my laboratory for 3 years (eventually Centocor ended up

supporting our research for a full 15 years) and to pay royalties to NYU on the sales of any products developed on the basis of technologies originating in my laboratory."[29]

The first study to test the hypothesis that anti-TNF treatment (infliximab) would benefit rheumatoid arthritis patients was performed by Feldmann and colleagues at Charing Cross Hospital in London (supported by grants from the Arthritis and Rheumatism Council of Great Britain, the Arthritis Foundation of Australia, and the Royal Australasian College of Physicians).[30,31] A second trial with infliximab followed shortly, performed at Charing Cross Hospital, and public hospitals in Germany, the Netherlands, and Austria (funded by a grant from the Arthritis and Rheumatism Council and Centocor).[30,32] A third trial, run by the same centres, was funded by the proprietor pharmaceutical company Centocor.[33] The pivotal Phase III trial was run at the same centres, funded by Centoctor.[34] In commentary soon after the approval of infliximab, one of the key inventors, Marc Feldman, commented that competitions will be important for bringing down prices – although he identified competition as being among different anti-TNF agents.[30]

Etanercept

Etanercept is a soluble version of a TNF receptor, often described as a 'decoy' for TNF.

Bruce Beutler's team at University of Texas-Southwestern, with NIH funding, developed and patented the prototypical fusion protein that formed the basis of etanercept.[35–42] The key publication by Immunex scientists describing the new molecule cites the key paper by Beutler's team in recognising the key step in increasing the effectiveness of the anti-TNF activity (creating a dimer by fusing two recombinant TNF receptors with one humanized Fc).[43] The University of Texas sold all rights to Beutler's key patent to a Immunex in 1998.[44] (in some sources, Beutler is quoted as saying they directly invented the final molecule.[42]) Bruce Beutler was awarded a Nobel Prize in 2011 for related work.[42]

Another key technique used in manufacturing etanercept was developed at Massachusetts General Hospital, where Brian Seed had developed key techniques in forming fusion proteins, which were essential to the development of etanercept (that work appears to have been funded by private investments).[45–47]

The Phase 1 and 2 trials were funded by the proprietor, Immunex. Some post-approval trials, important in finding different indications for etanercept, were run by Leeds University, with originator company funding.[49,50]

Etanercept is considered to be a case study of a 'patent thicket', where a great number of patents (potentially) cover a medicine, making it difficult for potential competitors to determine when patent protection will expire, or the precise scope of protection. Relatedly, etanercept is considered a case of evergreening.[37,48]

**Factor Xa inhibitors (apixaban and rivaroxaban)**

Rivaroxaban and apixaban are anticoagulants (blood-thinners) that work by inhibiting Factor Xa, a key enzyme involved in coagulation.

Factor Xa was validated as a drug target for anticoagulation in studies of antistasin and tick anticoagulant peptide (TAP),[51] funded by the US pharmaceutical company MSD, grants from the US Government through the Department of Health Services and National Cancer Institute, as well as

grants from charitable organisations (WW Smith Charitable trust, American Cancer Society, and the American Heart Association).[51–59]

Early exploratory work looking for FXa inhibitors was done at the labs of the University of North Carolina at Chapel Hill School of Medicine (funded by the US Government, American Heart Association, and North Carolina Heart Association), the German Democratic Republic publicly owned enterprise, and the Japanese pharmaceutical company Daiichi.[60–62] This work identified compound families that were effective as FXa inhibitors but not orally bioavailable. This work was key in informing the strategies taken by developers in the 1990s.[51,63]

Further work at the Washington University School of Medicine and the University of The Free State (Bloemfontein, Republic of South Africa) found that targeting Factor Xa was particularly promising because it would inhibit some clotting but not too much clotting – a key issue when developing blood thinning medications.[51,64–66] That work was funded by the pharmaceutical company MSD, the US National Institutes of Health and grants from the Monsanto/Washington University Biomedical Research Agreement.[51,64–66]

Rivaroxaban

The rivaroxaban molecule was identified at Bayer.[51] Some preclinical studies validating its effectiveness in vitro were done by Bayer collaborating with scientists at Pierre and Marie University and the University of Amsterdam.[51,67,68]

The Phase I and Phase II trials were carried out by Bayer.[69,70] Pivotal Phase III trials were led by European and UK academics and funded by Bayer and J&J.[71]

Apixaban

Discovery and optimization of apixaban was done by the proprietor pharmaceutical company, BMS.[72] Key Phase 3 clinical trials were funded by BMS and Pfizer, and run largely by the Duke Clinical Research Institute.[73]

**Pembrolizumab**

Pembrolizumab is a PD1 inhibitor, approved for use in a wide range of cancers, including melanoma, types of lung cancer, types of lymphoma, renal cancer, oesophageal cancer, types of breast cancer, endometrial cancer, and cervical cancer.

PD1 is a protein present on the surface of T cells, a key type of immune cell. In health, PD1 is stimulated by interaction with other immune cells as part of an inflammatory response and stimulation of PD1 leads to immune cell death. This is believed to serve as a regulatory mechanism against autoimmunity – once the T cell has served its role in recognising a foreign organism or a tumour and delivered an immune response, the T cell should die, in order to avoid immune overactivation. However, T cells are also a key way in which the human immune systems protects against tumours: where T cells detect a protein associated with cancer in a cell, they will bind to that cell and induce cell death, halting the progression of early tumours.[74] Thus, in certain cancers, inhibiting the action of PD1 'releases the brakes of the immune system' by allowing anti-tumour T cells to live for longer, substantially strengthening the immune response to tumours and leading to tumour shrinkage (remission).[75]

PD1 was discovered in 1991, in a laboratory of Kyoto University, Japan.[75,77] The work was financed by grants from the Ministry of Education, Science and Culture of Japan and the Ciba-Geigy Foundation, a philanthropic arm of the Ciba-Geigy pharmaceutical company that later became Novartis.[76,77] Further work at Kyoto University and the Japanese Science and Technology Corporation (a government research institution), from 1991 to 2002, elucidated the role of PD1 in immune cell regulation as well as the role of PD1 inhibition in strengthening immune response to tumours, supported by grants from the Japanese government.[75,78,79] Tasuku Honjo, the professor overseeing this work, was awarded the Nobel Prize for the discoveries in 2018.[80]

Pembrolizumab was developed by the US-based biotech Organon. (Organon the human healthcare arm of Akzo Nobel, a Dutch corporation whose main business was manufacturing paint.)[81,82] Organon's candidate compound was a murine antibody. In order to develop a humanized version, Organon in 2007 used the services of the UK charity LifeArc (Medical Research Council Technologies).[83,84] LifeArc has received substantial royalties for this work.[85]

LifeArc is a UK charity that grew out of MRC Technology (which was the key technology transfer organisation involved in the spin-out of Cambridge Antibody Technology, which developed the antibody humanization technique discussed above under adalimumab), and now operates a self-funded charity offering antibody humanization services and reinvesting earnings through research grants.

Note: Medarex has developed a humanized antibody (nivolumab) based on the genetic sequence of PD1 as published by the team at Kyoto University.[75]

Trials co-led by UK ICR (funded by the originator pharmaceutical company) led to approval.[86]

**Lenalidomide**

Lenalidomide is a treatment for multiple myeloma, a type of blood cancer in which B-cells, part of the immune system, proliferate abnormally.

Lenalidomide was discovered by Robert D'Amato, a researcher at Harvard Medical School, US, with funding from the Howard Hughes Medical Institute, a philanthropic medical research funder, in the early 1990s. D'Amato was investigating the effects of thalidomide on blood vessel and blood cell growth. He created modifications of the thalidomide molecule in a search for molecules with greater potency in inhibiting abnormal blood cell development and identified the amino-EM-12 analogue of thalidomide, which became lenalidomide, and secured certain patents on thalidomide derivatives.[87–90]

Celgene researchers were investigating the lenalidomide molecule at a similar time, though with a focus on anti-TNF effects and solid tumours (not multiple myeloma).[91]

Rights to IP relevant to lenalidomide were licenced by Boston Children's Hospital to Celgene.[92] Celgene – the current proprietor of lenalidomide – has been involved in royalty disputes with Boston Children's Hospital over the inventorship of lenalidomide, which resulted in Celgene paying a settlement of $198.5 million to Boston Children's Hospital.[93,94]

A US government investigation found that Celgene "contributed very little to the science first establishing that drugs like Revlimid could be an effective treatment for multiple myeloma. Rather, Celgene benefited from the acquisition of a decades-old product, academic and non-profit research, and at least eight federally funded studies."[90]

The first trial of thalidomide in patients with multiple myeloma was carried out by researchers at the University of South Carolina, the University of Arkansas, and Rockefeller University, with funding from the National Cancer Institute (while Celgene provided the study drug free of cost).[91,95]

The first trial of lenalidomide in patients with multiple myeloma was carried out in 2002, by researchers from Harvard Medical School and Celgene, with funding from the National Institutes of Health, the Multiple Myeloma Research Foundation, the Myeloma Research Fund, and the Doris Duke Distinguished Clinical Research Scientist Award.[91,96]

**Trastuzumab**

Research in the early 1980s, funded by the NIH, showed that inhibiting the HER2 growth receptor would reverse tumour growth in vitro.[97,98]

In 1985, scientists at Genentech identified the HER2 receptor, described its genetic sequence, and predicted that it was a gene whose overexpression was involved in causing cancer (an oncogene).[99] Axel Ullrich from Genentech collaborated with Dennis Slamon at the UCLA School of Medicine, who had a library of tumour samples, to demonstrate that HER2 is overexpressed in some breast tumours.[100] Similar discoveries were made simultaneously at the US National Cancer Institute and the University of Tokyo.[101] Genentech then demonstrated that HER2 plays a key causative role for a proportion of breast cancer.[101] With support from the US National Cancer Institute, Slamon and colleagues from the University of Texas Health Sciences Center showed that a monoclonal (murine) antibody specific to the HER2 receptor, created by Genentech working with Slamon,[102] could slow the growth of breast cancer cells in vitro.[103]

The strategy – of identifying and blocking growth receptors – also built on research at UCSD investigating the strategy of blocking growth receptors to fight cancers.[104] One antibody candidate, identified at UCSD as blocking tumour growth, later became cetuximab.[104]

Using funding from Revlon, a cosmetics company, Slamon tested the murine mAb in 20 volunteer breast cancer patients and undertook further research demonstrating that combining it with a conventional chemotherapy agent – cisplatin – produced a synergistic effect.[102] About US$13 million from Revlon funded Slamon's early work at UCLA.[102] Slamon was later quoted as saying that "[t]he science that ultimately led to the development of the drug would not have happened when it did without the support of Revlon" and the "Revlon grant helped accelerate the research that led to Herceptin by as much as ten years."[102]

After the early murine antibody candidate (MuMAb-4d5) showed promise, Genentech hired a researcher who had recently learned the technique of antibody humanization at the MRC LMB,[102] using the method of Winter et al,[105] to develop trastuzumab, a humanized version of MuMAb-4d5.[102] Genentech then collaborated with UCLA, UCFS, and MSKCC, to undertake Phase I-III trials, mostly with Genentech funding.[102,106–108]

Soon after approval, Genentech wrote to Congress to emphasise how important R&D tax credits had been in enabling financing of clinical trials for trastuzumab.[109] Tax credits can be seen as being similar to a government grant, as the credit granted by government 'forfeits' a proportion of tax revenue the government would otherwise earn from the company. It is also interesting to note that one historical analysis of the development of trastuzumab put the cost of development at "ultimately more than $150 million" – perhaps a surprisingly low figure.[102]

## 3. Estimated manufacturing costs

Data on sales of the raw, unformulated pharmaceutical (active pharmaceutical ingredient, API) were extracted from a proprietary database of exports from India. Data on API cost were analysed and converted into estimated generic prices using a methodology that has previously been applied to a range of medicines, described in numerous earlier peer-reviewed articles.[110–117] Caveats to the estimation method are outlined in the cited earlier analyses.[110–117]

Data on API costs were available for rivaroxaban, apixaban, and lenalidomide, but were not available for the other 7 drugs, that is, the biologics.

Estimates for the cost of API for biologics can be made using reported ranges of mAb manufacturing cost per gram.[117–122] (Costs of manufacturing fusion proteins (e.g. etanercept) are similar to those of mAbs.[118]) The average COGS at current mAbs manufacturing plants is estimated to be around US$100/g.[119,123] In the early 2000s, average COGS were reported to be around $300/g.[118,120] The manufacturing cost estimates below take a conservative (cautious) approach, by presenting a range of plausible costs based on per-gram costs ranging US$100-300.

Assumptions:

- Formulation costs (in vial or pre-filled injection) of $1-2.5 per unit for injectable formulations.[116,117,124]
- A margin for logistics of 20%.
- A profit margin of 10-50%.

Costs of R&D (or biosimilar development) are not included in the estimated cost-based prices, though for many or all of these drugs, originator R&D costs will likely have been recouped in the first year of global sales.

Comparison of current prices to estimated cost-based prices reveals that, for most medicines, a policy approach enabling early or immediate generic/biosimilar entry, and robust competition, could (have) allowed billions in savings.

| medicine | mg per unit * | Price per unit (GBP)** | Estimated cost-based price (GBP) | estimated price as % of current price | Savings over 2012-22 if available at cost-based prices (GBP)*** |
|---|---|---|---|---|---|
| apixaban | 5 | 0.56 | 0.017-0.024 | 3.1-4.2% | 985,304,070–996,826,354 |
| rivaroxaban | 20 | 1.06 | 0.04-0.05 | 3.4-4.6% | 822,049,164–832,686,945 |
| lenalidomide | 25 | 123 | 0.38-0.52 | 0.3-0.4% | 918,096,359–919,144,908 |
| adalimumab | 40 | 186.912 | 5.28–15.31 | 2.8%–8.2% | 2,501,532,740–2,647,776,192 |
| aflibercept | 4 | 481.44 | 1.48–3.91 | 0.3%–0.8% | 1,786,868,635–1,795,956,904 |
| etanercept | 50 | 96.76 | 6.34–18.48 | 6.5%–19.1% | 1,106,711,208–1,278,401,306 |
| infliximab | 120 | 223.02 | 13.73–40.66 | 6.2%–18.2% | 1,019,797,398–1,170,381,418 |
| ranibizumab | 3 | 449.049 | 1.37–3.59 | 0.3%–0.8% | 1,076,599,696–1,081,959,269 |
| pembrolizumab | 50 | 775.85 | 6.34–18.48 | 0.8%–2.4% | 1,065,150,245–1,082,229,327 |
| trastuzumab | 120 | 143.96 | 13.73–40.66 | 9.5%–28.2% | 604,729,872–762,363,323 |
| | | | | Total | 11,886,839,387–12,567,725,946 |

*Formulation with the lowest price per mg used, as a conservative assumption.

**'Indicative price' reported in March 2022, adjusted for confidential discounts assumed to be 38%, see appendix. The lowest available price is used, as a conservative assumption.
***Assuming prices reported in March 2022 have been constant over this period.

This is a highly hypothetical exercise and reflects a scenario in which

- Rights to manufacture the medicine were shared openly and globally before 2012, and
- Robust global competition rapidly emerged after rights were shared.

It is also important to note that 5 of the 7 biologics in the 'top 10' list now have biosimilars on the market in the UK, and the current prices listed in the table above are the lowest price available for that dosage formulation across originators and biosimilars. In high-income countries, biosimilar prices are still far above estimated costs of manufacture, likely due to

- Relative lack of competition due to recent market entry
- A high 'starting point' set by originators.

## References


1 Anti-VEGF therapy for wet macular degeneration. 2010 Lasker~DeBakey Clinical Medical Research Award. https://laskerfoundation.org/winners/anti-vegf-therapy-for-wet-macular-degeneration/.

2 Ferrara N. Vascular endothelial growth factor and age-related macular degeneration: from basic science to therapy. *Nat Med* 2010; **16**: 1107–11.

3 Aiello LP, Pierce EA, Foley ED, *et al.* Suppression of retinal neovascularization in vivo by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF-receptor chimeric proteins. *Proceedings of the National Academy of Sciences* 1995; **92**: 10457–61.

4 Park JE, Chen HH, Winer J, Houck KA, Ferrara N. Placenta growth factor. Potentiation of vascular endothelial growth factor bioactivity, in vitro and in vivo, and high affinity binding to Flt-1 but not to Flk-1/KDR. *J Biol Chem* 1994; **269**: 25646–54.

5 Ferrara N, Chen H, Davis-Smyth T, *et al.* Vascular endothelial growth factor is essential for corpus luteum angiogenesis. *Nat Med* 1998; **4**: 336–40.

6 Gerber H-P, Vu TH, Ryan AM, Kowalski J, Werb Z, Ferrara N. VEGF couples hypertrophic cartilage remodeling, ossification and angiogenesis during endochondral bone formation. *Nat Med* 1999; **5**: 623–8.

7 Gerber HP, Kowalski J, Sherman D, Eberhard DA, Ferrara N. Complete inhibition of rhabdomyosarcoma xenograft growth and neovascularization requires blockade of both tumor and host vascular endothelial growth factor. *Cancer Res* 2000; **60**: 6253–8.

8 Kuo CJ, Farnebo F, Yu EY, *et al.* Comparative evaluation of the antitumor activity of antiangiogenic proteins delivered by gene transfer. *Proc Natl Acad Sci U S A* 2001; **98**: 4605–10.

9 Holash J, Davis S, Papadopoulos N, *et al.* VEGF-Trap: A VEGF blocker with potent antitumor effects. *Proc Natl Acad Sci USA* 2002; **99**: 11393–8.

10 Saishin Y, Saishin Y, Takahashi K, *et al.* VEGF-TRAPR1R2 suppresses choroidal neovascularization and VEGF-induced breakdown of the blood–retinal barrier. *Journal of Cellular Physiology* 2003; **195**: 241–8.

11 de Oliveira Dias JR, de Andrade GC, Novais EA, Farah ME, Rodrigues EB. Fusion proteins for treatment of retinal diseases: aflibercept, ziv-aflibercept, and conbercept. *Int J Retin Vitr* 2016; **2**: 1–9.

12 Harrison C. Patent watch. *Nat Rev Drug Discov* 2012; **11**: 98–9.

13 Ricci V, Ronzoni M, Fabozzi T. Aflibercept a new target therapy in cancer treatment: a review. *Critical Reviews in Oncology/Hematology* 2015; **96**: 569–76.

14 Kim ES, Serur A, Huang J, *et al.* Potent VEGF blockade causes regression of coopted vessels in a model of neuroblastoma. *Proc Natl Acad Sci U S A* 2002; **99**: 11399–404.

15 Huang J, Frischer JS, Serur A, *et al.* Regression of established tumors and metastases by potent vascular endothelial growth factor blockade. *Proc Natl Acad Sci U S A* 2003; **100**: 7785–90.

16 Frischer JS, Huang J, Serur A, *et al.* Effects of potent VEGF blockade on experimental Wilms tumor and its persisting vasculature. *International Journal of Oncology* 2004; **25**: 549–53.

17 Inai T, Mancuso M, Hashizume H, *et al.* Inhibition of Vascular Endothelial Growth Factor (VEGF) Signaling in Cancer Causes Loss of Endothelial Fenestrations, Regression of Tumor Vessels, and Appearance of Basement Membrane Ghosts. *Am J Pathol* 2004; **165**: 35–52.

18 Schmidt-Erfurth U, Kaiser PK, Korobelnik J-F, *et al.* Intravitreal Aflibercept Injection for Neovascular Age-related Macular Degeneration: Ninety-Six–Week Results of the VIEW Studies. *Ophthalmology* 2014; **121**: 193–201.

19 Van Cutsem E, Tabernero J, Lakomy R, *et al.* Addition of Aflibercept to Fluorouracil, Leucovorin, and Irinotecan Improves Survival in a Phase III Randomized Trial in Patients With Metastatic Colorectal Cancer Previously Treated With an Oxaliplatin-Based Regimen. *JCO* 2012; **30**: 3499–506.

20 Marks LV. The lock and key of medicine: monoclonal antibodies and the transformation of healthcare. New Haven London: Yale University Press, 2015.

21 Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B. An endotoxin-induced serum factor that causes necrosis of tumors. *Proc Natl Acad Sci U S A* 1975; **72**: 3666–70.

22 Beutler B, Milsark IW, Cerami AC. Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effect of endotoxin. *Science* 1985; **229**: 869–71.

23 Monaco C, Nanchahal J, Taylor P, Feldmann M. Anti-TNF therapy: past, present and future. *International Immunology* 2015; **27**: 55–62.

24 Kempeni J. Preliminary results of early clinical trials with the fully human anti-TNFalpha monoclonal antibody D2E7. *Annals of the Rheumatic Diseases* 1999; **58**: i70–2.

25 Lu R-M, Hwang Y-C, Liu I-J, *et al.* Development of therapeutic antibodies for the treatment of diseases. *J Biomed Sci* 2020; **27**: 1.

26 McCafferty J. The long and winding road to antibody therapeutics. *mAbs* 2010; **2**: 459–60.

27 UK BioIndustry Association. Celebrating UK bioscience: unravelling the stories behind UK bioscience success. http://www.bioindustry.org/document-library/celebrating-uk-bioscience/1celebrating-uk-bioscience.pdf (accessed Aug 4, 2017).

28 Knight DM, Trinh H, Le J, *et al.* Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. *Molecular Immunology* 1993; **30**: 1443–53.

29 Vilcek J. From IFN to TNF: a journey into realms of lore. *Nat Immunol* 2009; **10**: 555–7.

30 Feldmann M. Development of anti-TNF therapy for rheumatoid arthritis. *Nat Rev Immunol* 2002; **2**: 364–71.

31 Elliott MJ, Maini RN, Feldmann M, *et al.* Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor alpha. *Arthritis Rheum* 1993; **36**: 1681–90.

32 Elliott MJ, Maini RN, Feldmann M, *et al.* Repeated therapy with monoclonal antibody to tumour necrosis factor α (cA2) in patients with rheumatoid arthritis. *The Lancet* 1994; **344**: 1125–7.

33 Maini RN, Breedveld FC, Kalden JR, *et al.* Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998; **41**: 1552–63.

34 Maini R, St Clair EW, Breedveld F, *et al.* Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *The Lancet* 1999; **354**: 1932–9.

35 Peppel K, Crawford D, Beutler B. A tumor necrosis factor (TNF) receptor-IgG heavy chain chimeric protein as a bivalent antagonist of TNF activity. *Journal of Experimental Medicine* 1991; **174**: 1483–9.

36 Bruce A Beutler, Karsten Peppel, David F Crawford. DNA encoding a chimeric polypeptide comprising the extracellular domain of TNF receptor fused to IgG, vectors, and host cells. .

37 Jonathan Gardner. A three-decade monopoly: How Amgen built a patent thicket around its top-selling drug. BioPharma Dive. 2021; published online Nov 1. https://www.biopharmadive.com/news/amgen-enbrel-patent-thicket-monopoly-biosimilar/609042/.

38 The Center for the Genetics of Host Defense UTSW. Meet Our Director. https://www.beutlerlab.org/director.html.

39 Steensma DP, Shampo MA, Kyle RA. Bruce Beutler: Innate Immunity and Toll-Like Receptors. *Mayo Clinic Proceedings* 2014; **89**: e101.

40 Dikshit M. Drug Discovery and Drug Development: The Indian Narrative. Springer Nature, 2021.

41 Kathryn Claiborn. Bruce Beutler wins the 2013 ASCI/Stanley J. Korsmeyer Award. 2013; published online April 1. https://www.jci.org/articles/view/69412.

42 The Nobel Prize. Bruce A. Beutler: Biographical. https://www.nobelprize.org/prizes/medicine/2011/beutler/biographical/.

43 Mohler KM, Torrance DS, Smith CA, *et al.* Soluble tumor necrosis factor (TNF) receptors are effective therapeutic agents in lethal endotoxemia and function simultaneously as both TNF carriers and TNF antagonists. *The Journal of Immunology* 1993; **151**: 1548–61.

44 The University of Texas Administration. Chancellor's Docket No. 93. 1998; published online April 6. https://www.utsystem.edu/sites/default/files/offices/board-of-regents/board-meetings/dockets/5-1314-1998.pdf.

45 Christopher Rowland. Drug firm, MGH fight over royalties. The Boston Globe. 2005; published online June 28. https://archive.boston.com/business/articles/2005/06/28/drug_firm_mgh_fight_over_royalties/.

46 Massachusetts General Hospital Translational Medicine Group. Who We Are. https://tmg.mgh.harvard.edu/about/who-we-are.

47 Report by the Office of Congresswoman Katie Porter (CA-45). Killer Profits: How Big Pharma Takeovers Destroy Innovation and Harm Patients. 2021; published online Feb 5. https://porter.house.gov/uploadedfiles/final_pharma_ma_and_innovation_report_january_2021.pdf.

48 Storz U. The Cabilly patents. *mAbs* 2012; **4**: 274–80.

49 Hunt L, Emery P. Etanercept in the treatment of rheumatoid arthritis. *Expert Opinion on Biological Therapy* 2013; **13**: 1441–50.

50 REF2021. Improving drug-induced remission in rheumatoid arthritis, and safely stopping the long-term use of drugs without disease flare. https://results2021.ref.ac.uk/impact/20fae694-ff2d-4717-baba-71e17d2c6edd?page=1.

51 Perzborn E, Roehrig S, Straub A, Kubitza D, Misselwitz F. The discovery and development of rivaroxaban, an oral, direct factor Xa inhibitor. *Nat Rev Drug Discov* 2011; **10**: 61–75.

52 Tuszynski GP, Gasic TB, Gasic GJ. Isolation and characterization of antistasin. An inhibitor of metastasis and coagulation. *Journal of Biological Chemistry* 1987; **262**: 9718–23.

53 Nutt E, Gasic T, Rodkey J, *et al.* The amino acid sequence of antistasin. A potent inhibitor of factor Xa reveals a repeated internal structure. *Journal of Biological Chemistry* 1988; **263**: 10162–7.

54 Dunwiddie C, Thornberry NA, Bull HG, *et al.* Antistasin, a Leech-derived Inhibitor of Factor Xa. *Journal of Biological Chemistry* 1989; **264**: 16694–9.

55 Waxman L, Smith DE, Arcuri KE, Vlasuk GP. Tick Anticoagulant Peptide (TAP) Is a Novel Inhibitor of Blood Coagulation Factor Xa. *Science* 1990; **248**: 593–6.

56 Nicolini FA, Lee P, Malycky JL, *et al.* Selective inhibition of factor Xa during thrombolytic therapy markedly improves coronary artery patency in a canine model of coronary thrombosis: *Blood Coagulation & Fibrinolysis* 1996; **7**: 39–48.

57 Vlasuk GP, Ramjit D, Fujita T, *et al.* Comparison of the In Vivo Anticoagulant Properties of Standard Heparin and the Highly Selective Factor Xa Inhibitors Antistasin and Tick Anticoagulant Peptide (TAP) in a Rabbit Model of Venous Thrombosis. *Thromb Haemost* 1991; **65**: 257–62.

58 Lynch JJ, Sitko GR, Mellott MJ, *et al.* Maintenance of canine coronary artery patency following thrombolysis with front loaded plus low dose maintenance conjunctive therapy. A comparison of factor Xa versus thrombin inhibition. *Cardiovascular Research* 1994; **28**: 78–85.

59 Sitko GR, Ramjit DR, Stabilito II, Lehman D, Lynch JJ, Vlasuk GP. Conjunctive enhancement of enzymatic thrombolysis and prevention of thrombotic reocclusion with the selective factor Xa inhibitor, tick anticoagulant peptide. Comparison to hirudin and heparin in a canine model of acute coronary artery thrombosis. *Circulation* 1992; **85**: 805–15.

60 Tidwell RR, Webster WP, Shaver SR, Geratz JD. Strategies for anticoagulation with synthetic protease inhibitors. Xa inhibitors versus thrombin inhibitors. *Thrombosis Research* 1980; **19**: 339–49.

61 Stürzebecher J, Markwardt F, Walsmann P. Synthetic inhibitors of serine proteinases XIV. Inhibition of factor Xa by derivatives of benzamidine. *Thrombosis Research* 1976; **9**: 637–46.

62 Nagahara T, Yokoyama Y, Inamura K, *et al.* Dibasic (Amidinoaryl)propanoic Acid Derivatives as Novel Blood Coagulation Factor Xa Inhibitors. *J Med Chem* 1994; **37**: 1200–7.

63 Pinto DJP, Wong PC, Knabb RM, Wexler RR. Case History. In: Annual Reports in Medicinal Chemistry. Elsevier, 2012: 123–41.

64 Prager NA, Abendschein DR, McKenzie CR, Eisenberg PR. Role of Thrombin Compared With Factor Xa in the Procoagulant Activity of Whole Blood Clots. *Circulation* 1995; **92**: 962–7.

65 McKenzie CR, Abendschein DR, Eisenberg PR. Sustained Inhibition of Whole-Blood Clot Procoagulant Activity by Inhibition of Thrombus-Associated Factor Xa. *ATVB* 1996; **16**: 1285–91.

66 Kotzé HF, Lamprecht S, Badenhorst PN, Roodt JP, Van Wyk V. Transient Interruption of Arterial Thrombosis by Inhibition of Factor Xa Results in Long-term Antithrombotic Effects in Baboons. *Thromb Haemost* 1997; **77**: 1137–42.

67 Gerotziafas GT, Elalamy I, Depasse F, Perzborn E, Samama MM. In vitro inhibition of thrombin generation, after tissue factor pathway activation, by the oral, direct factor Xa inhibitor rivaroxaban. *J Thromb Haemost* 2007; **5**: 886–8.

68 Biemond BJ, Perzborn E, Friederich PW, Levi M, Buetehorn U, Büller HR. Prevention and treatment of experimental thrombosis in rabbits with rivaroxaban (BAY 597939)--an oral, direct factor Xa inhibitor. *Thromb Haemost* 2007; **97**: 471–7.

69 Kubitza D, Becka M, Wensing G, Voith B, Zuehlsdorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939--an oral, direct Factor Xa inhibitor--after multiple dosing in healthy male subjects. *Eur J Clin Pharmacol* 2005; **61**: 873–80.

70 Kubitza D, Becka M, Voith B, Zuehlsdorf M, Wensing G. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. *Clin Pharmacol Ther* 2005; **78**: 412–21.

71 Eriksson BI, Borris LC, Dahl OE, *et al.* A Once-Daily, Oral, Direct Factor Xa Inhibitor, Rivaroxaban (BAY 59-7939), for Thromboprophylaxis After Total Hip Replacement. *Circulation* 2006; **114**: 2374–81.

72 Wong PC, Pinto DJP, Zhang D. Preclinical discovery of apixaban, a direct and orally bioavailable factor Xa inhibitor. *J Thromb Thrombolysis* 2011; **31**: 478–92.

73 Granger CB, Alexander JH, McMurray JJV, *et al.* Apixaban versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med* 2011; **365**: 981–92.

74 Raskov H, Orhan A, Christensen JP, Gögenur I. Cytotoxic CD8+ T cells in cancer and cancer immunotherapy. *Br J Cancer* 2021; **124**: 359–67.

75 Chamoto K, Yaguchi T, Tajima M, Honjo T. Insights from a 30-year journey: function, regulation and therapeutic modulation of PD1. *Nat Rev Immunol* 2023; published online April 25. DOI:10.1038/s41577-023-00867-9.

76 Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *The EMBO Journal* 1992; **11**: 3887–95.

77 The NOVARTIS Foundation (Japan) for the Promotion of Science. Our Story. https://japanfoundation.novartis.org/en/about/index.html.

78 Nishimura H, Minato N, Nakano T, Honjo T. Immunological studies on PD-1 deficient mice: implication of PD-1 as a negative regulator for B cell responses. *Int Immunol* 1998; **10**: 1563–72.

79 Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci U S A* 2002; **99**: 12293–7.

80 The Nobel Prize. Tasuku Honjo: Facts. https://www.nobelprize.org/prizes/medicine/2018/honjo/facts/.

81 Meet the Dutch Scientists who Invented Keytruda, "The President's Drug". Labiotech. 2022; published online June 24. https://www.labiotech.eu/interview/interview-keytruda-cancer-inventors/.

82 David Shaywitz. The Startling History Behind Merck's New Cancer Blockbuster. Forbes. 2017; published online July 26. https://www.forbes.com/sites/davidshaywitz/2017/07/26/the-startling-history-behind-mercks-new-cancer-blockbuster/#564e9965948d.

83 LifeArc. Keytruda: a new generation of cancer treatment. https://www.lifearc.org/case-studies/keytruda-new-generation-cancer-treatment/.

84 LifeArc. Organon and MRC Technology sign antibody development agreement. 2007; published online July 25.

85 Andrew McConaghie. Research charity LifeArc cashes $1.2bn royalty from Keytrud. PMLive. 2019; published online May 21. https://www.pmlive.com/pharma_news/research_charity_lifearc_cashes_$1.2bn_royalty_from_keytruda_1288841?SQ_ACTION=clear_design_name&full=true.

86 Burtness B, Harrington KJ, Greil R, *et al.* Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *The Lancet* 2019; **394**: 1915–28.

87 D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci U S A* 1994; **91**: 4082–5.

88 David Altman. From Thalidomide to Pomalyst: Better living through chemistry. 2013; published online April 2. https://www.damatolab.com/from-thalidomide-to-pomalyst.

89 Robert D'Amato. Methods and composition for inhibition of angiogenesis. https://patents.google.com/patent/US8012996B2/en?oq=US8012996.

90 U.S. House of Representatives Committee on Oversight and Reform. Drug Pricing Investigation – Celgene and Bristol Myers Squibb—Revlimid. 2020; published online Sept.

https://oversightdemocrats.house.gov/sites/democrats.oversight.house.gov/files/Celgene%20BMS%20Staff%20Report%2009-30-2020.pdf.

91 Bartlett JB, Dredge K, Dalgleish AG. The evolution of thalidomide and its IMiD derivatives as anticancer agents. *Nat Rev Cancer* 2004; **4**: 314–22.

92 Celgene Corporation. Form 10-K. Annual Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934. 2007. https://www.sec.gov/Archives/edgar/data/816284/000095012308001878/y49949e10vk.htm.

93 Menendez for Senate and Ryan Alexander. Greedy Bob Hugin Stiffs Children's Hospital of $200M, Sued for Lying to Investors. 2018; published online Oct 10. https://menendezfornj.com/greedy-bob-hugin-stiffs-childrens-hospital-of-200m-sued-for-lying-to-investors/.

94 Tracy Staton. Celgene, Boston Children's play tug-of-war over Revlimid royalties. FiercePharma. 2014; published online Jan 6. https://www.fiercepharma.com/legal/celgene-boston-children-s-play-tug-of-war-over-revlimid-royalties.

95 Singhal S, Mehta J, Desikan R, *et al.* Antitumor Activity of Thalidomide in Refractory Multiple Myeloma. *N Engl J Med* 1999; **341**: 1565–71.

96 Richardson PG, Schlossman RL, Weller E, *et al.* Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. *Blood* 2002; **100**: 3063–7.

97 Swain SM, Shastry M, Hamilton E. Targeting HER2-positive breast cancer: advances and future directions. *Nat Rev Drug Discov* 2023; **22**: 101–26.

98 Drebin JA, Stern DF, Link VC, Weinberg RA, Greene MI. Monoclonal antibodies identify a cell-surface antigen associated with an activated cellular oncogene. *Nature* 1984; **312**: 545–8.

99 Coussens L, Yang-Feng TL, Liao Y-C, *et al.* Tyrosine Kinase Receptor with Extensive Homology to EGF Receptor Shares Chromosomal Location with *neu* Oncogene. *Science* 1985; **230**: 1132–9.

100 Slamon DJ, Clark GM, Wong SG, Levin WJ., Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987; **235**: 177–82.

101 Lasker Foundation. 2019 Lasker~DeBakey Clinical Medical Research Award: Herceptin — a targeted antibody therapy for breast cancer. https://laskerfoundation.org/winners/herceptin-a-targeted-antibody-therapy-for-breast-cancer/.

102 Robert Bazell. Her-2: The Making of Herceptin, a Revolutionary Treatment for Breast Cancer. Random House, 1998.

103 National Cancer Institute. HER2's Genetic Link to Breast Cancer Spurs Development of New Treatments. https://www.cancer.gov/research/progress/discovery/her2.

104 Memorial Sloan Kettering Cancer Center. Remembering John Mendelsohn, a Pioneer of Targeted Therapy for Cancer. 2019; published online Jan 11. https://www.mskcc.org/news/remembering-john-mendelsohn-pioneer-targeted-therapy.

105 Carter P, Presta L, Gorman CM, *et al.* Humanization of an anti-p185HER2 antibody for human cancer therapy. *Proc Natl Acad Sci U S A* 1992; **89**: 4285–9.

106 Slamon DJ, Leyland-Jones B, Shak S, *et al.* Use of Chemotherapy plus a Monoclonal Antibody against HER2 for Metastatic Breast Cancer That Overexpresses HER2. *New England Journal of Medicine* 2001; **344**: 783–92.

107 Baselga J, Tripathy D, Mendelsohn J, *et al.* Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. *JCO* 1996; **14**: 737–44.

108 Cobleigh MA, Vogel CL, Tripathy D, *et al.* Multinational Study of the Efficacy and Safety of Humanized Anti-HER2 Monoclonal Antibody in Women Who Have HER2-Overexpressing Metastatic Breast Cancer That Has Progressed After Chemotherapy for Metastatic Disease. *JCO* 1999; **17**: 2639–2639.

109 145 Cong. Rec. S12227 - RESEARCH AND EXPERIMENTATION TAX CREDIT. 1999; published online Oct 7. https://www.govinfo.gov/content/pkg/CREC-1999-10-07/pdf/CREC-1999-10-07-pt1-PgS12227.pdf.

110 Hill A, Barber MJ, Gotham D. Estimated costs of production and potential prices for the WHO Essential Medicines List. *BMJ Global Health* 2018; **0**: e000571.

111 Hill A, Gotham D, Fortunak J, *et al.* Target prices for mass production of tyrosine kinase inhibitors for global cancer treatment. *BMJ Open* 2016; **6**: e009586.

112 Hill A, Simmons B, Gotham D, Fortunak J. Rapid reductions in prices for generic sofosbuvir and daclatasvir to treat hepatitis C. *J Virus Erad* 2016; **2**: 28–31.

113 Hill A, Redd C, Gotham D, Erbacher I, Meldrum J, Harada R. Estimated generic prices of cancer medicines deemed cost-ineffective in England: a cost estimation analysis. *BMJ Open* 2017; **7**: e011965.

114 Gotham D, Fortunak J, Pozniak A, *et al.* Estimated generic prices for novel treatments for drug-resistant tuberculosis. *Journal of Antimicrobial Chemotherapy* 2017; : dkw522.

115 Barber M, Gotham D, Hill A. Potential price reductions for cancer medicines on the WHO Essential Medicines List. *European Journal of Cancer* 2017; **72**: S119.

116 Gotham D, Barber MJ, Hill AM. Estimation of cost-based prices for injectable medicines in the WHO Essential Medicines List. *BMJ Open* 2019; **9**: e027780.

117 Gotham D, Barber MJ, Hill A. Production costs and potential prices for biosimilars of human insulin and insulin analogues. *BMJ Global Health* 2018; **3**: e000850.

118 Kelley B. Industrialization of mAb production technology: The bioprocessing industry at a crossroads. *mAbs* 2009; **1**: 440–9.

119 Mahal H, Branton H, Farid SS. End-to-end continuous bioprocessing: Impact on facility design, cost of goods, and cost of development for monoclonal antibodies. *Biotechnol Bioeng* 2021; **118**: 3468–85.

120 Abdullah Baaj, Kenneth I Kaitin, Mari Serebrov. Manufacturing Strategy for Diverse Biologic Pipelines of the Future. Tufts Center for the Study of Drug Development. 2017; published online Oct. https://www.fdanews.com/ext/resources/files/2017/11/11-20-17-Tufts.pdf?1511557822.

121 Gotham D. Cell line access to revolutionize the biosimilars market. *F1000Research* 2018; **7**: 537.

122 Ronald Rader, Eric Langer. Biosimilars Paving The Way For Cost-Effective Bioprocessing. Biosimilar Development. 2017; published online Aug 23. https://www.biosimilardevelopment.com/doc/biosimilars-paving-the-way-for-cost-effective-bioprocessing-0001.

123 Whaley KJ, Zeitlin L. Emerging antibody-based products for infectious diseases: Planning for metric ton manufacturing. *Human Vaccines & Immunotherapeutics* 2022; **18**: 1930847.

124 Melissa Barber, Dzintars Gotham, Christa Cepuch, Helen Bygrave. Cost of production for insulins, GLP1 receptor agonists, and SGLT2 inhibitors. (unpublished). 2023.

## Methodological appendix

Data analysis was done with datasets made publicly available by the NHS, with manipulation done in *R*.

Available data on NHS drug expenditures

Up to 2020, NHS Digital previously published an annual report titled "Prescribing Costs in Hospitals and the Community". From 2004 up to and including the 2017/18 financial year, NHS Digital published the total annual cost (at list price) for all medicines positively appraised by NICE, across the primary and secondary care sectors.[1] Annual cost broken down by individual medicines was not published in the 2018/19 and 2019/20 editions, and the report was no longer published after 2020.[2]

Then, for about two years, NHS BSA published secondary care medicines data (SCMD) files monthly, from January 2019 to December 2022.[3] For the period January 2019 to April 2021, the published files report the volume of individual medicines procured, but not costs or prices (though prices would have been available in Drug Tariff files). NHS BSA now publishes secondary care medicines data with indicative price (SCMD WIP) files monthly, starting in April 2021, with January 2023 being the most recent available.[4] For period with no reported prices, costs were estimated for this period by assuming indicative prices were the same as they are reported in the April 2021 SCMD WIP file, and combining these indicative prices with monthly volumes.

For medicines dispensed in the community (i.e. not hospital), costs aggregated by INN are available in 'prescription cost analysis' (PCA) files for every year back to 2014.[5] For the years 2019/20, 20/21, and 21/22, community costs from PCA were added to the secondary care costs.

This leaves a gap in available data on (hospital) procurement volume and costs between April 2018 and April 2019, for medicines used in secondary care. Data *are* available for this period for primary care spending. However, in order not to disproportionately count primary care medicines for the purposes of this analysis identifying medicines with top spend, primary care data in this period are omitted.[6] Costs in this year were estimated as the average of the cost in the year before and the year following.

A small proportion of drugs that have been discontinued or are procured through parallel importation or 'special orders', no longer have a matching SNOMED code, and were therefore excluded.

Aggregating by INN

As mentioned above, the main dataset that is currently published for drug costs in secondary care is "Secondary Care Medicines Data (SCMD) with indicative price" (SCMD WIP) files.[7]

This is published as monthly data. It includes product name (exact product/formulation including brand name) and SNOMED code, but not the molecule name (INN).

For the purposes of this analysis, cost aggregated by INN is needed.

In order to add the INN name to the SCMD WIP files, a VMP-to-VTM-to-INN map was created by extracting the corresponding lists from a dm+d TRUD file (version of April 17, 2023). This 'map' is then applied to the SCMD files to generate an 'INN' column.

NICs were then aggregated by molecule (INN) and sorted by cost.

Estimation of confidential discounts

ABPI and DHSC publish joint top-level data on the magnitude of confidential discounts.

Table. Total NHS medicines expenditure at list prices versus actual (confidentially discounted) prices, 2018-2021, GBP billions.

| | 2018 | 2019 | 2020 | 2021 |
|---|---|---|---|---|
| Cost at list price | 17.2 | 18.8 | 20.3 | 22.9 |
| Branded medicines sales after confidential discounts | 11.6 | 11.8 | 12.2 | 13.4 |
| VPAS+SS payments | 0.638 | 0.931 | 0.597 | 0.585 |
| Net cost after subtracting confidential discounts and VPAS+SS payments | 10.962 | 10.869 | 11.603 | 12.815 |
| Net costs as % of total cost at list price | 64% | 58% | 57% | 56% |
| Corresponding average discount for branded medicines | 36% | 42% | 43% | 44% |

*Source: DHSC ABPI Waterfall chart medicine sales 2021, available from https://www.abpi.org.uk/publications/dhsc-abpi-waterfall-chart-medicine-sales-2021/ .*
*VPAS –voluntary scheme for branded medicines, pricing, and access; SS – statutory scheme.*

From 2018-21, the average discount (confidential price discounts plus payments under VPAS or SS) was 41%. This average amount is applied across all years (2012-2022) in the analysis, in order to estimate net cost. In part, this average is used because, while payments under PPRS are published, we were not able to identify published information on final payments under the statutory scheme (SS).

API costs

Average costs for active pharmaceutical ingredient exported from India were calculated using methods described previously.[9] A linear regression model was used to model trends in price, and the model output at 1 Dec 2022 was used as the assumed API price:

Apixaban US$1,919/kg
Rivaroxaban US$1,543/kg
Lenalidomide US$17,040kg

**Notes**

[1] NHS Digital. Prescribing Costs in Hospitals and the Community. https://digital.nhs.uk/data-and-information/publications/statistical/prescribing-costs-in-hospitals-and-the-community
[2] https://digital.nhs.uk/data-and-information/publications/statistical/prescribing-costs-in-hospitals-and-the-community/2018-2019 ; https://digital.nhs.uk/data-and-information/publications/statistical/prescribing-costs-in-hospitals-and-the-community/2019-2020
[3] NHS Business Services Authority. Open Data Portal. Secondary Care Medicines Data (SCMD). https://opendata.nhsbsa.net/dataset/secondary-care-medicines-data
[4] NHS Business Services Authority. Open Data Portal. Secondary Care Medicines Data (SCMD) with indicative price. https://opendata.nhsbsa.net/dataset/secondary-care-medicines-data-indicative-price
[5] https://opendata.nhsbsa.net/dataset/prescription-cost-analysis-pca-annual-statistics
[6] https://opendata.nhsbsa.net/dataset/prescription-cost-analysis-pca-annual-statistics
[7] https://opendata.nhsbsa.net/dataset/secondary-care-medicines-data-indicative-price
[8] https://www.abpi.org.uk/value-and-access/uk-medicine-pricing/nhs-medicine-spend/
[9] Hill A, Barber MJ, Gotham D. Estimated costs of production and potential prices for the WHO Essential Medicines List. *BMJ Global Health* 2018; **0**: e000571.

Global Justice Now is a UK campaign to tackle the root causes of global poverty and inequality. We mobilise people in the UK for change, and act in solidarity with those fighting injustice, particularly in the global south.
www.globaljustice.org.uk

Just Treatment is a patient-led campaign fighting to ensure everyone gets the healthcare they need by challenging the power of the pharmaceutical and health industries, and demanding that the government acts to put patients before corporate profits.
www.justtreatment.org

STOPAIDS is a UK-based HIV, health and rights network that supports UK and global movements to challenge systemic barriers and inequalities to end AIDS and ensure people around the world can realise their right to good health and wellbeing.
www.stopaids.org.uk