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PERSPECTIVE

A novel perspective on pharmaceutical R&D costs: opportunities for reductions

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ABSTRACT

Introduction: R&D costs as an element of medicines' pricing play a prominent role in the discussions regarding the affordability of medicine. This paper investigates the details of R&D costs and the potential for reductions.

Areas covered: The manuscript focuses on the constitution of R&D costs in relation to medicines' pricing and its potential developments. This manuscript builds on a cost-of-opportunity approach to explore the results of potential changes in drug development and its possible economic, political, and societal impacts.

Expert opinion: The cost of capital is the largest cost category that could be affected by authorities. Public institutions can affect these costs by increasing public investments in R&D and reducing the amount of development time that is associated with a high capital need. In order to affect the cost of failure, it is key to understand its drivers. A government taking risks as the funder of early innovation yields an opportunity to introduce an alternative model for medicine development. Next, to control pricing, it is important to adequately reward innovation in order to ensure improved quality of care, access, and affordability of systems. Innovation, high-quality care, access, and affordability require entrepreneurial and changing positions of governments, authorities, public institutions, and the pharmaceutical industry.

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Affordability; cost-based pricing; cost of capital; cost of failure; drug development; R&D costs; transparency; value-based pricing

1. Introduction

R&D costs in relation to medicine pricing has become an important ingredient in societal discussions on healthcare spending [1–3]. This paper builds on collaborative work by the Gupta Strategists and the Fair Medicine Foundation on the topic of R&D investments in medicine development [4]. Here, we specifically focus on the determination and composition of R&D costs to further explore the results of an alternative fair pricing model for medicines and its potential effect on medicine prices as well as its potential economic, political, and societal impact.

In the USA, the mean price of the top-100 specialty products for non-orphan medicines increased from 13,810 USD per patient per year to 33,654 USD and for orphan medicines from 1,11,124 USD to 1,50,854 USD between 2010 and 2018 [5,6]. Overall, the share in product launches of specialty medicines in the US was estimated at 61% in 2018. In the US, the EU5 (i.e. France, Germany, Italy, Spain, and the UK), and other major developed countries taken together, the share of projected spending for specialty medicines, in total, is expected to rise between 2019 and 2023 [7]. In particular, for orphan products, the share of new product launches in the U.S. has increased from 34% in 2008 to 44% in 2018 [7]. Increases in specialty medicines have come with high prices and increased pressure on healthcare budgets in many countries, which has led to discussions on affordability and pricing [7–11]. The trends of an increasing share of specialty medicines, high prices, and associated spending on medicines are likely to continue considering the current medicine pipeline development [8,10,12,13]. In particular, oncology and orphan drugs are subject to discussions regarding medicine pricing, and healthcare spending often focus on these categories [10,12–15].

Pricing trends for medicines are often strongly aligned with the value-based pricing principle, for which the added value of the product compared to the competitor or standard of care is determinative for the product price [16]. Cost-effectiveness is presented as the cost per Quality-Adjusted Life Year (QALY) and the willingness-to-pay threshold generally leads to a higher price setting than warranted by cost-based pricing approaches. Value-based pricing propositions may have led to situations in which potentially cost-effective medicines were considered to pose affordability challenges from both health-system and societal perspectives. Such considerations indicate the current major healthcare challenge that concerns affordability issues and, with that provide instrumental input for the political and societal debates. Notably, the political and societal pressures on the price-setting of medicines potentially has an impact on patients' access to them. Next, to value-based considerations, the current reasoning behind product pricing

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Article highlights

- The costs of capital and failure, on average, account for 93% of the total R&D costs and are therefore considered as the most suitable cost category that could be targeted for reducing R&D costs.
- A more entrepreneurial government as a co-investor in early innovation yields an opportunity to impact the current medicine development model.
- A reduction in failure costs can be achieved by organizing multi-stakeholder coalitions that evaluate product development steps with corresponding investments.
- An innovative method for medicine pricing ensures a fair price and transparency in publicly funded medicine development.
- Alternative models for medicine development that could address the current accessibility challenges and affordability critiques need to be considered within future public-private investment in product development in order to ensure affordable healthcare and patient access to innovative medicines.
- Application of alternative models seems to be most suitable for low-volume, high-cost medicines, such as rescue antibiotics and (ultra-) orphan products.

is sometimes characterized by the justification of the price pointing to the requirements for innovative medicines and associated high R&D costs as well as the high risks of medicine development. However, in general, the relation between R&D investments and pricing is not transparent for (valid) business reasons. This is often related to the global differential pricing that is used to achieve the optimal rate of innovation and R&D investments (e.g. dynamic efficiency) [17]. However, this enhances the aforementioned increasing societal and political pressure and questioning of the conventional model of medicine development.

The 'toolbox' of authorities to deal with rising medicine spending, increase in volume and strain on the healthcare budget is expanding into a broad spectrum of possibilities [18]. Examples of this are the horizon scanning that is performed to identify medicine with potentially high prices or impact on the healthcare budget; delinkage of R&D costs for antibiotics; recent COVID-19 vaccine development; performance-based entry and payment agreements for medicines with high prices and/or uncertain added value; multi-criteria decision analysis conducted by authorities and decision-makers; and proposed models for fair pricing [8,15,18–22]. These interventions can be divided into pre, peri, and post launch interventions. Managed entry agreements, proposed models for pricing validation, indication-based pricing, differential pricing, joint international negotiations, and initiatives have thus far focussed on quantifying the value of new medicine [18]. While the peri and post launch activities are valuable tools to deal with an increased strain on the budget, it might be more beneficial to install prelaunch activities to be proactive rather than reactive. Therefore, we aim to focus on early, prelaunch interventions during development and to propose a methodology for fair pricing following the development of medicines as an alternative to value-based pricing approaches.

Recently, in response to the COVID-19 pandemic, many vaccines were developed within a relatively short period of time with initiation of a vaccination within 10 months [22]. It was estimated that 61% of all vaccine development costs were paid with taxpayers' money and only 25% was paid by the pharmaceutical industry [22]. The remainder is funded by wealthy benefactors [22]. Discussions on the adequate pricing of these vaccines have, among others, focused on these distributions. The recent pandemic stimulated strong initiatives in public-private funded development with the ultimate goal of quick access following market authorization and reimbursement arrangements. Several procurement agreements anticipate supply issues and secure sufficient availability of vaccines, illustrating the possibilities of success for alternative models of development.

In response to the increasing discussion regarding the current model of medicine development, alternative development, and pricing models are being explored with an important focus on fair pricing, transparency, access, and affordability. The suggested R&D and pricing framework could offer solutions for product-market combinations for which – from a return-on-investment perspective – it remains ambiguous whether the current pharmaceutical model will efficiently deliver the innovation. Notably, in this context, the 'real-option rate of return' pricing model is suggested including all relevant costs in the final price-setting of medicine. This includes the three broad R&D cost categories discussed in this paper. This approach may afford opportunities for increased transparency in pricing and reduced R&D costs, potentially translating into a lower price setting.

2. Methods

This paper builds further on a published Cost of Opportunity report [4]. The data that was used was derived from the Evaluate Pharma database and represents the worldwide spending on pharmaceutical products by pharmaceutical companies between 1990 and 2017 [23]. This includes all spending from preclinical development up to and including registration and phase 4 investments. The investments included are limited to pharmaceutical investments and do not include academic and governmental investments.

In order to obtain insight into the new molecular entity's (NME) total R&D costs, data on drivers of R&D costs was derived from a literature search aimed at identifying original research papers discussing R&D costs per NME published between 2000 and 2017. In addition to this, a literature search was performed on published manuscripts regarding R&D costs and its most important drivers. These drivers included number of subjects per trial, trial duration, success rate and weighted average cost of capital (WACC).

2.1. The cost of opportunity approach

The total R&D costs per NME was defined as the sum of the out-of-pocket costs spent on the successful product, the out-of-pocket failure costs, and the cost of capital. The calculated costs per cost category were calculated for the preclinical phase, phase 1, phase 2, and phase 3 trials, and the approval phase. Formulas for the cost of opportunity approach are shown in equation 1a-e below.

Equation 1a-e: Calculation of the different cost categories (derived from the Cost of Opportunity report) [4].

$$a)\quad Oop\,suc = (Oop\,suc\,PC) + (Oop\,suc\,Ph1) + (Oop\,suc\,Ph2) + (Oop\,suc\,Ph3) + (Oop\,suc\,appr)$$

$$b)\quad Oop\,fail = (Oop\,fail\,PC) + (Oop\,fail\,Ph1) + (Oop\,fail\,Ph2) + (Oop\,fail\,Ph3) + (Oop\,fail\,appr)$$

$$c)\quad Oop\,fail = (Oop\,succ\,PC) * \frac{1}{PPC * Pph1 * Pph2 * Pph3 * Papp} - Oop\,succ\,PC$$

$$d)\quad CoC = CoC\,PC + CoC\,Ph1 + CoC\,Ph2 + CoC\,Ph3 + CoC\,appr$$

$$e)\quad CoC\,Pc = (Oop\,success\,pc + Oop\,Pc) * ((1 + WACC)^{TPC+Tph1+Tph2+Tph3} - 1$$

OoP: Out-of-pocket, PC: pre-clinical, phx: Phase 1, 2 or 3, Appr: Approval, Px: success rate for phase x (100% – failure rate for phase x), CoC: Cost of capital, Tx: Duration of phase x (years), T: Time of development in years, WACC: Weighted average cost of capital, Suc: success, Fail: failure

The formulas shown above are the basis of the costs-based price determination that we will propose in the results. Reported success rates, duration per phase, and weighted average cost of capital (WACC) were the primary drivers in the cost determination [4].

To establish futureproof R&D models, we explore the methodology for alternative R&D and pricing models, the real-option rate of return model, as well as regulatory and reimbursement frameworks. Its possible implications are described and discussed in the next sections. The goal of the developed real-option rate of return model is to calculate a fair price. We defined a fair price for medicine in accordance with the definition by the WHO: 'one that is affordable for health systems and patients and that at the same time provides sufficient market incentive for industry to invest in innovation and the production of medicines' [24].

3. Results

3.1. R&D costs opportunities for reductions

The average R&D costs per NME were estimated at 2.5 billion USD, which is in line with the estimate by Dimasi 2016 et al. [3]. The R&D costs estimates range between 0.5 billion USD for biologic orphan products and 6.5 billion USD for an oncology small molecular entity. While the Cost of Opportunity report substantiates the analysis by Dimasi et al. (2016), it also demonstrates the widespread R&D cost estimates between indications. Other estimates commonly used in the discussion regarding R&D costs are from Prasad 2017 et al. (757.6 mln 2017 USD, range: 203.6 mln – 2,601.7 mln) [2]. While this article does raise a fair question with regard to transparency of R&D cost determination published by Dimasi et al., their method for calculating R&D costs makes it possible to not include all R&D costs, such as failure costs.

As shown in Figure 1, the costs of capital (53%) and failure (40%) account, on average, for 93% of the total R&D costs. Therefore, these cost components seem most suitable for initiatives aiming at the reduction of R&D costs and, with that the product price. The cost of success (7%) is the direct investment in the development of a successful pharmaceutical product. Since this money has been invested in successful product development, the R&D costs are attributed to all stages of this development (Figure 1).

3.2. Cost of capital

The cost of capital is the largest cost category that could be affected by national or international authorities by rules and regulations and public institutions through funding and affecting the cash need of projects. Additionally, university medical centers (UMCs), other hospitals, and universities can impact

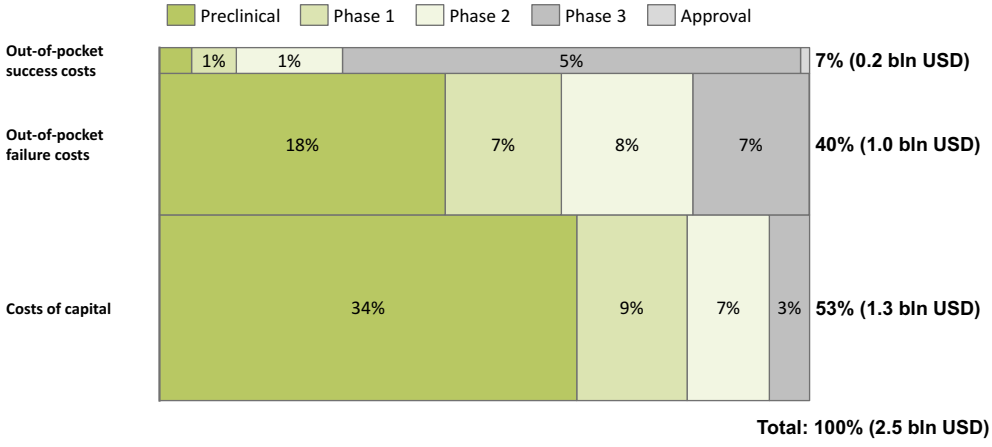

Figure 1. *Composition of R&D costs per NME across cost components and phase of development up to and including product registration based on worldwide Evaluate Pharma data between 1990 and 2010 (2017 dollar) (figure derived from the Cost of Opportunity report) [4]. (NME= new molecular entity, bln = billion, USD = United States Dollar).*

the funding and cash needed through publicly funded early research and valorization. These institutions can affect the cost of capital in two ways: public investments in R&D for medicines and a reduction of the time spent on (early) development phases for which there is a high need for capital. A reduced requisite for capital can be achieved by prolonging the phase in which public institutions develop medicines. This requires additional (public) funding mechanisms to be made available to these institutions with social responsibility in mind and possible restrictions on price [25]. Another potential way to change preclinical development is by preclinical information sharing to accelerate drug discovery [26]. These are examples of the application of the push and pool mechanisms, using public investments to make a project more interesting and create a potential delinkage of R&D costs depending on the conditions of investments. This could occur in collaboration with industry partners. Notably, there is a relatively minimal need for private investment in the early development phases.

Total funds that are capitalized can be reduced by enhancing public investments or implementing zero costs tech transfer from public institutions under-predefined conditions (delinkage of R&D costs). Figure 1 shows that 34% of the total R&D costs relate to the preclinical cost of capital. Therefore, reducing spending in that phase has much more effect on total costs than a reduction of costs in later development phases. Therefore, the structural use of public funding sources in the earliest phases of development yields potential opportunities to decrease capital costs accumulated during the early development phases.

Investing public capital in medicine development is possible in two forms. Firstly, the same conditions as those that apply for private money can be enforced combined with influence on market entry conditions for the public party involved. Secondly, even better conditions than private money may be applied combined with some strict predefined conditions on pricing. These are both viable options to potentially allow for substantial cost reductions. Direct return on public capital can be achieved by using the revenues generated by the products but also from societal gains in terms of health benefits and averted economic burden. Depending on the conditions, the cost of capital could, for example, be partly reduced or redistributed to public institutions as a return on their investment and used for future investments.

The time over which funds are capitalized can potentially be reduced by more extensive preclinical development by public institutions or by decreasing the amount of time until and investment requirements for market introduction. For the latter, we see a possibility reduce the time to market by accepting early reimbursement with early (provisional) approval (e.g. managed entry agreements) before phase 3. This could be especially appropriate for specific products such as orphan drugs and those for serious conditions and the end-of-life phase because the need for new treatments and the burden of disease is significant. Next, to a reduced cost of capital accumulation, additional benefits may occur for patients that achieve earlier access than otherwise would have been the case. The underlying principle is shown in Figure 2 that the total cost of capital increases primarily in later years.

3.3. Cost of failure

In order to affect the cost of failure, it is crucially important to understand the key drivers of failure. The concept of failure is not a rigid definition but occurs in multiple forms with numerous consequences. It consists of the chance of failure, time until failure, and capital loss. Furthermore, it occurs in all the phases of development and can therefore affect the involved parties differently [4]. The various results of failure can be primarily attributed to the different sources of funding and stakeholders involved. The failure costs are calculated by multiplying the direct investments by one divided by the chance of future success [4]. Understanding why and where in medicine development this occurs, and the identification of potential interventions, could lead to risk reduction and subsequently lower R&D costs.

Early failure occurs at academic institutes and start-ups as a result of their involvement in the early pioneering phases when the chance of failure is the greatest. Failure of these parties means not receiving a patent or generating a proof-of-concept. This phase is primarily funded with subsidies, grants, and public capital through academic institutes [27,28]. For start-ups, failure could mean that the business must be liquidated as they are generally funded by government subsidies, grants, and also venture capital [27,28]. Start-ups with faster economic potential are usually funded with venture capital. In general, the financial support for start-ups for preclinical or early clinical development is derived from grants and subsidies [27–29]. While we discuss ways to reduce the chance of failure and, with that, reduced costs of failure, it is important to note that interventions related to managed entry agreements also affect the failure profile of medicine development. Conditional or accelerated approval or payments based on limited or preliminary data are associated with additional costs (post launch studies) and a risk that patients do not receive the optimal treatment, and there is uncertainty of the outcomes [30]. The possibility of failure to achieve desired results for approval or full payment is attributed to a higher failure rate in the approval phase with greater costs associated with this. A high failure rate late in the development process substantially increases the cost of failure. Therefore, a review of the early access system in this context would be advised with its possible effect on R&D costs and health outcomes. The national authorization and reimbursement systems would benefit from more cooperation between countries in data collection, post-marketing research, as well as data analysis, and interpretation [30].

Failure of large pharmaceutical companies means that the development of a specific pipeline product is being delayed or terminated, which does not directly affect other R&D projects and does not necessarily have an immediate impact on the company, as this is implicitly part of the R&D investment and decision-making process. The later phases of development are fully funded by the pharmaceutical company or venture capital [27,28]. Types of failure within medicine development can be largely divided into two categories: biological or medical reasons and economic or strategic reasons. Failure for economic or strategic reasons is related to the business and earnings model. As time progresses, successful medicine

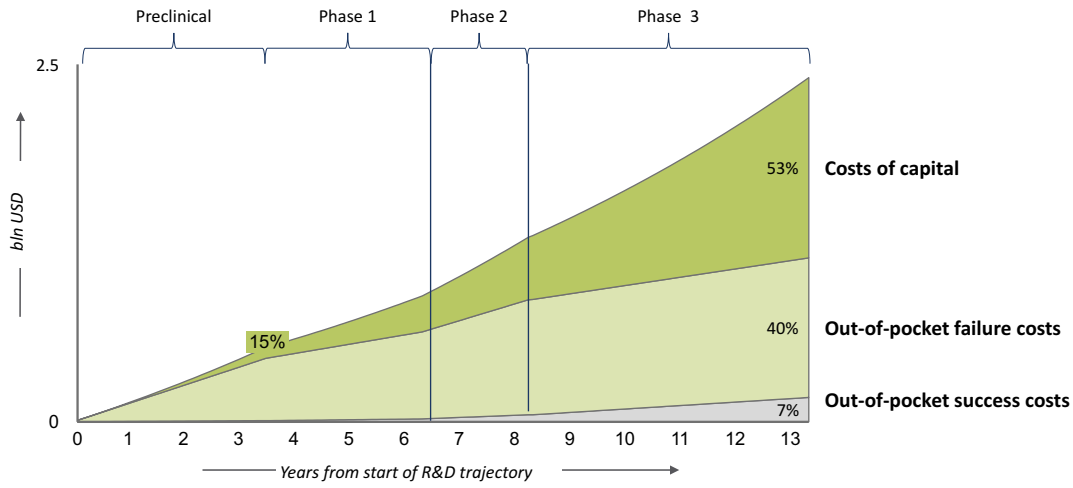

Figure 2. *Cumulative R&D costs during an average R&D trajectory of 10–15 years, modeled based on the average costs of medicine development (figure derived from the Cost of Opportunity report)* [4].

development is becoming more difficult due to significant scientific and economic challenges. Understanding the different sources of funding and types of failure possibly creates an opportunity to affect the failure costs and the conditions under which capital is invested.

As shown in Figure 1, the largest part of the cost of failure is attributed to the preclinical phase, accounting for 18% of the total R&D costs. Figure 2 illustrates that the failure costs also rise most in this phase. It is important from a public investment perspective and a public-private collaboration perspective to identify ways to affect the early failure rate and, subsequently, the failure costs to partly de-risk medicine development for the specified indications. Removing the risk in early development will primarily be related to development and valorization from academic institutes to start-ups. First, with regard to business opportunity reasons, the authorities can influence the overall failure rate by relaxing the approval criteria for prespecified products. A more entrepreneurial government taking risks as the primary funder of early innovation has the opportunity to significantly impact the current medicine development model. A government and other research funders apply both push (fund early research; delinkage) and pull (milestone payments such as tax breaks, capital gains, patents, or data exclusivity) mechanisms can enormously benefit the development risk profile [31]. This is even more interesting if a government is able to gain a direct or indirect return on its investment. A direct return on investment would be a monetary return on investment through the sale of medicines from which it is potentially difficult for governments and research funders to profit. Therefore, including the indirect returns might be more suitable. Indirect returns can be derived from classic health technology assessment outcomes: health benefits gained (e.g. QALYs) or negative outcomes averted (e.g. hospitalizations), fiscal returns for governments (e.g. tax revenues and reduced social benefits), and fair product prices saving direct medicine spending [32]. These aspects could be an inherent component of a public pharmaceutical investment proposal. Second, a reduction in failure costs can also be achieved by organizing coalitions in which multiple stakeholders evaluate the product and make the decision invest. As described in a paper published by Smietana et al., pharmaceutical co-development of medicines increases the success rate of a project by approximately 7% [33]. While the effect of a higher success rate on the total R&D costs is highly dependent on the phases in which it occurs, an improvement of 7% in the overall success rate leads to more than 10% savings in total R&D costs. Therefore, it could be interesting to include multiple ecosystem parties during the R&D process instead of just the obvious pharmaceutical companies. This is in accordance with public investments in the development of medicines. It is expected that the increase in the success rate is in line with Smietana et al. for pharmaceutical co-development and possibly higher [33]. In addition to this, the moment of failure might occur earlier with better decision-making. Both of these factors will reduce the total cost of failure.

3.4. Pricing model: translate savings into price reductions

In 2014, the Fair Medicine Foundation (Amsterdam, the Netherlands) was founded to develop and implement such alternative business models and pricing methods, with the determination of R&D costs considered as the key factor [34]. This 'real-option rate of return' pricing method aims to transparently determine the price based on all relevant current and future costs. The two key factors in the real-option rate of return model are the goal to include all relevant current and future costs (real-option) and base the price on these costs including a prespecified rate of return.

Equation 2a-d: Calculation of the price per patient per year (real-option rate of return) and calculation of the three cost categories

$$a)\quad pppy = \left(\frac{R\&D\ cost}{Average\ \#\ of ppy * patent\ period} + production\ costs\ pppy\right) * (1 + profit\%)$$

b) R&D costs = (Out of packet costs + Failure costs +Cost of capital)

c) $Failure\ costs = (Oop\ costs\ per\ phase) * \left(\frac{1}{cummulative\ succrss\ rate\ per\ phase}\right)$

d) Cost of capital = (R&D cost*(1 + WACC%)$^{avg\ t\ tillapproval}$) *(1-GDP deflator)$^{avg\ t}$

pppy: price per patient per year, OoP: Out-of-Pocket, WACC%: weighted average cost of capital %, GDP: Gross Domestic Product.

We propose implementing a general pricing model for global public goods, such as innovative and necessary medicine. This would be especially applicable to the products proposed in this manuscript, characterized by high prices that often lack competition [12,20]. For oncology medicine, when generics are introduced after patent expiration, substantial price reductions are observed [35]. Overall, the price of medicine reduces by 41% after 4 years, and higher price reductions are observed for medicines with high revenue prior to patent expiration [36]. Real-option rate of return pricing for orphan drugs for which competition is often lacking after patent expiration could potentially improve their worldwide availability and affordability and standard of care. On a worldwide scale, differential pricing would also be part of this model. Prices may be adapted per country or region based on gross domestic product while taking public funding into account.

As a consequence, initiatives to reduce investments or save costs will translate into lower market prices. The proposed, newly developed, and implemented pricing method includes all relevant costs related to medicine development, the three cost components, and projected sales. The three different cost components can be summarized as out-of-pocket costs spent on the successful product, failure costs, and costs of capital (Figure 1). By including all three cost components for the development of new medicine, the average R&D costs were previously estimated to amount to 2.5 billion USD (2017). The first part of the proposed pricing method is to map all relevant costs of development.

4. Discussion

The success of medicine development could be its potential downfall. Improving the general standard of care raises the entry barrier for medicines developed after that, which consequently creates pressure on healthcare budgets, affordability, as well as regulatory and reimbursement decision-making [37]. This could increase the need for direct public and private spending, time of development, and therefore the associated risk. Since healthcare affordability is a growing concern, alternative development, and funding models complementary to the current pharmaceutical model could create valuable opportunities for society and, more specifically, public, and private institutions. This is a novel perspective with regard to medicine development and pricing focussed on public-private collaboration where all parties invest and share in development risk and additional pricing methods for these products to possibly improve the proposed societal, political, and economic implications. To keep improving the quality of (pharmaceutical) care, access to medicines and healthcare affordability, it is important to continue rewarding innovation. Access and affordability to novel treatments require an entrepreneurial position and a transformation of governments, authorities, public institutions, and the pharmaceutical industry. We do acknowledge that how this can be operationalized is a difficult question that must be addressed in discussions with all the parties involved.

The financialization of the pharmaceutical industry is an example of a phenomenon that is expected to maintain the current trends of medicine prices [38]. The general definition used for financialization is "The description of the development of financial capitalism in which debt-to-equity ratios increased and financial services accounted for an increasing share of (national) income relative to other sectors" [38]. The rise in long-term debt and the redirection of profits away from operational activities to be used in mergers and acquisitions for which rising premiums are paid in expectation of future income might not always represent value. The manifestation of financialization is evident in an industry where shareholders are prioritized and dividend payments are funded through debt. In addition to this, the increase in intangible assets relative to total assets (e.g. a shift from fixed capital) to intangible assets (e.g. intellectual property and goodwill) is observed [38]. This increases the need for new alternatives that address the developments proposed in the recent SOMOS report [38]. These observations can be adequate starting points to improve the current development model to better fit society's needs. The current pharmaceutical model, with the increasing use of cheap debt instead of profit to fund R&D and pay dividends to shareholders, might be a precursor for increasing unsustainability [38]. While innovation should always be rewarding, supplying patients with high-quality, affordable care and reinvesting capital gains in R&D should be the primary focus.

Public institutions can reduce the total R&D costs in the preclinical development phase. In the current healthcare system, public capital is already invested in either early phases of research through subsidies, grants, universities, and hospitals, or at the end when products are reimbursed. Therefore, investing public capital in a more focused manner and implementing ways to remove regulatory hurdles for early access could yield an opportunity and viable option for providing patient access to affordable medicines. Governments or public institutions will be afforded the possibility to anticipate future reimbursement prices and will be able to give full transparency in justifying the official list price. When governments and public institutions can positively affect the primary drivers of R&D costs and reduce the total costs, they can receive a return from this. The return can be achieved through a direct return on investment and pricing transparency or health benefits gained or economic burden averted. Initially, products with potentially difficult business models such as rescue antibiotics and (ultra-) orphan products appear to be the most suitable due to the relevance of the availability of new antibiotics and ongoing discussions regarding medicine prices for orphan products and lower capital

requirements. The societal benefits and savings in the orphan market are expected to be substantial since it is often characterized by a highly emotive nature and excessive market power, which might be exploited, leading to excessive prices despite limited benefits of products [39,40].

4.1. Expert opinion

Authorities and governments have the choice to wait until producers bring products to the market and only can accept, negotiate, or reject prices. Negotiations are challenging as there are no clear and transparent criteria for price negotiation. There is mostly political and societal pressures involved when initial official prices are considered too high and when patients eligible for treatment do not receive reimbursed access. A more proactive and prelaunch position of authorities and public institutions in the drug R&D phases with academic centers and pharmaceutical companies will create more opportunities to jointly build on a focused R&D agenda and create an upfront agreement on price-setting. In particular, a clinical research fund could cover pre-investments that are mostly obtained from pharmaceutical and biotech companies with increasing acquisitions by other companies. This could promote public-private partnerships and reduce potential risks in a later phase of the development of new medicines and possibly introduce more competition in markets where this is currently lacking.

In the discussion around alternative models for the pricing of medicines, it is recommended to focus on the pricing method first rather than the costs of medicine development. Alternative models for medicine development that could address current problems and critiques need to be considered in the future product development. By implementing development coalitions and alternative funding and pricing models such as, with the real-option rate of return model, it is possible to impact the total investments required and share the risk and return with a variety of stakeholders. Developments within multi-stakeholder coalitions will aid in the acceptance and development of alternatives for R&D and pricing.

The future of healthcare and medicine development is determined by current choices. We propose to make these choices together with respect to the current drug development system, including underlying business models and decision-making. Changing the roles of current stakeholders both public and private, to invest in alternative R&D models with lower product prices should therefore be considered as a transformation process aimed at reducing healthcare expenditures. Changing the drivers of R&D costs does not directly translate into lower medicine prices, and possible changes to pricing and reimbursement might decrease prices, however, this does not mean this will result in lower prices. Therefore, it is important to also examine decision-making systems that can more effectively adopt healthcare innovations, like the increasing number of orphan products or innovative cell and gene therapies, than the current system. The decision-making system would benefit from a more structured and predictable approach in the assessment of cost-effectiveness, budget impact, and product price in addition to prelaunch interventions.

Due to the development and pricing characteristics, (ultra-)orphan products seem to be the most suitable as the first step in the development and early adaptation as well as alternative development and pricing models especially since these products for generally for patients with significant medical needs. In the long term, alternative development models for larger indications and expensive development trajectories could follow depending on the outcomes of the first alternatives. Since the range of R&D costs between indications is substantial (0.5 bln USD – 6.5 bln USD), we propose that, when discussing medicine pricing and R&D costs, the indication-specific R&D costs should be used if available.

Further theoretical and practical developments of alternative R&D funding, product pricing, and reimbursement models are necessary to further build on collaboration between all relevant stakeholders. Adoption by more stakeholders will soon require increased involvement of public and private parties. This can be achieved by using more proof-of-concept examples of different alternatives in medicine development and pricing. In our opinion, this early development of these alternatives is the primary responsibility of governments, and authorities. However, it could benefit from private case examples.

We expect that, within the coming years, the pharmaceutical and healthcare industries will most likely transform and lead to more sustained public-private collaborations. Though it is a joint effort, public institutions will be more involved as co-founders of early innovations, while private companies will primarily participate in the later development. All of these stakeholders who are involved will be part of the development within a public-private collaboration. To make an impact through public-private collaborations, there should be a trade-off on price, profit, and transparency with an upfront agreement on the return on public and private investment. The recent developments in response to the COVID-19 pandemic have not only shown the importance of public-private collaborations, but also proved the potential of a more collaborative model including the delinkage of R&D costs. Such a model ensures that all stakeholders, both public and private equally benefit, while accessibility and product prices are not a topic for discussion. The public investments in the COVID-19 vaccine, for example, the Oxford/Astra Zeneca vaccine was developed with the help of the UK government [22]. The public investments are profitable both through the availability of the vaccine (e.g. a reduction in drawbacks averted) and the relatively low and societally acceptable price during the pandemic (e.g. cost-savings) [22]. A proactive and entrepreneurial position of governments and public institutions in response to the COVID-19 pandemic has demonstrated that collaborative development, funding, and market authorization have a right to be part of the overall medicine development "toolbox." This is primarily applicable to vaccines and is expected to also benefit the development of orphan drugs and antibiotics.

It is expected that innovation in medicine development is related to the types of products being developed. The share of personalized medicine and platform technologies

such as gene therapies will increase in the future. These developments require alternative R&D models and are appropriate for this type of innovation. Alternative R&D models also require a change in how the market authorization and reimbursement systems handle this. Criteria that are used to accept new products in the healthcare and reimbursement system should change to adhere to the future needs of society, and innovation should be rewarded. If all this becomes true, these innovations will be instrumental to the transformation of healthcare.

5. Conclusion

Gaining insight into what drives the R&D costs and how this could translate into potential savings creates an opportunity to reduce medicine expenses. The alternative model is based on collaboration between both public and private stakeholders. The costs of capital and of failure are the two primary cost categories that can be affected by interventions in drug development.

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Author contributions

SvdS and FdL worked on the conceptualization of the paper and writing the early drafts. All authors contributed to the writing of the paper and approved the final manuscript.

Data statement

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