

Pills and profits

How drug companies make a killing out of public research



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Cover image: Over 1000 activists from the Fix the Patent Laws campaign march to the Department of Trade and Industry (DTI) in Pretoria. They are demanding that the DTI take urgent steps to fix South Africa's outdated patent laws so that everyone can get the medicines they need. © Shayne Robinson, Mutiny Media

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Glossary

Abiraterone	Drug that is used to treat advanced prostate cancer.
Access to medicines	Access to medicines, or accessibility, is defined as having medicines continuously available and affordable at public or private health facilities or medicine outlets that are within one hour of travel for patients.
Adalimumab	Drug that is used to a range of diseases including psoriasis and ankylosing spondylitis.
Affordability	The extent to which something is affordable; in this report it specifically relates to the capacity of public or private health services or individual patients to buy a medicine for treatment without limiting further access. Affordability is one aspect of accessibility.
Alemtuzumab	Drug that is used to treat B-cell chronic lymphocytic leukaemia and multiple sclerosis.
Antimicrobial resistance	Microorganisms (such as bacteria and viruses) change when exposed to antimicrobial drugs (such as antibiotics and antivirals) so these drugs become ineffective to treat infectious diseases.
Bedaquiline	Drug that is used to treat multi-drug resistant tuberculosis.
Biologics	Biologics are medicines based on artificially produced antibodies (molecules that the human immune system uses to attack invaders).
Biosimilar	Biosimilars are the equivalent of generic medicines but for biological medicines. They are medicines that are designed to be as similar to the original biologic (known as the originator biologic) as possible, and undergo extensive testing to ensure that their effectiveness and safety are equivalent to the originator's.
De-link or de-linkage	Disconnecting the cost of R&D from the price of the medicine that is developed.
Generic medicines	A medicine that is equivalent to a brand-name product in dosage, strength, route of administration, quality, performance, and intended use.
Health product	Any medicine, vaccine or diagnostic.
Health technology	Any result of scientific research that is applicable for a use in healthcare, including medicines, vaccines and diagnostics (this may also be a patentable finding that is discovered earlier in the R&D process, such as a technology that helps identify new potential medicines).
Infliximab	Drug that is used to treat autoimmune diseases such as rheumatoid arthritis.
Intellectual property	A work or invention that is legally protected through copyright, trademark, or a patent. For the purposes of this report, intellectual property primarily concerns patents. Patents are government-issued rights to an invention, such that manufacture, use, or sale of the invention without the patent-holder's permission is legally prohibited.

Monoclonal antibodies	Antibodies that are artificially created to bind to a specific target.
Originator medicine	The version of a medicine that was first authorised (and normally patented) worldwide for marketing, having completed its efficacy, safety and quality requirements. Once the originator medicine is no longer protected by the patent, generic pharmaceutical companies can enter the market with a generic version of the originator medicine.
Open access	The products of research are freely accessible to all.
Product Development Partnerships (PDPs)	Nonprofit organisations that bring together stakeholders from the private and public sectors to research, develop and support access to new health technologies that target diseases disproportionately affecting developing countries.
Public funding	UK government financial support through direct grants, investments, tax credits or use of state facilities.
Trastuzumab	Drug that treats patients with HER2-positive breast cancer, marketed as Herceptin by Roche.
Trastuzumab emtansine	Drug to treat patients with certain HER2-positive breast cancers that have spread or come back. Marketed as Kadcyla by Roche.
‘TRIPS-plus’ provisions	Conditions that put more restrictions on intellectual property than required in the World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS agreement), such as extending the patent term to beyond 20 years or provisions that limit the use of compulsory licences or generic competition.

Acronyms

ARV	Antiretroviral
BBSRC	Biotechnology and Biological Sciences Research Council
BEIS	Department for Business, Energy and Industrial Strategy
BTG	British Technology Group
CAT	Cambridge Antibody Technology
CEWG	Consultative Expert Working Group
DFID	Department for International Development
DoH	Department of Health
DNDi	Drugs for Neglected Diseases Initiative
EFPIA	European Federation of Pharmaceutical Industries and Associations
HIV	Human immunodeficiency virus
ICR	Institute of Cancer Research
IMI	Innovative Medicines Initiative
IPR	Intellectual property rights
MDR TB	Multi-drug resistant tuberculosis
MRC	The UK Medical Research Council
MRC LMB	The UK Medical Research Council Laboratory of Molecular Biology
MS	Multiple sclerosis
NDPB	Non-departmental public body
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NIHR	National Institute for Health Research
OECD	Organisation of Economic Co-operation and Development
PDP	Product development partnership
PrEP	Pre-exposure prophylaxis
PSRI	Public sector research institution
RCUK	Research Councils UK
R&D	Research and development
RRMS	Relapsing-remitting multiple sclerosis
SDG	Sustainable Development Goals
TB	Tuberculosis
TNF	Tumour necrosis factor (a molecule important in inflammation)
TRIPS	Trade-related aspects of intellectual property rights
UN HLP	United Nations High-Level Panel on Access to Medicines
USAID	United States Agency for International Development
WHO	World Health Organization
WTO	World Trade Organization

Executive summary

UK taxpayers and patients worldwide are being denied the medicines they need, despite the public sector playing a pivotal role in the discovery of new medicines. The UK government is the second largest funder country, after the US, for research and development (R&D) in diseases that predominantly affect poor countries. Across all areas of health R&D, the UK government spent £2.3 billion¹ on health R&D in 2015 alone. Globally, it is estimated that the public pays for two-thirds² of all upfront drug R&D costs, with around a third of new medicines originating in public research institutions. On top of this, many medicines developed by pharmaceutical companies are often built upon a large body of scientific work undertaken and paid for by the tax payer.

This report illustrates that even when the UK government has funded a substantial proportion of the R&D for innovative medicines, there is no guarantee of an equitable public return on this public investment. That is to say, no guarantee that patients in the UK and beyond will be able to access the medicine at an affordable price, and be able to make use of the data, knowledge, and technologies generated in the research process.

In many cases, the UK taxpayer effectively pays twice for medicines: first through investing in R&D, and then by paying high prices for the resulting medicine once ownership has been transferred to a private company. The NHS spent more than £1bn last year alone on medicines developed with significant reliance on UK public research funding, while two of the five most expensive medicines for the NHS were developed in large part with UK publicly funded research (appendix 2).

The commercialisation of these discoveries by pharmaceutical companies has generated huge private profits from public funds. This situation is enabled by a global system of intellectual property rights that provide time-limited monopolies to companies, allowing them to charge high prices for products with relatively low production costs.

Monopoly on medicines

A patent gives companies exclusive rights to a new drug for 20 years. No other company can make or sell that drug during that patent period. Without competition, companies can demand whatever price they like. Sometimes patent protection can effectively be extended beyond 20 years, either by combining multiple patents or by receiving patent extensions from regulators to compensate for time taken in approving a medicine. Companies also engage in 'evergreening' where minor amendments are made to the medicine so that it can be re-patented.

Pharmaceutical companies claim that these high prices are needed to provide a commercial incentive for them to undertake further R&D for new medicines. But when the public purse is funding a large proportion of this R&D, the justification for monopoly pricing is hard to sustain. Moreover, pharmaceutical companies consistently spend more on sales and marketing than on R&D for new medicines³. Many companies also spend disproportionately more on shareholder dividends and buying back their own shares to artificially boost their share price than they spend on R&D⁴.

The high prices of new medicines are unsustainable for an already underfunded NHS, and put these treatments completely beyond the reach of patients in developing countries.



Campaigners protest the actions of pharmaceutical companies outside a pharmaceutical conference in London as part of 'Fix the Patent Law' campaign, March 2014

Conditions on UK public funding for R&D

There is a clear lack of safeguards to ensure the accessibility and affordability of medicines that derive from publicly funded R&D. Public funding for health R&D is predominantly managed by four government departments: the Department of Health; the Department for Business, Energy and Industrial Strategy; the Department for Education; and the Department for International Development. Though there are some guidelines on public funding in these departments, they are usually vague and fall far short of concrete guarantees that products developed with public funding will be made available at an affordable price to patients in the UK and beyond.

In addition to the absence of safeguards for access, funding for medical R&D is shrouded in secrecy. Though some funding streams and grants received by public research institutions can be identified, information on the decision-making processes regarding commercialisation of discoveries and the overall funding of a drug's discovery and clinical trials are rarely publicly available. This lack of transparency disrupts accountability and hampers the development of improved ways of financing R&D.

Corporate influence at the highest levels

Contact between the pharmaceutical industry and the government is necessary. But our findings indicate that the industry has significant influence on government. Employees of pharmaceutical companies hold key positions in research councils such as the Medical Research Council, Biotechnology and Biological Sciences Research Council, and the Council for Science and Technology. Two sub-groups within the Office for Life Sciences provide industry executives and lobbyists with direct access to ministers from the Department of Health, the Department for Business, Energy and Industrial Strategy, and key personnel from HM Treasury⁵. Professor John Abraham, one of the foremost experts on pharmaceutical policy concurs: *"the pharmaceutical industry was, and is, permitted to have privileged strategic access to, and involvement with, government regulatory policy over and above any other interest group"*⁶.

There is also a more pervasive form of influence, which assumes that what is good for the pharmaceutical industry is good for the public. This assumption is apparent in reports like the Witty

The influence of the pharmaceutical industry on UK health R&D policy calls into question whether funding is governed in the interest of corporations or public health

Review, which recommended that universities “should assume an explicit responsibility for facilitating economic growth, and all universities should have stronger incentives to (...) (work) together to develop and commercialise technologies which can win in international markets.”⁷ The influence of the pharmaceutical industry on UK health R&D policy calls into question whether funding is governed in the interest of corporations or public health.

The UK's response to global initiatives on access

Ensuring accessibility and affordability of medicines has increasingly become an international concern. In recent years a range of influential global actors have published reports on the topic, including the UN Secretary General's High-Level Panel on Access to Medicines. Recommendations, from across the reports, include:

- Transparency requirements must be attached to public R&D funding.
- Any intellectual property coming from public funding must be licensed in a way that protects access.
- The prices of medicines should be de-linked from their R&D cost.

The UK government has made commitments to ensuring access to affordable medicines in the Sustainable Development Goals and has engaged in the WHO's Consultative Expert Working Group on R&D. But these efforts are undermined by the UK government's resistance to the findings of the High-Level Panel report. The UK government has not been active in pushing for progress on global access to medicines and is particularly resistant to ensuring transparency of R&D costs.

UK public funding of specific medicines

UK public funding has played a substantial role in the discovery and development of highly effective and often life-saving treatments. The following examples show that the high prices charged by pharmaceutical companies for these very effective medicines have severely restricted access for the patients that need them, despite this upfront investment by tax payers:

Abiraterone is an effective drug for treating advanced prostate cancer. It was discovered and developed at the Institute of Cancer Research (a largely publicly funded UK research institute) before eventually coming under the ownership of Janssen, a division of the pharmaceutical giant, Johnson & Johnson. Janssen's sales of abiraterone reached £7.2 billion by the end of 2013⁸.

The use of abiraterone for patients on the NHS has been restricted for many years due to the high price of the drug. The drug has undergone a series of cost-effectiveness reviews and is now recommended by the National Institute for Health and Care Excellence (NICE) for use in certain categories of advanced prostate cancer patients. The second review (undertaken between August 2014 and March 2016) estimated that an additional 5,900 people a year would have benefitted from the drug if it was approved for use by the NHS⁹. During that time, such patients could only access the drug if they made a successful application to the Cancer Drugs Fund. Even though the use of this drug was then highly restricted, the NHS paid £172 million for abiraterone purchases from 2014 to 2016¹⁰. The taxpayer played a critical role in developing this drug and yet it is costly to the NHS and has been rationed in England.

A further review by NICE is now underway to decide on whether to expand the use of abiraterone to a wider set of patients.

Monoclonal antibodies (MABs) are artificially created antibodies and have been developed to treat a wide range of diseases - predominantly for cancers and autoimmune diseases, but increasingly for others too. The technologies that allow the production of MABs were developed at the UK Medical Research Council Laboratory of Molecular Biology (MRC LMB) in Cambridge, which is publicly funded via the UK Medical Research Council. Six of the top-ten all-time highest selling medicines have been MABs, and the discoveries were hailed as one of the biggest medical breakthroughs of the last decades.

The following three cases are examples of medicines that are based on the MAB technology developed at the MRC LMB:

Alemtuzumab was originally developed at Cambridge University and first approved for the treatment of B-cell chronic lymphocytic leukaemia (B-CLL). Cambridge scientists then led further investigations of its usefulness, at a smaller dosage, in treating multiple sclerosis (MS). Sanofi Genzyme, who had acquired the rights to the drug, removed it from the market as a B-CLL medicine and re-launched it as a medicine for MS. At the time of withdrawal there was speculation that the exercise was motivated by commercial reasons. When it was used off-label (i.e. used for a non-licensed purpose) for MS prior to being withdrawn from the market, the price in the UK was around £2,500 per MS treatment course in 2012¹¹. In 2017, it now costs £56,000 per treatment course – a 22-fold increase¹².

Adalimumab is an effective drug for treating a range of diseases including rheumatoid arthritis, psoriasis, and Crohn's disease. Also based on the MAB technology from the MRC LMB, the development of adalimumab was undertaken by a spin-off company formed by researchers from the MRC LMB, Cambridge Antibody Technology. Since then, this drug has become the second highest earning prescription medicine in history, with cumulative sales of GBP £71.6 billion through 2016¹³. Adalimumab has represented the highest expenditure on a single medicine by the NHS for the past two years running, with a total cost of nearly £800 million over this period¹⁴.

Infliximab is used to treat autoimmune diseases such as rheumatoid arthritis and was developed at New York University and the Kennedy Institute of Rheumatology (at the time part of Imperial College London), with clinical trials run via charity and industry funding. After the initial trials discovering and proving its effectiveness in rheumatoid arthritis, development was taken over by Centocor Biotech (now part of Janssen). Infliximab is the fourth highest-selling prescription medicine ever produced, with cumulative sales of US\$85.5 billion (£63.7 billion) up to the end of 2016. In 2014/2015¹⁵, it represented the fourth highest expenditure on a single medicine in the NHS, at £159 million. The following year the NHS spend on infliximab rose to £178 million¹⁶.

R&D initiatives that safeguard accessibility

The UK has made some positive progress towards models of R&D that offer better public returns. The UK is the largest contributor to the Drugs for Neglected Diseases initiative (DNDi), which was set up to develop new medicines for diseases that predominantly affect people in the global south. Since its creation, DNDi has developed new easy to use, field adapted and non-patented medicines: two for malaria, two for visceral leishmaniasis, one each for Chagas disease and sleeping sickness, and has 13 new chemical entities in its development pipeline. As a result of these new treatments, an estimated 980,000¹⁷ lives were saved between 2009 and 2013. This model could be applied to other disease areas outside of neglected diseases but on its own does not address the underlying structural problems of the health R&D system.

Recommendations

The UK government should make changes in the following five areas to safeguard access to medicines developed using taxpayer's money:

Attach public interest conditions to R&D funding

- Government departments should demand, monitor and enforce public interest conditions in all contracts and agreements concluded with public and private sector stakeholders for health research. These should be based on the principles of affordability, accessibility, and equity.

Introduce transparency

- For each originator medicine procured by the NHS, develop and enforce standardised reporting requirements that ensure public availability of: the final negotiated 'net' price (after any discounts) charged to the NHS; the R&D costs attributable to the medicine and any public contributions to R&D costs; and manufacturing costs.
- Ensure all licensing agreements between public sector research institutions (such as a university) and other parties are available in a publicly accessible database.

Enable effective governance and accountability

- Develop guidelines for government departments that fund R&D to ensure public health interests are prioritised over commercial interests. The guidelines would include, for example, ensuring civil society representation in key decision-making bodies.
- Develop a clear monitoring and accountability framework for citizens to hold the government to account on the effectiveness of mechanisms to safeguard accessibility and affordability of health products developed with public funding.

Support de-linked R&D models

- Identify and implement de-linked funding mechanisms for R&D, that is, mechanisms that (1) de-link research activity from expected commercial returns, and (2) de-link R&D expenditures from the price of the final product to avoid monopolistic pricing as the central funding mechanism.

Drive international progress on R&D

- Actively encourage the World Health Organization (WHO) and its member states to support: (1) the development of biomedical principles for R&D; (2) the establishment of a global pooled fund for R&D; and (3) an accompanying global agreement to finance this fund in order to address global imbalances in R&D that lead to patients not getting the medicines they need.
- Encourage and enable international market entry for generic and biosimilar medicines by enforcing strict requirements for patent approval, combating business tactics that block or delay their market entry (such as 'pay-for-delay agreements'), reaffirming the right of WTO members to issue compulsory licenses, and avoiding 'TRIPS-plus' provisions in trade agreements.

Introduction

“High medicine prices have affected me very directly. I had to crowdfund to pay privately for cancer treatment to prolong my life as these expensive drugs were not available on the NHS at the time I needed them. I felt like I was having to beg for my life, but when you are 40 and have a small child you do whatever you can to try and raise your kids.”

Melanie Kennedy

Melanie Kennedy, a single mother to two boys aged five and sixteen, was diagnosed with incurable breast cancer in 2013. Following chemotherapy and surgery, there was only one drug left that could help prolong her life - trastuzumab emtansine (brand name Kadcyla), a second-line treatment for breast cancer. But with a price tag of £90,000 this drug was not available on the NHS until mid-2017 because it was too expensive and the drug company, Roche, refused for years to drop the price.^{18,19,20} In the end, Melanie had to crowdfund to raise the money to pay for treatment.

Melanie's story is not an isolated case. Patients in the UK and around the world are suffering or dying unnecessarily from illnesses where medicines exist but are unaffordable. Pharmaceutical companies are charging such high prices that patients, governments and public health authorities cannot afford them.

In the UK, the underfunded NHS is struggling to afford spiralling medicine prices. Sofosbuvir, a drug that cures hepatitis C, costs as much as £39,000 per 12 week treatment in the UK. Because of its high cost, the NHS has been forced to ration the medicine.²¹ The high prices charged by pharmaceutical companies are having a significant impact on national health budgets globally. Over all, NHS spending on medicines has risen 29% in the past five years and the National Institute for Health and Care Excellence (NICE) has struggled to regulate the price of medicines.^{22,23}

The problems of access are even worse on a global scale. Trastuzumab is included in the World Health Organization's (WHO) *Essential Medicines List*, a list of priority medicines required for a functioning healthcare system. However, trastuzumab is unavailable to the vast majority of women seeking care across the developing world because it is too expensive. In South Africa's private sector, for example, a 12-month course of trastuzumab costs almost £31,000.²⁴ For public health systems with limited budgets, highly priced medicines are simply not available.

High drug prices are a common barrier to accessing medicines all around the world. While generic competition has driven down the prices of many antiretrovirals (ARVs) to treat HIV, affordability barriers remain: if HIV positive patients experience side effects or become resistant to older, cheaper drugs, they require 'third-line' options that cost at least 18 times as much.²⁵ In Brazil, diabetes treatment can cost as much as £540 a month, equivalent to 82% of the average income.²⁶

High drug prices are not the only barrier to accessing medicines. The recent Lancet Commission on Essential Medicines Policies defined the five 'core' barriers as insufficient financing for medicines, unaffordability of medicines, assuring medicines' quality and safety, appropriate use (e.g. of antibiotics), and missing medicines – that is, gaps in the medical armamentarium.²⁷ Other factors of health systems can also affect access, such as the travel required to receive medicines.

Why are medicines so expensive? Pharmaceutical companies are able to charge high prices because new medicines are patented. This gives companies a monopoly on a newly created drug for 20 years. Without competition, companies can sell medicines at whatever price they want. This monopoly system is entrenched globally through the World Trade Organization Agreement on Trade Related Aspects of Intellectual Property Rights (the TRIPS agreement), which sets minimum requirements for pharmaceutical patent protection.²⁹

Some estimate that the public pays for two-thirds of upfront drug R&D costs

Pharmaceutical companies often justify high prices by claiming that they are necessary to recoup high R&D expenditures. However, evidence suggests that pharmaceutical companies often spend more on marketing costs and buying back their own shares than on R&D.^{30,31} Crucially, the contribution of the public sector to R&D of new medicines is often not recognised – about a third of new medicines originate in public research institutions.³² On top of this, many medicines originating from pharmaceutical companies are built upon scientific work done in the public sector. When all is considered, some estimate that the public pays for two-thirds of upfront drug R&D costs.³³ The scandal of expensive medicines is compounded by the significant contribution that public funding makes to the discovery of these new medicines in the first place. The NHS spent more than £1bn last year alone on medicines that received substantial UK public research funding, while two of the five most expensive medicines for the NHS were developed in large part by UK public funded research.

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Melanie Kennedy had to fundraise for her own breast cancer treatment as the medicine was too expensive for the NHS.

Many efforts to ensure access to medicines across countries of different income levels have therefore focussed on securing a strong public return for this public investment. This report considers equitable public return on public investment to mean, more specifically: broad, equitable access to affordable health products, as well as to the data, knowledge, and technologies generated in the research process. Multiple committees convened by intergovernmental bodies such as the WHO and UN have recognised the significant role of the public sector in R&D and have encouraged novel ways of financing R&D, as well as the safeguarding of affordable access to healthcare through (among other things) licensing agreements and transparency.

The UK government spent £2.3 billion on health R&D in 2015 alone, and is the world's second largest funder country for R&D in diseases that predominantly affect poor countries. Yet, few conditions are attached to UK government R&D investments to safeguard affordable access.

This report presents the case for the UK government to implement a robust public return for public investment approach to health R&D. **Chapter 1** provides an overview of current UK R&D spending, guidelines and conditions. It also identifies the limitations of existing guidelines as well as the lack of transparency and potential commercial conflicts of interest. **Chapter 2** provides specific examples of when and how UK public research has led to the successful development of medicines but where people still have limited access to them, particularly due to high pricing. **Chapter 3** then analyses positive examples of UK R&D initiatives that are making progress towards ensuring affordability and accessibility of the final product. Finally, **chapter 4** presents recommendations for the UK government to take action to ensure public health returns on public investments in medical R&D.

**The public are paying twice,
first for the research and then for
the high cost of these medicines**

"I strongly believe that if I can get this treatment I can live longer, see my two sons growing, see my grandson growing. I think governments should provide Herceptin [trastuzumab] to every woman living with HER2-positive breast cancer so that we, including myself, can live a longer life and not a scary life like the life I'm living now."

**Tobeka Daki, HER2+ breast cancer patient
(1967–2016)**

Tobeka, a mother to two and fearless activist from South Africa, was diagnosed with HER2-positive breast cancer in 2013. She was told that she needed trastuzumab (marketed by Roche as Herceptin) to fight the cancer and improve her chances of survival. But Tobeka was unable to access this essential treatment because it was too expensive. The cancer spread to her spine and, on 14 November 2016, Tobeka died in her home.²⁸





South Africa, 7 February 2017: Treatment Action Campaign members protest outside the offices of Roche in Johannesburg against the excessively high price of their breast cancer medication. The South African government has indicated that it cannot afford to purchase the medication as the cost is too high.

The current system of expensive medicines cannot continue – socially or economically. High prices for life-saving medicines are placing an unsustainable strain on the NHS budget. Meanwhile, pharmaceutical companies are profiting from public investment in R&D while leaving millions of patients across the world without access to vital medicines. Taxpayer-funded medical research has turned medicines into a 'luxury' that are increasingly beyond the reach of the patients who need them. The public are paying twice, first for the research and then for the high cost of these medicines. This report responds to this alarming picture by clearly laying out the steps that should be taken to ensure that public institutions and funding lead to the development of life-saving medicines that are accessible for all those who need them.

1. Current UK government health R&D spending

The UK government is the second largest funder country of global health R&D after the US.³⁴ Every year the UK spends billions of pounds of taxpayer money on medical R&D,³⁵ but the conditions attached to this funding by the government are inadequate to safeguard access and affordability of the final products.

There is not enough transparency to allow proper scrutiny of access to individual medicines developed through public research. It is possible to identify some of the funding flows, usually those directly granted to public research institutions. However, the overall public contributions to the discovery and clinical trials of medicines, and the decision-making processes involved in transferring rights to the private industry, are very non-transparent. It is evident that the pharmaceutical industry has a pervasive influence on the UK government's policy-setting and funding allocation with regard to health R&D. It also appears that the UK government is failing to live up to its own commitments to safeguard access to medicines that have received public R&D funding despite setting some vague guidelines that aim to ensure 'value for money' and maximise societal return.

1.1 Overview of UK government health R&D spending

Health R&D in the UK is funded through a complex network of actors, each with their own priorities. Three key government departments manage health R&D funding, which is in turn administered by multiple non-departmental public bodies (NDPBs)ⁱ. In addition, there are numerous advisory bodies, each entering at a different point in the policy process.

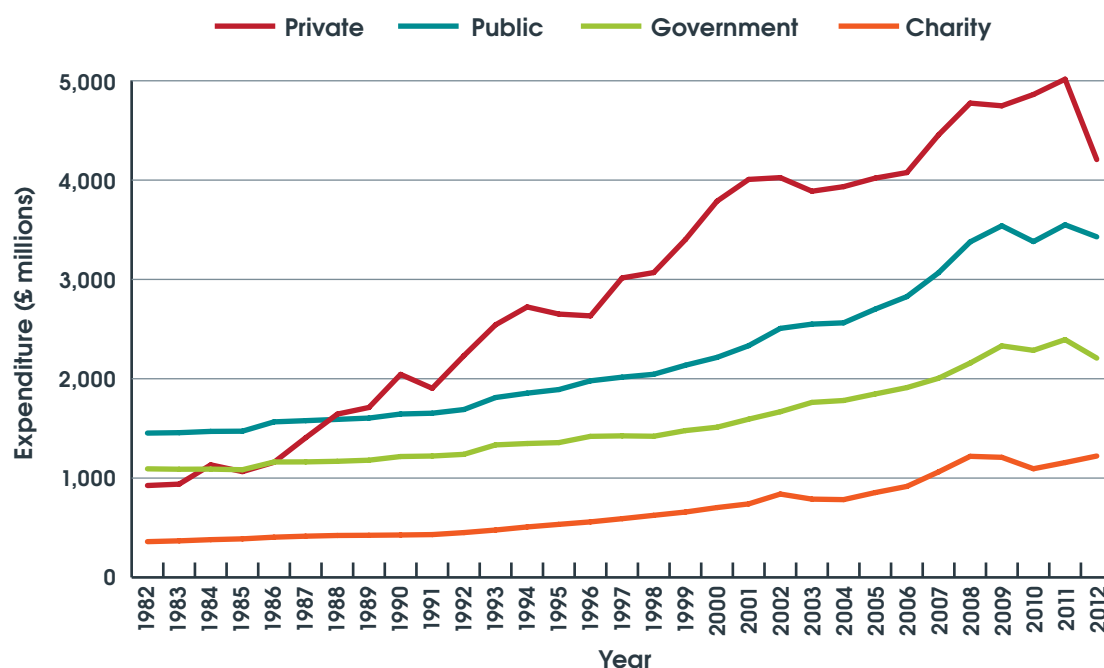
Sources of health R&D spending in the UK

A familiar narrative in public discourse is that the pharmaceutical industry contributes an overwhelming majority of health R&D investments. However, a recent study showed that from the early 2000s to 2012, combined government and charity spending in the UK represented about 40% of all health R&D expenditures (figure 1). Within R&D for cancer treatment, an area in which the industry's high prices have been particularly striking, combined funding from government and charity sources exceeded private sector investments in 22 of the 30 years from 1982 to 2012.³⁶

Whilst government funding as a proportion of total health R&D funding was at a low in 2002, it nevertheless increased over a ten-year period from 26% of the total in 2002 to 29% in 2012. In the same period, the proportion of health R&D funding contributed from the private sector decreased by 7%. As public funding, through both the government and charities, plays an increasingly important role in funding health R&D, public funders must consider strong safeguards for an equitable public return.

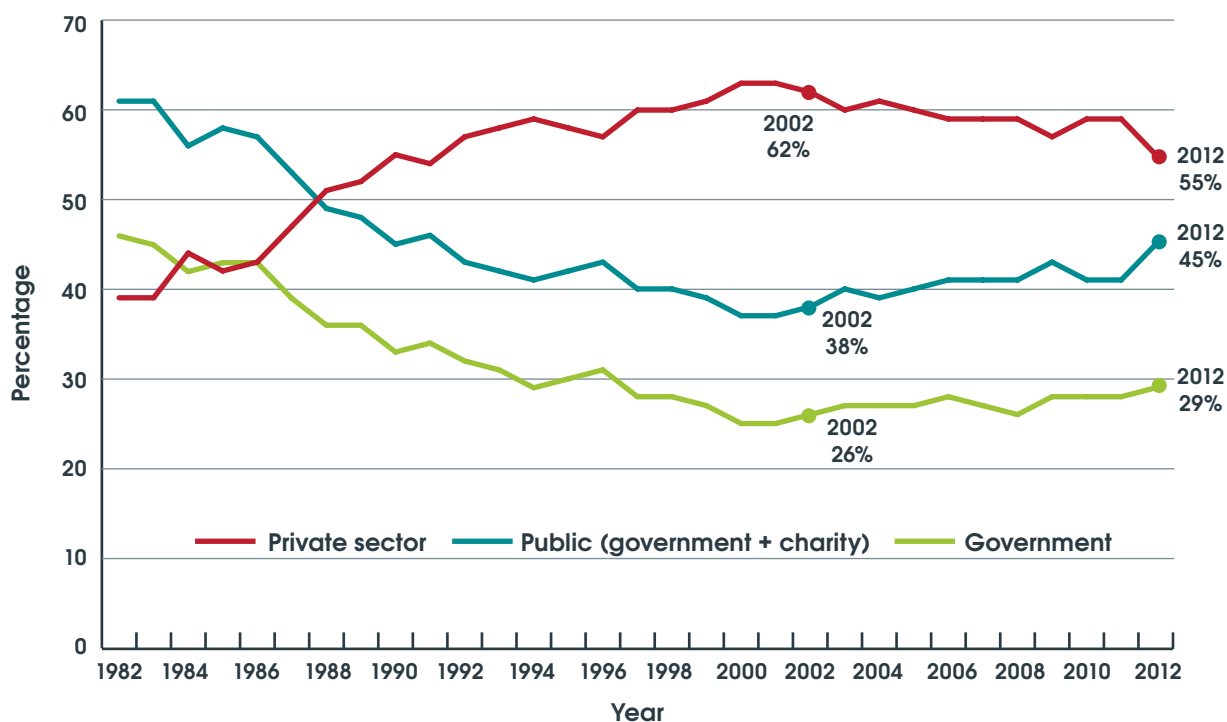
i. Including the Medical Research Council, Innovate UK, the National Institute for Health Research, the Council for Science and Technology, the Office for the Strategic Co-ordination of Health Research, the Office for Life Sciences and the Biotechnology and Biological Sciences Research Council

Figure 1: Health R&D spending by year and by funding sector (£millions)



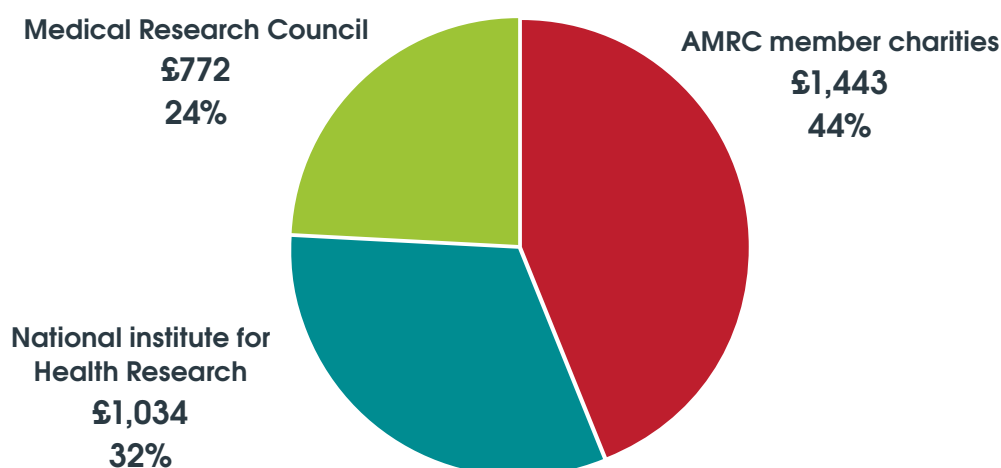
From Sussex et al.³⁷ not altered, used under a Creative Commons Attribution 4.0 International license (<http://creativecommons.org/licenses/by/4.0/>).

Figure 2: Percentage of total health R&D expenditure contributed by funding source



Graph based on data published by Sussex et al.³⁸

Figure 3: Non-industry spend on health R&D in 2015 (£millions)



Adapted from the Office for Life Sciences citing the Association of Medical Research Charities (AMRC) website.³⁹ AMRC members include all main charities that fund research in the UK. This assessment seems to exclude Innovate UK, DFID, and the Higher Education Funding Council, though their health R&D expenditures are significantly lower.

Trends in government health R&D spending across all departments

UK government R&D expenditure for health has grown from £1.4 billion in 2007 to £2.3 billion in 2015.⁴⁰ Health R&D has steadily and significantly increased as a percentage of total government R&D expenditure from 16% in 2007 to 23% in 2015.⁴¹ Most government health R&D funding in the UK comes from the Department of Health (DoH), the Department for Business, Energy and Industrial Strategy (BEIS) via the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (BBSRC), and the Higher Education Funding Bodies (also called 'UK Funding Councils').

In global health, the UK government appears to favour Product Development Partnerships (PDPs) (or perhaps, more broadly, public-private partnerships). Nearly half of the UK's global health R&D funding (45%) in 2015 went to PDPs.⁴³ One example of a PDP with substantial funding from the UK (via the Department for International Development (DFID)) is the Drugs for Neglected Diseases initiative (DNDi), discussed in chapter 3.

Forecast for UK R&D spend

The UK government is firmly committed to investing in and expanding R&D across all sectors, including health. The Conservative Manifesto 2017 commits: "we will spend more on research and development (...) so that overall, as a nation, we meet the current OECD average for investment in R&D – that is, 2.4 per cent of GDP – within ten years, with a longer-term goal of three per cent." Universities are positioned within the manifesto to lead the expansion of R&D capacity so that universities may "enjoy the commercial fruits of their research". There is also a commitment to "significantly increase our funding of UK-led medical and technical research into the biggest threats to global health."⁴⁴

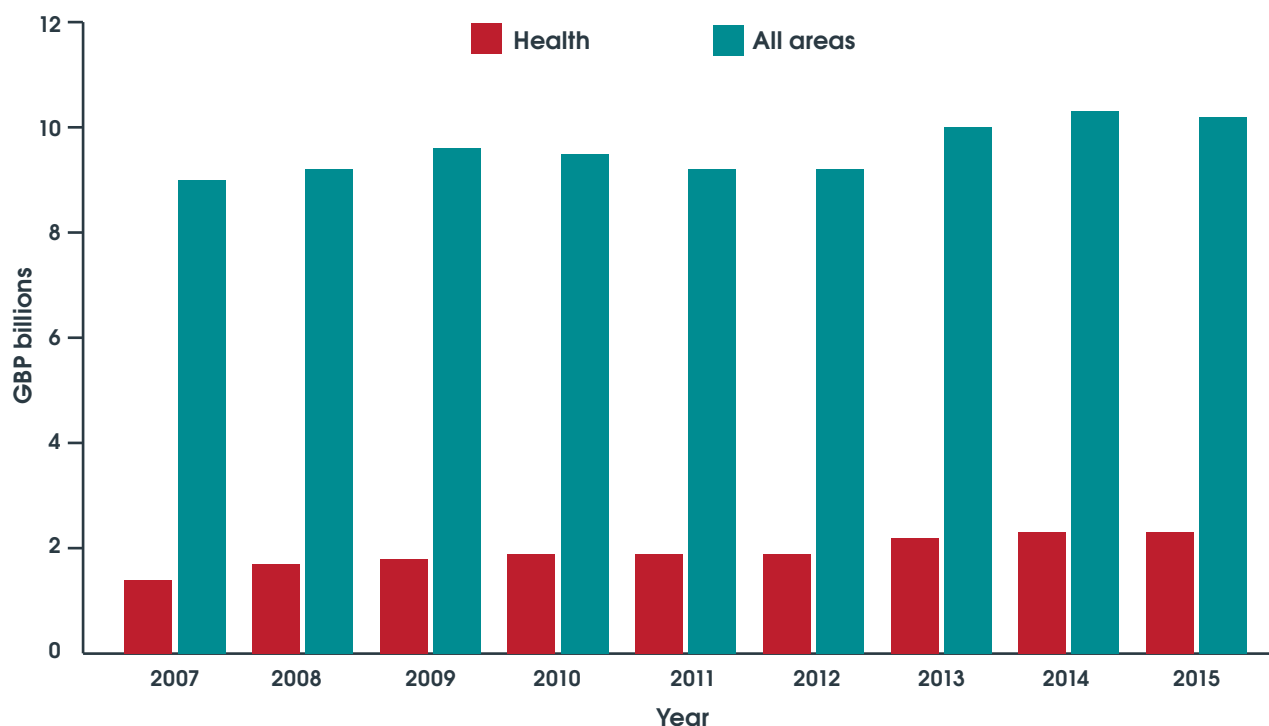
The Industry Strategy Green Paper (launched in January 2017) sets out a vision for an industrial strategy that includes investments in science, research, and innovation, and reaffirms a commitment "to maintaining and building on our strengths in R&D" as the UK leaves the EU. The Industrial Strategy Challenge Fund is a commitment to spend an additional £4.7 billion in R&D by 2020-21 to address industrial challenges and lists healthcare and medicines as one of the challenges identified.⁴⁵

The UK and the EU

In 2014/15 (most recent data available), more than 9% of all funding for research in higher education institutions in the UK came from EU sources. Clinical medicine was the top area of EU funding in absolute terms (£120 million) by a wide margin.⁴⁶ Between 2007 and 2013, the UK contributed €5.4 billion (\$4.8 billion) to the EU's research funding framework, but received a total of €8.8 billion (\$7.8 billion) from the EU (€3.4 billion (£3.0 billion) more than contributed).⁴⁷

In summary, the UK taxpayer is a medical R&D funder of global significance, and the UK government's approach to funding research and managing the results of research has the potential to significantly affect the health and wellbeing of people around the world.

Figure 4: UK government R&D expenditures on health (£billions)



Most recent available data from ONS.⁴² R&D expenditures categorised as having the socio-economic objective of 'health'.

1.2 UK commitments to public return on R&D investment

Ensuring accessibility and affordability of medicines has increasingly become an international concern. In recent years a range of influential global actors have published reports on the topic, including the UN Secretary General's High-Level Panel on Access to Medicines,⁴⁸ the Lancet Commission on Essential Medicines Policies,⁴⁹ the Council of the European Union,⁵⁰ the UK All-Party Parliamentary Group on Global Tuberculosis, and WHO's Consultative Expert Working Group on Research and Development (CEWG).

Recommendations, from across the reports, include:

- **Transparency requirements must be attached to public R&D funding.** The costs of R&D (particularly the public contributions to R&D) and the terms of licencing agreements made between public and private institutions should be publicly available.
- **Any intellectual property coming from public funding must be licensed in a way that protects access.** An approach to licensing that prioritises health needs and systematically incorporates provisions to safeguard access to medicines should be used.
- **The prices of medicines should be de-linked from their R&D costs:** The current health innovation model predominantly relies on the use of patents and profits arising from monopolies as a financial incentive for stakeholders to do R&D activities. There are calls for an alternative approach to be explored that de-links the costs of R&D from the final price of the end-product, aiming at the lowest sustainable price worldwide.⁵¹

The UK has supported some international commitments that aim to guarantee access to affordable medicines and better coordinate R&D efforts. Fundamentally, the UK supports the notion that *"the enjoyment of the highest attainable*

standard of health is one of the fundamental rights of every human being."⁵² The UK has endorsed the UN's Sustainable Development Goals (SDGs), which "will shape the world's approach to growth and sustainable development until 2030".⁵³ Targets 3.8 of the SDGs include references to ensuring access to affordable essential medicines and vaccines.ⁱⁱ

The UK has also supported international initiatives. It financially supported and engaged in the discussions of the WHO's CEWG on R&D, played a leading role in efforts to tackle antimicrobial resistance (AMR), and supported the declaration of the High-Level Meeting on Antimicrobial Resistance. The latter underlined that *"all research and development efforts should be needs driven, evidence-based and guided by the principles of affordability, effectiveness and efficiency and equity"* and acknowledged the importance of de-linking the costs of R&D from the price and volume of sales.⁵⁴

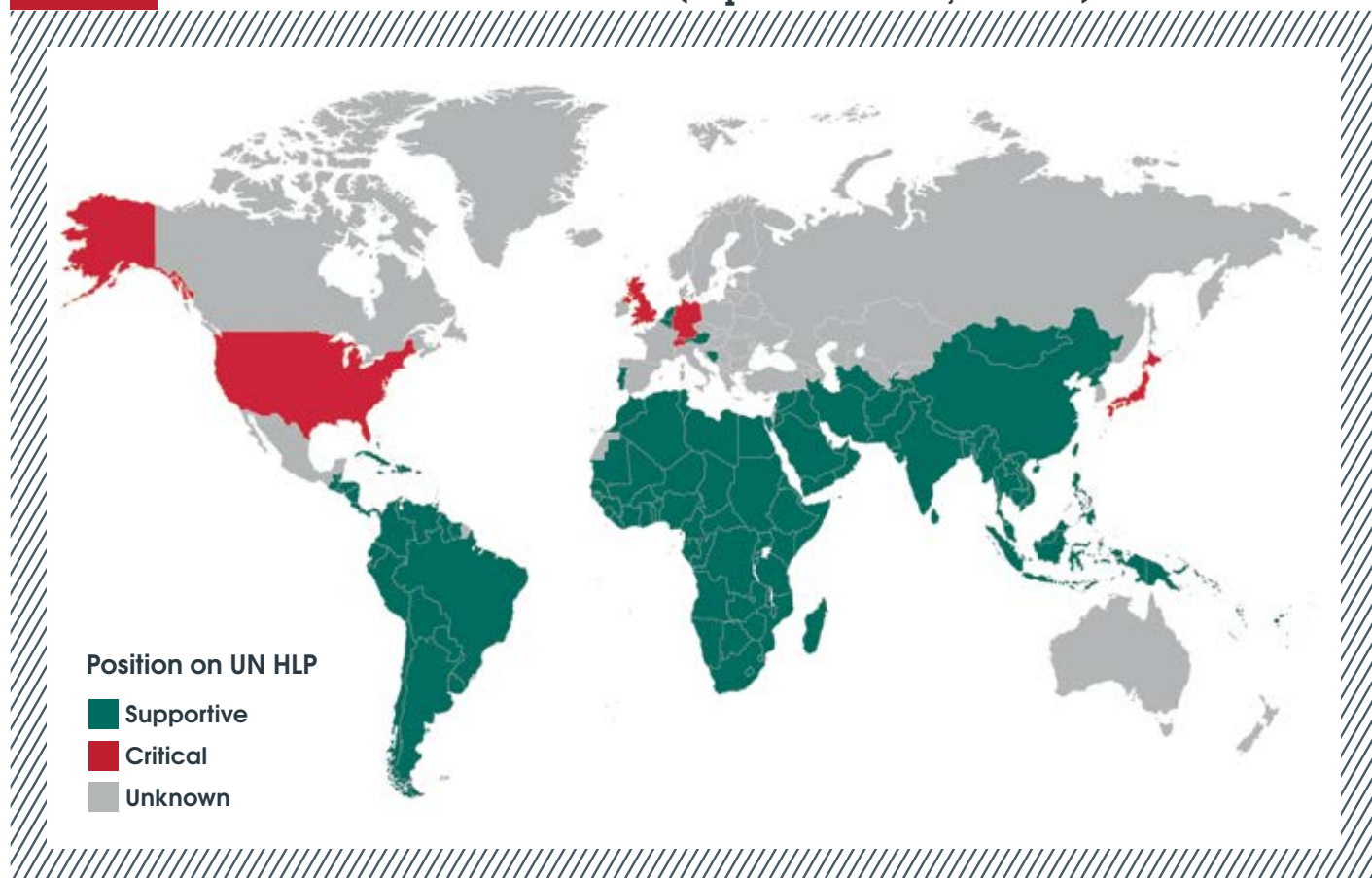
De-linkage

The current patent system enables pharmaceutical companies to charge high prices for medicines as an incentive to invest in R&D. The concept of de-linkage disconnects the costs of R&D from the price of the medicine that is developed. De-linkage models include paying for R&D upfront through grants and/or prizes and allowing the competitive production of resulting products. De-linking allows for ownership and control of health technologies to be kept in public hands, enabling decision-makers to prioritise public health over corporate profit.

ii. Target 3.8 includes "...access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all" and Target 3.B is to "Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health, which affirms the right of developing countries to use to the full the provisions in the Agreement on Trade-Related Aspects of Intellectual Property Rights regarding flexibilities to protect public health, and, in particular, provide access to medicines for all."

Figure 5:

Countries coloured by their response to the report of the UN High-Level Panel on Access to Medicines (September 2017, Oxfam).⁵⁸



This support by the UK government for new ways of financing R&D and safeguarding public returns on R&D is undermined by the government's resistance to the findings of the report by the UN High-Level Panel on Access to Medicines (UN HLP), released in 2016.⁵⁵ The UK Government's position on the HLP is that the WHO is "well placed to consider which recommendations add the most value",⁵⁶ but it is still unknown if and how the UK will encourage the WHO to prioritise taking specific HLP recommendations forward. This is despite that fact that the UN HLP report recommendations enjoy widespread support from national governments, many of which voiced their support for the recommendations, as demonstrated in the map above (figure 5) and at the 70th World Health Assembly.⁵⁷

The UK has been particularly resistant to transparency of R&D costs by casting doubt on the ability to calculate these. DFID has repeatedly commented that "*a disaggregation of costs in company product portfolios is very difficult to achieve particularly as companies work across many different countries, with multiple partners at different phases of development and delivery, and in often using multiple shared inputs*". However, it is clear that transparency in R&D spending is not impossible, given that the pharmaceutical industry have previously supplied, confidentially, data for an industry-sponsored study analysing per-drug R&D costs.⁵⁹

1.3 Conditions attached to UK R&D grants

A variety of conditions attached to UK R&D grants exist, which is unsurprising as R&D funding is administered by multiple bodies and departments. Our analysis shows that conditions attached to grants are not sufficient to guarantee that patients in the UK and beyond will be able to access the final medicines at an affordable price. On the other hand, there are guidelines to make the knowledge generated in the research process, as a result of UK grants, available to others.

All UK R&D spending is guided by an overarching, principle of “value for money” as set by HM Treasury “in the public interest”. However, the Treasury’s definitions and principles are vague, and predominantly focused on procurement costs rather than asserting human rights, such as the right to health. The Treasury confers certain expectations and obligations upon those administering public funds, including the systematic and continuous evaluation of the outcomes of funding as well as the willingness to seek advice and make changes if alternatives “would deliver better value”.⁶⁰

All UK R&D spending is covered by a policy called *The Research Governance Framework for Health*

and Social Care, which also applies to any research within the health system “undertaken by industry, charities, research councils and universities within the health and social care systems that might have an impact on the quality of those services.”⁶¹

DFID has one of the most detailed ‘value for money’ approaches, which aims to maximise “the impact of each pound spent to improve poor people’s lives”.⁶² Much of DFID’s internal guidance, such as their *Smart Rules* refers to aid and programme delivery rather than R&D, but DFID staff have informed us that, for DFID, a large profit margin on products developed from their research funding would not be acceptable within their ‘value for money’ principles.⁶³ However, DFID does not define what an acceptable profit margin is.

The Treasury recommends that public bodies “consider setting conditions’ on grants, such as the use of ‘clawback’ clauses in agreements regarding intellectual property rights”.⁶⁴

From our analysis of various public funding bodies, we have provided a traffic light summary overview of the conditions attached to UK R&D (table 1, below). The Treasury itself does not have any conditions that relate to the pricing or accessibility of assets derived from UK R&D spending^{65,66}

Table 1: Strength of conditions attached to UK R&D grants

	Access for NHS patients	Access for patients in developing countries	Transparency of R&D costs	Open access for research
Research Councils UK				
Medical Research Council				
Department for International Development				
National Institute for Health Research				
National Health Service				

Traffic Light summary analysis indicating strength of conditions attached to UK R&D grants.

- No provisions
- Vague guidelines
- Specific provisions, with scope for monitoring and enforcement
- Strong provisions, monitoring and enforcement⁴²



Youth Stop AIDS campaigners deliver a petition to UK Parliament calling for UK leadership on changing the way we research and develop medicines, May 2016.

Access for NHS Patients

The *Framework and Guidance on the Management of Intellectual Property in the NHS* requires the Secretary of State for Health and NHS Trusts to consider all benefits to NHS patients when managing intellectual property generated by NHS employees and NHS bodies. It explicitly notes that “it is not always the case that actually maximising income is best for the health service. There will always be other strategic priorities to consider such as improving health for the maximum number of patients and providing savings to the NHS.”⁶⁷

The NHS spent more than £1bn last year on medicines that have received substantial public R&D funding

However, it is unclear how this may influence the pricing of medicines developed with UK R&D funding.

No UK public sector research body includes specific provisions in their grant agreements relating to the pricing in the UK of medicines derived from UK taxpayers. MRC grants “do not include conditions

relating to the pricing and accessibility of pharmaceuticals”.⁶⁸ However, NHS policy does require that NHS organisations “consider the benefits” to NHS patients of any commercialisation agreement (e.g. between an NHS Trust and a pharmaceutical company) and that they “include, where possible, preferential terms of sale for NHS bodies not associated with the IP”.

Given that the NHS spent more than £1bn last year on medicines that have received substantial UK public R&D funding (appendix 2), it is questionable whether existing provisions are managing to safeguard the interests of the NHS.

Access for patients in developing countries

DFID does not attach affordability conditions to the grants it makes to PDPs but it does expect them to have a “business model” that includes access as a core consideration (DNDI is explored in Chapter 3). For example, when setting out the “business case” for their funding of the TB Alliance, DFID described as a “critical outcome” that the Alliance makes efforts to guarantee new medicines “once developed and approved, are affordable, accessible and adopted; especially in low income countries”.⁶⁹ DFID expects compliance with these aims to be internally regulated by the TB Alliance.

The NHS policy *Framework and Guidance on the Management of Intellectual Property* notes that when entering licensing negotiations NHS organisations “should seek to include terms that are likely to give patients in developing countries access to products at reasonable cost”.^{70,71} These terms include setting limits on the price charged in developing countries, and restricting the area of use or territory of the license.

The National Institute for Health Research (NIHR) uses standard contracts with organisations that receive funding. These place a responsibility on the contractor to consider “access to essential medicines in the developing world” and “prosecute patent applications in less developed countries only as necessary”.⁴³

Transparency of R&D costs

We did not find any provisions that required transparent reporting of R&D costs or the involvement of public contributions.

Open Access for Research

The Treasury recommends the use of ‘clawback’ clauses, in agreements regarding intellectual property rights (IPR).⁷² Clawback clauses give the funder certain rights over an asset produced as a result of the grant, giving them more influence to ensure “that public sector funds are used for the intended purposes”. All of the public sector funding bodies analysed in this study have conditions relating to the IP generated through public funding. These typically seek to protect intellectual assets and share research outcomes so that “arrangements for collaboration and/or exploitation (do) not prevent the future progression of research”.⁷³

The MRC has its own additional terms and conditions that strongly encourage “research use exemptions” on licenses to ensure IPR do not provide a barrier to further research. The MRC also includes conditions relating to the mandatory registration and the publishing of clinical trial data.⁷⁴

The strongest example of an open access policy belongs to Research Councils UK, which states that they “take very seriously their responsibilities in making the outputs from this research publicly available”. The official aim of the policy is “to ensure that the public investment in research secures the maximum economic and societal return”.⁷⁵

The UK government has made steps to ensure ‘value for money’ and sets a precedent for using conditions on UK R&D spending. In practice, the exploitation and licensing of IPR, including open access to research, are fairly commonplace. While health R&D appears to be a priority for the UK government, conditions concerning affordable access to the health technologies developed with UK public funds for NHS patients and beyond, or transparency of R&D costs, are either too vague or non-existent.

Within NIHR standardised research contracts, there are provisions for the Secretary of State for Health to monitor the effectiveness of IP management for public benefit and, in cases where this is not being achieved, give the Secretary of State the right to take control of the IP.⁷⁶

The lack of clarity caused by a patchwork of existing policies is compounded by the fact that there is little to no publicly available information about their effectiveness. This means that while some promising practices are reportedly in place (in DFID funding, for instance) there is little information available about their success. While this may be partly explained by already stretched departments wishing to avoid the extra administrative burden of carrying out evaluations, it is also indicative of the low priority given to affordable access to medicines and other health technologies. Reflecting on the specific cases of medicines that have received public R&D funding outlined in chapter 2, it is clear that strong safeguards are needed to protect the NHS and guarantee access for UK taxpayers or patients abroad, including in developing countries. Currently there is little evidence that such safeguards are effective and enforced.

For further detail about conditions and policies attached to public health R&D funding in the UK, see appendix 3.

1.4 A lack of transparency in UK medical R&D

Greater transparency in drug development and drug commercialisation is a key step towards a fairer R&D system. Companies often defend their high prices by citing high R&D costs, but do not provide details of how much a drug has cost to develop. A lack of transparency is unfortunately also present in UK government-funded health R&D.

In many cases, information about UK public funding of R&D is not easily available. For example, while the NIHR notes as an achievement on its website that *"in 2015/16 the NIHR-supported infrastructure received (funding) resulting in: 94 licences, 5 registrable and 62 non-registrable IP products, 15 spin-outs"*, it does not provide information on what these licences were for, or what these IP products and spin-outs were.⁷⁷ A freedom of information request for the details of these licences, IP, and spin-outs was unsuccessful, with the DoH noting that they do not hold this information. Other examples of lack of transparency are the lack of reporting of clinical trial expenditures and the proportion of UK government R&D spending in health that goes to private companies.⁷⁸

The lack of transparency in UK public R&D is no anomaly in the global system of pharmaceutical R&D. There is a profound lack of published data on how much it costs to develop new medicines from start to finish, with only broad estimates available. The most widely-cited study estimates an R&D cost of US\$2.6 billion (£1.99 billion) per medicine, but this industry-funded study has been widely criticised for biased and erroneous methodology.^{79,80} In a more recent analysis of ten cancer drugs, the median cost of developing a single cancer drug was found to be £480 million.⁸¹

At a much lower end of the range of estimates, the DNDi, who have developed six new therapies over the past decade, *"has estimated the cost to develop a new chemical entity in the field of neglected diseases at (£85-£131million)... including the cost of 'failures' – drug candidates that did not ultimately prove successful"*.⁸² As a figure from a PDP, this is not fully comparable to pharmaceutical company costs, but it does indicate that significant savings may be possible using an alternative, not-for-profit R&D model.⁸³

The confidentiality that clouds R&D costs as well as final price agreements and negotiations between national governments such as the UK and pharmaceutical companies creates an uncertain and uneven playing field for negotiators. It also reduces the power of citizens, civil society, and the media to engage in a conversation over the final price.

1.5 Commercial influence over UK government health R&D

The pharmaceutical industry is deeply enmeshed at all levels of the health R&D process in the UK. Professor John Abraham, one of the foremost experts on UK pharmaceutical policy, notes that *"the pharmaceutical industry was, and is, permitted to have privileged strategic access to, and involvement with, government regulatory policy over and above any other interest group"*.⁸⁴

"The Department (of Health) seems unable to prioritise the interests of patients and public health over the interests of the pharmaceutical industry"

2005 House of Commons Health Select Committee report

This relationship has a long history,⁸⁵ as recognised by a House of Commons Health Select Committee report in 2005. At the time, the DoH was jointly responsible for 'promoting the interests' of pharmaceutical companies and patients. The committee found that *"the Department (of Health) seems unable to prioritise the interests of patients and public health over the interests of the pharmaceutical industry"*, further adding that *"(t)he interests of patients, the NHS and industry can be at odds and we have no confidence that the Department is capable of achieving the balance required"*.⁸⁶ In response, the government simply asserted that the DoH would continue with a dual responsibility to promote pharmaceutical industry interests, and serve patients.^{87,iii}

People directly employed by the pharmaceutical industry hold key positions in the MRC, BBSRC, the Council for Science and Technology (an NDPB advising the Prime Minister on science and technology policy) and Innovate UK. Furthermore,

iii. The Committee recommended "that responsibility for representing the interests of the pharmaceutical industry should move into the remit of the Department of Trade and Industry to enable the DoH to concentrate solely on medicines regulation and the promotion of health", to which the Government responded that "(...) the interests of patients and the industry are not exclusive. (...) The Government believes that at present the Department of Health is the right place to balance all of these interests". Secretary of State for Health, "Government Response to the Health Committee's Report on the Influence of the Pharmaceutical Industry," September 2005, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/272177/6655.pdf.

two sub-groups within the Office for Life Sciences provide industry executives and lobbyists with direct access to ministers from the DoH, BEIS, and key personnel from HM Treasury.⁸⁸ The attendance for one of these, the Ministerial Industry Strategy Group, has included the Chief Executive the British pharmaceutical lobbying group ABPI, and executive staff from Pfizer, GSK, and AstraZeneca.⁸⁹

In July 2017 the DoH appointed a new commercial officer, Steve Oldfield, whose experience includes senior roles with pharmaceutical companies Sanofi and Teva, as well as being on the board of the Association of the British Pharmaceutical Industry.⁹⁰ Steve Oldfield will now be responsible for negotiating drug prices with pharmaceutical companies, despite having previously written to the former Prime Minister, David Cameron, stating it “is a prevailing myth that medicines are expensive”.⁹¹

Another example of corporate influence on UK government R&D is in Innovate UK, an NDPB

sponsored by BEIS, which describes itself as “the UK’s innovation agency”. Innovate UK is run by an executive management team and a governing board, whose members are appointed individually by the Secretary of State for BEIS. The chief executive of Innovate UK is Dr Ruth McKernan CBE, former vice president of the US pharmaceutical company Pfizer.

A major area of activity for Innovate UK is its ‘Catapult Centres’ of which there are 11 across the UK.⁹² ‘Catapult Centres’ provide businesses with access to manufacturing and testing facilities, as well as expertise. On the Board for the ‘Medicines Discovery Catapult’, five out of nine members come directly from working in the pharmaceutical sector.⁹³ Of the seven executive staff on the management team, six have previously had jobs in the pharmaceutical industry, for companies including Pfizer, Merck, and Astra Zeneca.⁹⁴ The Cell and Gene Therapy Catapult has a similar level of industry involvement on its executive board.

Corporate controversy in EU research

According to Corporate Europe Observatory, “*Big pharma enjoys semi-systematic access to decision-making in Brussels, facilitated by its vast lobby expenditure, complex web of actors, extensive meetings with policy-makers, and participation in advisory groups*”. In 2015 the declared lobbying spend by the pharmaceutical industry was almost £35 million.⁹⁶

The EU’s biggest public-private initiative is on health R&D. The Innovative Medicines Initiative (IMI) is a programme of public-private partnerships jointly managed by the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA). The EU contributes 50% of total funding in cash disbursements, while EFPIA members contribute 50% of funding through ‘in-kind’ (that is, mainly non-cash) contributions. The UK has seen a net gain in funding from IMI: “*between 2007 and 2013, the UK secured a total of €8.8bn in R&D funding, €3.4bn more than contributed*”.⁹⁷

The primary aim of IMI is to make drug development cheaper, quicker, and ‘better’.^{98,99} But the IMI has been the target of numerous critiques from project partners, academia, non-governmental organisations and the media for allegedly serving simply as a large subsidy to the pharmaceutical industry, and failing to safeguard affordable access to the end products of the research partnerships. The German publication Spiegel Online, Belgian newspaper De Standaard, and Swiss broadcaster SRF jointly investigated the IMI leading to a damning report by Spiegel Online in April 2015. By “*analyzing IMI’s structure, procedures and finances, (and interviewing) researchers, politicians and employees of pharmaceutical companies and non-governmental organizations*” the report found that the IMI is “*funded with more than €2.5 billion (...) in taxpayer money, (and) has been used almost exclusively to subsidize the pharmaceutical industry through the circuitous route of research*”.¹⁰⁰

BEIS has confirmed to us that *"the Catapults and Innovate UK do not attach pricing or accessibility issues (sic) to any products produced by companies with which it works"*.⁹⁵ This brings into question the ability of the industry to impartially contribute to regulating public funding of health R&D that they might have a commercial interest in.

To a certain extent, of course, contact and collaboration between the pharmaceutical industry and the government is necessary but our findings indicate that the industry exerts a further, more insidious and pervasive form of influence, which Professor John Abraham calls 'corporate bias'.¹⁰¹ For health R&D policy, this coalesces in the assumption and narrative that what is good for the pharmaceutical industry is good for the public. This assumption is obvious in reports like the Witty Review, which recommended that universities *"should assume an explicit responsibility for facilitating economic growth, and all universities should have stronger incentives to (...) (work) together to develop and commercialise technologies which can win in international markets"*.¹⁰² The assumption is also inherent in Innovate UK's 'business-led' stance, and in the way that public sector research institutions (PSRIs) boast of revenue gained from IP licences. This bias towards corporate interests, however, overrides public health interests and thereby creates problems of access and price.

The pervasive influence of the pharmaceutical industry over UK government health R&D begs the question of whether funding is governed in the interest of the public health, or large private companies. As the following chapter will show, company shareholders may ultimately be greater beneficiaries of some government health R&D than people in need of new treatments. Taxpayer-funded health R&D should first and foremost benefit people in need of new treatments and the governance of research funds should reflect that priority.

The Life Sciences Industrial Strategy

This strategy released in September 2017 was written by the Life Sciences Industrial Strategy Board, which is made up of companies like GlaxoSmithKline, Astra-Zeneca and Johnson & Johnson and the Association of the British Pharmaceutical Industry, as well as representatives from academia and charities.¹⁰³

The strategy promises an additional £146m to subsidise medical research – both through work undertaken by industry directly, and partnerships which will be commercialised by industry. The report notes that "issues of pricing were explicitly not included in the scope of the report".

2. UK contributions to R&D of specific medicines

Examples of medicines developed through public investment are not widely known, especially examples in the UK. Nevertheless, universities and public-sector research institutions are essential drivers in pharmaceutical innovation. Between 1998 and 2007, 31% of scientifically novel new drug registered in the US were discovered in a university.¹⁰⁴ Some have estimated that public funding is responsible for as much as two-thirds of pharmaceutical R&D.¹⁰⁵

To shine a light on the contributions of UK public investments to pharmaceutical R&D, this chapter details case studies where the UK has played a substantial role in the discovery and development of highly effective and often life-saving treatments that also represent some of the most expensive medicines in the UK and the world. Three of these examples stem from monoclonal antibodies, a discovery which is used in a third of all new medicines introduced worldwide.¹⁰⁶

The following case studies give an overview of what each drug is used for, the role of UK government funding in the R&D process through to 'commercialisation' and subsequently the controversies that surround the access to or price of the drug in the UK and elsewhere. In general, information on R&D expenditures (even in public research) and drug prices are limited and often confidential. As a result, the case studies could not fully describe R&D expenditures, the exact contributions of the private sector, nor the profits made on specific medicines (as, in general, only revenues are reported). These case studies are also unable to describe the full picture of UK public contributions to drug R&D. The full list of medicines owing a substantial part of their development to public research is likely to be significantly longer.

2.1 Abiraterone

Abiraterone is effective for treating patients with advanced prostate cancer, including those who are resistant to hormone therapies and both before and after chemotherapy.¹⁰⁷

UK government and abiraterone R&D

Abiraterone was discovered at the Institute of Cancer Research (ICR), a largely publicly funded UK research institute that is part of the University of London and works in close partnership with an NHS Trust. The ICR also led the clinical development of abiraterone, which was funded by multiple public funding sources, including the UK MRC and the charity Cancer Research UK, as well as by British Technology Group (see below) and a pharmaceutical industry licensee.

Data about private sector contributions to the R&D costs of specific medicines is not publicly available, making it impossible to know the total R&D cost. However, from the data available it is clear that abiraterone was discovered and predominantly developed by a UK public-sector research institution, with substantial public funding for Phase I, II, and III clinical trials.

British Technology Group

The British Technology Group (BTG) arose from the National Research Development Corporation set up by the UK Government in 1948.¹⁰⁸ While it originally held a 'right to first refusal' (i.e. the right to be the first to negotiate a licence) on discoveries made in UK academic institutions, this privilege was later removed.¹⁰⁹ It was privatised in 1992 and has since behaved as a private biotech company, including directly selling medicines.

The first patents on abiraterone were filed by the ICR in 1992, and rights to the patents were assigned to the British Technology Group (BTG). We have not been able to find details on arrangements between the ICR and BTG.

In 2004, BTG licensed abiraterone to Cougar Biotechnology (see box on *Licensing of patent rights to medicines*).¹¹⁰ Johnson & Johnson acquired Cougar Biotechnology for approximately £600 million in 2009.¹¹¹ The branded version of abiraterone is now marketed as Zytiga by Janssen, which is part of Johnson & Johnson.

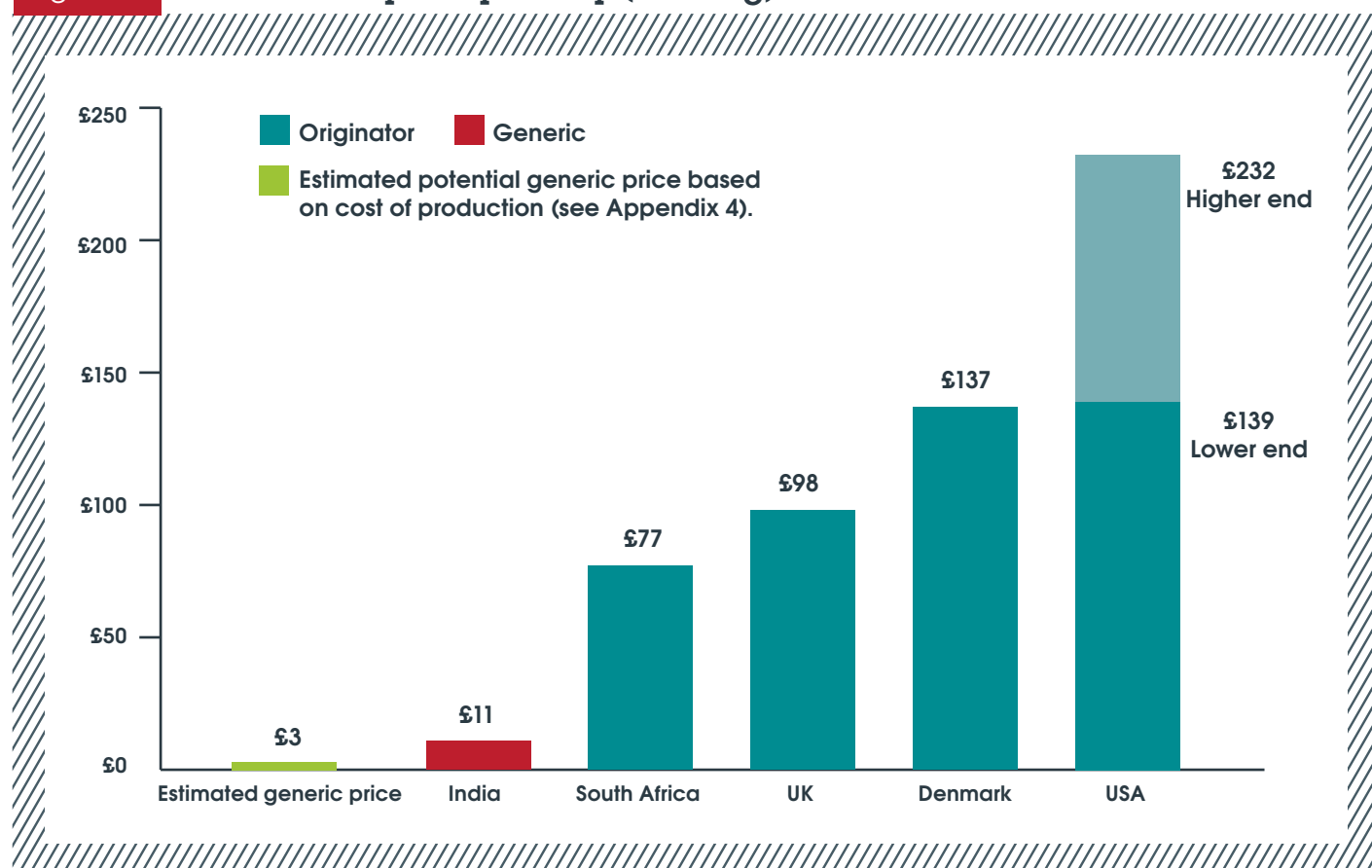
Access to abiraterone and controversies

A price comparison across countries are shown in figure 6, below (of these countries, only the Indian price represents a generic version^{iv}).^{112,113,114,115,116,117}

In the UK

About 423,000 people have prostate cancer in the UK.¹¹⁸ The price of abiraterone has led to repeated rejections by NICE for not being cost-effective. NICE assesses the cost-effectiveness of a drug by measuring the cost in pounds per additional quality-adjusted life year gained through treatment.

Figure 6: Abiraterone price per day (1000mg)



iv. Abiraterone was not found in the database of public procurement prices in South Africa (the private market price was therefore used), or in the database of public procurement prices for the Indian state of Tamil Nadu (private market price used). In the UK, the British National Formulary's "indicative price" was used. In the US, where drug prices are often very different in different contexts, two sources were used with the intention of being broadly representative: the higher end price represents the National Average Drug Acquisition Cost (NADAC), an average value reported by Medicaid, and based on the community pharmacies' average cost of procuring abiraterone; the lower end price represents the price as negotiated by the Veterans' Affairs Committee – commonly one of the lowest price-points seen in the US.

Licensing of patent rights to medicines

Typically, the rights to a discovery made in a public research institute are transferred to a private company with the understanding that the company will undertake further development and eventually market the drug (or vaccine, diagnostic, etc.). First, the discovering scientist, or the institute itself, patent their discovery. The rights to use this patented discovery are then sold to a private company usually through an exclusive licence, meaning all rights are transferred to a single licensee. These licences often include a small royalty to be paid back to the discovering institute.

While this reflects the common route for discoveries in the UK and other high-income countries, alternative approaches are possible that could safeguard affordable access to the final product – these are described in chapter 4.

In five years of negotiations spanning two reviews, abiraterone was recommended by NICE only after the price was lowered to push the cost of abiraterone marginally below NICE's upper limit of acceptable cost, and after significant public pressure from patient groups, the DoH, and others.

During the second NICE review of abiraterone, 5,900 people could have benefitted from abiraterone for each of the two years that NICE and Janssen were negotiating the price and 'cost-effectiveness' of the drug¹¹⁹, but were unable to access it through the NHS. In that time, eligible patients had to take their chances with getting the drug through the Cancer Drugs Fund,^v which rationed its use¹²⁰. For these untreated patients, abiraterone could have been life-saving: a recent trial has shown a 37% reduction in prostate cancer deaths three years after treatment.¹²¹

v. The Cancer Drugs Fund (CDF) ran from 2010 to 2016 and was specifically put in place to pay for cancer treatments deemed not to be cost-effective by NICE. Health care providers could make a request to the CDF to finance the cost of a treatment for a specific patient. During its five years of operation it cost the public purse £1.27bn.

Despite the role of UK public funding in R&D, abiraterone is sold in the UK at a price that poses a significant challenge for the NHS. The NHS spent £172 million on branded abiraterone from 2014 to 2016,¹²² despite a generic version being available in India for a price 85% lower.¹²³

By the end of 2016, Janssen's global sales of abiraterone had reached \$9.7 billion (£7.5 billion).¹²⁴ This is in stark contrast to the Institute for Cancer Research (the original discoverer of abiraterone), which had earned just £137 million in revenues by the end of 2017, or about two percent of Janssen's sales.¹²⁵

Globally

Based on recent positive results from using abiraterone for prostate cancer, the drug is in good standing for inclusion in the next (2019) WHO *Essential Medicines List*. However, it was previously rejected from the list, with a major factor being the high cost.¹²⁶

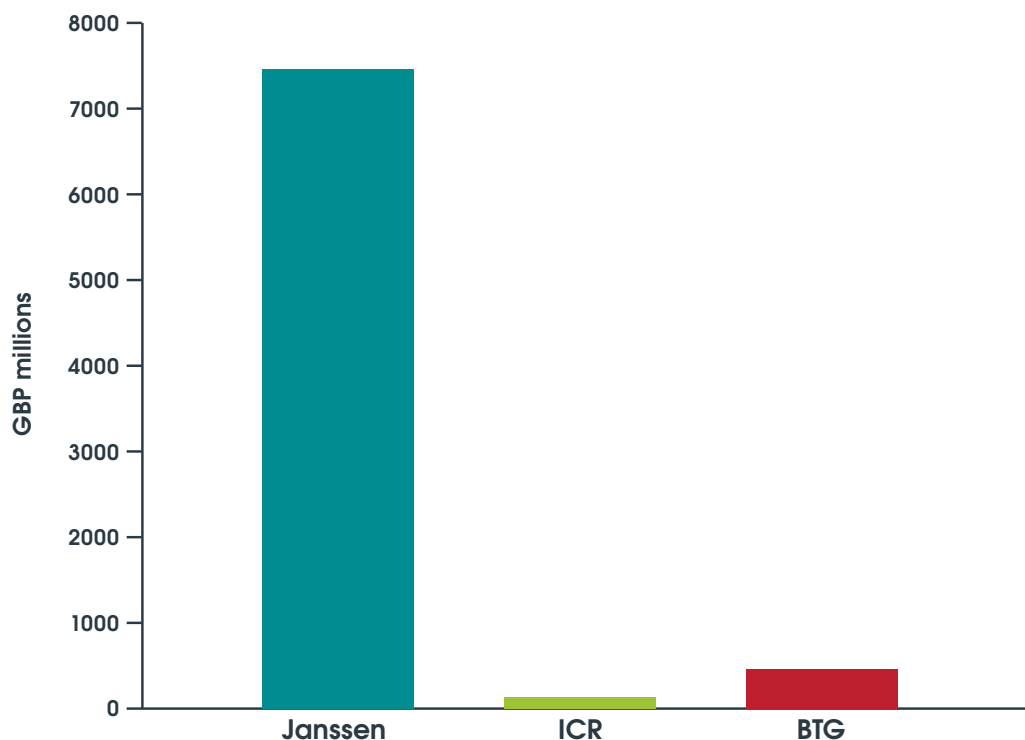
There is a disproportionately high rate of deaths from prostate cancer in sub-Saharan Africa compared to other regions.¹²⁷ While next to no published data are available on access to abiraterone, our study found that abiraterone is not available in the public sector in South Africa. We also know that the cost is only slightly cheaper in the South African private sector than in the UK, despite South Africa having a nearly eight times lower average income.^{128,129} In some parts of Asia, an anti-fungal agent is used instead of abiraterone (due to the latter's high price) though it has significant undesirable side-effects.^{130,131} Generic manufacture of abiraterone may be blocked in many parts of the world by patents lasting until 2027.¹³²

For further detail on the development and accessibility of abiraterone, please see appendix 4.

Income

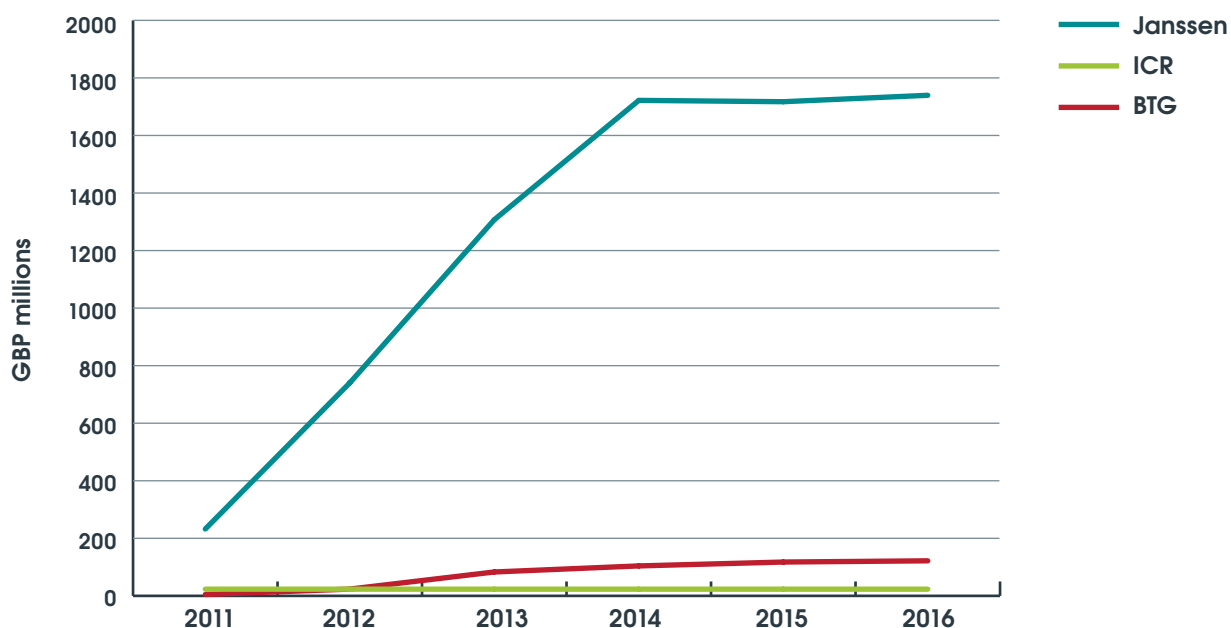
BTG receives income on abiraterone through licensing royalties. A comparison of the incomes of BTG and Janssen are shown in the graph below. Data from BTG and Janssen annual reports,^{133,134} and a response received from the ICR to a request made under the Freedom of Information Act.¹³⁵

Figure 7: Total income from abiraterone for Janssen, ICR and BTG (£millions)



Janssen and BTG incomes may be slightly underestimated as they are reported only to the end of 2016.

Figure 8: Income from abiraterone per year for Janssen, ICR and BTG (£millions)



Yearly income for ICR calculated as £137 million averaged over six years, based on total revenue from abiraterone of £137 million as of October 2017.

2.2 Monoclonal antibodies

Antibodies are molecules produced by cells in the human immune system; they attach to entities in the body that the immune system identifies as ‘foreign’, such as bacteria. Monoclonal antibodies (MABs) are antibodies that are artificially created to bind to a specific target. Different MABs have been developed to treat a wide range of diseases. They are used predominantly for cancers and autoimmune diseases, but increasingly for other types of diseases too.

UK government and R&D of monoclonal antibodies

The basic technologies for producing MABs were developed by Greg Winter in the 1980s and 1990s, predominantly at the the UK Medical Research Council Laboratory of Molecular Biology (MRC LMB) in Cambridge.^{136,137,138} The MRC LMB is funded primarily by the UK Medical Research Council.¹³⁹

Since the development of MABs and MAB humanisation in Cambridge, the market has grown dramatically: more than 40 MABs are now available in Europe and the US,¹⁴⁰ and six of the ten medicines with all-time highest sales have been MABs.¹⁴¹ The UK MRC receives royalties on many monoclonal antibody medicines developed based on their discoveries, but the royalties represent a very small proportion of the revenues earned by the companies selling the medicines.¹⁴²

An estimated 65% of therapeutic antibodies use the technologies developed at the MRC LMB,¹⁴³ including adalimumab (tradenname Humira), trastuzumab (Herceptin), bevacizumab (Avastin), infliximab (Remicade), and rituximab (Rituxan/MabThera).^{144,145,146,147} In the case studies of adalimumab, alemtuzumab, and infliximab, public research played a significant additional role in drug development, leading and/or funding clinical trials. These three case studies are explored in subsequent sections.

Controversy

Monoclonal antibody medicines are highly expensive. Access to these medicines in the developing world is low, and their prices strain health budgets in high-income countries.

The controversies around patenting monoclonal antibodies

Extensive controversies have surrounded the patenting of the MAB technologies developed at the MRC LMB.

In 1984, the year when César Milstein was awarded a Nobel Prize for his discoveries relating to MAB production, the MRC researcher was quoted as saying “*I think patents are financial swindles that prevent the public from access to information*”.¹⁴⁸

Geoff Hale and Herman Waldmann, who developed alemtuzumab (discussed later in this section) wrote that the decision not to patent some of the early discoveries at MRC LMB regarding MABs “*probably did more than anything else to facilitate the widespread use of monoclonal antibodies*”.¹⁴⁹

Global access

Little data is available on access to monoclonal antibody medicines in low- and middle-income countries. The recent Lancet Commission on Essential Medicines Policies considered that “*monoclonal antibodies used to treat cancers (are) another example of medicines whose prices present affordability challenges to all countries, regardless of income level*”.¹⁵⁰ Trastuzumab in particular has been the focus of recent campaigns highlighting the consequences of unaffordable prices in South Africa.¹⁵¹ In 2011, a group of regional experts estimated that in South-East Asian low- and middle-income countries only 15% of patients had access to bevacizumab and cetuximab for colorectal cancer and trastuzumab for breast cancer.¹⁵²

There is hope for increased access to MABs through the production of biosimilar MABs. Though in their infancy as market-authorised products globally, biosimilars have already demonstrated substantial cost savings of up to 70% in recent years.¹⁵³ Biosimilar MABs have been described as “game-changers” in extending access to these medicines.¹⁵⁴

Biosimilars are biologic medicines that are designed to be as similar to an originator biologic as possible. Due to the complexity of the manufacturing processes, they cannot be completely identical to the originator product, but the manufacturer of a biosimilar undertakes clinical trials to demonstrate that the safety and efficacy of a biosimilar is equivalent to that of the originator drug. In the context of pharmaceutical markets and treatment access, they are analogous to generics for non-biologic medicines.

2.2.1 Alemtuzumab

Alemtuzumab is used to treat B-cell chronic lymphocytic leukaemia and multiple sclerosis (MS). It is an effective drug for treating relapsing-remitting MS, the most commonly diagnosed type of MS. Trials have shown that alemtuzumab treatment results in a 48-61% reduction in severe relapses,¹⁵⁵ and 78% of previously untreated patients treated with alemtuzumab were relapse-free at two years.¹⁵⁶

Role of UK government in Alemtuzumab R&D

The discovery, lead optimisation, Phase I clinical testing, and first years of manufacture of versions of alemtuzumab were carried out at Cambridge University.¹⁵⁷ The discovery was eventually licensed to a subsidiary of the Wellcome Foundation.^{vi} With help from Greg Winter's team at LMB, a humanised version of the drug was created – Campath-1H, now known as alemtuzumab. The Wellcome Foundation abandoned the drug after finding that it suppressed certain types of immune cells beyond what was hoped for.¹⁵⁸

Use in multiple sclerosis

As Wellcome abandoned the drug, positive results for its use in MS were emerging.¹⁵⁹ The clinical

development of alemtuzumab for multiple sclerosis, from early clinical trials to regulatory approval, was led by academics working at the University of Cambridge.¹⁶⁰ As for all medicines, while the exact amount invested in the work is impossible to report due to difficulties in attributing block grants, coupled with corporate secrecy, the initial Phase I clinical trial exploring its use in relapsing-remitting MS appears not to have received funding from industry.^{161,162,vii} Cambridge University reported that the “key grants” from the pharmaceutical industry for Phase II and III clinical trials totalled less than £2 million.¹⁶³

Through a series of acquisitions, alemtuzumab eventually came under the ownership of French company Sanofi-Aventis.¹⁶⁴

Access to alemtuzumab and controversies

Access in the UK

MS affects about 107,000 people in the UK. 85% of cases are initially diagnosed with the relapsing-remitting type, the type for which alemtuzumab can be used.^{165,166}

Alemtuzumab was approved for use in B-CLL,¹⁶⁷ before it was approved for MS. However, during this time alemtuzumab was widely used off-label as a treatment of MS. At the time, the cost of use for MS over two years was nearly nine times less than treating one B-CLL case for a year as it required a much smaller dose.¹⁶⁸

In 2012 Genzyme (part of French company Sanofi-Aventis) withdrew the product from market and ‘surrendered’ its license for use in B-CLL, then subsequently re-licensed the product for use in MS at a far higher price per dose.¹⁶⁹ In a letter to healthcare providers Genzyme stated that, “(t)his action is not being taken for any reasons related to product safety, efficacy or supply, but as part of the Company’s plan for bringing alemtuzumab forward as a treatment for a new indication.”¹⁷⁰ However, at the time of withdrawal there was speculation that the exercise was motivated by commercial reasons and that the price would increase.¹¹¹

vi. The Wellcome Foundation LTD is a pharmaceutical company and subsidiary of GlaxoSmithKlein, previously known as Burroughs Wellcome & Company

vii. Apart from Wellcome Foundation support for the centre that was manufacturing the experimental MABs for use in the trials. In order to produce the relatively large amounts of Campath antibodies that were needed for various clinical trials, the Therapeutic Antibody Centre (TAC) was established, first at Cambridge before moving to Oxford University. This was funded by multiple sources including the MRC and Cambridge University, with the Wellcome Foundation providing a minority of the funding.

When alemtuzumab was used off-label prior to being withdrawn from the market, the price in the UK was around £2,500 per MS treatment course.¹⁷¹ The price of alemtuzumab is now about £56,000 per treatment course – a 22-fold increase.¹⁷²

While the drug was off the market, clinicians could obtain alemtuzumab for patients with leukaemia via a patient access programme.¹⁷³ It is not known how many patients who had been using alemtuzumab to keep their disease in remission suffered from a worsening of their condition during the one and a half years that the drug was taken off the market.

This market manipulation was met with only light criticism from editorials in the *Lancet* and *BMJ* medical journals,^{174,175} and received limited attention in the press.¹⁷⁶ Sanofi Genzyme has reported alemtuzumab sales of more than €950 million (£789.3 million) since 2012.¹⁷⁷ The NHS spent £19 million on alemtuzumab in 2014/2015 and £61 million in 2015/2016.¹⁷⁸

Despite its very high price, NICE has recommended the drug on the basis that it comes under their maximum “willingness to pay” threshold of cost-effectiveness compared to current alternative treatments.¹⁷⁹

Income

BTG receives income on alemtuzumab through licensing royalties. A comparison of the incomes of BTG and Genzyme are shown in the graph below. Data from BTG and Genzyme (Sanofi) annual reports.^{180,181}

2.2.2 Adalimumab

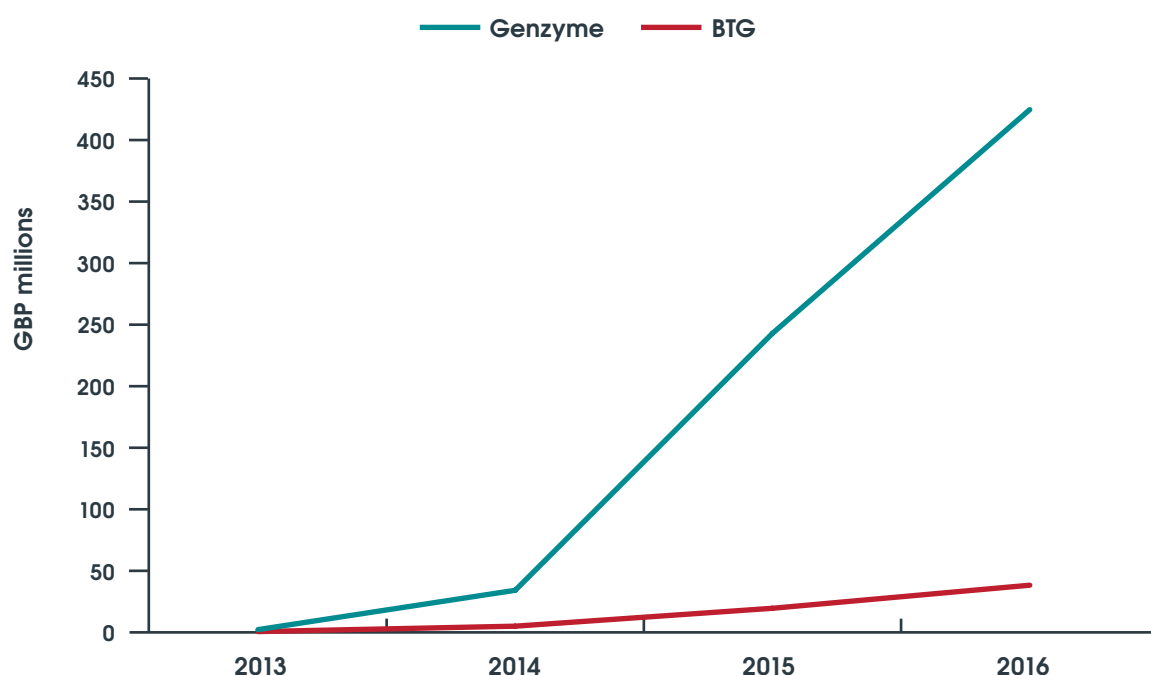
Adalimumab is an effective drug for treating a range of diseases including rheumatoid arthritis, psoriasis, and Crohn’s disease (see Appendix 5).

Role of UK government in Adalimumab R&D

The MRC LMB transferred exclusive rights to crucial parts of the MAB technologies to Cambridge Antibody Technology (CAT), a company set up by MRC LMB scientists (this type of company is called a ‘spin-off’).¹⁸² In 1993, a company called BASF Pharma Solutions commissioned CAT to develop a fully humanised MAB that would neutralise tumour necrosis factor (TNF, a molecule important in inflammation).¹⁸³

This resulted in adalimumab, which proved highly effective in treating rheumatoid arthritis. At the end of 2000, Abbott Laboratories bought the division of BASF Pharma Solutions that owned the rights to

Figure 9: Income from alemtuzumab for Genzyme and BTG per year (£millions)



adalimumab for \$6.9 billion (£5.13 billion). CAT has received between 2% and 5% of adalimumab sales as royalties.¹⁸⁴

Access to adalimumab

Adalimumab is the second highest-earning prescription medicine ever produced, with cumulative sales of \$95.6 billion (£71.6 billion) through 2016.¹⁸⁵ The UK price of adalimumab as indicated in the British National Formulary is about £900 per month.¹⁸⁶ Adalimumab represented the highest expenditure for a single medicine in the NHS in 2014/2015 and 2015/16, with a total spend of £371 million and £417 million respectively.¹⁸⁷ Expected EU patent expiry is 2018, and 2016 in the US.¹⁸⁸

One biosimilar of adalimumab has been approved in the US and EU, manufactured by US company Amgen. Two other biosimilars have been approved in India, and others are in development.¹⁸⁹

2.2.3 Infiximab

Infiximab is used to treat autoimmune diseases such as rheumatoid arthritis.

UK government funding of infiximab R&D

Infiximab was first developed at New York University.¹⁹⁰ At the time a particular set of MABs were being investigated for use in treating overwhelming bacterial infection (sepsis), and were regarded as unpromising by industry for use in rheumatoid arthritis.^{191,192} Despite scepticism, researchers working at the Kennedy Institute of Rheumatology (then part of Imperial College London) postulated potential efficacy of the agent in treating rheumatoid arthritis,¹⁹³ and undertook clinical trials to prove this, which were very successful. The funding for this early work, which included clinical trials at Charing Cross hospital, came predominantly from a UK charity (Arthritis Research Campaign) alongside a small industry grant.^{194,195} After this crucial initial proof of infiximab's effectiveness in treating rheumatoid arthritis, further work was undertaken by Centocor Biotech (now Janssen Biotech).¹⁹⁶

The Kennedy Institute owns two patents on the method of administering an anti-TNF antibody medicine (such as infiximab) together with what is termed a "disease modifying antirheumatic drug" (these are in

essence all the non-biologic treatments for rheumatoid arthritis, and are off-patent medicines^{viii}). This combination approach is a very common approach to treating the disease.¹⁹⁷ The Kennedy Institute has received "tens of millions of dollars in royalties for use of (this) patent" from Centocor Biotech, Abbott Laboratories, Amgen, and Wyeth (Pfizer).¹⁹⁸

Access to infiximab

There are about 370,000 people living with rheumatoid arthritis in the UK.¹⁹⁹

Infiximab is the fourth highest-selling prescription medicine ever produced, with cumulative sales of \$85.5 billion (£63.8 billion) up until 2016.²⁰⁰ In 2014/2015, infiximab represented the fourth highest expenditure on single medicine in the NHS, at £159 million. The following year the spend on infiximab rose to £178 million.²⁰¹

Following the expiry of the EU patent in 2015,²⁰² a biosimilar infiximab has become available in the UK. A recent audit by the Royal College of Physicians has confirmed that it is of equivalent efficacy to the originator medicine.²⁰³ The price of infiximab as indicated in the British National Formulary is about £600 per month when used for rheumatoid arthritis, or £377 per 100mg vial.²⁰⁴ The price of biosimilar infiximab has fallen modestly (by about 10%) compared to the originator price reported as £420 per 100mg vial in 2010.²⁰⁵

For further detail on the development and accessibility of the medicines based on monoclonal antibodies mentioned here, please see appendix 5.

2.3 How UK government R&D puts profits before patients

UK taxpayer-funded health R&D has led to some of the biggest advances in medicines in the past decades. By transferring the rights of such medical advances to multinational pharmaceutical companies, the UK government has enabled pharmaceutical companies to abuse their patent monopolies. As a result, the commercialisation of these medicines has put them out of reach of many patients in the UK and abroad. It has also financially benefitted multinational pharmaceutical companies whilst straining the NHS budget, which spent more

viii. Medicines which no longer have patent restrictions applied to them

Tuberculosis medicine

Tuberculosis is the leading cause of death among infectious diseases worldwide.²⁰⁶ Bedaquiline is used to treat multi-drug resistant tuberculosis, which is responsible for 5% of TB cases worldwide (480,000 cases annually), but 20% of TB deaths.

The bedaquiline molecule was not discovered through UK governmental funding. However, the UK government has contributed substantial funding towards Phase I, II, and III trials that are elucidating how bedaquiline can be used in the real world. Indeed most of the Phase III trials, which are generally the most expensive,²⁰⁷ either have been or are being undertaken by public research institutions. By making this contribution, the UK government has increased the number of patients eligible and therefore the overall use and market of bedaquiline. Many barriers to the widespread use of bedaquiline remain.

The drug company Janssen prices bedaquiline in three tiers, with a six-month treatment course priced at US\$900 (£672.75) for the lowest income bracket, US\$3,000 (£2,242.50) for upper-middle-income countries, and US\$30,000 (£22,425) for high-income countries.²⁰⁸ In contrast, MSF have stated that multi-drug resistant tuberculosis (MDR-TB) treatment should not cost more than US\$500 (£373.75) per patient,²⁰⁹ and research has shown that generic companies could profitably manufacture and sell bedaquiline for a price of less than US\$50 (£37.38) for a six-month course.²¹⁰ In 2015, Janssen began a programme donating 30,000 courses of bedaquiline treatment over four years through a collaboration with the United States Agency for International Development (USAID).²¹¹ Whilst the donation programme has been welcomed, it is not sustainable long-term. Despite the donation programme, there have been complaints about the small proportion of those needing the drug actually receiving it.²¹²

than £1 billion last year alone on medicines that received substantial UK public funding for R&D (appendix 2). Any royalties paid to UK institutions for the development of health technology are dwarfed by the costs to the NHS, not to mention patients and health services abroad.

Despite the lack of transparency around the total costs of developing medicines, it is clear from the case studies that the pharmaceutical industry enjoys huge profits from the medicines that UK taxpayers have made substantial contributions to research and develop. It is often assumed that private investment must be brought in to undertake clinical trials or that the expertise of the pharmaceutical industry is needed in order to bring a drug to market. However, considering the substantial involvement of public research funding, facilities, and academics to R&D, the high prices charged by industry are unjustified.

Even when the pharmaceutical industry does lead health R&D efforts, UK public funding can still play a

catalytic role in enabling these medicines to be used in the real world. As described in the boxes on TB and HIV medicines (above and opposite), UK taxpayers contributed substantial funding to expensive clinical trials that showed how the TB drug bedaquiline can be effectively used in tuberculosis treatment regimens, and established the efficacy of tenofovir and emtricitabine as pre-exposure prophylaxis (PrEP) to prevent HIV infections.

The UK government needs to drastically change the way R&D is funded to make sure new medical advances reach the patients who need them. Pharmaceutical companies are charging such high prices that the NHS is increasingly being forced to reject or ration new medicines developed in the UK. We should make sure that our public R&D funding leads to medicines that we can afford. There are examples of UK supported initiatives that are making positive steps towards addressing access issues from the start of the R&D process, and these are explored in the following chapter.



A Youth Stop AIDS campaign stunt outside UK Parliament as part of the It Ain't Over campaign, March 2017

HIV medicines

Treatment for HIV is known as antiretrovirals (ARV). These medicines help people with HIV live longer, healthier lives and substantially reduce the risk of HIV transmission.

Most of the academic drug discoveries in HIV were in US institutions.²¹³ UK taxpayers have been extensively involved in developing antiretroviral therapy through sponsoring or collaborating on 235 clinical trials (appendix 6). The UK MRC was crucially involved in developing the first lifesaving HIV treatment combinations (also known as regimens) that were recognised as safe and encouraged for widespread use²¹⁴ and the UK particularly invested in Phase I clinical trials for raltegravir, which is a lifesaving treatment for HIV positive patients who are resistant to or unable to take both first and second-line ARVs. The lowest possible price for third-line regimens that use raltegravir is £1,425 per person per year, which is 18 times the price of a first-line regimen. Many countries, especially middle-income countries, pay much more, making affordability a critical issue for HIV patients.

PrEP prevents HIV negative people from becoming infected. UK taxpayers have also had extensive involvement in developing the evidence base for PrEP. By demonstrating the effectiveness of PrEP, UK-funded research has substantially expanded the market (i.e. to non-infected people) and has prevented countless new HIV infections. Access to PrEP in the UK has been a rollercoaster in the past two years, with the cost of PrEP being central to the debate over whether NHS England or local authorities should provide it. Eventually, after a High Court ruling and unsuccessful appeal, NHS England announced it will provide PrEP to 10,000 people in a trial lasting three years.²¹⁵

3. Examples of UK contributions to new R&D financing models

The UK is leading or involved in a number of different R&D initiatives that are taking positive steps to secure affordable and accessible medicines. The DNDi is one example. It demonstrates the positive impact that an R&D model that prioritises accessibility and affordability can have on public health. Another example is the Longitude Prize, which uses a prize fund model and sets affordability conditions. However, even with these advances substantially more has to be done to ensure that medicines developed from publicly funded R&D are affordable and accessible to people in the UK and abroad.

Drugs for Neglected Diseases initiative

The DNDi is one of the furthest-developed examples of de-linked R&D. It was established in 2003 as a non-profit R&D organisation to develop treatments for neglected diseases.²¹⁶

DFID is at present DNDi's single largest individual funder across both governmental and private donors, having granted or committed £118 million.²¹⁷

Since its creation, DNDi has brought to market seven new treatments: two for malaria; two for visceral leishmaniasis; and one each for paediatric HIV/TB coinfection, Chagas disease, and sleeping sickness.²¹⁸ In calculations submitted upon request from DFID evaluators, DNDi estimated its impact in terms of lives saved at 980,000 over 2009–2013 (though DNDi noted significant limitations in its ability to accurately estimate this number).²¹⁹

DNDi uses "Target Product Profiles" to build in and consider accessibility, including affordability, from the very start of the R&D process. DNDi has delivered on its aims of keeping the treatments it develops affordable:

- The malaria treatment developed by a partnership between DNDi and the French pharmaceutical company Sanofi – ASAQ (artesunate + amodiaquine) – was launched at a price of US\$1 (£0.75) per adult treatment course and US\$0.50 (£0.37) per paediatric treatment course.²²⁰
- The treatment developed for stage two human African trypanosomiasis (sleeping sickness) is 50% cheaper than the previous mainstay therapy.²²¹
- In visceral leishmaniasis, clinical trials undertaken by DNDi provided the evidence for adopting a new treatment regimen, which reduced treatment time from 30 to 17 days and drug costs from US\$56 (£41.91) to US\$44 (£32.93).²²²

DNDi is a PDP and is an example of a de-linked model of drug development in which equitable and affordable access to the end product is built in from the start. The DNDi model could be applied to other disease areas outside of neglected diseases,²²³ but doesn't solve all the problems of the health R&D system. DNDi recognises that its model is not a comprehensive solution to all of the problems in the current R&D system. Rather, *"to fully address the scale of public health needs, public leadership is needed to redefine the 'rules of the game'"*.²²⁴ Fully de-linked pharmaceutical R&D would require an 'open science' approach in which financial incentives such as milestone prizes are used to encourage innovation, but where the products of innovation are fully public and there are no barriers such as patent monopolies.

Longitude Prize

The Longitude Prize, launched in 2014, is a jointly funded initiative between Innovate UK and the non-profit Nesta Foundation.²²⁵ It specifically focuses on developing a diagnostic test for bacterial infections, suitable for use anywhere in the world.²²⁶

The £10 million prize has rules and conditions which all applicants must adhere to in order to be eligible to win. One of the major criteria for winning the award is affordability, which is considered as satisfying the following three criteria:

- “Reflects value for money for the intended users (patient, doctor, health service).”
- “Is cheaper than any competing diagnostic test or method of similar performance characteristics.”
- “Where feasible and realistic, it should aim to be cheaper than the treatment cost that the test might save (e.g. the price of a course of antibiotics).”²²⁷

The test must be affordable in ‘global markets’, including low income settings. Furthermore, the terms and conditions of the prize give Nesta and Innovate UK the right to “*a non-exclusive royalty-free, worldwide, perpetual, irrevocable, sub-licensable right to use, develop and exploit or to appoint a third party to use, develop and exploit*” IP related to the project, in cases where the IP has not been ‘exploited’ or ‘commercialised’ satisfactorily.²²⁸ This is a useful safeguard to protect the public investment should the prize winner decide not to make the test sufficiently available.

Taken together these conditions send an important market signal to developers that they should factor in affordable access from the start. However, the Longitude Prize does not set out to fully finance the R&D costs involved with the development of these diagnostics, only to act as an additional incentive. Nor do the conditions explicitly prevent the winner from recouping R&D investments through sales. Nevertheless, the Longitude Prize remains a rare example of a prize fund in operation where affordability has been considered up front. Its outcomes will be watched closely around the world.

Recommendations

The government should consider how new mechanisms can be put in place to ensure maximum public health returns on public investments in R&D. This report illustrates that even when the UK government has funded a large part of the R&D underlying an innovative and effective medicine, there is no guarantee that this medicine will be accessible to patients in the UK or worldwide. Instead, the commercialisation of these discoveries has generated huge private profits from public funds. As a result, the UK government is effectively paying twice for medicines; firstly through investing in R&D and secondly by paying monopoly prices for medicines far above the cost of production.

Publicly funded medical R&D should first and foremost serve patients. The following five thematic recommendations will help the UK government to safeguard access to publicly funded medicines. These recommendations are specifically directly to the UK government but they could also apply to other funders of R&D such as charities and philanthropic funders who likewise benefit from public investment through the use of state facilities and tax breaks.

1. Attach public interest conditions

As a first step to safeguard public return on public R&D investments, donors should build in robust public interest conditions for every point of engagement in the R&D process. To do so, the UK government should:

- **Demand, monitor and enforce public interest conditions in all contracts and agreements** conducted with public and private sector stakeholders for health research. These should be based on the principles of affordability, accessibility, availability and equity.

Public interest conditions should, at a minimum, cover the following:

- a) Development of an access strategy, which considers the potential barriers to access and how to mitigate and/or overcome these. For example, a target and ceiling price that is affordable to patients in all endemic countries should be set.
- b) Patenting should be avoided unless necessary to ensure that a technology will be developed or produced or to avoid others patenting the technology. The ideal case is that the end product will be available as a public good and royalty-free. Any IP derived from publicly funded research should be managed proactively to safeguard accessibility and affordability.
- c) Open access policies that give third parties rights to access and use the research or discoveries made in a public research institution.
- d) Existing regulations on clinical trials transparency should be followed and all clinical study reports should be made available online.²²⁹
- e) Transparent reporting of R&D costs in all stages of development.

- f) Abuse or failure to carry out, on reasonable terms, any of the access provisions should lead to a suspension or cancellation of funding and/or licence, as applicable, or use of a compulsory license.

Public interest conditions should be carried through so that all subsequent R&D that uses publicly funded research are subject to the same public interest conditions. Where public funds seek to finance only late stage development (e.g. clinical trials), funding criteria should aim to achieve these public interest conditions, prioritising access in low- and middle-income countries,^{ix} with very few exceptions.

2. Introduce transparency

Knowledge and evidence of the true costs of R&D, including the involvement of public funds, would allow informed national and international discussions on what constitutes a fair price and how new models of R&D financing can be designed. Knowledge of R&D costs and of existing price agreements would also empower procuring entities, such as NHS England, in pricing negotiations. The UK government should:

- **Enforce standardised financial reporting measures for each medicine procured by the NHS**, including: final price paid; R&D costs; manufacturing costs;^x market costs; and transparent declarations of public contribution to R&D costs (through grant funding or tax breaks).
- **Ensure that all licensing agreements are added to a publicly accessible database**, which includes information on patent statuses.

The UK should end confidentiality clauses in price agreements that obscure the final price from the public.

3. Enable effective governance and accountability

To ensure that there is progress on ensuring a public return on R&D investments, mechanisms for citizen-led accountability and addressing commercial conflicts of interests need to be put in place. The UK government should:

- **Develop guidelines for departments that fund R&D on prioritising public health over commercial interests**. These guidelines should include **civil society representation in key decision-making bodies**, such as the new UK Research and Innovation agency and introducing regulation to avoid commercial conflicts of interest across all funding bodies.
- **Develop a clear monitoring and accountability framework for citizens to hold the government to account on the use of public interest conditions and demands for transparency**.

4. Support de-linked R&D models

Medicines are expensive because of monopolies. Where medicines are supplied in a competitive market, the price in general falls dramatically. The granting of monopolies is part of a societal contract whereby the public accepts to pay artificially high prices for products on the understanding that in so doing they are paying for the cost of R&D as well as the cost of producing the product itself. This is a system of linkage. It links the incentive to undertake R&D to the promise of high prices that can be charged in the absence of competition. However, this report has shown that the current patent system that grants monopolies is not working for public health. De-linked R&D models do not seek to pay for R&D through sales revenue. Rather they pay for R&D upfront through grants and/or prizes and allow the competitive production of resulting products.

ix Middle-income countries: despite the name given to this group by the World Bank, mostly have average incomes less than a quarter of the average incomes in high-income countries in Western Europe and, North America, Australia, and Japan. On top of this, significant income inequalities in middle-income countries distort the average income figures. These countries are home to 73% of the world's poor and face the dual challenge of disappearing bilateral and multilateral donor support and having to meet WTO requirements that limit generic competition.

x. In this context, production costs are often referred to as 'cost of goods sold'

De-linking allows for ownership and control of health technologies to be kept in public hands, enabling decision-makers to prioritise public health over corporate profit. To support these models, the UK government should:

- **Identify and implement de-linkage approaches to R&D**, such as the use of grants and prizes that fully cover the cost of R&D and do not allow for high product prices as a mechanism to finance drug development.

5. Drive international progress on R&D

The recommendations above would represent significant steps in ensuring equitable access to the benefits of publicly funded scientific progress. However, there needs to be global political leadership and coordination on R&D; leadership which is not undermined by IP commitments in trade negotiations.

The UK government should:

- **Actively encourage the WHO to support the establishment of a global biomedical R&D convention**, to include a **Code of Principles for Biomedical R&D**, thereby building in accessibility throughout the R&D process.
- **Encourage and enable generic and biosimilar market entry internationally** by: enforcing strict requirements for secondary or supplementary patent approval; reaffirming the right of WTO members to issue compulsory licenses under TRIPS flexibilities; and avoiding 'TRIPS-plus' measures in post-Brexit trade agreements.

Compulsory licensing is when a government allows someone else to produce a patented product or process without the consent of the patent owner.²³⁰

Appendices

Appendix 1: Methodology

This research was conducted using secondary data gathered, where possible, from publicly available sources. Where sources were incomplete we contacted public officials personally and used freedom of information requests.

Quantitative data were extracted from the DFID Development Tracker database, the Gateway 2 Research database, the G-FINDER survey, and annual departmental accounting reports. Information regarding patents was taken from the US Food and Drug Administration Orange Book. Figures on the epidemiology of conditions and the effectiveness of treatments were collected from the scientific literature.

For these case studies, public contributions were identified by tracing the funders for individual steps of the R&D process, as well as by identifying the centres at which research was undertaken and by referring to other research interviewing those involved in the development process.

Qualitative sources also included the gov.uk publications database, the UK National Archives online, websites of (and internal documentation from) public and private organisations, interviews and electronic correspondence with relevant personnel.

Following this research, we consulted government, civil society, patient groups and stakeholders working on access to medicines and/or R&D through one-to-one discussions, a discussion workshop in London and individual reviews.

Appendix 2: Medicines with the highest NHS England expenditures in 2015/16

Table 2: Medicines with the highest NHS England expenditures in 2015/16

Ranking by cost to NHS England	Medicine	Expenditure (in £000)
1	Adalimumab	£416,647.8
5	Infliximab	£178,179.2
6	Rituximab	£155,893.3
7	Trastuzumab	£152,037.6
15	Abiraterone	£74,148.7
	Alemtuzumab	£61,000
	Total	£1,037,906,600

Costs are from <http://www.content.digital.nhs.uk/catalogue/PUB22302/hosp-pres-eng-201516-report.pdf> except Alemtuzumab, which is from <http://www.content.digital.nhs.uk/catalogue/PUB22302>.

Appendix 3: Accessibility and affordability conditions applied to UK grants

The Department of Health

Conditions relating to IP generated from health related R&D within the NHS are set out in the policy, *The NHS as an Innovative Organisation: A Framework and Guidance on the Management of Intellectual Property in the NHS*, enacted by the DoH in September 2002. This guidance “commits the NHS to ensuring that new technologies are identified and developed in the interests of NHS patients and society as a whole”. The guide also explains the powers of the Secretary of State for Health and NHS trusts to exploit IP generated through the NHS. The guidelines state: “The statutory purpose of exploiting IP is to make more income available for the health service, and this must be the case when an invention is exploited successfully.”²³¹

These terms include setting limits on the price charged in developing countries, and restricting the area of use (or ‘territory’) of the license.

The National Institute for Health Research uses standard contracts for all research grants, which are provided by the DoH.²³² These contracts are between the Secretary of State for Health and the organisation receiving the funding (e.g. a university, NHS Trust, or commercial company). The template commercial contract for the Invention 4 Innovation (i4i) programme contains the following clauses, 16.2.4 and 16.2.5:

16.2.4 “The Authority is mindful of the importance of the development and distribution of new health-related technologies for less developed countries. The Authority’s policy on patenting is to prosecute patent applications in less developed countries only as necessary (for example, to provide development and marketing leverage for new products, or to exert leverage over global licensees)”.

16.2.5 “in exercising the rights in Condition 16.2 the Contractor takes due consideration of the Authority’s attitude to the inappropriate use of patents which it considers detrimental to scientific endeavour or to advances in healthcare.

According to clause 16.4, this can be monitored by the ‘Authority’ (i.e. the Secretary of State) who has the right to “monitor the operation and effectiveness of the Contractor’s procedures for the management of Intellectual Property in such ways as the Authority

considers reasonably necessary to ensure that any Foreground IP generated is disseminated and/or exploited for the public benefit”. Section 16.4 also provides the contractor with an obligation to simultaneously “promote the dissemination of results to maximise the benefits to the NHS, patients and the public”.

This is further emphasised in clause 16.6 which states that, in the case of a ‘Contractor’ seeking to commercialise ‘Foreground IP’ (IP developed during the research) that:

16.6 “the Contractor (and/or Collaborator) must take due consideration of the Authority’s attitude to access to essential health related technologies including medicines in the developing world. The Authority is mindful of the importance of the development and distribution of new health-related technologies for less developed countries. The Authority’s policy on licensing is to grant licences with provisions that seek to increase the availability of medicines at affordable prices to less developed countries (examples include dividing up territories between a commercial and a not-for profit partner, providing for developing world territories to revert to the institution if not exploited by the commercial partner or requirements for products to be supplied to the developing world at or close to cost)”.²³³

Department for International Development

DFID’s approach to affordable access is as follows:

“All other aspects of pricing and accessibility are based on individual funding competitions and subsequent negotiations with organisations that receive funding. When DFID funding competitions are launched, the criteria that will be used to assess bids are published. Many competitions go for a two-stage process. The criteria for the first stage are published, and details for the second stage are shared with the individual organisations that are asked to prepare a full bid. DFID uses standard agreements when organisations are awarded funding, and these agreements are published on the DFID website. There are also systems and procedures within DFID to ensure that accessibility (and pricing if relevant) is considered during programme assessment processes”.²³⁴

Appendix 4: Abiraterone

Discovery

In the early 1990s, researchers working at the ICR in London noted that high doses of the antifungal agent ketoconazole suppressed androgen synthesis and had been used to treat prostate cancer, but had numerous undesirable effects which limited the drug’s clinical usefulness. The team synthesised and tested several compounds, different from ketoconazole’s molecular structure but with a similar mechanism of action, identifying a compound that held promise for further development: this became abiraterone. This work was financed by the Cancer Research Campaign (later to become part of Cancer Research UK) and the MRC, with additional support from the British Technology Group and Cancer Research Campaign Technology.^{235,236}

Background on the Institute of Cancer Research

The Institute of Cancer Research is a higher education institution and constituent college of the University of London, and works in close partnership with the Royal Marsden NHS Foundation Trust.²³⁷ A total of 45% of the ICR’s funding comes from individual donations or endowments and research grants from the charities Cancer Research UK and Breast Cancer Now, as well as the Wellcome Trust and the UK MRC. A further 40% of the ICR’s funding comes from royalties and sales of rights to future royalties. Of the remainder, 14% comes from government funding for its work as a higher education institution and from tuition fees.²³⁸

Clinical trials

Phase I, II, and III trials were led by the ICR, with multiple public funders for the clinical trials, alongside industry funding (see table 3, below).²³⁹ Abiraterone received market authorisation in the EU and the US in 2011.^{240,241}

Patents

Abiraterone is under patent protection until March 2018 in Australia and Europe. Due to a patent protecting the use of abiraterone together with a steroid, which is the method of use for which it is licensed, generic competition for abiraterone may effectively be blocked until 2027 in Australia, Europe (including the UK), and the US.²⁴⁶

Access in the UK

Metastatic prostate cancer is generally treated with hormonal therapies (androgen deprivation therapy), followed by the addition of chemotherapy if and when the disease progresses.²⁴⁷

Abiraterone was initially assessed by NICE for use in patients with metastatic prostate cancer that were resistant to hormone therapies, and for use after chemotherapy had failed. The initial draft assessment by NICE found that abiraterone was not cost-effective.²⁴⁸ After significant pressure from various groups, an offer of a discount from Janssen, and applying special separate criteria used for ‘end of life’ treatment which allow higher costs than elsewhere, NICE recommended abiraterone for use as a second-line after failure of chemotherapy in May 2012.²⁴⁹

Table 3: Funding for clinical trials using abiraterone

Stage	Funding
Phase I	Cougar Biotechnology, Cancer Research UK, the UK MRC, the Prostate Cancer Research Foundation, the Royal Marsden Hospital Research Fund, an Experimental Cancer Medicine Centre grant, and the Bob Champion Cancer Trust. ²⁴²
Phase I/II	Cougar Biotechnology, Cancer Research UK, the DoH, and others. ²⁴³
Phase III	“(s)upported by Ortho Biotech Oncology Research and Development (a unit of Cougar Biotechnology) and grants from the (UK MRC), Experimental Cancer Medical Centre (a partnership between NHS trusts and universities), National Institute for Health Research Biomedical Research Centre, and Prostate Cancer Foundation (funding for one of the study authors)”, and took place in numerous countries. ^{244,245}

Six months later, in 2013, a trial showed that abiraterone was also effective in patients who were resistant to hormone therapies, but before chemotherapy.²⁵⁰ For these patients, however, NICE determined in August 2014 that the drug was not cost-effective.²⁵¹ This decision was described as “a kick in the teeth” by the charity Prostate Cancer UK.²⁵² In March 2016, NICE reversed this decision after further negotiations on discounts with Janssen, which involved lowering the list price from £2,930 for a month of treatment (120 tablets) to £2,300, as well as providing the treatment free after the first 10 months of treatment.²⁵³

A recent Phase II/III trial showed significant benefit when starting abiraterone at the same time as hormone therapy, instead of starting only when the cancer had become hormone-resistant. In this trial, starting abiraterone at the same time conferred a 37% survival benefit. This trial was sponsored mainly by the UK MRC, as well as Cancer Research UK, Astellas Pharma, Clovis Oncology, Janssen, Novartis, Pfizer, and Sanofi-Aventis, and was run predominantly in NHS hospitals.^{254,255} A third NICE assessment is now expected.

Access globally

As part of the 2015 WHO *Essential Medicines List* review cycle, the Union for International Cancer Control undertook a review, in 2014, of all cancer medicines to identify promising candidates for addition to the list. The UICC reviewed (among others) two new, promising, oral treatments for metastatic prostate cancer – enzalutamide and abiraterone – concluding that “*these agents are still in development and currently have shown a relatively small magnitude of benefit and their current costs limit the use of these agents in resource-limited settings*”.²⁵⁶ Three years after this review, data from a trial has been published that demonstrate a 37% improvement in overall survival when abiraterone is added to standard (androgen-deprivation) therapy in metastatic prostate cancer. It seems likely that these new findings will put abiraterone in good standing for inclusion in the next (2019) WHO *Essential Medicines List*.

While studies have shown disproportionately high rates of prostate cancer mortality in black African men, access to chemotherapy is often limited by costs.^{257,258} While prostate cancer causes 7.8 deaths per 100,000 people per year worldwide, in sub-Saharan Africa

and the Caribbean the mortality rate is around 2.5 to 3 times higher.²⁵⁹ Abiraterone appears not to be publicly procured in South Africa, and in the private market costs only slightly less than in the UK.²⁶⁰

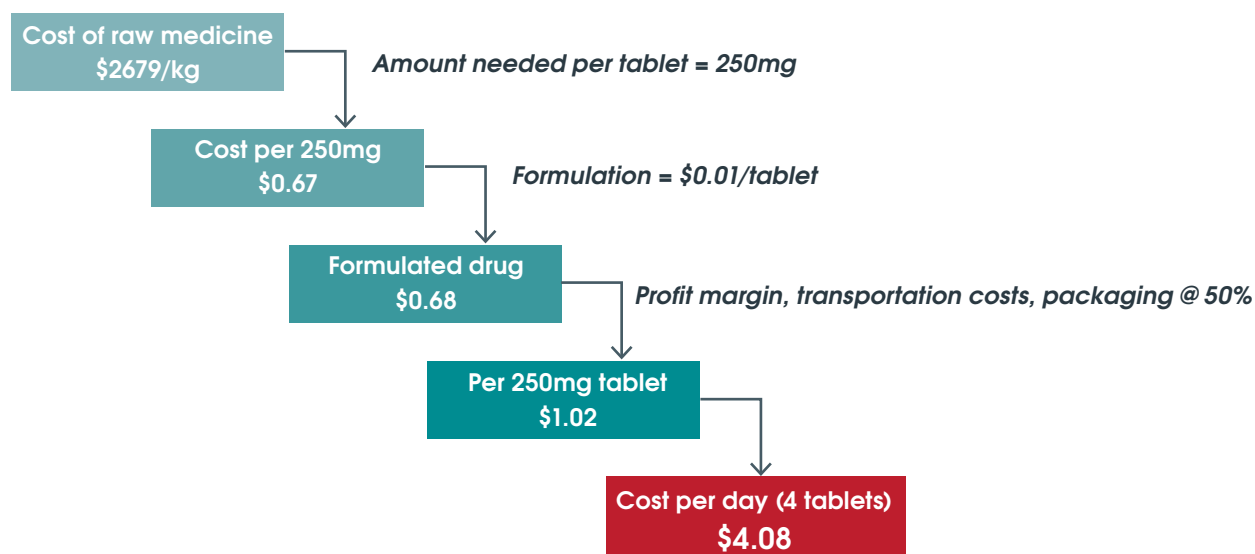
Resource-stratified guidelines drafted at the Asian Oncology Summit in 2013 categorised abiraterone as a medicine reserved for countries with a “maximum level of healthcare resources”, and noted that in some parts of Asia, ketoconazole is used instead due to prohibitive cost.²⁶¹ Ketoconazole (mentioned earlier in this case study) has a similar mechanism of action, but has potentially dangerous side-effects and is not recommended for use in prostate cancer in European guidelines.²⁶²

Cost of production

We used prices of raw abiraterone (i.e. the active pharmaceutical ingredient) exported from India to calculate the potential generic of abiraterone. The average price of the raw drug substance was US\$2,679 (£2,019), meaning the cost of the raw drug in one 250 mg tablet is US\$0.67 (£0.51). Using methodology that has been previously published^{263,264}, we estimate that a generic version could be profitably manufactured for US\$1.02 (£0.77) per tablet, or US\$4.08 (£3.08) or a standard daily dose of four tablets.

Data on shipments of active pharmaceutical ingredient (API) exported from India was extracted from customs data available in the online database www.infodriveindia.com. Data was cleaned to censure non-API exports (e.g. exports of finished pharmaceutical product). Linear regression was used to model the trend in prices, weighted by the size of each individual export. Calculations were done in Stata/MP 14.0 for Mac. The resultant model was used to predict an average API price per kilogram for November 1, 2016, which is when the dataset ends due to changes in customs law in India. This price, US\$2679/kg, was multiplied by the per-tablet dosage (250mg) of abiraterone. We added an assumed cost of US\$0.01 per tablet to account for formulation costs, based on confidential contact with a large Indian manufacturer. We added a conservative (large) assumed markup for overheads and profit of 50% to give an estimated per-tablet sustainable generic price. Lastly, we multiplied this by 4 to give an estimated daily cost, as the standard daily dosage for abiraterone is 1000mg. This resulted in an estimated daily cost of US\$4.08.

Figure 9: Estimation of generic price of abiraterone based on cost of production



Appendix 5: Monoclonal antibodies

Discovery of monoclonal antibodies

Antibodies are molecules produced by cells in the human immune system, which attach to entities in the body that the immune system identifies as 'foreign', such as bacteria. Important characteristics of antibodies are that any one strain (termed a 'clone') can only attach to a unique target, and different strains can be produced to 'recognise' a wide range of targets.

In biopharmaceuticals, these characteristics can be used to attach to and (usually) inactivate entities that are central to disease processes, thus treating the disease. Antibodies that are produced artificially to bind (attach to) a specific target are termed monoclonal antibodies or 'MABs'.

Different MABs have been developed to treat a wide range of diseases: predominantly for cancers and autoimmune diseases, but increasingly in other areas too.

Georges Köhler and César Milstein, researchers working in the MRC LMB in Cambridge, first developed a technique for the large-scale production of customised monoclonal antibodies. In 1984, they were awarded the Nobel Prize for this work.⁹⁰ In that year, Milstein was quoted as saying "*I think patents are financial swindles that prevent the public from access to information*".^{265,266,xi} The LMB is funded primarily by the UK MRC.²⁶⁷

xi. Geoff Hale and Herman Waldmann later wrote that "(the decision not to patent Köhler and Milstein's discoveries) probably did more than anything else to facilitate the widespread use of monoclonal antibodies". Geoff Hale and Herman Waldmann. From Laboratory to Clinic: The Story of CAMPATH-1. In *Diagnostic and Therapeutic Antibodies*, ed. AJT George and CE Urch (Springer Science & Business Media, 2000).

The first MABs were developed in mouse cells, and their efficacy was limited by the fact that when used in humans they would be inactivated by the human immune system (which recognised the substance as 'mouse'), and could cause dangerous side effects and allergic reactions. The next scientific step was to make MABs more similar to the antibodies produced naturally by the human immune system.

Researchers working under the leadership of Greg Winter at the MRC LMB subsequently developed a technique called 'CDR grafting', which enabled the production of antibodies that were highly similar to human antibodies ('humanised'), and then a technique called 'phage display', which enabled the production of fully human antibodies.²⁶⁸ In both cases, the antibodies could be made to attach to a target selected by a researcher.

The LMB's patents on these techniques have since been licensed to more than sixty companies.²⁶⁹

Multiple blockbuster medicines have been developed using this technology, relying on the MRC's intellectual property. An estimated 65% of therapeutic antibodies use the technologies developed at the LMB by Greg Winter,²⁷⁰ including adalimumab (trade name Humira), trastuzumab (Herceptin), bevacizumab (Avastin), infliximab (Remicade).^{271,272} Other examples are given in table 4, below; this list is unlikely to be exhaustive, as the MRC and spin-off companies maintain complex networks of licenses to various companies for the use of the technology.²⁷³ Both chimeric and humanised antibodies were developed at the MRC LMB.²⁷⁴ Another scientist at the LMB, Michael Neuberger, developed an alternative method, which has also been used in the development of many MABs.²⁷⁵

Table 4: Medicines that use the UK MRC's monoclonal antibody technology

Medicine	Therapeutic use and notes	List price in the UK
Adalimumab	Numerous autoimmune conditions, see later in text	£900 per month
Alemtuzumab	Multiple sclerosis	£56,000 per treatment course (two treatment cycles 1 year apart)
Infliximab	Rheumatoid arthritis Crohn's disease	About £600 per month when used for rheumatoid
Raxibacumab	Anthrax <i>"Stockpiled by US government for treatment of anthrax infections"</i>	No price available
Tocilizumab	Rheumatoid arthritis, juvenile idiopathic arthritis	£700 per month
Belimumab	Lupus (systemic lupus erythematosus) <i>"First new treatment of systemic lupus erythematosus (SLE) for fifty years"</i>	£2,500 per month
Certolizumab pegol	Crohn's disease	£1,000 per month
Ranibizumab	Wet age-related macular degeneration (a leading cause of blindness in the elderly)	£2,000 per year*
Eculizumab	Paroxysmal nocturnal haemoglobinuria	£6,300 per week
Natalizumab	Multiple sclerosis	£1,100 per month
Pembrolizumab	Melanoma, lung cancer	£4,000 every three weeks

List not exhaustive. Examples and notes in quotation marks compiled from the Gateway to Research database and other sources.^{278,279,280,281} List prices are compiled from the online British National Formulary,²⁸² and are approximate as exact cost will vary according to patient-specific factors affecting dosage regimen used. Perfect vial sharing assumed.

Since the development of MABs and MAB humanisation in Cambridge, the market has grown dramatically. More than 40 MABs are now available in Europe and the US,²⁷⁶ and many of the world's top-selling medicines have been MABs (see below). In 2015 it was reported that the MRC has earned nearly £600 million in royalties from medicines developed using this technology.²⁷⁷ In addition to MRC-developed technologies being central to many high-impact medicines, the involvement of public research extended far beyond this in a number of examples (described below) in which the University of Cambridge, its researchers and its spin-offs led the development of these medicines through clinical trials to market approval.

Global access to MABs

In India and Peru, biosimilar rituximab was launched at 50% of the originator price.²⁸³ As multiple biosimilar manufacturers enter markets, even greater price reductions are expected.

Recognising the potential impact of affordable biosimilars for MABs, in May this year the WHO announced that it would be piloting the inclusion of biosimilars in its Prequalification Programme, through which hundreds of low-cost generic medicines for HIV have gained quality approval and thus become eligible for international procurement. The first two MABs for which the WHO is inviting submissions for prequalification are trastuzumab and rituximab (both on the *Essential Medicines List*).^{284,285} In the associated press release, the previous WHO Assistant Director General for Health Systems and Innovation, Dr Marie-Paule Kieny, noted *"Innovator biotherapeutic products are often too expensive for many countries, so biosimilars are a good opportunity to expand access and support countries to regulate and use these medicines,"* and Dr Suzanne Hill, WHO's Director of Essential Medicines and Health Products, noted *"Biosimilars could be game-changers for access to medicines for certain complex conditions"*.²⁸⁶

ALEMTUZUMAB

Discovery and early development

Herman Waldmann, an immunologist working at Cambridge University, became interested in MABs as a potential treatment for a syndrome termed 'graft-versus-host disease', a major complication of organ transplants. With MRC funding, he and his team developed rat antibodies specific to a type of cell in humans that was responsible for GVHD. They termed these antibodies 'Campath', short for Cambridge Pathology.²⁸⁷ Aside from the potential use in bone marrow transplants, Campath MABs were subsequently investigated as a potential therapy in leukaemias, lymphomas, numerous rare autoimmune diseases, rheumatoid arthritis, and eventually, multiple sclerosis.²⁸⁸

The discovery, lead optimisation, Phase I clinical testing and first years of manufacture of Campath were conducted at Cambridge.²⁸⁹ The discovery was eventually licensed to a subsidiary of the Wellcome Foundation. With help from Greg Winter's team at MRC LMB, a humanised (and consequently safer) version of the drug was created – Campath-1H, now known as alemtuzumab. Wellcome abandoned the drug after investing about £50 million and years of trials, due mainly to the finding that it suppressed certain types of immune cells beyond what was hoped for.²⁹⁰

Access to alemtuzumab

While work was ongoing to investigate alemtuzumab's role in the treatment of MS, alemtuzumab was approved in 2001 for use in B-CLL.²⁹¹ Before alemtuzumab was approved for use in MS (in 2013 in the EU and 2014 in the US) it was already being widely used off-label for treatment of MS.²⁹² Alemtuzumab received marketing approval from the European Commission on 17 September 2013, and was recommended by NICE for treatment of MS on 4 April 2014.

In 2014, the University of Cambridge reported that it had received £18.6 million in royalties for alemtuzumab.²⁹³

A Chinese manufacturer has entered into an agreement with a US-based company to develop biosimilars for alemtuzumab, among other MABs.²⁹⁴

ADALIMUMAB

Development

Adalimumab was first approved by the FDA in 2002 for use in rheumatoid arthritis,²⁹⁵ a debilitating condition that causes pain, stiffness, and destruction of the joints. Adalimumab's approved indications have since expanded to include:

- Psoriatic arthritis (2005) – a joint condition associated with psoriasis, a condition causing scaly skin lesions.
- Ankylosing spondylitis (2006) – a joint condition mainly affecting the lower back.
- Crohn's disease (2007) – a potentially fatal inflammatory gastrointestinal disease often requiring repeat surgeries and hospitalisations.
- Psoriasis (2008).
- Juvenile idiopathic arthritis – a joint condition affecting children.
- Ulcerative colitis (2012) – a condition with similarities to Crohn's, but affecting lower parts of the bowel.²⁹⁶

Table 5:

UK prevalence of disease for which adalimumab has been approved as a treatment

Disease	UK prevalence
Psoriasis	929,000 ²⁹⁷
Psoriatic arthritis	130,000*
Ankylosing spondylitis	492,000**
Crohn's disease	7,000**
Juvenile idiopathic arthritis	10,000 ²⁹⁸
Ulcerative colitis	146,000 ²⁹⁹

* Estimated by multiplying 2015 prevalence as reported in the Global Burden of Disease study psoriasis prevalence by psoriatic arthritis prevalence reported by Helliwell.³⁰⁰

**Estimated by multiplying UK population by 0.75% prevalence estimate from Hamilton et al (ankylosing spondylitis)³⁰¹ and 10.6 per 100,000 estimate from Molodecky et al (Crohn's)³⁰²

Appendix 6: HIV medicines (antiretrovirals)

Table 6: Number of clinical trials with UK PSRI collaborators, by medicine and trial phase

Medicine	Early Phase I	Phase I	Phase I/II	Phase II	Phase II/III	Phase III	Phase IV	Not specified	All phases
Tenofovir disoproxil	1	6			1	4	9	5	26
Ritonavir		7		2	1	2	13		25
Efavirenz	1	5		2	2	4	6	3	23
Emtricitabine	1	6				4	8	3	22
Raltegravir		10		2		3	2		17
Darunavir		6		1		1	6		14
Lamivudine	1	2			2		5	2	12
Lopinavir		3		1	1	2	5		12
Maraviroc		3					6		9
Nevirapine		1		1			6	1	9
Dolutegravir		3			1		4		8
Ribavirin		3		1		1	2	1	8
Atazanavir		3				1	3		7
Rilpivirine		3	1			1	2		7
Abacavir		1					4		5
Cobicistat		4					1		5
Zidovudine		2			1		1	1	5
Etravirine		1				1	1		3
Elvitegravir		1					1		2
Saquinavir							1		1
Stavudine							1		1
Total	4	70	1	12	10	28	91	19	235

Most trials were Phase IV (post-market authorisation trials), with the second largest number of trials in Phase I (initial safety or pharmacokinetics trials).

More recently UK public sector research institutions have also had extensive involvement in developing the evidence base for PrEP:

- The PARTNER study was funded by National Institute for Health Research (NIHR)^{xii}.
- The PROUD study was funded by the MRC Clinical Trials Unit, Public Health England, and the NIHR Clinical Research Network. Medicines used in the trial were provided free by Gilead Sciences.³⁰³

xii. The study coordinating centre also received support from the Danish National Research Foundation.

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This report is endorsed by the following organisations:

