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Promoting population health through pharmaceutical policy

The role of the UK Voluntary Scheme

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Summary

Since 2018, the National Health Service (NHS) spending on branded medicines has been increasing annually by over 5 per cent, excluding expenditure on COVID-19 vaccines and treatments. In the fiscal year 2021-22, the total cost of prescription medicines to the NHS in England, after accounting for confidential discounts and rebates, reached £17.2 billion. A significant portion of this growth can be attributed to increased expenditure on hospital-prescribed medicines. From 2018 to 2022, NHS spending on hospital-prescribed medicines, net of confidential discounts, increased by 35 per cent from £6.7 billion to £9.1 billion.

The top-5 therapeutic areas, categorised by the British National Formulary (BNF), drove the highest growth in hospital spending during the 2018-2022 period, surpassing £2 billion. Notably, the malignant disease and immunosuppression category, which includes cancer drugs, accounted for £904 million of the increase since 2018 representing a 43 per cent change, whereas the respiratory system category accounted for £587 million representing a 279 per cent change.

Overall, a small number of products played a significant role in the hospital setting's spending growth between 2018 and 2022. Specifically, within the malignant disease and immunosuppression category, the top three products in terms of spending growth accounted for £333 million of the increased expenditure. Additionally, within the respiratory system category, the top three products contributed to a substantial growth of £561 million in hospital spending between 2018 and 2022.

The United Kingdom (UK) adopts two main mechanisms to control pharmaceutical spending. The first is a voluntary agreement between the government and the pharmaceutical industry exerting direct spending controls in the form of industry repayments to the government (ie, rebates). The 2019 Voluntary Scheme for Branded Medicines Pricing and Access (VPAS) includes a 2 per cent annual growth limit on branded medicines' sales during the 2019-2023 period. The second involves the evaluation of new medicines by the National Institute for Health and Care Excellence (NICE), which makes recommendations for their adoption by NHS England. NICE conducts cost-effectiveness analysis to estimate the additional cost required to gain an additional year in good health (Quality Adjusted Life Year, QALY) from the use of a new medicine compared to a comparator, known as the incremental cost-effectiveness ratio (ICER). If the incremental cost per QALY is below NICE's approval threshold, the medicine is considered cost-effective. The approval threshold is an important driver of pharmaceutical prices as companies typically discount their drugs to the point that they meet this threshold for reimbursement.

NICE's approval threshold has historically ranged from £20,000 to £30,000 per QALY, however an increasingly broad set of exemptions permit many products to price at a level consistent with approval thresholds of £50,000 per QALY or more. These approval thresholds are not evidence-based and fail to represent the benefits forgone from displaced care elsewhere in the healthcare system, known as opportunity cost. The most robust and extensively peer-reviewed estimate of healthcare system opportunity costs is approximately £15,000 per QALY, significantly lower than NICE's current approval threshold. The implication is that funding new medicines could actually reduce overall population health due to the extent of displacement of other forms of healthcare.

The pharmaceutical industry argues that the UK government's existing affordability mechanisms, particularly the VPAS requirement to cap spending growth at 2 per cent per year, may have unintended consequences. These include limited or delayed availability of new medicines in the UK, negative impacts on UK Research and Development (R&D) activity, and a reduction in the UK's contribution to global pharmaceutical R&D. We examine the plausibility of these arguments in this report.

Availability of medicines: Despite concerns about companies not launching products or prioritizing the UK market after Brexit, the UK remains an attractive market with new products receiving a 3-year exemption from the VPAS repayment. The Medicines and Healthcare products Regulatory Agency (MHRA) is one of the fastest regulators globally and is expected to increasingly rely on international regulators to further speed up its assessments. NICE appraises all new products, with a high percentage of positive recommendations. Medicines with positive recommendations have NHS funding mandates. In 2019, NHS England introduced the Commercial Framework to more routinely facilitate access to medicines that exceed the approval threshold by providing more complex commercial arrangements and confidential discounts.

R&D in the UK: The pharmaceutical industry claims that capping spending growth and increasing VPAS repayment rates would reduce industry R&D investment in the UK, resulting in a significant long-term loss to society. However, this projection is based on self-reported data from the industry collected during a period leading up to negotiations with the NHS. The link between national pricing policy and the location of industry's R&D investment is not consistent with the available evidence. Only a small portion of returns from R&D investment directly benefit the UK economy in terms of jobs and tax revenues, as most returns accrue globally. Additionally, some returns would still benefit the UK regardless of where the R&D took place, as patients in the NHS would derive benefit from the health benefits of products developed elsewhere.

UK contribution to pharmaceutical innovation: Another argument raised by the pharmaceutical industry is that the UK is not adequately contributing to global pharmaceutical innovation. Establishing an appropriate pricing level that balances maximizing population health within the NHS and making a fair contribution to global R&D is crucial. Recent research assessing the benefits of different pricing levels, considering their impact on current and future health through innovation and drug development, suggests that current pricing levels in the UK are likely too high. Based on available evidence, offering manufacturers approximately one quarter of the long-term value of new pharmaceutical products would represent an optimal share.

As the government starts negotiations for the next iteration of the voluntary agreement with the industry, it should strive to strike a better balance between health and industrial policy objectives. Claims that increasing VPAS repayment rates would have unintended consequences on industrial strategy are overstated. Ensuring the efficiency and affordability of medicines spending is essential to prevent resources from being diverted away from other vital services in the NHS while fostering future health gains through innovation.

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Abbreviations

ABPI	Association of British Pharmaceutical Industry
BEIS	Department for Business, Energy and Industrial Strategy
BNF	British National Formulary
CDF	Cancer Drugs Fund
DHSC	Department of Health and Social Care
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
FDA	Food and Drug Administration
GDP	Gross Domestic Product
ICER	Incremental Cost-Effectiveness Ratio
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE	National Institute for Health and Care Excellence
PPRS	Pharmaceutical Pricing Regulation Scheme
QALY	Quality Adjusted Life Year
R&D	Research and Development
UK	United Kingdom
VAT	Value Added Tax
VPAS	Voluntary Scheme for Branded Medicines Pricing and Access

Background

Over the past few years, approval and adoption of expensive new technologies has threatened the financial sustainability of healthcare systems (1). Spending on pharmaceuticals, both as a share of total economic output and on a per capita basis, has increased in many high-income countries (2).

Since 2018, the net sales of branded medicines to the National Health Service (NHS) in the United Kingdom (UK) have been growing annually by over 5 per cent, excluding centrally procured vaccines and COVID-19 treatments (3). In England alone, the total cost of medicines, including generics, to the NHS reached £17.2 billion in the fiscal year 2021-22, after accounting for confidential discounts and central rebates (4). Hospital spending on prescription medicines, which contributes significantly to the overall spending growth, saw a change from £6.7 billion in 2018 to £9.1 billion in 2022 for the NHS (net of confidential discounts and excluding central rebates). This represents a 35 per cent change or a compound annual growth rate of 7.8 per cent. Table 1 shows costs for hospital-prescribed medicines according to the British National Formulary (BNF) therapeutic categorisation, ranked by growth between 2018 and 2022 (5).

The top-5 therapeutic areas, based on BNF categories, accounted for the highest growth in hospital spending during the 2018-2022 period, exceeding £2 billion. These areas corresponded to malignant disease and immunosuppression (£904 million, 43 per cent change), respiratory system (£587 million, 279 per cent change), skin (£220 million, 177 per cent change), nutrition and blood (£204 million, 39 per cent change), and cardiovascular system (£135 million, 42 per cent change). **Figure 1** illustrates the spending growth trends for these top-5 BNF categories.

Identifying and attributing precise growth drivers in NHS hospital spending on prescription medicines is challenging due to the requirement to keep discounted prices confidential and the use of generic names in prescribing. While the market entry of new expensive medicines and their uptake in the NHS are expected to be major contributors to spending, deals regarding drug portfolio access with manufacturers also seem to play a significant role, as suggested by the data. For example, spending for respiratory system prescription medicines more than doubled from 2019 (£224 million) to 2020 (£482 million). This increase coincided with a commercial deal between NHS England and Vertex Pharmaceuticals, enabling the availability of three new cystic fibrosis therapies (6),

Another significant trend observed during this period is the expansion of indications for existing medicines. One notable example is pembrolizumab, which was initially approved by the European Medicines Agency (EMA) in 2015 for the treatment of advanced melanoma in adults. Pembrolizumab has since substantially expanded its licensed indications to a current count of 11, likely contributing to the increase in cancer drug spending in the hospital setting (7).

Overall, a large proportion of the 2018-2022 spending growth in the hospital setting can be attributed to a small number of products. Specifically, within the top-5 therapeutic areas listed above, a total of five medicines accounted for £983 million of the spending increase. Similarly, in the malignant disease and immunosuppression and respiratory system BNF categories, the top-3 products by spending growth were responsible for £333 million and £561 million of their increased spending, respectively.

Figure 1. Growth in net NHS spending on hospital prescribed medicines in top-5 BNF categories, 2018-2022

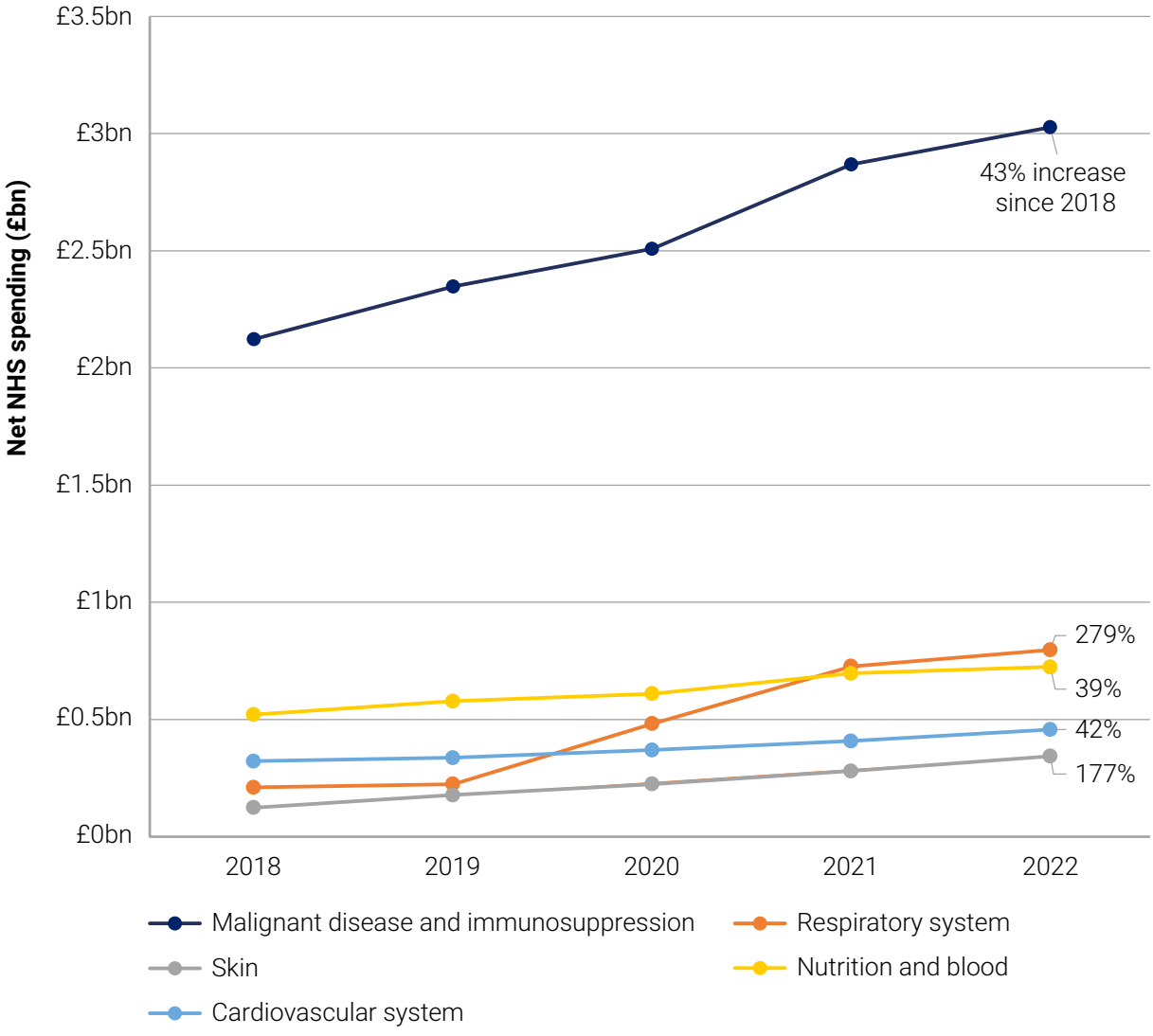


Table 1. NHS hospital spending on prescription medicines according to BNF categories ranked by growth in spending, 2018-2022.

	Year					Spending (£)	
BNF Category	2018	2019	2020	2021	2022	Total spending	Growth in spending
Malignant disease and immunosuppression	2,123,166,063	2,346,990,356	2,507,868,916	2,869,220,089	3,027,263,176	12,874,508,599	904,097,114
Respiratory system	210,522,582	223,908,721	481,897,318	726,635,180	797,177,706	2,440,141,508	586,655,125
Skin	123,746,669	177,812,996	224,086,588	280,406,037	343,386,578	1,149,438,867	219,639,909
Nutrition and blood	521,065,033	577,991,945	610,181,810	696,540,310	724,668,764	3,130,447,861	203,603,731
Cardiovascular system	322,533,024	336,582,994	369,325,394	407,857,786	457,132,608	1,893,431,805	134,599,584
Gastro-intestinal system	116,340,398	143,680,596	170,610,399	210,379,080	247,302,705	888,313,178	130,962,307
Immunological products and vaccines	210,308,330	219,487,544	246,883,187	274,895,355	333,823,327	1,285,397,743	123,514,997
None	283,779,543	303,914,995	292,339,550	340,547,888	372,779,837	1,593,361,814	89,000,294
Eye	467,806,401	511,878,002	441,084,379	520,240,459	543,071,561	2,484,080,802	75,265,159
Central nervous system	221,092,488	225,546,520	218,889,041	240,708,365	279,232,114	1,185,468,529	58,139,626
Endocrine system	168,023,301	179,462,158	177,859,771	198,517,105	209,911,117	933,773,451	41,887,816
Anaesthesia	89,956,726	91,933,452	90,128,590	110,684,586	111,365,906	494,069,260	21,409,180
Preparations used in Diagnosis	50,564,995	53,536,800	45,341,436	55,041,393	66,327,204	270,811,828	15,762,209
Drug Tariff Appliances	19,316,518	19,647,867	20,926,908	23,324,983	24,036,037	107,252,313	4,719,519
Other Drugs and Preparations	5,215,078	5,939,982	6,076,047	7,151,509	6,769,922	31,152,538	1,554,844
Ear, nose, and oropharynx	7,214,121	7,981,309	6,326,347	6,700,102	7,482,406	35,704,285	268,285
Incontinence Appliances	34,933	33,971	28,768	18,172	13,109	128,952	-21,824
Stoma Appliances	1,218,676	1,059,778	887,539	883,170	780,081	4,829,243	-438,596
Drug Tariff Dressings	9,361,535	8,375,771	6,813,528	7,251,173	7,442,139	39,244,146	-1,919,396
Obstetrics, gynaecology, and urinary-tract disorders	58,009,054	60,485,408	43,916,553	48,991,546	52,151,177	263,553,738	-5,857,877
Musculoskeletal and joint diseases	884,361,797	675,849,521	695,119,330	830,005,691	830,063,035	3,915,399,373	-54,298,762
Infections	821,212,074	665,208,026	604,445,463	598,856,441	616,625,261	3,306,347,264	-204,586,813

Source: Spending figures were provided by NHS England following a data request by the authors.

Mechanisms for ensuring affordability and efficiency in pharmaceutical spending

The UK employs two main mechanisms to control pharmaceutical spending. The first is a voluntary agreement between the government and the pharmaceutical industry. Such an agreement was first introduced in 1957, with both price and profit controls. Over time, it has undergone several changes, including an initial shift from both price and profit controls to a focus solely on profit controls (8). Since 2014, the Department of Health and Social Care (DHSC) and the Association of British Pharmaceutical Industry (ABPI) have been setting caps on the annual growth of branded medicines' net sales to the NHS over approximately five-year periods. The latest agreement, known as the 2019 Voluntary Scheme for Branded Medicines Pricing and Access (VPAS), followed the previous 2014 Pharmaceutical Pricing Regulation Scheme (PPRS), and included a 2 per cent limit on the annual growth of branded medicines' net sales during the 2019-2023 period (9). Spending beyond this level is repaid to the government by industry in the form of rebates. The scheme's aims were to speed up access to cost-effective branded medicines while maintaining affordability and predictability for NHS spending (10). Companies not participating in the voluntary agreement are subject to a statutory scheme. It should be noted that centrally procured vaccines and COVID-19 treatments are excluded from VPAS, and also that net sales are not equal to NHS spending, as the former excludes distribution costs and Value Added Tax (VAT) which are applied in secondary hospital care.

The second mechanism is the evaluation of new medicines by the National Institute for Health and Care Excellence (NICE). NICE conducts health technology evaluations on behalf of the NHS to promote efficient allocation of NHS resources (11), complementing the direct spending controls that aim to ensure affordability in NHS spending. Created in 1999, NICE appraises the clinical and cost-effectiveness of new health technologies by examining whether additional costs are justified by their added clinical benefits. NICE conducts cost-effectiveness analysis, a type of economic evaluation, to estimate a health intervention's incremental cost required to gain an additional Quality Adjusted Life Year (QALY), versus a comparator, known as an Incremental Cost Effectiveness Ratio (ICER). If the incremental cost per incremental QALY, ie, ICER, of a health technology is below NICE's approval threshold then it is considered a cost-effective use of resources. These evaluations drive NICE's recommendations to the NHS for the adoption of new health technologies.

Since 2000, NICE has conducted a total of 878 technology appraisals, with the majority (84 per cent) resulting in positive recommendations (including 'optimised' decisions as well as those included in the Cancer Drugs Fund, CDF) (12). From 2017 to 2022, NICE evaluated 346 pharmaceuticals, resulting in 157 positive recommendations and 145 optimised recommendations for smaller patient groups than the licenced indication. Additionally, four technologies were recommended only for research (12). Negative decisions accounted for only 11.5 per cent (40 appraisals) during this period.

Health system objectives of pharmaceutical policy

A primary objective of the NHS is to maximize population health given limited resources. In order to achieve this, national pharmaceutical policies should promote equitable access to safe and effective medicines at an affordable cost, while ensuring their rational use (13). The efficient allocation of resources is critical to optimizing population health and societal welfare. This requires prioritising technologies that provide good value-for-money and recognising the concept of opportunity cost – given budget constraints every investment made in one technology is associated with sacrificed benefits that could have been accrued from investing in alternative technologies (or treatments or services).

The concept of opportunity cost is central to understanding the role of cost-effectiveness analysis within the NICE decision-making process. Because the NHS operates within a constrained budget which is de facto insufficient to cover all health interventions for all patients, funding some interventions will displace the resources needed for funding others, together with their resulting benefits (14). Therefore, the 'ethics of opportunity costs' provides an ethical framework for NICE when evaluating the acceptability of funding some health technologies over others, to justify recommendations for the NHS (14, 15).

NICE's approval threshold and its health and non-health impacts

Approval thresholds play a central role in NICE's decision making as the benchmark for what NICE will consider to represent value for money. As reimbursement is conditional upon setting a price consistent with this threshold, companies are incentivised to offer (confidential) discounts that place the cost per QALY of their product just below the approval threshold (16). NICE's approval threshold is therefore a key mechanism for pharmaceutical price control in the UK.

Approval thresholds set by NICE should reflect the opportunity cost of investing in a new health technology, corresponding to the benefits forgone from displaced health interventions across the healthcare system (17). However, in reality NICE's approval thresholds are not evidence-based and fail to represent opportunity costs.

Historically, NICE has used an arbitrary approval threshold of £20,000-£30,000 per QALY, without empirical basis (18-20). This range was adopted in NICE's Methods Guide and the 2019 voluntary agreement between the government and the pharmaceutical industry.

In reality, NICE's approval threshold is now frequently substantially higher than £20,000 to £30,000 per QALY (20). In 2009, the End of Life treatments guidance increased NICE's approval threshold to £50,000 per QALY for treatments that offered at least three additional months of survival for patients with less than 24 months of life expectancy, which mostly corresponded to cancer treatments (21, 22). The End of Life treatments approach was replaced by a more broadly applicable disease severity value modifier in 2022 following the latest update of NICE health technology evaluation methods (11). This new disease severity modifier can increase the approval threshold to around £51,000 per QALY for conditions considered to be highly severe. In addition, in the 2017 guidance for Highly Specialised Technologies programme targeting ultra-rare diseases, the approval threshold was increased to £100,000-£300,000 per QALY (23).

In 2015, a study funded by the Medical Research Council and the National Institute for Health and Care Research estimated the health opportunity cost in the UK. The study evaluated the changes in overall NHS expenditure and changes in health effects in primary care trusts across programme budget categories and associated disease specific mortality. The study estimated a central maximum approval threshold of £12,936 per QALY (17), which has since been updated to ~£15,000 (24), representing the most robust and extensively peer-reviewed empirical estimate available to date about opportunity costs at the healthcare system level. Latest estimates suggest that the marginal cost of generating a year in good health in the NHS may have decreased in more recent years, to between £6,000 and £8,000 (25). It is worth noting, however, that these studies have some limitations and methodological assumptions related to data availability that may impact their findings (26). The £15,000 per QALY estimate is used as a benchmark in DHSC impact assessments (27, 28).

Notably, this estimated ICER threshold is significantly lower than the current approval threshold adopted by NICE, which raises concerns about funding new medicines at a level higher than healthcare system's opportunity cost. While NICE's current threshold may benefit some patients who would otherwise have no access to therapies that are not cost-effective, it would unavoidably disadvantage other patients due to the displacement of more cost-effective therapies offering larger clinical benefits for the money spent, thereby reducing overall population health (29). For example, oncology drugs funded between 2009 and 2011 under the End of Life treatments criteria are estimated to have contributed fewer QALYs to advanced stage cancer patients than those lost amongst other NHS patients due to care being displaced by additional drug expenditure (30).

Displaced NHS healthcare services not only impact patient health but also has significant implications for UK productivity (31, 32). For every £10 billion spent on new medicines, reduced funding for other NHS services and the consequent impact on population health is expected to reduce UK productivity by £8 billion (See **Box 1** for details) (32). Notably, these estimates stand in stark contrast to industry claims that new medicines deliver productivity benefits in addition to clinical benefits, and that these benefits would offset the costs of new medicines through increased tax payments. A recent PwC analysis sponsored by the ABPI reported that the wider adoption of NICE-recommended therapies would lead to significant broader benefits to the economy and society, due to greater patient, carer and NHS productivity (33). However, this analysis only looked at a selective sample of drugs affecting relatively young patients and ignored the opportunity cost of paying for new medicines, therefore failing to account for the significant productivity implications of displaced NHS care (see **Box 1**). Furthermore, many NICE-recommended drugs focus on diseases that primarily affect older individuals who may not return to work even if their health is improved by new medicines. For example, in 2022-23, 50 per cent of NICE Technology Appraisals were of cancer drugs for advanced or metastatic disease (34).

Box 1: Estimation of the medicines' spending impact on UK productivity

Current evidence suggests that the NHS is able to generate a QALY per £15,000 of expenditure (24). Allocating £10 billion of the NHS budget to new medicines would therefore be expected to result in around 670,000 QALYs lost due to care being displaced elsewhere in the NHS.

Previous comprehensive analyses by the Department of Health and Social Care estimated that for every QALY gained through healthcare, UK productivity increases by £11,600 (32). This is estimated as production net of any effects of the QALY on consumption.

Allocating £10 billion of NHS budget to new medicines is therefore expected to result in an £8 billion productivity loss associated with displaced NHS care (670,000 QALYs lost multiplied by a £11,600 per QALY loss in productivity). This needs to be carefully weighed up against any productivity benefits directly associated with access to new medicines.

Source: calculated from authors based on DHSC Impact Assessment estimate of health opportunity cost of £15,000/QALY (27, 28) and estimates of productivity impacts of NHS activity reported within Claxton et al (32).

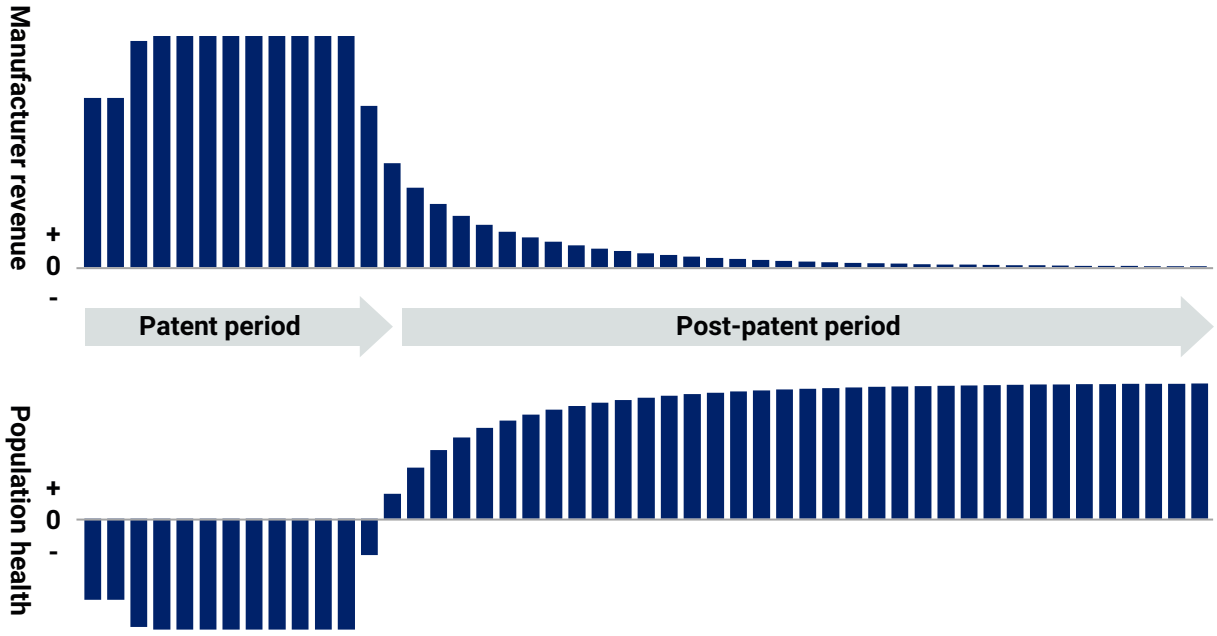
How is the value of new medicines shared between pharmaceutical companies and patients?

The value of a new medicine is typically attributed to the health improvement it provides to patient populations throughout its life cycle. A medicine's life cycle includes both the on-patent period when the manufacturer holds patent rights, and the off-patent period when generic or biosimilar versions of the originator become available (35). In addition to the medical value of a medicine in terms of improved patient health outcomes, manufacturers also receive a financial value from the medicine in the form of sales revenue following its licensing and market entry. Industry revenues are important to fund future pharmaceutical innovation, as companies invest in R&D based on expected future profits, although R&D spending from the largest companies is lower than what they spend on other non-R&D activities (36). Therefore, the total value of a new medicine is shared between patients in terms of improved health and manufacturers in terms of revenue.

Figure 2 shows how a medicine's value is distributed between the manufacturer and NHS patients over its life cycle. During the on-patent period, revenue mainly accrues to the manufacturer due to the drug's monopoly protection. During this period, NHS patients experience a health deficit as the new medicine's benefits are outweighed by the impact on other NHS services. After the patent period, NHS patients start receiving significant net benefits from the availability of cheaper generic or biosimilar versions of the medicine.

A study of 12 NICE-appraised medicines found that manufacturers received between 6 per cent to 260 per cent of a new medicine's value over its life cycle (35). In seven out of the 12 cases, the manufacturer received more than 100 per cent of the medicine's value. This means that the negotiated prices (including confidential discounts) had an overall negative impact on the health of the NHS patient population due to displacement of other more cost-effective services. NICE's current approval threshold makes it unlikely for the NHS to receive a net positive value from new medicines, even during the off-patent period. To address the growing budgetary pressures on the NHS, it is crucial to prioritise affordable spending on medicines taking into account opportunity costs, but also considering the incentivizing impact it might have on the development of new medicines.

Figure 2. The value profile of new pharmaceuticals from a manufacturer and NHS perspective



Potential unintended consequences of spending controls

Governments need to balance the population health objectives of healthcare systems with industrial policy considerations. Industrial policy focuses on promoting economic activity and generating economic output beyond the healthcare sector. The life sciences industry is an important sector of the UK economy, with over 6,500 businesses employing 280,000 people (37). The UK's Life Sciences Strategy aims to maintain and improve the country's attractiveness for industry as a location for investment, throughout the life cycle of medicines from basic research to clinical development to commercialisation (38, 39). However, balancing the interests of the NHS and the pharmaceutical sector is complex. Industry's objective of charging high prices and increasing revenues often conflicts with the NHS's goals of promoting affordability and delivering health for all.

The pharmaceutical industry claims that the UK government's existing affordability mechanisms, especially the VPAS requirement to keep branded medicines' sales growth capped at 2 per cent a year, may have unintended consequences. As outlined earlier, net spending on branded medicines in the NHS grew at approximately 5 per cent a year since 2018 (excluding COVID-19 vaccines and treatments). To bring recent spending back in line with the agreed growth level, the government has established the industry repayment rate, ie,, rebate, for 2023 at 26.5 per cent of companies' yearly revenues (compared to 5 per cent to 10 per cent between 2019 and 2021). This increase in repayments has sparked opposition within the industry, presumably due to concerns that it might indicate a long-term trend for industry repayments (40). Two US pharmaceutical companies pulled out of the voluntary agreement between the government and industry in protest at the rise in repayment rates (41). One of the companies said the clawback has a "punishing" impact on innovation which would lead to the UK falling behind other countries, and the other company warned that the scheme would affect the company's ability to operate in the country. This was in addition to another big pharmaceutical company stating that it would reduce its UK footprint and jobs, and another that it could divert investment away from the UK.

Overall, industry assertions include that spending controls will contribute to **(1)** limited or delayed availability of new medicines in the UK, **(2)** negative impacts on R&D activity in the UK, and **(3)** the UK failing to contribute a fair share to global pharmaceutical R&D. We examine the plausibility of and evidence base for these concerns in the sections below.

Availability of medicines

Recent headlines have highlighted concerns raised by drug companies about a "penalising rebate" levy designed to limit the NHS's medicines bill. According to a report in the FT, "At least two drug companies have privately warned ministers that they will cease or curtail operations in the UK" unless they are spared the levy (42). These concerns have added to the anxieties among policymakers that companies would not launch their products or prioritise the UK market following Brexit.

However, these concerns overlook a range of system-level factors that make the UK an attractive market for launching products. To begin with, there is a 3-year exemption period whereby new products do not attract the VPAS payment.

Importantly, the regulatory environment is favourable to industry. The Medicines and Healthcare products Regulatory Agency (MHRA) is among the fastest regulators worldwide and is expected to become even speedier. In 2021, the MHRA launched the Innovative Licensing and Access Pathway, which allows manufacturers to benefit from early and frequent interactions with the agency and NICE (43). Additionally, the MHRA recently announced a new international recognition framework for the rapid sign-off of medicines already approved by regulatory authorities in other high-income countries (44, 45). These expedited approval pathways complement other existing regulatory mechanisms for faster routes to market, such as the conditional marketing authorisation pathway which provides access to medicines for which comprehensive clinical data is not yet available. However, these mechanisms are not without trade-offs, as outlined in **Box 2**.

NICE now appraises all new products, with a high percentage of positive recommendations. All medicines with a positive recommendation have a funding mandate in the NHS. In addition to routine commissioning through NICE, several exceptional mechanisms exist for access to new medicines whose value is surrounded by uncertainty due to immature or incomplete data, including the Cancer Drugs Fund (46), and the new Innovative Medicines Fund (47), though these come with a number of concerns about the value they provide to patients and the NHS (48, 49).

The UK's public national health system provides universal healthcare coverage, and as a result, companies seeking to enter the market must only negotiate with NHS England as the single payer. This differs from many other countries where companies must negotiate with multiple payers, which can create additional access hurdles and administrative burdens. In 2019, NHS England introduced the Commercial Framework to more widely facilitate access to medicines whose cost-effectiveness exceeds the approval threshold by providing more complex commercial arrangements and confidential discounts (50).

Efforts are also underway to accelerate the adoption of new technologies that offer significant benefits for patients. The Accelerated Access Collaborative has established the Rapid Uptake Products program, which identifies and promotes promising new technologies that address important unmet needs in the NHS (51).

Apparently, the debate surrounding new product launches in the UK assumes that the rapid and widespread adoption of all new medicines is an inherently desirable health policy goal. However, this assumption fails to differentiate between drugs that offer therapeutic benefits and those that do not. The Office for Life Sciences' Competitiveness Indicators evaluate the uptake of new medicines, but do not account for their clinical effectiveness. While delayed or non-launch of new and effective drugs can negatively impact individual patients, the impact of access on population health is less clear cut when drug prices are at the levels currently observed in the UK. As shown in **Figure 2** access during the patent period typically reduces overall population health due to the new medicines' impact on other NHS services. This is particularly true for new medicines with uncertain effectiveness and cost-effectiveness, and those recommended at high prices as evident via NICE's increasingly higher approval thresholds of £50,000 per QALY or more. Ultimately, it is essential to recognise that patients, healthcare systems, and society do not require access to all new medicines, but timely access to therapeutically superior medicines that are cost-effective. The notion of opportunity cost is central to this, as adoption of expensive new medicines priced at the higher end of the current NICE approval thresholds will lead to a net reduction in population health.

Promoting population health through pharmaceutical policy

Box 2. Knock on effects of regulatory conditions on health technology assessment

New medicines are licensed for use in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA). In recent years, the duration of clinical development and regulatory review has shortened globally, resulting in uncertainty associated with the clinical benefits and harms of new medicines at the time of market entry (52). Regulatory approval is increasingly based on clinical trials that measure the drug's effect on so-called surrogate endpoints, which are intermediate measures that have a variable association with patient-relevant outcomes such as overall survival and health-related quality of life (53). The growing reliance on surrogate endpoints, particularly in areas like advanced cancers, has been controversial and has led to the market authorization of drugs that ultimately had unfavourable benefit/risk profiles (54). One notable instance involved bevacizumab, which received accelerated approval in the US in 2008 for the treatment of metastatic breast cancer (55). The approval was based on promising results showing improvement on a surrogate endpoint, progression-free survival. However, subsequent confirmatory trials failed to demonstrate an overall survival benefit, leading to the US Food and Drug Administration (FDA) revoking the drug's licence for that indication in 2011. More recently, several cancer drugs were withdrawn from the market due to post-approval studies demonstrating no beneficial effects on overall survival, despite earlier studies finding promising results on surrogate endpoints (56).

Therefore, NICE's assessments rely on an increasingly uncertain evidence base regarding the benefits, harms, and cost-effectiveness of new medicines (57). Although NICE has strategies in place to account for uncertainty, it remains unclear whether and how committees are considering all relevant evidence and related uncertainties within their decisions (58).

Strikingly, cancer drugs assessed by NICE which had mature overall survival data were less likely to be recommended for funding compared to indications with immature survival data (59). In fact, NICE did not reject any indications with immature survival data as extrapolation beyond trial follow-up protected against ruling out potential survival gains that could justify the incremental costs associated with the drugs. In such cases, greater uncertainty due to immature survival data benefited the manufacturers.

Industry R&D investment in the UK

Another concern is that the government's medicines affordability mechanisms will cause pharmaceutical companies to pull back their R&D investments from the UK. A recent ABPI survey to its members explored past (2021), current (2023) and future (2028) R&D investment intentions under four different repayment (ie, rebate) scenarios, ranging from less than 10 per cent to 20-30 per cent. According to the survey, companies indicated that they would decrease their R&D footprint in the UK by as much as 20 per cent if the VPAS repayment rate remains at current levels of 20 per cent-30 per cent. An ABPI-commissioned report using these survey results estimated that such a reduction in domestic R&D activity between 2023-2028 would equal £5.7 billion of R&D investment (60).

The ABPI-commissioned report indicates that the potential loss of UK industry R&D could have a significant impact on the national economy. The report suggests that the economic benefits of industry R&D activity are so substantial that a higher payment rate to the NHS could be a 'false economy' (60). The report concludes that the loss of long-term UK tax revenues that would result from a reduction in R&D investments by pharmaceutical companies could outweigh any potential savings to the NHS from higher repayments. In other words, the report claims that setting a higher VPAS repayment rate would result in a net loss to public sector finances. These conclusions do not hold up to scrutiny on two broad grounds (see **Box 3** for further detail).

Firstly, the projections based on self-reported data about R&D investment in the UK may be overstated and do not align with established drivers of domestic R&D investment. There is no empirical evidence supporting an association between national pricing policies and location of R&D investment decisions (61, 62). The DHSC concluded in its Impact Assessment report that the supply side factors such as availability of expert scientific labour and favourable tax conditions are the primary drivers of R&D location, not demand or procurement for pharmaceuticals in the local market (28). Similarly, the European Federation of Pharmaceutical Industries and Associations (EFPIA) highlighted the importance of supply-side factors for the location of industry R&D investment in a recent report. The EFPIA report recommended incentivising the creation of innovation hubs and enhancing public R&D funding as strategies for boosting the attractiveness of Europe for industry R&D activity (63).

Secondly, the report predicts that a £5.7 billion withdrawal of R&D would result in a £54.3 billion loss in UK Gross Domestic Product (GDP). These large losses reflect the wider consequences of reduced R&D investment, the majority of which accrue to the pharmaceutical sector (64). Only a small share of these returns would directly benefit the UK economy in the form of jobs and tax revenues, as the majority of the returns would accrue globally.

However, while the evidence does not support a direct link between national pricing policies and R&D location decisions, there is a possibility that some pharmaceutical companies may still choose to relocate R&D activities from the UK as a political move to deter other countries from adopting similar pharmaceutical pricing policies that may impact their revenues. This would be a politically motivated decision rather than a financially driven one.

Box 3. Would promoting affordability of medicines via spending controls in the UK represent a false economy?

Between 2023-2028, increasing the VPAS repayment rate from less than 10 per cent to 20-30 per cent would generate an additional £11.9 billion in revenues for the NHS. During the same period, the ABPI members reported that increasing the repayment rate from less than 10 per cent to 20-30 per cent would reduce industry R&D investment in the UK by £5.7 billion. According to the report, the reduction in industry R&D in the UK would result in a sizeable loss to society over the long-run, which would be worth £54.3 billion due to returns to R&D foregone. The report further estimated that the losses in tax revenues over the long-run would exceed the gain in revenue to the NHS by £18.1 billion, representing a false economy. This finding can be challenged on five grounds.

1 The £5.7 billion projected reduction estimate in R&D investment is based on self-reported data from industry collected during a period leading up to negotiations with the NHS, therefore potentially suffering from direct conflicts and motivational biases.

2 The link between national pricing policy and the location of industry's R&D investment is not aligned with the broader literature.

3 The findings of the report are based on the assumption that industry R&D will generate a perpetual annual return of £0.5 for every £1.00 invested. However, these returns accrue to global companies and global shareholders. Based on an analysis of trade information from the Department for Business, Energy and Industrial Strategy (BEIS), only 10 per cent of UK sales revenues remains in the UK. Using this figure, and adjusting the ABPI findings accordingly

- **a** As opposed to £54.3 billion, £5.4 billion would be lost in terms of economic activity.
- **b** As opposed to £18.1 billion, £1.8 billion would be lost from UK tax revenues.

4 It is also important to consider alternative ways to encourage industry R&D in the UK. The NHS savings through repayments could be reinvested in public R&D that would predictably stimulate industry R&D investment. According to conversative estimates, £1 in public R&D spending stimulates £2.2 in private R&D investment (64). Therefore, less than a quarter of the NHS savings (£2.6 billion) would need to be reinvested as public R&D to avoid any loss in industry R&D in the UK between 2023-2028.

UK contribution to pharmaceutical innovation

Another argument put forth by the pharmaceutical industry in response to pharmaceutical spending controls is that the UK is not fulfilling its responsibility as a 'global citizen' and adequately contributing to global pharmaceutical innovation. The industry's investment in R&D is influenced by expected global lifetime revenues, taking into account drug development costs and factors influencing prescription drug demand (65). Research indicates a positive correlation between projected future profits and R&D activity (66, 67). Various studies suggest that market growth, such as expanded insurance coverage, can significantly impact the number of new drugs developed by pharmaceutical companies (68, 69).

Lowering drug prices worldwide would inevitably result in reduced revenues and could have a negative impact on industry R&D. Available evidence from the academic literature and a recent analysis by the US Congressional Budget Office suggests that a 10 per cent decrease in revenues for pharmaceuticals is expected to result in a decrease in the number of new drugs developed in the region of 5 per cent (70, 71).

However, it is important to note that the relationship between industry revenues and R&D activity is primarily observed in large markets like the US, which accounts for around 40 per cent of the global pharmaceutical market in terms of sales. In contrast, the UK represents only 4 per cent of the global market. Therefore, the concern that lower drug prices in the UK would have a negative impact on global R&D and innovation is unsupported. If the UK seeks to fulfil its role as a responsible 'global citizen' and contribute to global R&D, it is important to determine an appropriate pricing level that balances the objectives of maximizing population health within the UK and making a fair contribution to global R&D.

Recent research has addressed this question by evaluating the benefits of different pricing levels, considering both their impact on current net population health and their effects on future net health through their influence on R&D and drug development (70). This analysis suggests that even when accounting for the influence of pricing on innovation and assuming the UK fulfils its role as a responsible 'global citizen', current pricing levels in the UK are likely to be too high. This raises the question of what proportion of the total long-term value of a new pharmaceutical should be offered to manufacturers as an incentive for future innovation and the value it generates.

Based on the available evidence, offering manufacturers roughly one quarter of the long-term value of new pharmaceutical products would represent an optimal share. This could be achieved via a range of payment mechanisms including a lower NICE approval threshold, higher VPAS repayments or innovative models such as subscription payment approaches (70).

Conclusions

The affordability of medicine spending in the UK faces challenges stemming from various system-level and societal factors. One significant factor is the global decline in regulatory evidence standards, leading regulatory agencies, including those in the UK, to expedite approval decisions (72). Consequently, a considerable number of new drugs enter the market with limited evidence regarding their clinical benefits and potential harms. Most new drugs do not offer any additional therapeutic advantages over existing alternatives (73, 74). In the context of cancer treatment, for instance, the majority of newly introduced drugs lack evidence of extending overall patient survival, which is the most direct measure of drug efficacy (75).

NICE has seen an increase in the number of product reviews due to the 2019 voluntary agreement that mandates the appraisal of all new drugs and new uses of existing drugs. Alongside this, there has been a gradual rise in the proportion of positive recommendations by NICE, which come with funding mandates within the NHS. A concerning trend has been the utilization of approval thresholds by NICE that are too high and disconnected from the actual opportunity costs of the healthcare system (29). Specifically, there is a growing share of NICE recommendations based on approval thresholds exceeding £30,000 per QALY. Without a significant reduction in NICE's approval threshold, access to new medicines is likely to have adverse effects on population health.

As the government starts negotiations for the next iteration of the voluntary agreement with the industry, it should strive to strike a better balance between health and industrial policy objectives. Ensuring the efficiency and affordability of medicines spending is essential to prevent resources from being diverted away from other vital services in the NHS. Industry claims that increasing VPAS repayment rates would hinder the availability of new product launches or diminish industry investments in R&D within the UK are unlikely to hold. Although drug pricing plays a crucial role in fostering future health gains through innovation, the available evidence suggests that current pricing levels likely surpass the optimal threshold, even when considering the benefits of future innovation (70).

Policymakers tend to be hesitant to deny access to new treatments, particularly when these treatments are already accessible in other countries. This tendency is further influenced by the powerful role of the pharmaceutical industry, which maintains strong financial ties with governments, patient organizations, healthcare professionals, and healthcare organizations (76-78). The industry has effectively positioned access to new technologies as the central focus of the debate, creating a contentious political climate surrounding access to new medicines. Notably, both NHS England and NICE have increasingly employed promotional language in their press releases when referring to new treatments, further shaping public discourse on access to these medicines (79).

It is important for NICE and NHS England to better communicate the underlying principles and values guiding their decision-making process for pricing and reimbursement of medicines. Such communication would improve public understanding that these decisions are made with fairness, efficiency, and sustainability as the guiding principles, serving society's best interests. A new social contract is needed, emphasizing the improvement of population health for all rather than prioritizing the development and access to new technologies as the primary objective.

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