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SCOPING REVIEW

# Mechanisms Considering Public Investment in Pricing and Reimbursement Decisions of Medicines and Other Health Technologies: A Scoping Review

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## Abstract

**Background** Pricing and reimbursement (P&R) systems do not normally use public investments in research and development (R&D) as criteria when negotiating the prices and reimbursement of health technologies.

**Objective** The objective was to find mechanisms that consider public investment in R&D when negotiating P&R or obtaining a fair return on this public investment

**Methods** We conducted a scoping review. A total of four databases (PubMed, Embase, Scopus and Web of Science) and a grey literature information source (Google Scholar) were searched. Eligible articles were published before 2024 and described how public sector investment in R&D is considered in price negotiations or how the public sector can obtain a return on R&D investment.

**Results** The review found 28 papers referring to mechanisms that take into account public investment in R&D to reduce prices in the P&R negotiation (e.g. delinkage R&D model, advance purchase agreement and government patent use), to obtain a fair return on investment (e.g. royalties and venture philanthropy) or to save costs or share risks (e.g. social impact bonds and prize fund). Examples are provided of health technologies that used these mechanisms.

**Conclusions** Policymakers have several resources they can draw from to ensure a fair and efficient use of public R&D funds. However, there is little evidence that these instruments are widely used in practice, and there is no political consensus on what mechanism is the most appropriate and why. In view of the above, it is essential to create a common framework that will ensure a fairer and more affordable system for public health budgets.

## 1 Introduction

The relationship between research and development (R&D) costs and medicine pricing has become an important topic of social debate, particularly in relation to healthcare expenditure [1]. Innovative medicines (defined as one representing real clinical or therapeutic progress and providing measurable added value compared with current options [2]) are fundamental for improving patient outcomes, but there is concern about high prices, increasing economic pressure on health systems and prompting discussions on sustainability, affordability and pricing policy [1, 3]. This has sparked a debate about whether high medicine prices can be justified by the cost of R&D, especially since public and philanthropic funders are also involved in this process [4]. It has been estimated that public institutions are responsible for one- to two-thirds of all R&D costs [5]. Consequently, several experts argue that taxpayers pay twice for medicines; first, through public investment in R&D to support basic and translational research and then through high prices at the time of purchase [4–8]. The main crux of the 'pay twice' argument is that taxpayers receive an insufficient return on their public investment in R&D of a medicine. In 2019, a NY representative on a US committee argued that the government acts as an early investor in medicine development with public money, which then becomes privatised, resulting in a poor return on investment (ROI) [7]. However, it should be noted that, aside from public money invested in R&D for new drugs, there is also indirect public funding of research, such as public costs in training scientists and researchers, public costs in funding hospitals where research takes place and tax credits to pharmaceutical companies undertaking research [6].

High medicine prices are adding to pharmaceutical policy challenges. A study by the IMS Institute of Healthcare

Extended author information available on the last page of the article

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**Key Points for Decision Makers**

Governments need research and development (R&D) and pricing models that focus on fair pricing and affordability to avoid taxpayers paying twice for medicines through public investment in R&D and purchasing.

Alternative mechanisms can consider public investment in medicines R&D in pricing.

These mechanisms achieve price reductions, better returns on investment and cost savings.

estimated that, from 2014 to 2018, global pharmaceutical spending increased by 30% to nearly US$1.3 trillion. Specifically, high medicine prices also extend to rare diseases, which affect approximately 10% of the population. Cohen and Felix identified 11 drugs approved for rare diseases by the Food and Drug Administration (FDA) that cost over US$225,000 per patient per year [3].

As a result, the price of medicines is rising year by year, causing unsustainability of national health systems, mainly as a result of the current R&D system [9, 10]. The monopoly created by the patent system has been questioned. While patents incentivise innovation by allowing companies to recoup R&D costs, they also limit access to medicines, creating allocative inefficiency and reducing consumer surplus [9, 10].

The pharmaceutical industry justifies high drug prices because innovation requires substantial and prolonged R&D investment, and there is a need for adequate incentives to offset the risk of failure [1, 3, 9]. However, this approach often prioritises economic profit over public health needs [5, 9, 11]. Thus, greater focus is placed on high-incidence chronic diseases than on orphan medicines, neglected diseases, diseases affecting low-income countries, potential explorations that are not patentable and non-drug interventions that are less profitable [5, 11]. For example, in the last 40 years, only two treatments have been produced for tuberculosis, a disease that kills 1.5 million people annually [9].

In addition, there are other explanations for the high prices of medicines. First, this system favours the creation of 'me-too' medicines, which are medicines with limited therapeutic advantages over existing drugs but are sufficient to obtain a patent. In this context, pharmaceutical companies often prioritise profit-maximising tactics instead of pursuing 'breakthrough' innovations [5, 9, 12]. For example, only 7% of new medicines approved between 2000 and 2013 were considered to offer a real advantage over existing ones [9]. Second, pharmaceutical companies game the system, for example, through drug switching or 'pay to delay' vis-à-vis their competitors [3]. Third, pharmaceutical companies try to extend patents through the process of evergreening by introducing a minor alteration to obtain a second patent [3, 5]. Finally, this system provides the pharmaceutical industry with generous intellectual property provisions as government incentives for innovation, leading to a major problem of lack of transparency of information [3, 5, 9, 11].

In 2014, the Tufts University Centre for the Study of Drug Development estimated that bringing a new drug to market costs about $2.6 billion, where $1.4 billion were for out-of-pocket expenses for research and investment and the remaining $1.2 billion became the ROI needed to attract investment in medicines. However, these estimates were criticised for the lack of transparency [3, 4]. Another study, which estimated the net cost of manufacturing 100 million doses of coronavirus disease 2019 (COVID-19) vaccines, found that their cost (US$ 0.54–0.98 per dose) was considerably lower than their pricing (e.g. the AstraZeneca vaccine was sold at US$2.15 in Europe, US$3–4 in the USA and US$5.25 in South Africa) [4, 13]. In this regard, it should be noted that, according to the industry's argument and the theory of innovative companies, revenues are used to reinvest in R&D for new medicines and not to recover the costs of the medicine that has been manufactured [14]. Despite this, a study has shown that large pharmaceutical companies allocate most of their profits to distributing them among their shareholders rather than increasing pharmaceutical innovation [14]. Therefore, the latter and the price difference in the example fuel the debate on the lack of transparency and secrecy surrounding manufacturing costs and the contribution to development costs, caused by exclusive data protection and the failure of private entities to publish the breakdown of R&D costs [1, 4, 5, 9, 15].

This lack of transparency also leads to inefficiency in terms of expenditure of financial resources and potential scientific duplication, and it complicates price negotiation for public payers, as they do not know the true R&D costs of medicines [4, 5, 9, 11]. Greater transparency about R&D would reduce information asymmetry between buyer and seller and would facilitate evaluation of the product, negotiation of prices and other conditions of market access [16]. Given the lack of transparency about the scientific studies used to develop new health technologies, the World Health Assembly adopted in 2019 the resolution 'Improving the transparency of markets for medicines, vaccines and other health products', which states that 'policies that influence the pricing of health products and that reduce barriers to access can be better formulated and evaluated when there is reliable, comparable, transparent and sufficiently detailed data across the value chain' [11, 17]. In this way, greater

transparency in the drug R&D process could be a key step towards a fairer system.

Although several scientists may perceive the preceding introduction as overly critical of the pharmaceutical industry, it is important to acknowledge that private firms play a central role in R&D of new medicines. Moreover, the return on public investment should also be measured in the enormous health benefits that people receive from new drugs. Finally, the pay twice debate may negatively affect the important efforts of the pharmaceutical sector that are necessary for the population [7].

In response to the growing debate regarding the current model of medicines development, there are alternative development and pricing models that focus on fair pricing, transparency, access and affordability. This research aims to review mechanisms that consider public investment in R&D of medicines and other health technologies to obtain public health benefits. We studied how these mechanisms consider public R&D investment in pricing and reimbursement (P&R) negotiations or if they provide a way for the public sector to obtain a return on R&D investment. In addition, we also examine ways to use public contributions to incentivise R&D in ways that achieve lower prices or cost savings for health services.

## 2 Methodology

To carry out this scoping review, we followed the methodology described by Arksey and O'Malley [18] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews (PRISMA-ScR) checklist [19]. We focused on seeking evidence on the utilisation of mechanisms that consider public investment in medicines and other health technology R&D, the use of this information in P&R negotiations and mechanisms that ensure return on public R&D investment.

### 2.1 Search Strategy

A search strategy was implemented in PubMed, Embase, Scopus and Web of Science (WOS)–Core Collection. Google Scholar was explored to identify grey literature. Additionally, the snowballing technique was employed to find any additional publications (i.e. the references of relevant papers identified from the search were reviewed). The full search strategy is available in Supplementary Table 1. The time period searched extended until 17 January 2024, without restriction on the start date. There were no restrictions by language or country.

### 2.2 Inclusion and Exclusion Criteria

The selection of the relevant articles was based on the following criteria: (1) publications describing how public sector investment in R&D is considered in price negotiations or (2) publications describing how the public sector can obtain a return on R&D investment. We excluded articles commenting on 'pay-twice' critique but not describing any proposal regarding how public sector investment in R&D should be considered in price negotiations nor how the public sector could recover the investment made in R&D.

### 2.3 Article Selection

The Rayyan software (https://www.rayyan.ai/) was used for the review management. The study selection process was implemented in two stages: an initial selection was made on the basis of titles and abstracts, followed by a full-text reading of potentially selected studies. The selection process was conducted independently by two reviewers (M.G. and Z.S.) who were blinded to each other's decisions. Disagreements were documented and resolved by a third reviewer (J.E.). Reasons for exclusion were documented. The results of the scoping review were synthesised as follows. First, a brief description was provided of how the mechanisms work, how they consider public investment and the results obtained in favour of health systems within each mechanism. Second, examples were introduced for those mechanisms that had real-life use cases.

## 3 Results

Initially, 2145 articles were retrieved, and 28 references were finally included in the review (Supplementary Table 2). Figure 1 shows a flow chart of the review selection process.

A total of nine different mechanisms that consider public investment in price or reimbursement negotiation leading to either lower purchase price of healthcare technology or to return on public investment made in earlier R&D stages were identified in these 28 publications. In total, six of these mechanisms are already used in practice, and their description is followed by examples of their application in P&R negotiations. The remaining three are proposals only that have not been applied in practice to date. The principal characteristics of each mechanism are summarised in Table 1.

### 3.1 Advance Purchase Agreements

Advance purchase agreements (APAs) are contracts under which pharmaceutical companies will subsequently supply a certain agreed quantity at prices that only cover the cost of production [20]. In 2020, the US government provided

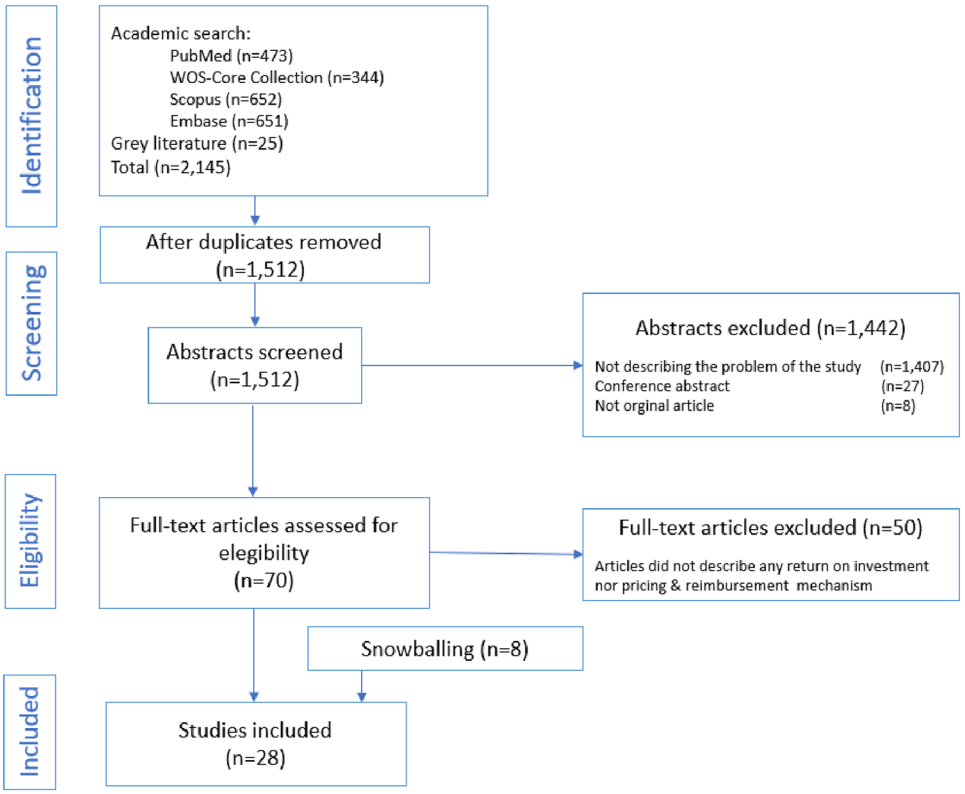


**Fig. 1** Flow chart of the study selection process

funding up to US$2.1 billion for the development and delivery of an initial 100 million doses of a COVID-19 vaccine developed by Sanofi Pasteur and Glaxosmithkline Biologicals, US$1.95 billion for 100 million doses of a BioNTech–Pfizer vaccine, US$1.6 billion for 100 million doses of a NovaVAx vaccine and US$1.2 billion for 300 million doses of an AstraZeneca–Oxford vaccine. This investment marked a major milestone in vaccine development, testing and licensing [35].

A variation of APAs is the R&D funding contract. The key difference between APAs and R&D funding contracts is that, while the latter focuses exclusively on supporting technology development without the purchase of products and specifically for new technologies, the former explicitly commits to purchasing products in the technology development process [20]. An example of a R&D funding contract is the agreement between the US Department of Health and Human Services and Moderna. This contract covered the costs associated with early stage vaccine development through to registration, with an option for scale-up of domestic manufacturing. It included a cost/price ceiling that the contractor could exceed at their own risk: therefore, the government was not obliged to reimburse the contractor for costs incurred in excess of the costs/prices agreed at the time of award [20, 36].

### 3.2 Royalties

According to Hyman and Silver [21], given the current patent system, the obvious solution for the government when there is public investment to fund a medicine development is to demand a royalty for the future sales in negotiation with the pharmaceutical company with intellectual property (IP) rights that could approximate the risk-adjusted value of the government's contribution to the final product. If the medicine is successful, this would generate funds that could be used, for example, to meet the cost of future research funded by public investment or to subsidise the costs of treating the drug in question. This royalty could also be used to reduce the price to beneficiaries of government-funded health programmes or for other budgetary issues [21]. Such is a case of Taxol for cancer treatment; the National Institute of Health (NIH) in the USA made large investments to R&D to Bristol Myers Squibb and, through a cooperative research and development agreement (CRADA), the NIH was allowed to receive royalty payments at a rate equal to 0.5% of the worldwide sales of Taxol. In their negotiation, the NIH considered factors such as the public health benefit, the stage of product development, the contribution of the NIH to the product, the type of product, the patent coverage, the market timing and the uniqueness of the materials [37].

Danziger and Scott [22] propose different types of royalties depending on the route of public financing in R&D,

**Table 1** Main characteristics of mechanisms (and their variations) that consider public investment in pricing and reimbursement decisions

| Mechanism | Primary objective | Where does R&D funding come from? (Example) | Who is compensated for this contribution to R&D? | Type of funding | Type of compensation | Condition on compensation | Time sequence | References |
|---|---|---|---|---|---|---|---|---|
| Advance purchase agreement | To reduce the purchase price of the health technology | Government | For-profit-companies | Contract (the purchase price of the technology is set at the time of the agreement) | Purchase of the product by the public body is guaranteed | Pharmaceutical companies provide agreed quantity of vaccines at prices that only cover the cost of production | Contract is prior to investment | [20] |
| R&D funding contract | To reduce the purchase price of the health technology | Government | For-profit companies | Contract covered the costs of vaccine development | | Pharmaceutical companies provide agreed quantity of vaccines at prices that only cover the cost of production | Contract is prior to investment | [20] |
| Royalties | To reduce the purchase price of the healthcare technology, to recoup a return on investors' investment, to subsidise the treatment costs or to cover the cost of future publicly funded search | Government | Government | Royalty | Reflects the risk-adjusted value of government's contribution to the product, | N/A | Investment prior to compensation (royalty) | [21] |
| Direct financing (intramural research) | | Government | For-profit companies | Royalty | e.g., profitability exceeding a stated threshold | License for using the technology | Investment prior to compensation (royalty) | [22] |
| Indirect financing (extramural research) | | Government agency (NIAID) | Federal agencies' laboratories (CDC, FDA, VA) or universities | Royalty | Percentage of future sales | Sufficiently successful commercialisation of technology | Grant is negotiated before the compensation | [22] |
| Venture philanthropy | To recoup a return on investors' investment | Philanthropic foundations (Cystic Fibrosis Foundation) | For-profit companies | Royalty | Percentage of future sales | | Investment is prior to the negotiation of royalty | [23, 24] |
| **Prize fund[a]** | **To incentivise pharmaceutical companies to invest in R&D of drugs for neglected diseases** | **Philanthropic foundations** | **For-profit companies (first producer of a technology)** | **Prize** | | **Additional therapeutic value of a new therapy over the already existing ones** | | [25] |

**Table 1** (continued)

| Mechanism | Primary objective | Where does R&D funding come from? (Example) | Who is compensated for this contribution to R&D? | Type of funding | Type of compensation | Condition on compensation | Time sequence | References |
|---|---|---|---|---|---|---|---|---|
| Prize fund[a] | To incentivise pharmaceutical companies to invest in R&D of drugs for neglected diseases by delinking the price of medicines from the fixed costs of innovation | Government, charitable foundations, international taxes (Health Impact Fund) | For-profit companies | Prize | Annual reward payments | The more a new medicine improves or lengthens human lives, the more money the innovator earns | Investment prior to compensation | [26] |
| Delinkage R&D model[a] | To reduce prices of medicines | Government/philanthropic foundation (Drugs for Neglected Diseases Initiative) | For-profit companies | Prize | Combination of research grants, subsidies and cash rewards | Marginal cost pricing | Investment prior to compensation | [27, 28] |
| Advance market commitment[a] | To reduce the purchase price of the health technology | Government or private foundations | For-profit companies | Prize | | To provide the vaccines at a price affordable to developing countries | Investment prior to compensation | [29] |
| **Prize system[a]** | **To reduce the purchase price of the health technology** | **Government or philanthropic foundations** | **For-profit companies (determined by an auction)** | **Prize** | | **Compensation is linked to delivered benefits Pharmaceutical companies can only charge the marginal cost of production** | **Investment prior to compensation** | [21] |
| Reasonable pricing clauses | To reduce the purchase price of the health technology | Government | Government | Contract containing a reasonable pricing clause | | Price of a healthcare technology should be comparable to the global market | Public funding and 'compensation' are negotiated at the same time | [17, 30, 31] |
| Social impact bonds (pay-for-success mechanism) | To transfer investment risk from the public sector to the private sector | Philanthropic foundation/for-profit companies | Philanthropic foundation/for-profit companies | Bond (operates over a fixed period of time but does not offer a fixed rate of return) | | Achievement of contractually agreed outcomes (i.e. positive social results and cost savings for the taxpayers) | Investment prior to compensation | [32] |

**Table 1** (continued)

| Mechanism | Primary objective | Where does R&D funding come from? (Example) | Who is compensated for this contribution to R&D? | Type of funding | Type of compensation | Condition on compensation | Time sequence | References |
|---|---|---|---|---|---|---|---|---|
| Government patent use | To reduce the purchase price of the healthcare technology | Government | For-profit companies | | Percentage of sales (under Section 1498) | | No obligation for prior negotiation of compensation (under Section 1498) | [33] |
| **Real-option rate of return model** | **To increase transparency in pricing, reduce R&D costs and potentially reduce prices of medicines** | **Government or public institutions** | **Government or public institutions** | **N/A** | **Reduced total R&D costs** | **Reduction of primary drivers of R&D costs (i.e. costs of capital, out-of-pocket failure costs and out-of-pocket success costs)** | **N/A** | [1] |
| **Publicly funded clinical trials of prescription drugs** | **To improve efficiency of the healthcare system by setting the prices of products at the marginal cost of production** | **Government** | **Companies carrying out the clinical trials with public money** | **Contract** | | **N/A** | **N/A** | [34] |
| **Direct tax credits** | **To reduce the purchase price of the health technology** | **Government** | **For-profit company** | **Direct tax credit** | **Direct tax credit is proximate to the social value of the innovation** | **Marginal cost pricing** | **Investment is prior to compensation** | [10] |

The "bold" is for mechanisms that have not been applied in practice to date. It should be noted that the characteristics of each mechanism were taken from the corresponding reference

*NIAID* National Institute of Allergy and Infectious Diseases, *CDC* Centers for Disease Control and Prevention, *FDA* Food and Drug Administration, *VA* Department of Veterans Affairs, *R&D* Research and Development, *N/A* not applied

[a]These mechanisms are subtypes of the prize system/delinkage R&D model

i.e. direct or indirect financing. When R&D is carried out by public institutions (intramural research), royalties for health innovations and granting of the patent to develop the technology must be negotiated at the same time. Thus, the technology transfer offices of the agencies that are in charge of royalty negotiation processes could intervene to negotiate those royalties for patented innovations. For example, the NIH negotiated the patent and royalties for the drug-eluting coronary stent with Angiotech Pharmaceuticals. Where direct public funding has been allocated to research through universities or other organisations (extramural research), as in the case of the R&D developed by the National Institute of Allergy and Infectious Diseases for the anti-viral remdesivir, the universities' (or other organisations') technology transfer agreements would be responsible for negotiating royalties. However, government royalties on the contribution to extramural research funding would not be triggered until such transferred technologies have been sufficiently successfully commercialised, with the criterion of 'sufficient' defined by the royalty policy as, for example, exceeding a threshold of profitability on the basis of experiences from other inventions where extramural research has been carried out [22].

A model that uses royalties is Venture Philanthropy [23, 24], a funding model proposed to impact investment in which a non-profit organisation makes investments in pursuit of its own goals. Despite being a non-profit organisation, this investment model has the potential to generate a financial ROI, which will be reinvested in a virtuous circle to support the mission of the non-governmental organisation (NGO). An example is the case of Kalydeco. The NGO that applied Venture philanthropy for Kalydeco's R&D investment was the Cystic Fibrosis Foundation (CFF). This agreement included an ROI for the CFF through royalties as a percentage of future medicine sales. The main objective of the CFF was to accelerate the development of new treatments for cystic fibrosis by funding promising scientific research in academia and in the biotechnology and pharmaceutical industries. In 2014, the CFF sold Kalydeco's future royalties to Royalty Pharma for US$3.3 billion that could be immediately reinvested to support the foundation's mission, i.e. activity-based payments to align incentives among stakeholders and ensure that progress is made for the benefit of patients [23, 24].

### 3.3 Prize System/Delinkage R&D Model

Stiglitz and Jayadev [25] proposed, among other things, the prize fund mechanism as a solution to the lack of incentives for pharmaceutical companies to invest in R&D for effective and new drugs for neglected diseases due to insufficient potential revenues. The guaranteed prize this mechanism provides to the first producer of a therapy for a neglected disease is subject to the amount of additional therapeutic value of a new therapy; if there is only reduced benefit over the already existing therapies, the compensation from the fund is reduced [25].

The prize system proposed by Hyman and Silver introduced the possibility to take an auction to determine which manufacturer is willing and able to supply the drug to its beneficiaries [21]. The delinkage R&D model is based on the idea that the costs and risks associated with the R&D process should be rewarded. However, the reward should be based on financial returns rather than used as an R&D incentive for developers (and, thus, based on high drug prices). This model implies paying for R&D through a combination of research grants, subsidies and cash rewards (innovation inducement prizes, market entry rewards or open-source dividends). These prizes would be innovation-inducement alternatives to a patent monopoly and would allow experimentation with a generic competition market that could lead to prices close to the marginal cost of production. In the USA, it became clear that replacing the patent model with the delinked R&D model would result in paying competitive prices and making significant savings. In 2005, Senator Bernard Sanders put forward a proposal called the Medical Innovation Prize Fund through which he required the US government to create a fund of 0.55% of the US gross domestic product (GDP) to finance, through rewards, researchers and drug developers to achieve public health goals of public need [38]. However, this proposal was not adopted in the end. A case in which the delinkage R&D model is used and accessibility and affordability are prioritised from the beginning of the R&D process from a public-health-needs point of view is a case of neglected diseases, namely the Drugs for Neglected Diseases initiative [5, 7, 27, 28]. Other successful implementations of prize fund are Gavi, the Vaccine Alliance [29] and the Health Impact Fund [26, 39, 40].

### 3.4 Reasonable Pricing Clauses

The reasonable pricing clauses model was designed for high-priced, publicly funded medicines. These clauses are a contractual provision, and, although varying in their requirements, they all impose some type of price limitations on the exercise of any rights governing a publicly funded medical product. Their inclusion is justified on the basis of criteria

of reasonableness, equity and non-discrimination regarding other prices paid abroad [30]. They must be included when negotiating transfer agreements involving the participation of publicly funded academic institutions to ensure a fair return on public investment while providing incentives for the private sector to innovate. Additionally, they must be defined by a transparent multi-parametric analysis considering the investments made and production costs incurred by the manufacturer, the added medical value over the already existing treatments and the public investments that supported academic research [17]. In the USA, a reasonable price clause was first created in 1989 requiring 'a reasonable relationship between the price of a licensed product, the public investment in that product and the health and safety needs of the public' [7]. In September 2023, the US Department of Health and Human Services included a reasonable price clause in the negotiation of a US $326 million public investment contract with Regeneron for the R&D of monoclonal antibody therapy against COVID-19. Since then, the principles of obtaining fair and reasonable prices have been considered by the Biomedical Advanced Research and Development Authority (BARDA) and Centers for Disease Control and Prevention [31, 41]. Another example where a reasonable clause was applied was in the development of a Zika vaccine in 2016 [30].

### 3.5 Social Impact Bonds

Social impact bonds (SIBs), also called pay-for-success contracts, are a mechanism that enhances innovation and the cost-effectiveness of such innovation by incentivising investors to contribute to the provision of public goods and services. According to the Non-Profit Finance Fund [32], SIBs are defined as pay-for-success financing arrangements where private investors provide seed capital for the provision of services and are repaid by an end or outcome payer (usually a government), if contractually agreed outcomes are achieved. The main purpose of this mechanism is that the investors, not service providers nor payers, bear the financial risk. Additionally, investors underwrite service providers only if they are probably able to bring about positive social results (i.e. positive health outcomes) and cost savings for the taxpayers [32].

In the pharmaceutical sector, SIBs have been used in the R&D of off-patent/generic medicine repurposing. Since the function of SIBs is to increase private investment in public goods and services, this mechanism will serve to counteract market failures in medical treatments that are viable using SIBs but not financially viable through traditional patent system investment. The first case of SIBs for medicines was used in 2016 in England by Bruce Bloom, president of Cures Within Reach (a non-profit organisation with the drug repurposing goal), for a generic medicine-repurposing SIB model. This model involved four main stakeholders: impact investors (who finance the clinical trials aiming for obtaining an ROI), healthcare payers (who pay on the basis of successful agreed outcomes), service providers (who conduct the clinical trials and determine the criteria set for results evaluation) and researchers (who propose the methodology for the clinical trial) [32].

### 3.6 Government Patent Use

Government patent use (28 US Code §1498) is a legal mechanism that allows governments to bypass the patent held by a pharmaceutical company for a product that has received public funding and to procure that product competitively. This enables federal procurement agents to accept bids for different deals regardless of the patent status, and the patent-holding companies can do nothing to prevent this. This mechanism is particularly attractive in cases where there are urgent public health needs, such as COVID-19. For example, after the anthrax attacks in 2001, the US government used this mechanism to reduce the price of antibiotics necessary by half to guarantee an adequate supply [7, 33].

Given that it was the only antiviral that showed efficacy in an emergency situation such as COVID-19 and benefited from substantial public sector funding and research collaboration, this mechanism could be used in the case of remdesivir, with the objective to get a reasonable price and ensure that taxpayers receive a fair return on public investment. There are suppliers of generic versions of remdesivir in China, Bangladesh and India. Thus, the US Department of Health and Human Services, which distributes the drug, considering that it has made substantial public investments and that remdesivir obtained emergency use authorisation in the US, could seek additional competitive bids for the active ingredient remdesivir, and the government could accept the most competitive bids. In this case, the right holder company could negotiate fair compensation for both the public and private investment. In the event of a failure to reach an agreement, the pharmaceutical company could claim compensation in the Court of Federal Claims. By invoking section 1498, the pharmaceutical company and government would obtain a fair price taking into account research and development costs as well as certain terms of the patent it holds [33].

### 3.7 Publicly Funded Clinical Trials of Prescription Drugs

This mechanism consists of public funding of clinical trials of medicines through contracts with companies capable of conducting these clinical trials. The main objective is to leverage high bargaining power to achieve prices close

to the marginal cost of production. These contracts would enable several contractors to carry out clinical trials with public money, thereby replacing the clinical trials currently conducted by private pharmaceutical companies.

For this, there would be a public agency in charge of managing these contracts with the responsibility of ensuring efficiency, effectiveness and ethical standards of everything related to the development of clinical trials, which would lead to greater public health benefits. Having different contractors with overlapping responsibilities ensures competition and reduces the likelihood of overlooking potentially promising medicines. One of the most important benefits of this system is the elimination of conflicts of interest.

This would be achieved by maintaining a strict separation between the companies contracted to conduct the clinical trials and the pharmaceutical companies holding intellectual property rights that will market the drug. This separation prevents any financial interest or bias, and there would be an obligation to publish all trial results and all communications between the parties publicly.

Other benefits of this mechanism are that (a) fewer resources would be devoted to the development of drugs that offer a small net incremental benefit over existing drugs; (b) there would be no motivation to fund projects where there is no evidence to show any public benefit rationale for continuing the R&D process; (c) it would benefit certain drugs that lead to the replacement of other drugs that cause adverse reactions; (d) it would discourage pharmaceutical companies from conducting their own clinical trials, as the price they will receive from public payers would be the same as the price received by companies participating in this system; (e) a full public breakdown of research results would allow more information to be learned and analysed for future studies and (f) it would eliminate inappropriate payments by the pharmaceutical industry to doctors participating in public trials, which often include a component of future prescribing of the drug being studied [42]. This would remove the incentive for doctors to prescribe specific medicines and, in the absence of such payments, lower the cost of clinical trials.

There is no evidence of any real-world experience in which this mechanism has been used; however, the author demonstrated, through real data and under plausible assumptions, that this mechanism allows savings to be made by reducing the price of medicines and other additional benefits [34].

### 3.8 Real-Option Rate of Return Model

Van der Schans et al. [1] propose a model that aims to conduct pricing in a fair, transparent and sustainable way, potentially translating into a lower price setting. It considers all relevant costs at the pricing stage, including three types of R&D costs: out-of-pocket costs, failure costs and cost of capital. Thus, the model calculates all relevant current and future R&D costs (real option) and derives the price on the basis of these costs considering a predetermined rate of return. In other words, the model translates cost savings, due to increased transparency in pricing and reduced R&D total costs, into price reduction [1].

According to the author, the model has additional implications. Pricing based on the real rate of return, in the case of orphan drugs that lack competition after patent expiry, would improve availability, affordability and the level of care. In addition, this model would allow medicine prices to be adapted on the basis of each country's gross domestic product and the public investment that has been made. Finally, in case of failure, the governments would share the risk with the development company [1].

### 3.9 Direct Tax Credits

Under this mechanism, the objective of the governments is to obtain a price equal to marginal cost in exchange for providing tax incentives to the innovating firm through direct tax credits that are quantified by external experts approximating the assessed value of the innovation. If this agreement were to be adopted by pharmaceutical companies in a certain nation, price disparities between different customer segments would disappear, and any monopoly pricing would be eliminated, thereby increasing consumer surplus and access. Moreover, even eliminating the patent system would maintain the incentives for pharmaceutical companies to invest in R&D and not disrupt the development of innovation by transferring the risk inherent in pharmaceutical research to the taxpayer rather than to private companies, because it would be the taxpayers who would pay for R&D through direct tax credits. This system would maintain financial incentives for the innovator, similarly to the social value of the innovation, while improving access through marginal cost pricing at the same time. The social value of innovation (i.e. the amount of direct tax credits and that corresponds to the sum of the consumer and the producer surplus) would be assessed by the forces of the market and calculated on the basis of a function of a benchmark year of sales at market prices reflecting the private value of innovation. Hence, there will be a first year of monopoly price for the innovator with intellectual property rights which will be used as a benchmark for the social value of the innovation, and that benchmark year will be considered to quantify the amount of direct tax credits, which will be received for 12 years. From then on, the generic competition will begin. Therefore, the calculation of the direct tax credits will be higher the higher the incremental therapeutic benefit [10].

## 4 Discussion

To the authors' knowledge, this is the first review providing evidence of different mechanisms that consider public investment in medicine and other health technology R&D. A considerable number of articles mentioning a 'pay-twice' critique was identified. However, they did not propose any solution; therefore, they did not accomplish our inclusion criterion and thus had to be excluded from a full-text review. Final results identified nine mechanisms; most of them focus on reducing purchase prices [1, 10, 20, 21, 27, 29, 30, 33, 34], while others aim at ensuring a fair ROI [21–24, 37], incentivising companies to invest in R&D [25, 39] or transferring investment risk from the public sector to the private sector [32]. Theses mechanism can also be categorised into those currently used in practice and those that are proposals, whether as variations of existing mechanisms (e.g. the prize system proposed by Hyman and Silver [21] and the real-option rate of return based on a mathematical model [1]) or novel concepts (e.g. publicly funded clinical trials of prescription drugs [34] and direct tax credits [10]).

### 4.1 Implications of Identified Mechanisms and Possible Solutions to Pay-Twice Critique

APAs are a type of mechanism designed to finance global public good in situations where there is a global health need (e.g. antiviral treatment molnupiravir) [43]. The use of APAs has been notably effective during the COVID-19 pandemic, where significant funding from the US government led to the development and delivery of vaccines mainly at prices covering only the production costs. The use of APAs has also been implemented in Europe through the agreement signed between the European Commission and several pharmaceutical companies to secure the supply of COVID-19 vaccines for European Union (EU) member states. These agreements were made with companies such as AstraZeneca, BioNTech–Pfizer, Moderna and Johnson & Johnson. The commission committed significant funds to support the research and development of these vaccines and to ensure the delivery of doses once approved. Similar to the USA, APAs in Europe stipulated that pharmaceutical companies would provide an agreed quantity of vaccines at prices covering only the production costs. These agreements included provisions for accelerated delivery and prioritisation of doses based on public health needs. The main impact of this mechanism was the rapid vaccine deployment and incentives for innovation, facilitating the rapid development of vaccine in record time. The main limitation of APAs is that they require substantial upfront public investment and careful management to ensure that negotiated prices reflect true production costs without compromising quality or accessibility. Moreover, there are only experiences of their use for the financing of global public good such as vaccine. However, there is some dispute about the last European Commission APA with Pfizer (2024–2027) because it is a 'traditional' contract and it is not under the definition that has been used in this review for APAs.

R&D funding contracts, on the other hand, are used in countries such as the USA, which do not have a global public healthcare system where medicines are publicly funded nationally. Therefore, in the case of the USA, there is no mandatory purchase, and such purchases can be made by health insurers or public health insurance programs such as Medicare.

Royalties are designed to provide an ROI for the licensors who have invested in the R&D of a medicine, allowing them to recoup costs and potentially profit from their innovations. However, they have several limitations. First, the complexity in negotiation: negotiating the appropriate royalty percentage can be complicated, as it must equitably reflect public investment and R&D costs. This requires a detailed and transparent evaluation, which is not always easy to achieve. Negotiations can lead to legal disputes between the government and pharmaceutical companies over fair compensation and payment terms. Second, delays in investment recovery: royalties are paid over time based on the drug's sales, meaning the recovery of public investment can take many years. This can be a disadvantage compared with other mechanisms that offer quicker returns. Third, limited impact on initial prices: royalties do not necessarily reduce the initial price of the drug. Pharmaceutical companies may set high initial prices to maximise revenue, as royalty payments are tied to future sales.

Reasonable pricing clauses aim to balance fair pricing with public investment; however, their implementation faces significant challenges. These include defining and enforcing reasonable prices, ensuring compliance, addressing potential disincentives for innovation, managing complex negotiations and dealing with global access and market uncertainties. Moreover, reasonable pricing clauses are probably difficult to apply owing to the complexity of defining 'reasonable'. Previous examples have linked 'reasonable' with 'be equal to or less than its retail price in comparable markets globally' (Regeneron case), assuming that international reference pricing is a fair method for setting the price [31]. Therefore, careful consideration and management of these limitations are crucial to achieving the intended outcomes of reasonable pricing clauses in pharmaceutical pricing and reimbursement.

SIBs offer an innovative approach to funding public health interventions, including drug pricing and reimbursement. However, they come with significant limitations. These include the complexity of structuring agreements, challenges in measuring and attributing outcomes, financial

risks, high transaction costs, alignment of incentives, scalability issues, equity concerns and questions about long-term sustainability. Addressing these limitations is crucial to effectively leveraging SIBs for public investment in the pharmaceutical sector.

In the real-option rate of return model, the price per patient per year (real-option rate of return) is calculated by adding to R&D costs a margin in terms of the rate of profit [1]. Even this model is described by the author as a novel concept; however, it is nothing less than a cost-plus pricing that determines the price of medicines by estimating the production costs and adding a profit margin. A problem with 'cost-plus' models is information asymmetry, or 'hidden information', for example, it is not clear who decides the cost and how costs are measured, and there may be an incentive for the seller to inflate his declared costs. Additionally, as prices are relatively stable, they may not consider market fluctuations, such as changes in currency exchange rate. This model is actually not recommended by the World Health Organization for setting the price of pharmaceutical products [44]. Another issue regarding real-option rate of return as described by van der Schans [1] is that it seems that with 'real option' the author refers to the fact that the rate of return is based on future profits that are estimated as well as possible to reflect the real profits. However, the term 'real option' as used by the author can be quite misleading, as a real option value is a concept in financial services and refers to a right (but not an obligation) to make a business decision. 'Real' makes reference to a tangible asset instead of financial instrument [45]. Following this definition, there is no real-option valuation in the proposed model.

Under the publicly funded clinical trials of prescription medicines, model prices would be close but not equal to marginal cost of production. This is because when a development of a medicine comes to a publicly funded clinical phase, there is already a pharmaceutical company with intellectual property rights (this is because this company discovers the medicine in stages prior to the conduct of a clinical trial). Additionally, the prices should not drop down to a marginal cost of production because it is important that the private companies have an incentive to innovate [34]. However, it should be noted that this model should contribute to private companies' reduced incentives to innovate. A similar idea is also supported by the health technology assessment agencies of Belgium and the Netherlands; they propose a scenario under which a health technology would become public good; thus, the existence of patents and monopolies would no longer be justified as R&D of medicines, and other health technology would be a public enterprise [9]. Another idea proposed by the above-mentioned agencies is creating a fund jointly by a consortium of European countries that would be responsible for both buying out of the patents for promising drugs and completing the last phases of research. Research and development would delink from manufacturing and sales and, as a result, the price of medicine would fall to be more affordable and fair [9].

Pharmaceutical companies are important players in R&D of medicines; however, they are often criticised for charging too-high prices to consumers and public institutions [4, 5, 7]. On occasion, they can sell medicines in developing countries at marginal cost of production, but we cannot expect them to be charities. In this respect, the prize system could be a solution, as it has different benefits. First, R&D is funded by governments or philanthropic foundations, organisations, corporations or institutions, and, because the incentives for pharmaceutical companies come from public funds rather than the high prices made possible by a patent, the direction of drug innovation is driven by public health needs identified by and for public interests [5, 27]. Second, a prize system has the capability to eliminate the prospect of pharmaceutical companies seeking monopoly rents and tax exemptions that cause researchers to develop treatments for rare diseases and to establish the efficacy and safety of drugs before trial requirements have even been announced [21]. Third, given that, under this system, universities would no longer be able to patent discoveries, the fact that public investment for R&D has been involved could require open access to all results, thus increasing transparency and eliminating trade secrecy. This would eliminate the huge private profitability of publicly funded research and facilitate cooperation between scientists owing to open data [21]. Fourth, under the prize system, there is self-selection, i.e. those who believe they are expected to succeed compete [25]. Last, but not least, foundations working on the basis of the prize system are transparent; the information regarding the origin and destination of their funds can be easily accessed from their official webpages [26, 28, 29].

Pursuing the above idea further, the winner of the Office of Health Economics (OHE) Innovation Policy Prize launched in 2022 by the OHE—in which the posed question was 'how can policymakers design a system to generate fair prices that balances access and innovation throughout the lifecycle of medicine?'—proposed a so-called 'optional delinked reward system (ODRS)'. It is a supplement to existing insurance systems, offering pharmaceutical companies an alternative payment model, where, instead of traditional pricing, companies can opt for the ODRS, receiving a unit price equal to production and distribution costs and a reward based on the drug's incremental health benefits (measured in quality-adjusted life years). A fixed reward would be paid over 10 years, and, after this period, generics would be allowed. Under this system, the 'fair' price of new medicines meets three objectives that are currently not accomplished: (a) the price is 'fair' between buyers and sellers (i.e. the price ensures that the poor buyers can afford the medicine at the same time as the rewards of the firms for

**Table 2** Definition, advantages and disadvantages of the main mechanisms that consider public investment in pricing and reimbursement decisions

| Mechanism | Definition | Advantages | Disadvantages |
|---|---|---|---|
| Advance purchase agreement | A contract under which pharmaceutical companies will subsequently supply a certain agreed quantity of vaccines at prices that only cover the cost of production | Accelerates innovation in emergencies<br>Ensures rapid access<br>Pricing based on actual production costs | Requires substantial upfront public investment<br>Mostly limited to public goods (e.g. vaccines) |
| Royalty | Payments negotiated with the rights-holder company for having developed the medicine with public investment (often in the form of a percentage of sales generated from the licensed product) | Enables return on public investment<br>Promotes public–private collaboration<br>Can generate long-term revenue | Slow recovery of investment<br>No effect on initial drug price<br>Negotiation can be complex and legally sensitive |
| Prize system/delinkage R&D model | Rewards for pharmaceutical innovators subject to results of additional therapeutic value of new therapies. It is an alternative to the patent system that achieves prices close to marginal cost | Promotes access and affordability<br>Aligns R&D with public health needs<br>Increases transparency and open science | Requires significant public funding<br>Defining fair rewards is difficult<br>Limited real-world experience |
| Reasonable pricing clauses | A contractual provision setting conditions for fair pricing on publicly funded medical products | Seeks fair return on public investment<br>Can be enforced through licensing agreements<br>Encourages transparency | Ambiguity around defining 'reasonable'<br>May discourage private partners |
| Social impact bonds | Pay-for-success financing arrangements where private investors provide seed capital for a provision of services and are repaid by an end- or outcome payer if contractually agreed outcomes are achieved. | Transfers financial risk to investors<br>Encourages innovation and efficiency<br>Incentivises positive social outcomes | Complex to structure and monitor<br>Difficult to measure outcomes accurately<br>High transaction costs and scalability issues |
| Government patent use | Legal mechanism allowing governments to bypass the patent held by a pharmaceutical company for a product that has received public funding and to procure that product competitively | Reduces prices during public health emergencies<br>Enables competitive bidding<br>Already established in law | Potential legal disputes<br>Politically sensitive<br>Rarely used in practice |
| **Real-option rate of return model** | **The model that translates costs savings (due to an increased transparency in pricing and reduced R&D total costs) into price reduction** | **Promotes transparency and cost-based pricing**<br>**Shares risk between public and private sectors** | **Limited flexibility to market changes**<br>**WHO does not recommend these types of 'cost-plus' pricing** |
| **Publicly funded clinical trials of prescription drugs** | **Public funding of clinical trials of medicines through contracts with companies capable of conducting these clinical trials** | **Eliminates conflicts of interest**<br>**Allows prices near marginal cost**<br>**Mandatory publication of results** | **No real-world implementations to date**<br>**May reduce private innovation incentives**<br>**Requires capable public infrastructure** |
| **Direct tax credit** | **Consists of obtaining a price equal to marginal cost in exchange for providing tax incentive to the innovating firm through direct tax credits approximating the assessed value of innovation** | **Maintains R&D incentives without monopoly pricing**<br>**Encourages access and equity**<br>**Value-based incentive structure** | **Complex valuation of social benefit**<br>**Risk of public over-subsidisation**<br>**Requires strong oversight and auditing** |

Source: own elaboration based on the references used in the manuscript

The "bold" is for mechanisms that have not been applied in practice to date

their investments are ensured), (b) the price is 'fair' among sellers (i.e. the rules for rewards are clear and not randomly set) and (c) the price is 'fair' between countries (i.e. each country contributes appropriately to the global investment in innovation). The system would be budget-limited, encouraging competition based on health outcomes. Assessment relies on clinical trial data adjusted for real-world use, not on individual patient outcomes [46]. Thus, it seems that a prize system/delinkage R&D model in some of their form proposed could stop the increasing prices of medicines.

The main advantages and disadvantages of each mechanism are presented in Table 2.

This scoping review reveals the existence of several instruments that can be considered in P&R negotiations. However, it should be noted that, currently, there are only two countries in Europe that have introduced the criterion of considering public investment in R&D for the P&R negotiation: Italy and France. Italy was the pioneer country in Europe to introduce a requirement for pharmaceutical companies to declare the breakdown of public contributions, subsidies and incentives they have received for the R&D of medicines during the P&R negotiation. These new criteria have been applied by the Agenzia Italiana del Farmaco (AIFA) since 24 July 2020 [47]. Since these measures are recent, there have not been significant drops in domestic prices or compared with other countries. For its part, in 2021, France registered Article 79 of the Loi de Financement de la Sécurité Sociale, requiring pharmaceutical companies to declare to the Comité Économique des Produits de Santé (CEPS) the amount of public investment in R&D from which they have benefited [48]. The measures are having a very limited impact, as very few pharmaceutical companies are reporting public investments, and those that do are declaring lower amounts than the actual ones [49].

### 4.2 Limitations of the Scoping Review

This scoping review has several limitations. First, although the search was comprehensive and included multiple databases and grey literature sources, it is possible that relevant publications were missed, particularly unpublished reports or documents not indexed in the selected databases. Second, while the review aimed to include international evidence, most of the mechanisms identified and described are concentrated in high-income countries, particularly the USA and Europe, which may limit the generalisability of the findings to low- and middle-income countries.

In addition, several of the mechanisms identified are conceptual or have been applied only in limited or exceptional cases, meaning that the assessment of their effectiveness, feasibility and impact is based on theoretical or preliminary data rather than robust empirical evaluation. Moreover, the classification of mechanisms and their categorisation into practical versus proposed models were based on authors' interpretation of available evidence and may be subject to change as new examples emerge. Finally, as the field of pricing and reimbursement policy is evolving rapidly, several newer initiatives or mechanisms might not yet be captured in literature, especially if they have not been formally documented or evaluated.

## 5 Conclusions

This review has identified mechanisms that can be used for the development and financing of healthcare technologies with public R&D investment. Several of these have the objective of setting prices that are closer to the marginal cost of production. Others do not result in lower prices; instead, they provide an instrument to obtain a return on public investment, costs savings or risk sharing in R&D. However, we also find that these mechanisms are rarely used in R&D or P&R decisions in practice. Thus, policymakers and health economists should propose a framework to present alternatives to the patent system, such as the identified mechanisms, for those medicines and other health technologies that have received substantial public investment. In this way, decision-makers could adapt to different R&D scenarios to offer a fairer and more sustainable system for taxpayers.

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