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Public contributions to R&D of medical innovations: A framework for analysis

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ABSTRACT

Background and Objective: Article 57 of the proposed European Union (EU) Pharmaceutical Legislation (PL, Directive) will require market authorization applicants to publicly declare any direct financial support for R&D received from public authorities. Our research aims to identify the categories needed to capture direct or indirect public contributions to R&D, provide a framework for standardized reporting of public contributions, and reduce ambiguity in the interpretation of "direct" and "indirect" public contributions.

Methods: An iterative mixed-methods approach is applied: a targeted literature review was conducted, complemented by interviews with representatives of different stakeholder groups to identify categories of public contributions to R&D, followed by searches for relevant data sources.

Results: 26 publications on primary data relevant to analyses of public contributions were identified, finding that between half of all drugs approved and >90 % of drug targets are associated with public sector institutions and/or their spin-outs. Eight categories of public contributions to medical innovations were identified along the value chain (from basic research to post-market surveillance).

Discussion and conclusion: The framework offers a structured and systematic approach for identifying data on public and philanthropic contributions to developing medical products (medicines and devices). This information is often not comprehensively documented. Therefore, aligned public policies enforcing transparent and standardized reporting in sufficient granularity on R&D investments and conditions are key.

1. Introduction

Public contributions to the development of medical innovations have been discussed for several years, inspired by M. Mazzucatós book on "Public vs Private Sector Myths" [1], and are strongly supported by several detailed analyses [2–7]. The evidence for public and philanthropic contributions to the development of medical products (medicines and devices) is not disputed. In the media, this observation is referred to as "the public pays twice" and "risks are socialised and rewards are privatised" [8]. However, even with increasing evidence, corresponding public policies (such as conditionalities) are still lacking. In 2019, the World Health Assembly stressed the need for transparency in their Resolution on "Improving the transparency of markets for medicines, vaccines, and other health products" [9]. In April 2023, a proposal for a revision of the "Pharmaceutical Legislation" (consisting of a new Directive [10] and a new Regulation [11]) was published and will be negotiated in the coming years. The draft pharmaceutical legislation contains a transparency requirement regarding public financial support received for research and development (R&D) activities for a medicinal product. Article 57 of the proposed medicines Directive [10] will require market authorization (MA) applicants and MA holders (MAH) to publicly declare any "*direct financial support received from any public authority or publicly funded body*" about "*any activities for the research and development of the medical product*", without specifying the period during which funding was received.

The obligation is not restricted to only European Union (EU) financial support, so MAHs will also need to consider any funding from public authorities and publicly funded bodies outside the EU. The scope of the provision is very broad and covers direct funding for *any* R&D activities related to the medicinal product's development. This reporting obligation could, therefore, include funding received during pre-clinical and clinical stages. However, the recitals to the Directive do not stipulate indirect funding, such as a declaration of tax support [12]: "*The reporting obligation should only concern the direct public financial support such as direct grants or contracts.*" Within 30 days from the grant of the MA, the MAH must prepare an electronic report, which includes the amount of

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financial support received and the date of receipt, indicating the public authority or publicly funded body that provided the financial support and the legal entity that received it. The report must be (i) audited by an external auditor, (ii) accessible to the public via a dedicated webpage, and (iii) be updated annually [12].

However, "R&D" comprises a wide range of activities and different aims, starting with basic research aiming at mechanistic understanding of diseases and including pre-clinical research aiming at the investigation to create a new molecule, medical device or therapy. Development is about refining manufacturing techniques, and clinical research is mainly about generating evidence about the efficacy and safety of that therapy that will support regulatory approval and health technology assessment (HTA). Also, securing intellectual property (IP) is quite different at each phase: pre-clinical knowledge is protected by patent. Knowledge of development is sometimes protected by patents and sometimes by trade secrets. Clinical knowledge (after approval) is

Table 1
Multi-methods: Targeted literature search on public contributions to R&D for health innovations; Stakeholder groups interviewed on categories of public R&D; Data collections and exemplary data sources.

Literature: Public contributions to R&D of health innovations reported		
Search period	2010–2023	
Databases searched	Pubmed, Reference lists of key publications, key researchers	
Google Scholar	Grey literature	
Hand search	DNDi, KEI, SOMO, Public Eye, Doctors Without Borders (MSF)	
Search terms and search strategy	"publicly funded" OR "public contributions" OR "public investment" OR "philanthropic contributions" OR "philanthropic investment" OR "charitable research funding" OR "public R&D" OR "public research and development" OR "public sector financial support" OR "public sector research" OR "research spending" AND "drug development" OR "pharmaceutical drug development" OR "drug discovery" OR product development" OR "discovery" OR "development" OR "drug approvals" AND "biomedical research" OR "health research"	
Inclusion Criteria	English or German language Reporting of methods and sources Data in sufficient detail for extraction	
Results	26 publications: 11 (based on 5 datasets) on overall public contributions across drug approvals and 15 publications on 28 case studies on products.	
Interviews: Stakeholder groups, Topics and Inputs to categories		
Stakeholder Group	**Topics**	**Input on..**
Policy advocacy for affordable medicines	on medical innovation and public contributions	Basic & applied research, Changes in ownership, Support to clinical trials
	on experiences with reporting of public contributions in USA	Technology transfer, Changes in ownership
Pharmaceutical Industry	on EFPIA standard definition for declaration of R&D costs of member companies	Definitions on R&D
Research Policy and Impact	on Business Intelligence of Academia and Pharma, Technology Transfer	Technology transfer, Changes in ownership
	on research on licensing agreements and patents in SEC reports	Basic & applied research, Changes in ownership
Public Infrastructure for clinical trials	on cost estimates for clinical trials, attrition rates, factors that explain differences in costs, on screening for compounds	Applied & translational research, Support to clinical trials
Non-profit drug development	on attrition rates, on variables/ factors that explain differences in costs, on screening for compounds	Changes in ownership, Regulatory support
EC DG Research and Innovation	on EC funding of Research and Innovation, trial infrastructure and clinical trials	Applied & translational research, Support to clinical trials, RWD
Center for Clinical Trials at Medical Universities	on costing tools for clinical trials, on costs of trials, on cooperation with industry	Support to clinical trials Support to clinical trials
Clinical Researcher	on funding for clinical research	Basic research
	on stages of drug development and challenges	Basic & applied research
	on costing of academic or commercial clinical trials and refunding of use of infrastructure in commercial trials	Support to clinical trials
Research Funding Support	on EC grants for health and life sciences and on PPP-programs	Applied & translational research, Support to clinical trials
	on EC grants for SME and health innovations	Technology transfer, Business support to SME, Public Venture Capital
	on EC grants for Networks and Matchmaking	Technology transfer, Business support to SME, Public Venture Capital
Start-up biotechnology SME	on public grants in early-stage development and investors	Applied & translational research, Technology transfer
Consultation on R&D	on Antibiotics in development and public contributions, on R&D strategies, SME and public funding of bacterial and antifungal drug development	Applied & translational research antibiotics, Support to clinical trials
Data sources on categories of (direct and indirect) public contributions to R&D of health innovations		
Search period	2007 - 2023	
Public contribution by phase	**Topics and Data sources**	**Links**
Basic & translational research	EC-grants in Cordis Db,	https://cordis.europa.eu/de
	IMI/ IHI project database	https:// www.imi.europa.eu/projects-results/project-factsheets
	National research funders	National research agencies
Early-Stage Research in SME Biotech Companies	Spin-out/off companies	Google searches on Websites of Universities
	EC-Innovation support for Lifesciences, Biotech (EIC, EIE, EIT)	https://eic.ec.europa.eu/index_en; https://eismea.ec.europa.eu/programmes/european-innovation-ecosystems_en; https://eit.europa.eu/
Late-Stage Development in Corporate Companies	Changes in ownership	News: STATnews, FiercePharma, FierceBiotech, Investors News
	Trial Support by EC or national sponsors	https://cordis.europa.eu/de
Market Authorization, PLEG	Regulatory support	https://www.ema.europa.eu/en
	SA and PLEG	https://www.eunethta.eu/
	RWE data collections	https:// www.imi.europa.eu/projects-results/project-factsheets; https://darwin-eu.org/
Inclusion Criteria	English or German language	

protected by market exclusivity and data protection rights.

This research aims to identify the categories needed to capture direct or indirect public contributions to R&D, to provide a framework for standardized reporting of public contributions to R&D and to reduce ambiguity in the interpretation of "direct" and "indirect" public contributions. In contrast to the legislation for medicine only, our scope is broader, intending to cover public contributions to any medical innovation. A comprehensive compendium of all public contributions is neither intended nor seems realistic. Still, a comprehensive system of categories is nevertheless aimed at applying to medicines, medical devices, and other health technologies.

2. Materials and methods

To approach the research questions on which public contributions to R&D might be considered, an iterative mixed-methods approach is applied: a targeted literature review was conducted complemented by interviews with representatives of different stakeholder groups to identify categories (see Table 1), followed by searches for relevant data sources for information on the categories. Interviews, literature, and data analyses complement each other and are not reported separately but together.

Literature Review: First, a hand-search for published articles and reports was carried out in February and March 2023 (period 2010 to 2023, any type of publication that reported the methods and sources of their analysis in sufficient detail for extraction was included, keywords "publicly funded", "public contributions", "public investment", "philanthropic contributions" etc., see Table 1), followed by screening of the reference lists of relevant articles until August 2023. Due to the targeted (selective) hand search, no Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting is presented. Also, no risk of bias (RoB) assessment was conducted due to the heterogeneity of the studies, their study designs and the reporting of information.

Data extraction (of literature): Of the 26 publications identified, the following information was extracted: authors and year of publication, number of compounds or products included in the analysis, results of analyses, sources and methodology, and categories of public contributions considered.

Interviews with stakeholder groups: As a first step, relevant stakeholders were identified by the authoring team (DF and CW), and additional researchers from the Austrian Institute for HTA (AIHTA) contributed to topic guides. Snowball sampling for key stakeholders was used to identify additional interviewees on specific topics. The interviews were semi-structured with a wide range of stakeholders, including academic experts, industry representatives, not-for-profit developers and clinical trialists. Semi-structured interviews were chosen to allow the interviewer to adapt the questions to the interviewee's knowledge and to allow follow-up questions. Interviews with 17 stakeholders (located in different European regions) were conducted between February 2023 and September 2023 either online via Zoom, MS-Teams or in person. Notes were taken, but no recordings were made. The interviews were designed to be informative and were not processed further (e.g., via content analysis) due to their topic heterogeneity. The following inputs were extracted from the interviews: relevant keywords for targeted literature searches, relevant authors in the field of interest (using 'snowballing'), unpublished materials and grey sources, defining the variables for the extraction tables, and defining the spectrum of public contributions and data sources.

Data collections and sources: Finally, for each of the categories identified in the targeted literature searches and interviews, sources for data collection to provide detailed information on the categories were identified, and pilot data collections were conducted. To do this, we first subdivided R&D contributions into four phases, from basic research to post-launch evidence generation, and second, we classified the direct and indirect public contributions into eight categories. Subsequently, several data sources (databases, websites, etc.) were screened and reviewed for direct and indirect public contributions. The data collections are meant to be exemplary (not exhaustive).

3. Results

3.1. On public contributions to R&D of health innovations reported in the literature

26 publications were identified that considered the nature and extent of public contributions to R&D of medicines (and other products such as medical devices) (see Table S1 in Supplement).

Study characteristics: Several data analyses of large Food and Drug Administration (FDA)-approved drug cohorts are reported. Stevens et al. conducted the first analysis in 2011 [13] and updated it in 2023 [14]. Cleary et al. report on different aspects of the same cohort: 2018 [15], 2021 [16] and 2023 [7,17]. Nayak et al. 2021 [18] analysed subsamples of a larger dataset [6]. Sampat et al. reported as early as 2011 on public contributions to 379 new molecular entities (NME) (approved 1988–2005) [19] and, most recently, Cleary et al. 2023 on 356 compounds (approved 2010–2019) [7]. In addition to these broad analyses across many different drug approvals and indications, more detailed investigations into single drug (and one in-vitro-diagnostic device) development histories could be found in the literature. All analyses originate in a few authoring teams at the Harvard Medical School (Division of Pharmacoepidemiology and Pharmacoeconomics) [2,6,18,20–25], the United States (US-) Institute for New Economic Thinking [7,15,16], authors from Columbia University [19,26], US-authoring teams [13,14] or Japan-based [27] from Technology Development, IP and Science Policy or Advocacy Groups such as Treatment Action Group [28,29] or United Kingdom (UK)-based Global Justice Now [30]. Only the AIHTA [3,4,31] authored several European publications. None of the authoring researchers or teams declared to have a conflict of interest. Science grants of diverse public or charitable funds financed all the research.

Public contributions to R&D across indications reported: The datasets analysed in the publications ranged from 1973 [13,14] to 2019 [7]. Across FDA-approved drugs (NMEs), the analyses found that around 42 % of all biologicals [18], half of all drugs approved [19,27], or even >90 % of drug target research [7,15,17] are associated with public sector institutions and/or their spin-offs. For drugs awarded "priority" or "expedited review" (indicating therapeutic importance), the proportion was 64.5 % [19] to 68 % [6]. 9 % of FDA-approved drugs hold public sector patents, rising to 17.4 % for "priority" review candidates [19]. Global Justice Now estimated in 2017 that the public pays for two-thirds of all "upfront" (before approval) R&D expenditures for the development of drugs and that around one-third of all medicines originate in research institutions in the public sector [30]. Public institutions have created all the important, innovative vaccines introduced during the past 25 years [13]. In addition to the dominance of the indirect public sector effect over the direct effect (patents), the sales for these "priority review" drugs based on publicly funded R&D were far higher than for "standard review" drugs [19]. Most analyses focused on public contributions to basic research. However, public contributions were found in at least one in four new drugs and also in late-stage development [6]. In Europe, 12.3 % of all European Commission (EC) Framework (FP) 7-Health awards were related to the funding of late-stage clinical research. Pharmaceutical products and vaccines together accounted for 84 % of these late-stage clinical development research awards and 70 % of its funding [4].

Public funding amounted to between $839 million (mil) (2018) [15] and $1.44 billion (bil) [7] per first-in-class drug approval on basic or applied research for products with novel targets or $599 mil [7] per approval when considering applications of basic research to multiple products. Two-thirds of drugs and vaccines are discovered in the US and Canada, whilst one-third in Europe (Germany, UK, Belgium, etc.), the Asia-Pacific region (Australia, Japan) or the Middle East (Israel) with on

average $ 0.77 bil (Belgium), $ 0.55 bil (United States of America (USA)), $ 0.23 bil (UK), $ 0.14 bil (Germany) or $ 1.06 bil (Israel) public (academic) expenditures per drug [14]. The top discovering public sector institutions include the National Institute of Health (NIH), University of California, Emory University (USA), Catholic University (KU) Leuven (Belgium), Hans Knöll Institute (Germany) and the Weizmann Institute of Science (Israel) [14]. One author concludes [7,16] that spending from the NIH was not less than industry spending once the total costs of these investments are calculated using comparable accounting.

Public contributions to R&D of specific therapies: Detailed analyses of development histories of products based on singular case studies strengthen the overall picture: The studies showcase the paths of development from basic research in academic settings to spin-offs or small biotech companies to late-stage acquisitions by large pharma companies and present the economic process (financialization) of buying academic knowledge and developing it with private equity resources to profitable therapies for costly gene therapies [24,25], for Sofosbuvir (Sovaldi®) [31,32], paediatric orphan drugs [4], Pregabalin (Lyrica®) [22] and Buprenorphine (Subutex®), Olaparib (Lynparza®) [3] Abiraterone (Zytiga®) [33], Alemtuzumab (Lemtrada®) and Infliximab (Remicade®) [30], Bedaquinile (Sirturo®) [28], Tenofovirdisoproxil (Truvada®) [23]. Most recently, the public contributions to the development of mRNA (messenger ribonucleic acid) vaccines have been discussed publicly [2,34,35].

Sources used in published analyses: Most authors searched in a key set of sources such as the FDA Database (for information on approvals and designation, e.g. orphan), the FDAś Orange Book for patents, patent citation data, citation analyses linking to funding and grants agencies, employment information of authors and the NIH RePORTER (for NIH funds). Most analyses so far have been conducted on US sources, only very few on European information and even less on failed development with public funds (public risk investments) [4] (see Table 2). Information on public sponsorship of clinical trials was obtained from two databases (International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov). The least well documented were public contributions to market authorization and post-market launch, probably because these sources (including national tax incentives, orphan drug incentives, tax deduction policies for donation programmes and post-launch data collections) are challenging to estimate.

Categories of public contributions considered in published analyses: The categories of public contributions to drug/medical product development considered in the publications identified are funds and grants for basic, pre-clinical and applied (or translational) research up to the point of institutional support for filing a patent and for technology transfer. Legal, technical and financial support to spin-outs/offs from universities or start-up small and medium-sized enterprises (SMEs) were mentioned but less often considered in the actual data analyses since information on these grants is not as readily available and accessible as research funds [36]. Ownership changes from academic institutions to SMEs and later multinational corporates were considered by Roy [31], Vokinger [25], and Newham/ Vokinger [24]. In more detail, late-stage development in the form of public support for clinical research was considered broadly in Nayak [6,18] and Schipper [36], showcasing the multitude of sub-categories of funding and sources. Finally, regulatory support in the form of technical assistance for registration, methodological guidelines, and the provision of priority reviews or vouchers are considered a form of public investment (due to their opportunity costs) in Gotham [28,29], as tax credits, post-launch data collections – real-world data (RWD) for generating additional evidence – are considered as public contributions.

To conclude, the research area of public contributions to health products is still in its infancy. However, it has gained increasing interest, and more analyses are expected.

Table 2
Sources used in published analyses.

Public contribution by phase	Sources
Basic &translational research	FDA Database on approvals: https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases Merck Index: https://merckindex.rsc.org/ AdisInsight: https://adisinsight.springer.com/ Therapeutic Target Db (TTD): https://db.idrblab.net/ttd/ FDA Orange Book: https://www.fda.gov/drugs/drug-approvals-and-databases/orange-book-data-files. NIH RePORTER: https://reporter.nih.gov/ EC-Funds and projects: https://cordis.europa.eu/ Citation data and employment information: https://pubmed.ncbi.nlm.nih.gov/ National funding of biomedical research Request to national research institutions based "freedom of information act"
Early stage research in SME Biotech Companies	Licensing survey on technology transfer activities of academic institutions: https://autm.net/surveys-and-tools/surveys/licensing-survey SEC-filings: https://www.*sec*.gov/edgar/searchedgar/companysearch Reports under The Sunshine Act: on manufacturers' payments to physicians and teaching hospitals: https://www.ama-assn.org/practice-management/medicare-medicaid/physician-financial-transparency-reports-sunshine-act Technology Transfer Websites from universities on spin-out/offs Press releases, News: FiercePharma, FierceBiotech, STAT Health for acquisitions and licensing agreements US, EC and national SME-grants National funding of SME -facilities, infrastructure Public venture capital funds
Late Stage Development in Corporate Companies	Clinical Trials: https://www.clinicaltrials.gov/ and https://www.who.int/clinical-trials-registry-platform Requests to investigators & MAH
Market Authorization, Post-Launch Evidence Generation	National tax incentives FDA Database on approvals on orphan drug incentives Taxation of donation programmes RWE-data collections

3.2. On categories of (direct and indirect) public contributions to R&D of health innovations

Eight categories of public contributions to R&D of health innovations were identified in publications complemented by the interviews (see Fig. 1). These are listed below, along with information obtained from publications about the value of public contributions for each category.

1. Public contributions to basic, applied and translational research: In 2022, 0.74 % (€ 117.4 bil) of the Gross domestic product (GDP) was devoted to government allocations for R&D across the EU, with the most significant share (35.5 %) directed to basic research at public universities and a further 8.3 % going to applied research in health [37]. Meanwhile, EC grants are reported transparently and in detail. At the same time, national expenditures on R&D for health research, life science, and biotechnology are highly untransparent and not reported in a standardized and detailed manner. A review of public and philanthropic health research funding institutions found no standardized classification system to report on funding [38]. FP7 (2007–2013, € 5.6 bil) generated 174 projects in biotechnology, leading to 107 patents and 15 spin-off companies, and 553 projects in translating research, leading to 126 patents and 19 spin-off companies. Horizon2020 (2014–2020, € 9.8 bil)

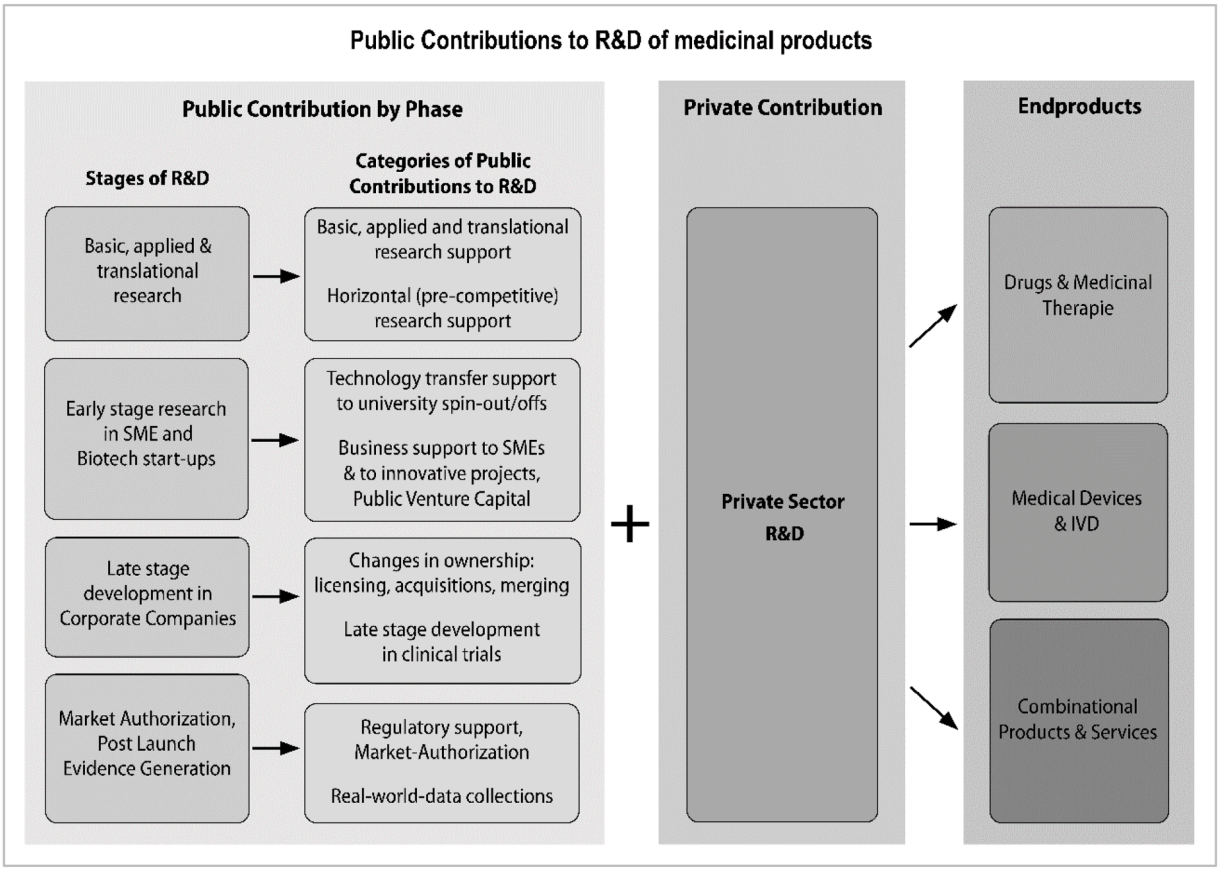

Fig. 1. Framework for analysis: public contributions to R&D of medical innovations.

supported 6571 projects in personalised medicine, infectious diseases and digital transformation in health care - an impact assessment of this funding stream is still ongoing. HorizonEurope (2021–2027, € 8.3 bil) supports 988 projects in non-communicable and rare diseases and tools and technologies for personalised medicine. Even if overall data does not provide enough granularity to estimate the public R&D contributions to the development of actual products, it is clear that funding for the knowledge and understanding of diseases is the prerequisite to product development. The attribution of public resources to the development of individual products can only be done on a case-by-case basis, such as the exemplary case studies of orphan drugs and antibiotics.

2. Public contributions to (pre-competitive) applied research: Cooperation agreements between competitors to collaborate in certain areas, such as R&D, can be pre-competitive, allowing companies to respond to competitive pressure and changing market dynamics. Pre-competitive cooperations share risk, save costs, increase investments, pool know-how, and speed up European innovation [39]. In Europe, the Innovative Medicines Initiative (IMI) (since 2022, the Innovative Health Initiative (IHI)) has been the most prominent example of extensive public contributions to such cooperations. The Innovative Medicines Initiative (IMI 1 2008–2013: € 1 bil of public contributions, IMI 2 2014–2020: € 1638 bil and IHI 2021–2027: € 1200 bil) generated methods, practical tools and supportive instruments for target identification and drug discovery; tools for predicting/ monitoring efficacy and/or safety, as well as for refining disease taxonomy/ biomarker-stratification; clinical trial designs; methods to process RWD; methods for benefit-risk assessment for the regulatory and HTA process; conduct of clinical trials; big data and knowledge management, digital health, artificial intelligence and support to clinical network building. A prominent (cross-indications) example is the "The European Lead Factory" (ELF) and its follow-up ESCulab (European Screening Centre: unique library for attractive biology), which has created a collection of some 550,000 compounds (small molecules) from private and public sources for target identification, drug discovery and lead optimization [40]. The EC invests in different public-private partnership (PPP) activities that ease the path to more efficient product development.

3. Technology transfer to university spin-offs/ spin-outs: Promising academic research with positive results is often patented and further developed in small BioTech start-ups founded by the patent holder or a group of researchers to prove the concept in clinical research. Most medical universities have "Technology Transfer" or "Patent Offices". The public sector is reimbursed directly for their discovery (private buy-out of spin-offs) or retains some IP rights. At first glance, the net impact is a financial benefit for the public R&D institutions; however, the total financial flows (later revenues) are rarely considered. Oxford University reports 15–20 new spin-off companies yearly and over £ 2.5 bil income through its spin-outs since 2010 [41]. Berkeley College of Chemistry reports $ 100 mil only for one gene therapy spin-out [42]. Since the small BioTech start-ups are often neither equipped with enough resources for the further development of their products nor with business intelligence to lead an enterprise, they receive public support. At this stage, many countries offer national business services in life science clusters that support developing a business plan, assessing the market and budgeting for early-stage clinical trials. National and European funds are granted for these categories of financial support.

4. Business support to SMEs and innovative projects, Public Venture Capital: The landscape of startup funding opportunities is vast, often organized by regions in EU member states or national institutions. For the phase before a life science company is set up, public funding is provided for the costs related to project development combined with tailored advice and support with targeted networking activities and match-making services with (international) investors. Once the

company is making a profit or is sold, financial support must be refunded. Customary securities usually needed for bank loans are not necessary. Additionally, the start-ups are partly funded through private (SeedFinancing) capital and national public venture funds. In the EC, the European Innovation Council (EIC) (with programmes like EIC Pathfinder, EIC Transition and EIC Accelerator) directly supports innovators throughout Europe. It bridges the investment gap in early-stage innovation. Around 35 % of all EIC activities are related to health and wellbeing. Innovations in Technology Readiness Levels (TRL) 2 to TRL7 can be funded [43]. TRL 8 (finishing the product development) and TRL 9 (manufacturing and scaling up) are only supported with EC resources in the form of equity shares of up to 25 % of the company shares. The EIC funds up to € 2.5 mil for TRL 2–6 and up to € 15 mil for TRL 6–8. Additionally, the European Institute of Innovation & Technology (EIT categories of funding: Attract to Invest, Bridgehead, Catapult, DiG-innovation, Jumpstarter, InnoStars Awards, etc.) was founded with a similar intention to support technology transfer (for spin-outs, spin-offs) and to strengthen the so-called 'knowledge triangle' – the principle that the optimal environment for innovation is when experts from business, research and education work together. At this stage, (Public) Venture Capital (VC) also comes into play. Despite a sizeable private venture capital market, governments are investing in risk finance of innovative start-ups to fill "funding gaps", esp. regarding innovation in specific targeted areas to capture public benefit [44,45]. The European Investment Fund (EIF) financially supports early-stage innovation specialists like e.g. BioGeneration Ventures (BCV). This investment is highly risk-prone since, realistically, it must be assumed that not all investments will lead to market maturity and reimbursement.

5. Changes in ownership: licensing, acquisitions, merging: According to the annual EU Industrial R&D Investment Scoreboard (2022), health industries (encompassing biotechnology, health providers, medical equipment, medical supplies and pharmaceuticals) are the most R&D-intensive sector, with 12.4 % of R&D investments [46]: The high costs for acquisitions of spin-outs/offs and licensing from academic institutions are rarely reported. Some authors and advocacy groups – such as Knowledge Ecology International (KEI) – regularly conduct detailed analyses and track details on licensing agreements, acquisitions, and expenses associated with clinical trials of individual companies. One can refer to the currently approved Advanced Therapy Medicinal Products (ATMP, including chimeric antigen receptor T (CAR-T) cell therapies and tissue-engineered products) as an example of the need for detailed, disaggregated data. As of September 2023, there are 18 ATMP approvals in Europe [47] and the USA. Nearly all originate from public research institutions, public-funded research, or charities [48]. The change of ownership happens most often after milestones in product development, e.g. early stage trials [36,49] have successfully been achieved and the risks of failure decrease. With each change of ownership, the company's price increases depending on the valuation of the product portfolios bought. This process – called "financialization" – has been covered in many case studies [31,50] and – it must be assumed, due to the aggregated presentation of the R&D data – that the costs for Mergers and Acquisitions (M&A) are covered under the industrial R&D expenses.

6. Public contribution to late-stage development in clinical trials: For more than a decade, universities or teaching hospitals have established their departments, called, for instance, "clinical trial coordination centres", which support academic trialists with planning and implementation (e.g. with costing tools [51,52]) and commercial trials with trial administration (recruiting, ethics committee' vote, accounting of costs etc.). To enable the costs incurred during commercial trials to be reimbursed, hospitals provide lists of prices for services delivered (staff cost, use of equipment, diagnostic monitoring, etc.) [53]. However, the commercial trialist only pays for extra costs, not standard treatment costs. Whether the maintenance of the technical equipment is adequately covered depends on the offer of the respective clinical trial coordination centres. The use and compensation of infrastructure is highly non-transparent. In diverse analyses of FDA/ European Medicines Agency (EMA)-approved medicines, it could be proven that the public plays not only a dominant role in funding the basic and translational research but also in later stage (phase 1–3 trials) research: about 25 % [6] to 40 % [18] of new approved biological drugs had evidence of public financial support for late stage development, the same holds for ATMPs. Between 80 % [54] and 91 % (DeWilde 2017 in [55]) of all CAR-T cell therapy trials are sponsored by academic sponsors, and conversely, only between 9 % [55] and 20 % [54] by the pharmaceutical industry. Charities also play an essential role in research funding, especially in the USA and the UK. However, their funding information is not easily searchable [56–58]. The coordination of 24 European Reference Networks (ERN) for rare diseases makes an essential public contribution to efficient recruiting, advancing methodologies in trial designs, outcome measurement and validation for improving and providing well-equipped infrastructure for conducting clinical trials.

7. Public contributions to regulation and marketing authorization: "Regulatory Science" has been developed to support regulatory assessments that inform both MAHs and HTA agencies. In 2011, the FDA published its first "Strategic Plan for Regulatory Science," followed by a detailed report on "Advancing Regulatory Science at FDA – Focus Areas of Regulatory Science (FARS)" in 2021 [59]. Several years later, in 2018, the EMA launched its strategy for "Regulatory Science to 2025″ [60], followed by a detailed list of "Regulatory Science – Research Needs" in 2021 [61]. Though private companies primarily finance the regulators EMA and the Notified Bodies (NB) through fees, the public contribution is substantial [62]: For 2023, the total budget of the EMA amounted to € 458 mil. Around 89.0 % derives from fees and charges to industry, 10.9 % from the EU contribution to public health issues and 0.1 % from other sources. Building capacities training modules [63], workshops on, e.g. patient registries [64] or real-world evidence, including registry data for regulatory purposes (e.g. [65].), and scientific events are publicly financed activities of EMA [66]. While the EMA coordinates the scientific evaluation of applications with the national medicines regulatory authorities in the EU Member States, the National Competent Authorities (NCA) have a remit far beyond contributions to market authorization. In recent years, the HTA agencies have become more important in providing Joint Scientific Consultation (JSC, formerly Early Dialogues/ ED) and Post-Launch Evidence Generation (PLEG). In contrast to EMA's Scientific Advice, they are provided free of charge. Finally, the public is not only providing methodological support for orphan medicines, paediatric medicines and ATMPs to optimise the generation of robust data, protocol assistance and accelerated approval via the PRIME (PRIority Medicines) Programme but also numerous fee-reducing instruments are in place at an opportunity cost, such as fee waiver, tax credits and longer market exclusivity.

8. Public contributions to post-launch evidence generation (RWD collections): With the rise of regulatory instruments such as Adaptive Pathways – intending to improve faster access – and the conditional approval of medicines based on early-stage (Phase 1/2 or Phase 2) pivotal trials, the demand from payer-institutions for a generation of evidence after market-authorization has increased significantly. EC grants and national initiatives have supported evidence collection to supplement clinical trial data to confirm the cost-effectiveness of products following conditional approvals based on early data (surrogate endpoints) and short follow-up periods. Data and governance concepts are developed in national HTA agencies [67,68]. For example, the European Bone Marrow Transplantation (EBMT) CAR-T registry is working with a budget of € 12.7 mil, partly derived from public sources; the SMArtCARE registry (platform to collect real-life outcome data of patients with spinal muscular atrophy) is fully sponsored by the MAH of the three available therapies; however, the study protocols and -plans for data collections accompanying the use of these therapies are conducted in public agencies [69,70]. Additionally, the EC has launched several programs to support post-market evidence generation, such as DARWIN EU (Data Analysis and Real World Interrogation Network); IMI/ IHI has contributed to establishing reference networks to facilitate a common

understanding of how to diagnose and treat rare diseases and for faster patient recruitment and long-term monitoring through patient registries.

4. Discussion

Analysing public contributions to medical product development as an area of research enquiry started to evolve about a decade ago and has gathered momentum in recent years. However, it so far lacks a standardised methodology. Our research intended to fill this gap and to offer a structured and systematic framework for data collection. We first divided the development of products into stages and searched – supported by targeted interviews with experts in the field – for categories of public contributions in the published literature. We identified eight categories. While supranational funding agencies (EC and NIH) report their expenditures on R&D very transparently, national expenditures are not available in a structured format. Similarly, commercial data on R&D spending are not available in enough detail. Additionally, no definition of what is reported (and what is not allowed to be covered) as R&D spending by companies exists. An absence of – or unstandardized – reporting of public expenditure and their output (measured in Key Performance Indicators (KPIs)) is part of the problem. It hinders the disclosure of public contributions to R&D for early as well as late-stage developments of health products.

While price records for the most expensive drugs are broken annually, the public sector has not had enough data to evidence the direct and indirect public contributions to basic, applied and translational research and contributions to new methodologies (e.g. trial designs or stratification of diseases). Our findings witness how product development takes place, namely research partnerships with public research organisations and small biotech start-ups, which are common. Major pharmaceutical companies send drug hunters and patent scouts to buy promising developments. The commissioning of Contract Research Organisations (CROs) to outsource development and clinical trials is increasingly being implemented in low-cost countries. Pharmaceutical companies pay research results according to defined milestones (asset transfer agreements). The global pharmaceutical companies then carry out the final approval and market introduction.

Estimates to date are based either on crude estimations across groups of products (primarily drugs) or on detailed analyses of individual case studies of products. The evidence for public and philanthropic contributions to the development of medical products (medicines and devices) is sufficiently robust, and the need for transparent reporting is too apparent. Aligned public policies enforcing transparency on R&D investments is key. Some countries – such as Italy, France and only recently Austria – are pioneers in implementing transparency requirements. Still, implementation remains toothless without clear definitions or sanctions in the event of non-compliance. For an implementation that is taken seriously, not only is transparent data relating to direct public contributions (leading to products) needed, but we also need good quality information regarding indirect funding, including tax breaks, methodology, tools, and techniques.

There is substantial scepticism that the call for increased transparency of development expenditures is nothing but a political statement without actual implications. To counter this justified scepticism on a lack of practical implications and, therefore, lack of relevance of the proposed framework, one must reflect on what potential consequences might be considered. On the one hand, the complementarity of public and private know-how in developing new drugs might replace the common myth that only private companies are innovators. A good example is the medial praise of BioTech/ Pfizer as developers of mRNA vaccines. Even if setting the facts on the role of public contributions in inventing major innovations is considered only an immaterial good, it might be valuable in democracies, increasing trust in the public sector. On the other hand, the feasibility of transparency clauses in purchasing contracts is already being probed (in Austria, Italy, and France) in some countries as a more manifest consequence. So far, however, it has had relatively little impact. The reasons might be found in the voluntary nature of the companies' provision of this data and the lack of regulatory embedding or enforcement of requirements to disclose this information. This might change with increased evidence and corresponding pressure on policy to react. The prerequisite for impacting price negotiations is robust data based on standardized reporting by all sectors, private and public (including EU member states reporting), philanthropic spending in all categories of R&D, and direct and indirect support. Corresponding reporting standards are the next step in logic to gain speed in implementation.

Public and private funding of the development of medicinal products are complementary ventures [71], sharing a division of work and working with large amounts of risk capital. Public R&D expenditures have macroeconomic effects on the GDP and microeconomic effects on companies' revenues – it has been estimated that a 1 % increase in public sector expenditures is associated with a 0.81 % increase in private sector expenditure [72]. However, the strategic aims of public R&D in health, life sciences, and biotechnology must first and foremost serve public health interests, such as priorities for new health technologies that meet patients' needs and serve economic interests only secondarily. Thus, when therapies are not available to those in need due to unaffordable prices, this system of complementarity can be seen to have failed. There is a very strong argument that the public contributions to basic /translational science (the knowledge) funded by taxpayers should be seen as global public goods and should be made freely available because they generate spin-offs, positive externalities, and provide the impulse for private R&D. The EC has reacted to the ever more often expressed reproach [11,73,74] that the public pays twice for their medicines, with the requirement for transparency – as seen in Article 57 of the proposed medicines Directive [10]. It is the intention of our research project – to our knowledge, the first of its kind – to provide a structure and classification when considering what kind of categories of public contributions one needs transparent information for.

It is argued that if the public sector tried to monetize the benefits of basic research, it would be either 1) very costly in terms of transaction costs and 2) might be counter-productive since it would diminish the incentive to use that research and apply it. Moving down the value chain into clinical research and regulatory approval, the risk of "paying twice" decreases because the public sector contribution is either bought out by the private sector investor, paid for in fees, or the public sector retains some IP rights. Therefore, any analysis of the public contributions to innovation must count not only the costs but also the income (benefits) of the public sector: any royalties or other rewards from the contribution to the development of the product and the IP (revenue) must be considered. Furthermore, a large part of the costs of R&D is in clinical trials conducted in public hospitals that are paid a remuneration to recruit and manage patients in clinical trials. The products (drugs, devices) are usually provided for "free", therefore representing an R&D cost to the sponsor but a benefit for public sector patients. Therefore, the focus needs to be on both the revenues and the costs for each actor, public sector and private. Consequently, only mapping all potential financial flows into and out of the R&D ecosystem and considering all stakeholders in innovation & R&D provides a full picture.

The complementarity of "intelligence from public and private sectors" is based on an implicit agreement (so-called "social contract" [75]) between government, citizens, organizations and private commercial actors that there are mutual obligations of the contractual partners. Applied to the context of medicines (and other medical products), corporate companies commit to bringing medicines to the market that address health needs in exchange for profits that compensate for their investments [76]. The role of governments is – within this social contract – to provide the legal and regulatory framework. However, this social contract between the public and private sectors to complement each other in developing "public goods", which has worked well for a long time, seems "broken" or – on the contrary –it is argued that the market is

not broken, but rather works *too* well. The many pull incentives for orphan drugs and rare diseases and the RoI for orphan drugs are so high now that the attention placed on rare diseases is displacing investment capital from other areas. This displacement of capital and effort from broad public health problems to micro-diseases might explain the decreasing health impact of R&D and increasing prices. Legislation on orphan drugs and antibiotics are two examples where public contributions aim to fix broken markets and provide incentives. This is a public intervention to drive innovation to spaces where the market was not reactive. These intentional drivers should further be explored by defining public needs and expected outcomes under conditional contracts.

5. Limitations and research gaps

This research has several limitations:

- The major limitation to getting a full picture is the lack of accessibility and availability of national sources providing data in enough detail or a standardized format, especially in the EU-27 countries. While the NIH RePORTER is easily searchable and provides information in different formats, the Cordis Database is descriptive only. While US-based companies must provide annual financial statements (Security and Exchange Commission (SEC) reports), no such source is available in Europe.
- A lot of well-documented data and information regarding the public contribution to innovation and R&D, direct and indirect, has been provided. However, the information lacks links to products/projects to apportion public contributions and their impact.
- Another major limitation is that some areas have not been covered by this research. Information on taxes, especially reduced taxes for commercial R&D, national and regional support to companies to settle in a certain region, overhead expenses for national and European services providing consultancy on EC-research funding and funding for innovation expenses like patenting, is lacking.
- The provision of publicly funded skills and training, essential prerequisites for settling companies in certain regions, has not been covered since these are intangible public contributions not solely targeted at health innovations.
- Some public contributions were assigned – for pragmatic reasons – to one individual category and only mentioned in another (such as methodology advancement in collecting and handling real-world data). This leads to some overlap between the eight categories identified, which can be considered a limitation of the approach of categories.
- The information we report on is not exhaustive and provides only examples. While a general impression can be given, a generalisation across all therapies, medicines and medical products is impossible. In particular, the areas of medical product development and me-too drugs are under-researched. Very few authors have researched technologies other than drugs.
- Additionally, most research is based on approved medicines and on following their development backwards rather than analysing public R&D and the licenced and patented outputs also to capture the public risk investments.
- Finally, we searched for and used only publications in English and German.

6. Conclusion

The question is not so much why we need to consider public contributions, but how to capture the substantial amounts of public funding in particular from European as well as from US-based public institutions. The conditions attached to public R&D grants are not sufficient [77]. The proposal for the new PL includes transparency requirements on the reporting of direct public R&D received. However, – as was shown here – the indirect public contributions are as relevant as the direct ones. Identifying the direct and indirect public contributions along the proposed categories seems easy compared to finding a way to reflect these contributions in pricing. Furthermore, the conditions for transparency requirements are not yet in place to allow for checking and monitoring. Several policy options are proposed as conclusions of this paper:

- Standardized reporting of public and philanthropic R&D spending, not only on the European level, but also for national funders, incl. their outputs (patents, spin-outs, …), would increase reporting granularity of data and projects' outputs.
- Compulsory requirements of R&D reporting for industry with clearly defined in-/ and exclusion criteria for increased comparability between public and private of R&D expenditures is recommended.
- Public availability is crucial: the reports supplied by the MAHs must be made available to the public, providing access to the data in a format that is easy to filter and interact with and potentially allows users/researchers to download, analyze and verify the files.
- Detailed contractual options for conditionalities and requirements attached to public support to research and further development of innovations – such as a "reasonable pricing clause", open access to intellectual property rights, profit-sharing or repayment of the initial investment or royalty payments to the public – are needed.

Finally, the role and willingness of political decision-makers to use any transparent information on public contributions that may be established need to be stressed. Otherwise, the transparency requirement clause will stay "dead paper" instead of advocating for a paradigm change. We intend not only to develop the framework and to pilot it in use cases but to finally provide (in due time) an instructive manual for policy-makers to support them in price negotiations.

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Contributions

Claudia Wild (CW) conducted the research and wrote the first draft, Ozren Sehic supported the data collections, Daniel Fabian (DF) and Louise Schmidt contributed with comments on the draft. The final version of the manuscript was agreed upon by all authors.

CRediT authorship contribution statement

Claudia Wild: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Ozren Sehic:** Investigation. **Louise Schmidt:** Writing – review & editing. **Daniel Fabian:** Writing – review & editing, Methodology.

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The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplementary materials

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