HEALTH INNOVATION NEXT GENERATION PAYMENT & PRICING MODELS (HI-PRIX):

Balancing Sustainability of Innovation with Sustainability of Health Care

D2.1: Guidance (Handbook) on estimations (ranges) of cost elements along the value chain for demanding detailed information in price negotiations

WP2 – Role of Public Contributions to the Development of Health Innovations and its Integration in Value Assessment and Pricing/Reimbursement Decisions

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COVER PAGE

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ABBREVIATIONS

ATMPs	Advanced Therapy Medicinal Products
ACC	Abramson Cancer Center
AMR	Antimicrobial Resistance
AWS	Austrian Wirtschaftsservice Gesellschaft
BARDA	Biomedical Advanced Research and Development Authority
BCV	BioGeneration Ventures
BERD	Business enterprises expenditures on R&D
BES	Business Enterprise
CARB-X	Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator
CLL	Chronic Lymphocytic Leukemia
CMRI	Centre for Medicines Research International
CRADA	Cooperative Research and Development Agreement
CROs	Clinical Research Organizations
DB	Database
DFG	German Research Foundation
DNDi	Drugs for Neglected Diseases Initiative
EBMT	European Bone Marrow Transplantation
EC	European Commission
EDCTP	European and Developing Countries Clinical Trial Partnership
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHDS	European Health Data Space
EIC	European Innovation Council
EIE	European Innovation Ecosystems
EIT	European Institute of Innovation & Technology
EJP RD	European Joint Programme on Rare Diseases
ELA	Exclusive License Agreement
ELF	European Lead Factory
EMA	European Medicines Agency
ESCulab	European Screening Centre: unique library for attractive biology

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EUnetHTA	European Network for Health Technology Assessment
FARS	Focus Areas of Regulatory Science
FDA	U.S. Food and Drug Administration
FET	Future & Emerging Technology
FFG	Austrian Research Promotion Agency
FIH	First Time in Humans
FP6	6th Research Framework Programme
FP7	7th Research Framework Programme
FWF	Austrian Science Fund
GARDP	Global Antibiotic Research and Development Partnership
GBARD	Government Budget Allocations for R&D
GDP	Gross Domestic Product
HES	Higher Education
HTA	Health Technology Assessment
IHI	Innovative Health Initiative
IMI	Innovative Medicines Initiative
IP	Intellectual Property
IPR	Intellectual Property Rights
JCA	Joint Scientific Consultation
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
KCE	Belgium Health Care Knowledge Center
KEI	Knowledge Ecology International
LA	Licensing Agreement
MA	Market Authorization
MAH	Market Authorization Holders
MDA	Muscular Dystrophy Association
NB	Notified Bodies
NCA	National Competent Authorities
NCE	New Chemical Entity
NCI	National Cancer Institute
NIAID	US National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NMEs	New Molecular Entities
OD	Orphan Drug

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OECD	Organization for Economic Cooperation and Development
OMP	Orphan Medicinal Product
OOPD	Office of Orphan Products Development
PDP	Public Private Development Partnerships
PI	Principal Investigator
PLEG	Post-Launch Evidence Generation
PNP	Private Non-Profit
PPP	Public-Private-Partnership
PrEP	HIV pre-expositions prophylaxis
PRIME	PRIority Medicines
RIS	Regional Innovation Scheme
RoI	Return on Investment
RWE	Real World Evidence
SEC	US Security and Exchange Commission
SMA	Spinal Muscle Atrophy
SMEs	Small and Medium Enterprises
TRL	Technology Readiness Levels
UPenn	University of Pennsylvania
VC	Venture Capital
WHA	World Health Assembly

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1 Introduction

1.1 Background

New pharmaceutical products are getting increasingly more expensive [1]. As a result of this trend accessibility of pharmaceuticals may decrease. Novel treatments especially for orphan diseases (EU definition: below 1 out of every 2000 EU citizens affected [5]) are ever more often unaffordable - even for high income countries in the European Union and their public healthcare systems [1, 2] sometimes without showing either none or modest clinical benefits or improvements of life [3, 4]. Many orphan drugs and ATMPs (Advanced Therapy Medicinal Products) are currently under development that will likely have a high estimated price. Public health care systems in Europe are faced with increased costs and increased expenditure [1, 2]. Pharmaceutical companies used to mainly justify the high prices with their expenditures for research and development (R&D). A shift towards pricing according to the added value novel treatments bring (value-based pricing) occurred. Greater transparency around R&D costs is essential for analysts and policymakers to check the veracity of claims by companies that the steep price increase of new drugs is driven by high development costs [5]. Policymakers throughout the world are calling for more transparency on actual costs and expenditures for R&D. Most notably in the European Commission's newly proposed revision of the pharmaceutical legislation [6] and the World Health Assembly's (WHA) 2019 resolution WHA72.8 on "Improving the transparency of markets for medicines, vaccines, and other health products" [7]. The EC has funded this research project as part of the Horizon Europe project "Health Innovation Next Generation Payment and Pricing Models" (HI-PRIX, Grant Number 101095593, 2023-2025). A part of the HI-PRIX project aims to increase the transparency of direct and indirect public contributions as well as the unbundling of the value chain of pharmaceutical R&D to understand how expensive pharmaceutical R&D actually is.

There are voices not attributing all innovation to pharmaceutical companies [8]. Subsequently, the role of public institutions like universities, university spin-offs, and publicly funded biotech start-ups is largely being disregarded at the price negotiations [8]. Public measures in form of research grants, tax incentives, use of clinical infrastructure or regulatory measures such as scientific assistance or fast-track-approvals have a large impact: in the US, the Food and Drug Administration (FDA) approved 248 drugs between 2009 and 2017 containing one or more new molecular entities (NME) of which 19% had origins in publicly supported institutes, and 6% originated in spin-offs of publicly supported programs [9]. From 1970 to 2009 153 FDA approved medicines entered the market that originated in public sector research institutes [10]. For the European counterpart, the European Medicines Agency (EMA), no such numbers are available due to a lack of transparency on reporting of public contributions. A study - sponsored by Pfizer and conducted by the Tufts Center for the

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Study of Drug Development - analysed pharmaceutical R&D and emphasized the importance of academia and public contributions to basic research [11].

The costs of clinical trials are rarely publicly available, or if they are, the validity of data being published might be suboptimal [12]. Publicly accessible data from not-for-profit organisations such as the Drugs for Neglected Diseases Initiative (DNDi) or the Global Alliance for TB Drug Development [13] show that their R&D costs are far lower than what studies on average costs of pharmaceutical R&D estimate [14]. Not-for-profit pharmaceutical companies are mostly focusing on neglected diseases of the Global South [14] where developed products are unlikely competing with great alternatives and therefore, development of new drugs may be far cheaper than what for-profit pharmaceutical company are developing. Despite that key difference, due to transparency we know the development cost of DNDi's products, but we do not know the actual R&D costs of for-profit-pharmaceutical companies.

There is little evidence whether transparency of private R&D would necessarily lead to lower consumer prices since, currently, there are no "transparency policies" in place [8, 15]. Even in the case that transparency will not lower prices, Riccaboni et al. (2020) [16] state "It is agreed upon that transparency in decision-making is beneficial to the functioning of the innovative pharmaceutical market as it supports good governance, enhanced decision-making and efficiency" [16]. Transparency is needed for policymakers to work towards improving public health and accomplishing the goals defined in Sustainable Development Goal (SDG) 3 – good health and well-being. If implemented, the newly proposed pharmaceutical legislation of the EC would increase transparency [6] and would work towards affordability, accessibility and availability (triple A strategy) [6].

There is a substantial lack of knowledge of public institutions and governments on their contributions to the R&D process. Funds are given without binding conditions on access and affordability of the final products. After funding (pharmaceutical products, vaccines, medical devices and diagnostics) R&D, there is no mandatory periodic review of the status of development that the receiving party has to submit to the funding one [17]. Public funds are most often given unconditionally and with a severe lack of transparency. In the US and in Europe alike [18].

Ever more often the allegation is raised that the public "pays twice" [15]. Despite the fundamental role public institutions play in the R&D process of innovative medicines, when it comes to paying for the final product those investments are being overlooked by pharmaceutical companies and public social welfare programs alike [19]. After a product is developed successfully and received EMA approval, the pharmaceutical company enters into negotiations with public healthcare programs. At those confidential negotiations, public contributions do not play a role in determining the price the public pays for products they help to development, but the "value" does. Cost-effectiveness studies as well as Health Technology Assessment (HTA) aid the public in decision making.

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There is an information asymmetry in the negotiations: Private pharmaceutical companies know how much they spent to develop the product, how high the production costs are as well as detailed estimates on their expectations on Return on Investment (RoI) of the value-based pricing and associated profits then are communicated to the investors. Public negotiators lack this information and have no reliable, unbiased sources of cost estimates. Furthermore, they lack the knowledge of the extent of public contributions and therefore, are unable to use this information in price negotiations. In neoclassical economics information asymmetry is a leading cause for market failure. Simplified: by increasing transparency the risk of market failure would decrease. The intention of this paper is to bring transparency into pharmaceutical R&D by firstly analysing the actual costs of pharmaceutical R&D. Secondly, to analyse the extent of public contribution to it. Public contributions will then be put in relation to the findings from the first part on estimating the costs of pharmaceutical R&D. Thirdly, to analyse the importance of mergers & acquisitions and the patent system.

1.2 Definitions and concepts

Pharmaceutical research and development (R&D) is a complex and lengthy process aimed at discovering, developing, and bringing new pharmaceutical products to the market to cure diseases, increase the efficacy of existing products and reduce side effects of drugs. It involves various stages, including preclinical research, clinical development, regulatory approval, and post-marketing surveillance/ collection of Real-World Data (RWD). Here's a step-by-step overview of the process of pharmaceutical R&D as the EMA classifies and defines different stages [20]:

Discovery and Target Identification: Scientists and researchers identify potential disease targets, such as specific proteins or molecular pathways involved in a disease. They explore various sources like scientific literature, genetic studies, and molecular biology to find potential drug targets.

Drug Discovery: In this stage, researchers work to identify or design molecules that can interact with the target and modulate its activity. They use techniques like high-throughput screening, computer modeling, and medicinal chemistry to identify potential drug candidates.

Preclinical Research: Once potential drug candidates are identified, they undergo extensive preclinical testing. This involves in vitro (cell-based) and in vivo (animal) studies to assess the drug's efficacy, toxicity, pharmacokinetics (how the body absorbs, distributes, metabolizes, and excretes the drug), and potential side effects. Preclinical studies provide initial data to support the decision of advancing a candidate (new molecule or therapy) to clinical trials.

Investigational New Drug (IND) Application: If the preclinical data is promising, the drug developer submits an IND application to the regulatory authorities, such as the

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U.S. Food and Drug Administration (FDA). The IND includes preclinical data, proposed clinical trial plans, and information on the drug's manufacturing, formulation, and safety.

Clinical development - Phase I: Phase I trials involve a small number of healthy volunteers to assess the drug's safety, dosage range, and potential side effects. These trials also evaluate how the drug is metabolized and excreted in the body.

Clinical development - Phase II: Phase II trials include a larger group of patients to assess the drug's effectiveness and further evaluate its safety. These trials provide preliminary evidence of efficacy and help refine dosage regimens.

Clinical development - Phase III: Phase III trials involve many patients and compare the investigational drug to existing standard treatments or placebos. These trials provide critical data on the drug's safety, efficacy, and potential adverse reactions. Positive results from Phase III trials are crucial for regulatory approval.

Attrition rate: The entire process, from discovery to market, takes several years and involves significant investments in research, scientific infrastructure, clinical trials, and regulatory agencies. Not all drug candidates are developed successfully and make it through each stage due to various reasons like safety concerns, lack of efficacy, or commercial viability. When many drug development projects are suspended (scientific attrition for efficacy and commercial attrition for financial reason) the success rate is low, while the attrition rate is high.

New Drug Application (NDA) Submission: If the Phase III trial results are positive, the drug developer submits an NDA to the regulatory authorities (FDA in US/ EMA in the EU), providing comprehensive data on the drug's safety, efficacy, manufacturing process, and proposed labeling.

Regulatory Review: Regulatory agencies review the submitted data and evaluate whether the drug's benefits outweigh its risks. They assess the drug's safety, efficacy, quality, and labeling information. This stage can involve multiple rounds of questions, clarifications, and negotiations between the drug developer and regulatory authorities.

Approval and Post-Marketing: If the regulatory agency is satisfied with the data and the drug's benefits outweigh the risks, it grants marketing approval. Once approved, the drug can be marketed and distributed to healthcare providers and patients. Post-marketing surveillance continues to monitor the drug's safety, identify rare side effects, and gather additional data on its long-term effects.

Collection of Real World Evidence (RWE): RWE is gathered to gain insights into a product's performance in real-world settings. This data can be collected from diverse sources such as patient registries or observational studies. The objective is to gather a comprehensive understanding of a pharmaceutical product's effectiveness, safety profile, and patient outcomes beyond the controlled environment of clinical trials.

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From funding basic research to providing the clinical infrastructure for conducting the pivotal trials public resources are involved at every stage of pharmaceutical R&D. As guidance for our research on transparency, we developed a scheme (see Figure 1.4-1) to provide a more detailed overview of the elements along the value chain of the development of medicines and to structure our approach to search for relevant information.

Before examining why, the public should be interested in increasing transparency in R&D, we must first define R&D. Depending on who you ask, the definitions can vary greatly. The definition matters because in various European countries there is legislation incentivizing high R&D activity by granting tax benefits in accordance to R&D spending [21-23]. The lack of a precise agreed definition of R&D lead to inefficiencies emerging from the use of a variety self-defined concepts for what R&D is and which activities can fall under this concept. Acquisitions of SMEs or patents, opportunity cost of capital as well as Phase IV studies aiming at increasing market shares ("Seeding trials") could be included in R&D expenditure reporting of for-profit pharmaceutical companies but may not fall under the public's understanding of R&D.

There is no binding definition or framework that companies must use to disclose their R&D definitions and costs. In 1963, the Organization for Economic Co-operation and Development (OECD) published the "The Proposed Standard Practice for Surveys of Research and Experimental Development" commonly known as the Frascati Manual [24]. It defines what R&D is and what it is not for most sectors but leaves room for interpretation. The most recent edition of 2015 includes a specific definition of R&D in the context of pharmaceuticals. It is the most commonly used framework to assess whether an expenditure is R&D or not and is regarded as the gold standard to assess expenditures for R&D. In assessing R&D, the European Union refers to the Frascati Manual and we therefore will use the Frascati definition as it is the most well-known and developed definition for R&D.

According to the Frascati Manual, R&D in pharmaceuticals refers to "creative work undertaken systematically to increase the stock of knowledge about substances intended for use in the prevention, diagnosis, or treatment of disease and to develop new applications of this knowledge for practical purposes." [24]. The definition encompasses the scientific and technological activities aimed at discovering, developing, and improving pharmaceutical products, including drugs, vaccines, and therapeutic agents.

The definition recognizes that R&D in pharmaceuticals involves both basic research (fundamental scientific exploration) and applied research (targeted at specific practical objectives) [24]. It emphasizes the goal of expanding knowledge related to substances used in disease prevention, diagnosis, and treatment, as well as the application of this knowledge to develop practical solutions.

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1.3 The Problem: Decline of productivity ("patent cliff") and strategies to tackle the decline

A pharmaceutical product can have varied forms of protection from copying at various stages of the development process. Pre-clinical knowledge about a molecule is protected by a patent. Development knowledge can be protected by a patent or by trade secret. Once a drug received approval from the responsible approval agencies, is protected by market exclusivity rights and data protection rights. The term "patent cliff" refers to the phenomenon of patent expiry and a subsequent abrupt decline in sales for a group of products, while no further products are in the research pipeline to fill in. The pharmaceutical industry had to face such patent cliffs based on a decline of productivity from 2005 and 2011, which was reflected in a lower number of novel drugs (new molecular entities/ NMEs) approved by the FDA or EMA in these years[18, 19, 25, 26] (see Figure 1.3-1). The problems of the pharmaceutical industry were described by Scannel et al. (2012) [27] in detail: In their analysis, evergreening (a term describing the strategy to marginally modify a drug to prolong its patent protection) is not counted as a novel medicine and several factors are used as an explanation for the problems in the pharmaceutical industry. Scannel et al. (2012) [27] identified three phenomena: The 'Better than the Beatles' problem, the 'Low hanging fruit' problem and the 'Throw money at it' tendency.

- The "Better than the Beatles" problem describes the perceived problem for the pharmaceutical industry where new medicines have to be better than the current standard of care to be successful. While the back catalogue of generic options - with only small profit margins - is growing, the research pipeline for patent-protected medicines is small. This problem deters R&D activity in certain therapeutic fields and crowds R&D activity in others. Emblematic of this trend is the field of oncology, which has seen an increase of investment like no other field has [28] (regardless of the evidence on the benefit on survival or quality of life [3]). In addition, orphan diseases are interesting to pharmaceutical companies, since there are no treatment options on the market and less post-launch competition expected [25]. If there is an excellent standard of care for a disease in place, pharmaceutical companies are less likely to invest in R&D in that field since they want to avoid competing against the 'Beatles'.
- The "Low Hanging fruit" problem is an explanation used by the pharmaceutical industry to justify high costs of novel treatments due to high R&D costs [27]. The understanding here being that all the easy-to-cure diseases have been cured and 'fruits higher up on the tree need more effort to pick'. According to Scannel et al. [27], between 1950 and 2010, the average cost of bringing a new drug to the market doubled every 7 years. This increase cannot be simply explained by inflation alone and, therefore, would support the existence of the 'low hanging fruit' problem.

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- The 'Throw money at it' tendency" [27] describes a habit by companies to continue business as usual if a business strategy is working. Imagine a pharmaceutical company spending 1 billion Euros for one new pharmaceutical product that is a true innovation and incredibly successful in monetary terms. The logic of the company is that by doubling their R&D expenditures, they will generate double the revenue of the first pharmaceutical novelty. In real-world settings, this tendency exists to a lesser degree, but it follows that logic. Investment in pharmaceutical R&D can take decades for a new product regardless of how much money you 'throw at it'.

A study that analysed the top 12 innovation-driven pharmaceutical companies defined the quintessential "blockbuster" era of the pharmaceutical sector from 1995-2015 [29]. The pharmaceutical industry reacted with various strategies to its problems: A shift from 2005 onwards towards speciality drugs and biologics (often with orphan designation) targeting medical indications with little or no therapies (also called "unmet medical needs" by the pharmaceutical industry) can be observed as a direct result of legislation incentivising research in these fields [29, 30]. Also "evergreening" (a term describing the strategy to marginally modify a drug to prolong its patent protection) is a persisting trend [31] and public-private-partnerships with academia and in-licensing as well as acquisitions of smaller companies with promising drug candidates became ever more common [32, 33].

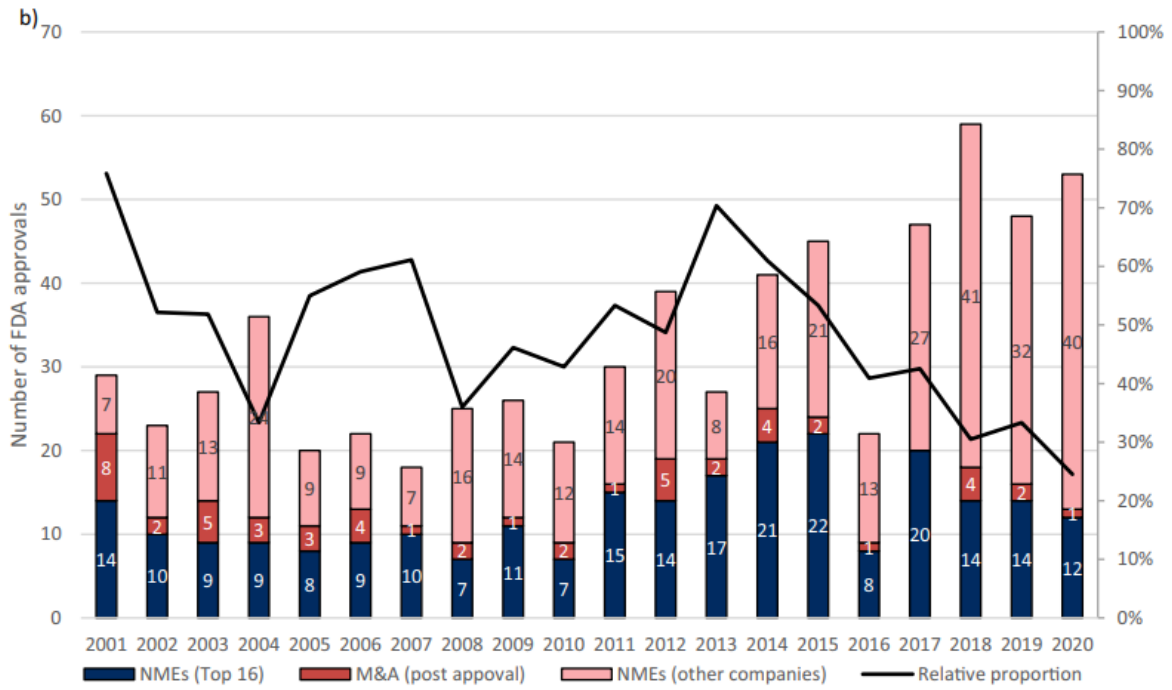

Figure 1.3-1: Patent Cliff and Decline of Productivity – NME approvals 2001 to 2020 by FDA (Graph by Schuhmacher et al. [26])

The concept of rare or orphan diseases gained prominence in the 1980s and the associated orphan drug regulation (launched in 2000), but also the decoding of the

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genome (2001) leading to biomarker discoveries and improved stratification of patients (also called "personalized or precision medicine") contributed to the structural changes in the pharmaceutical industry. In response to the challenges faced by pharmaceutical companies in developing new treatments for broad chronic diseases, the orphan drug regulation (ODR) incentivizing drug development for rare diseases was welcomed. Additionally, governments around the world implemented policies providing financial incentives, such as tax credits and grants, and granting market exclusivity. Data requirements for orphan drugs were also lowered with FDA/ EMA approval possible after completed phase II studies [34]. Now, 20 years later already two thirds of all drugs approved in the US are orphan designated products [35] many of them in oncology. This development induced by now possible biomarker-based dissection of diseases is often called "orphanisation" referring to the exploitation of the orphan drugs legislation by drug developers [36].Orphan drugs are associated with high costs leading to issues on affordability and challenges in healthcare reimbursement systems [30].

Though the increased attention and investment in rare diseases has led to advancements in understanding of those diseases and in improved diagnostic capabilities [30], an evaluation of the impact of the orphan drug legislation brought disillusion on actual new drugs [37]. Between 2007 and 2017, 131 medicines were approved by EMA as orphan drugs for 107 rare diseases: 22 drugs were approved for two or more indications and for different periods of market exclusivity - and with significant return on investment (RoI) over very long periods [37]. 28% of the orphan drugs were oncology drugs [37] (e.g. for Acute Myeloid Leukaemia/AML or gliomas), i.e. indication areas where other therapeutic options were already available. Different voices on this either portray the existing orphan drug legislation as working effectively [38, 39] and others that critique it [36].

Scientific progress in general, changes in the market and in public R&D incentive systems have contributed to the development of these new orphan drugs. In addition to the general trend of "orphanisation" of drugs and indications, there is a noted trend for large pharmaceutical companies not to conduct research themselves, but to buy up late-stage developments from small biomedical companies (often spin-offs from universities) - also known as the strategy of "search and development" (rather than R&D [40]). According to a study by Pammolli et al. [41] this trend speeds-up development time and increases productivity.

The productivity crisis in the pharmaceutical sector is over and shows – since 2013 - an upward trend on multiple frontiers according to Pammolli et al. [41]. The number of newly approved drugs has increased and attrition rates for most large pharmaceutical companies have decreased. The reduction of attrition rates was a driving factor for productivity [41]. However, in a recent study, the 16 largest pharmaceutical companies (by revenue) were analysed on their productivity with the result that between 2011 and 2020, 57% of all new drug launches were unprofitable [26]. To offset the loss, mergers and acquisitions are being used as a cost containing and risk

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mitigating strategy [25] to increase productivity and revenue [26]: from big pharmaceutical companies that used to conduct research themselves to leaner and more specialized companies [29]. Cooperations between academia and pharmaceutical companies are also partly responsible for reducing risks for pharmaceutical companies (especially for ATMPs [42]). The flexibility of academic inquiry across a wide range of biological disciplines holds great promise for developing new products [43]. Public Private Partnerships (PPPs) have increased in numbers and became a more common practise [44].

1.4 Methodology

1.4.1 Overall methodology

This paper aims to put a spotlight on the costs of pharmaceutical R&D and public contributions to it. For achieving this aim, R&D elements along the value chain (see Figure 1.4-1) will be scrutinized for detailed information on contributors and beneficiaries, expenditures, and costs. The approach to the analysis on cost of developing pharmaceuticals and the public contributions to product development follows the following general methodology that will be described in more detail in this chapter below:

- First, the R&D process is considered along the value chain from private expenditure to identify the key items of R&D funding (Chapter 2) and then those items were adapted to the kinds of contributions public entities typically make to R&D (Chapter 3) (see Figure 1.4-1).
- Then a mixed-methods approach is applied using an iterative procedure for identifying relevant information and data sources by conducting qualitative interviews with experts in their respective fields (Table 1.4-1), followed by targeted literature searches on the topics identified and a systematic analysis and synthesis of the literature and data found.
- Interviews, literature, and data analyses complement each other and are not reported separately.

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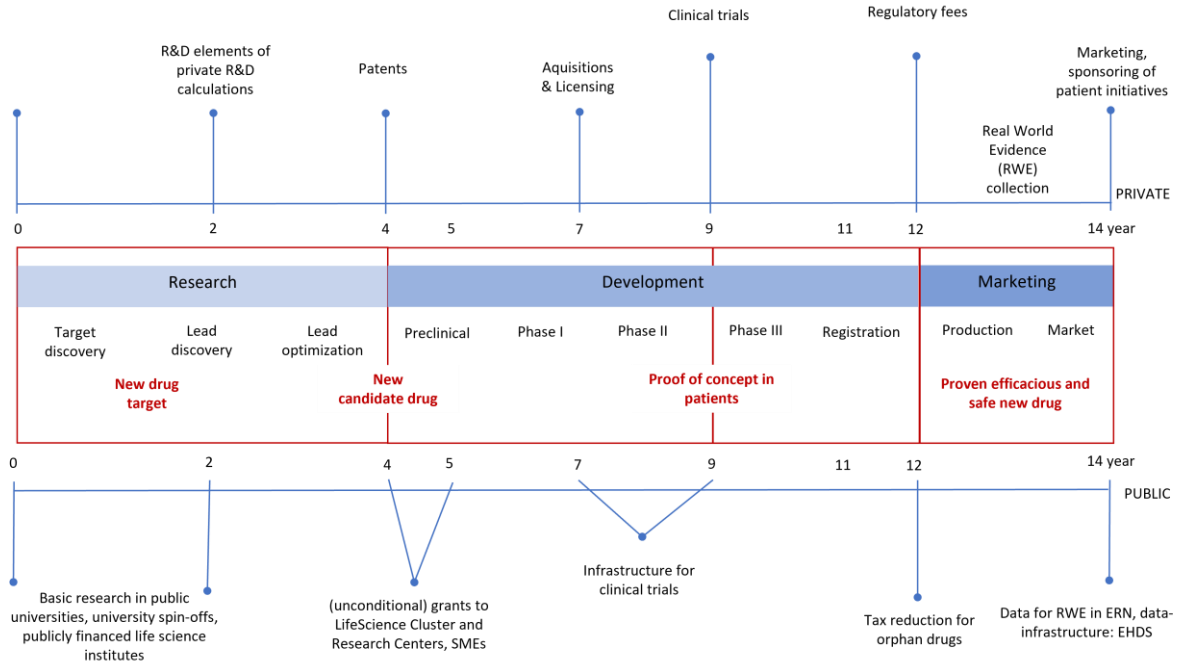

Figure 1.4-1: R&D Process of a drug in development

1.4.2 Research questions (RQ)

The following research questions (RQ) led our research:

- RQ1: What is the R&D cost of bringing a new drug to the market?
- RQ2: Which factors influence these costs of R&D for pharmaceuticals?
- RQ3: Which public contributions to R&D of (medicinal and other) products are reported in the literature?
- RQ4: Which categories of (direct and indirect) public contributions to R&D of (medicinal and other) products can be identified and supported by data?

1.4.3 Details on the methodologies to answer the RQ

To answer the four research questions the following methodologies were applied in an iterative manner. Figure 1.4-2 presents the overarching methodology: a mixed-methods approach was applied using an iterative procedure for identifying relevant data and information.

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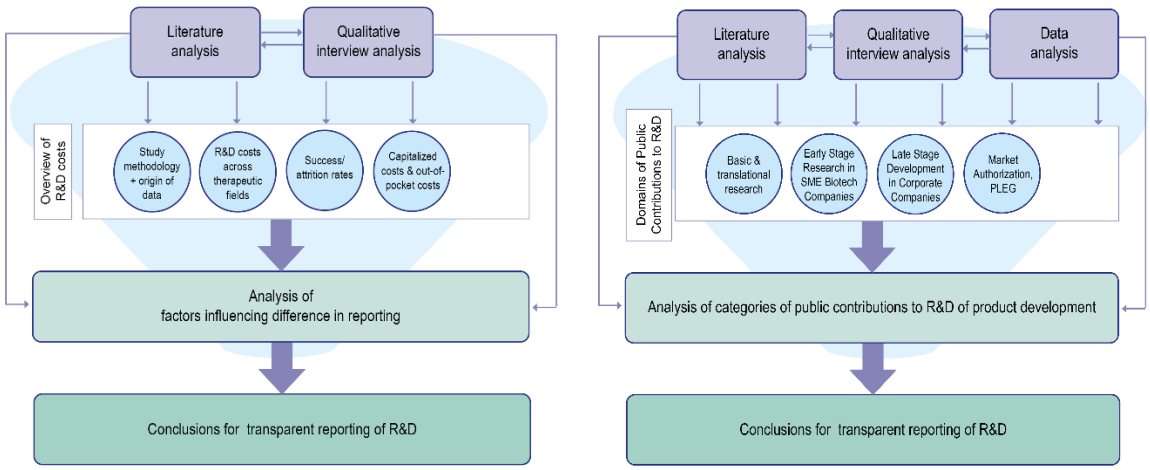

Figure 1.4-2: Methodological approach in chapter 2 and chapter 3

1.4.3.1 Interviews with stakeholder groups

Identification of experts: As a first step the stakeholder groups essential for giving input and insights were identified by the authoring team (DF and CW) and additional researchers from AIHTA (Ingrid Zechmeister-Koss, Christoph Strohmaier) complemented by topics to discuss. Further on snowball sampling for key stakeholders was used to identify additional interviewees on more specific topics.

Semi-Structured interviews - questions and documentation: The interviews were prepared based on a preliminary orientation in the literature: for cost estimations the review of Schlander et al. (2021) [45] (chapter 2) and for public contributions a book from Mazzucato "Public vs Private Sector Myth's" [46] (chapter 3) were used. The interviews were conducted in a semi-structured manner with academic experts, pharmaceutical industry representatives and not-for-profit pharmaceutical developers (see Table 1.4-1) intending to cover and include many different stakeholder-groups. Semi-structured interviews as a method was chosen to allow the interviewer to adapt the questions to the interviewee's knowledge as well as to allow follow up questions. The interviews were conducted between February 2023 and September 2023 (and are still ongoing) by two researchers (DF, CW) either online via Zoom or in person. All of the 17 interviews but six were conducted by two researchers together and minutes were taken by both interviewers, combined, and documenting the interviews in a joint document. However, no recordings were taken, and the interviews were not processed further (e.g., in a content analysis) due to their heterogeneity in topics and contents and the only informative character: The interviews held were intended to support in identifying variables that influence R&D costs and to gain insights in the spectrum of public contributions to the development of products. .

Inputs from the interviews (see Figure 1.4-1) were taken to identify:

- Relevant aspects and key words for targeted literature searches

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- Relevant authors in the field of interest (using 'snowballing')
- Unpublished materials and grey sources
- Defining the variables for the extraction tables
- Defining the spectrum of public contributions and data sources
- Assessing factors that might influence the differences in the reported data

The questions asked are listed in Appendix B Chapter 2.

Table 1.4-1: Identification of Interviewees according to stakeholder groups

Stakeholder Group	Topics	Input for Chapter 2	Input for Chapter 3
Policy advocacy for affordable medicines	on medical innovation and public contributions	R&D Cost estimates, Clinical trials, Screening, Attrition rates	Basic & applied research, Changes in ownership, Support to clinical trials
	on experiences with reporting of public contributions in USA	Clinical trial size, Attrition rates, Basic research, Keyword identification	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	Affiliations of researchers, total R&D spending, Cost of Capital	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	Clinical trials, Attrition rates, Financialization	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	Financialization, Screening, Attrition rates, Clinical Trials, Public Private Development Partnerships	Changes in ownership, Regulatory support
EC DG Research and Innovation	on EC funding of Research and Innovation, trial infrastructure and clinical trials	Screening	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	Clinical trials	Support to clinical trials
		Clinical trials	Support to clinical trials
Clinical Researcher	on funding for clinical research	Basic 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

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Start-up biotechnology SME	on public grants in early-stage development and investors	Clinical development stages, Clinical trials	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	PDPs	Applied & translational research antibiotics, Support to clinical trials

DNDi – Drug for Negelected Diseases Initiative, EC DG – European Commission Directorate General, ECRIN- European Clinical Research Infrastructure Network, EFPIA- European Federation of Pharmaceutical Industries and Associations, EIC - European Innovation Council; EIE - European Innovation Ecosystems, FFG – Forschungsförderungsgesellschaft (Austrian Research Promotion Agency), IMI/ IHI – Innovative Medicines Initiative/ Innovative Health Initiative, KEI - Knowledge Ecology International, KKS - Kompetenzzentrum für Klinische Studien (Compenetnce Centre for Clinical Studies), MUW – Medizinische Universität Wien (Medical University of Vienna), PDP- Public Private Development Programs.; PPP-Private-Public-Partnerships, RWD -real world data

1.4.3.2 Targeted Literature Search

For answering RQ1 and RQ2 the systematic review of pharmaceutical R&D cost estimates conducted by Schlander et al. (2021) [45] was updated with articles published since 2021. The same search strategy – as used in Schlander et al. was used.

- First a hand-search for published articles and reports was carried out, followed by screening of the reference lists of relevant articles to update the Schlander et al. (2021) publication [45].
- Then, for each of the subchapters (domains) that were identified in the interviews as factors influencing the costs additional targeted literature searches were conducted (reported as subchapters of chapter 2).

The details can be found in Table 1.4-2.

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Table 1.4-2: Targeted literature search on costs of R&D for pharmaceuticals (Update of [45]) for RQ1 and on factors influencing costs of R&D for pharmaceuticals for RQ2

RQ1: What are the costs of R&D for pharmaceuticals to bring one new drug to the market?	
Search period	2020 - 2023
Databases searched	PubMed, Embase, EconLit
Google scholar	Grey literature
Hand search	DNDi, KEI, TB Alliance, OECD, EC, EFPIA, Evaluate Pharma, Reuters, StatNews, SOMO, RAND, Economist Intelligence Unit (EIU), Office for Health Economics (OHE), National Institutes of Health (NIH), World Health Organization (WHO), statista
Search terms and search strategy	"drug research and development" AND "costs" OR "drug research and development" AND "expenditure"
Inclusion Criteria	English or German language Use of original data
Results	2 additional studies + 22 from [45]
RQ2: Which factors influence these costs of R&D for pharmaceuticals?	
Search period	No limitation
Databases searched	PubMed, Embase, EconLit, google scholar
Google scholar	Grey literature
Hand search	DNDi, KEI, TB Alliance, OECD, EC, EFPIA, Evaluate Pharma, Reuters, StatNews, SOMO, RAND, Economist Intelligence Unit (EIU), Office for Health Economics (OHE), National Institutes of Health (NIH), World Health Organization (WHO), statista, PhRMA
Inclusion Criteria	English or German language Use of original data
Search terms and search strategy	"drug research and development" AND "Costs for orphan drugs" OR "Costs for non-orphan drugs" OR "Costs of self-Originating drugs" OR "Costs for in-licensed drugs" OR "Costs by Phase of R&D" OR "Attrition rates" OR "Failure rate" OR "Abandonment rate" OR "Costs associated with study design" OR "size of clinical trials" OR "probability of success" OR "pre-clinical costs" OR "basic research"
Results	Costs for orphan vs. non-orphan: 2 studies Self-Originated vs. licensed/ acquired: 10 studies Costs by Phase of R&D: 9 studies Attrition rates: 16 studies Study Designs and Size of Trials: 11 studies

Due to the targeted hand search, no PRISMA reporting is presented.

Risk of Bias (RoB): No risk of Bias assessment was conducted due to the heterogeneity of the studies and the reporting of information. However, we analysed the information according to the data transparency and the comprehensibility of the calculations.

Data extraction: Of the 22 publications reported in Schlander et al. (2021) [45], 14 analyse mixed therapeutic fields and 8 examine specific therapeutic fields. 2 additional publications were identified; one from an interview with DNDi and one from a literature review on google scholar and PubMed. Three additional publications were identified for attrition rates specifically [47-49]. We extracted – as a first step - the following information for publications on mixed therapeutic fields and specific therapeutic fields:

- Drug inclusion period
- Sample of drugs included
- Reported success rates in percentage
- Average out-of-pocket and capitalized cost estimate to bring one new drug to the market

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- Origin of the data the cost estimates are based
- Methodology of the studies: accounting for failed trials
- Stage of start of cost estimates: whether basic research is included in the cost estimates or not;

In a second step, the same 24 publications were disaggregated in sub-tables and further information was extracted on:

- Self-originating vs licensed
- Costs of clinical trials
- Compound screening
- Average development time
- Per clinical development stage attrition rates
- Per clinical development stage cost estimations

For answering RQ3 on public contributions to R&D of product development a targeted search for published articles and reports was conducted:

- First a hand-search was carried out, followed by screening of the reference lists and of key researcher in the field.

The details can be found in Table 1.4-3.

Table 1.4-3: Targeted literature search on public contributions to R&D for pharmaceuticals for RQ3

RQ3: Which public contributions to R&D of (medicinal and other) products are reported in the literature?	
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), etc.
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 details for extraction
Results	25 publications: 10 (based on 5 datasets) on overall public contributions across drug approvals, and 15 publications on 28 case studies on products.

Due to the targeted hand search, no PRISMA reporting is presented.

Risk of Bias (RoB) and Data extraction (of literature): No risk of bias assessment was conducted due to the heterogeneity of the studies and the reporting of information.

Data extraction: Of the 25 publications identified, the following information was extracted:

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- Authors and year of publication
- Data basis of analysis: number of compounds or product
- Results: effects of public contributions
- Sources and methodology
- Categories of public contributions considered

1.4.3.2 Data collections and sources

For answering RQ4 the value chain (see figure 2-1) was for reasons of practicality

- First subdivided in four phases of research and development from basic research to post-launch evidence generation and
- Subsequently, several data sources (databases, websites, etc.) were screened and exploited for direct and indirect public contributions identified in interviews and publications. The data collections are meant to be exemplary (not exhaustive).
- Lastly the categories of direct and indirect public contributions were accordingly classified into eight categories. The categories are eventually – at this stage of the research - not exhaustive.

The details can be found in Table 1.4-4.

Table 1.4-4: Data collections and exemplary data sources for RQ4

RQ4: Which categories of (direct and indirect) public contributions to R&D of (medicinal and other) products can be identified and supported by data?		
Search period	2007 - 2023	
Public contribution by phase	**Topics and Data sources**	**Links**
Basic & translational research	EC-grants in Cordis Db, IMI/ IHI project database National research funders	https://cordis.europa.eu/de https:// www.imi.europa.eu/projects-results/project-factsheets see Table A 1, in Appendices Chapter 2
Early Stage Research in SME Biotech Companies	Spin-out/off companies EC-Innovation support for Lifesciences, Biotech (EIC, EIE, EIT)	Google searches on Websites of Universities 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 Trial Support by EC or national sponsors	News: STATnews, FiercePharma, FierceBiotech https://cordis.europa.eu/de see Table A 1, in Appendices Chapter 2
Market Authorization, PLEG	Regulatory support SA and PLEG RWE data collections	https://www.ema.europa.eu/en https://www.eunethta.eu/ https:// www.imi.europa.eu/projects-results/project-factsheets; https://darwin-eu.org/
Inclusion Criteria	English or German language	

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2 R&D costs and on factors influencing the costs

2.1 Results: Overview of R&D costs

This section intends to answer RQ1 on the costs of R&D for drugs. Several research groups conducted studies on the costs of R&D to bring one new drug to the market. The novelty of our approach is the disaggregation of R&D cost estimates. Starting from basic research to the discovery phase, to preclinical and onwards to Phase 1-3 of clinical trials, this paper aims to present cost estimates with a specific focus on factors, influencing the differences between the reporting of researchers with industry/ governmental/ not-for-profit or academic affiliations (origin of data, methodologies, bias). As an overarching theme, attrition rate plays a pivotal part, specifically the differentiation between the medical and financial reasons for abandonment of further activities (scientific and commercial attrition rates).

Three main elements that make up R&D cost estimates are identified by Sussex et al. [50]. Firstly, 'Out-of-pocket (OOP)' costs of R&D. OOP costs entail the actual costs of bringing one new drug to the market. Secondly, the aspect of financing R&D. Namely, cost of capital, opportunity costs and costs of acquiring patents or licenses. Thirdly, attrition rates in % that describe how many projects succeeded and how many failed. Capitalized cost estimates are the accumulation of all costs accrued along the value chain which includes the OOP costs, the costs associated with financing and the development time, as well as the attrition rates. Each of these will be analysed in the following sections (See Figure 2.1-1 on the elements that make up the total R&D costs for pharmaceuticals).

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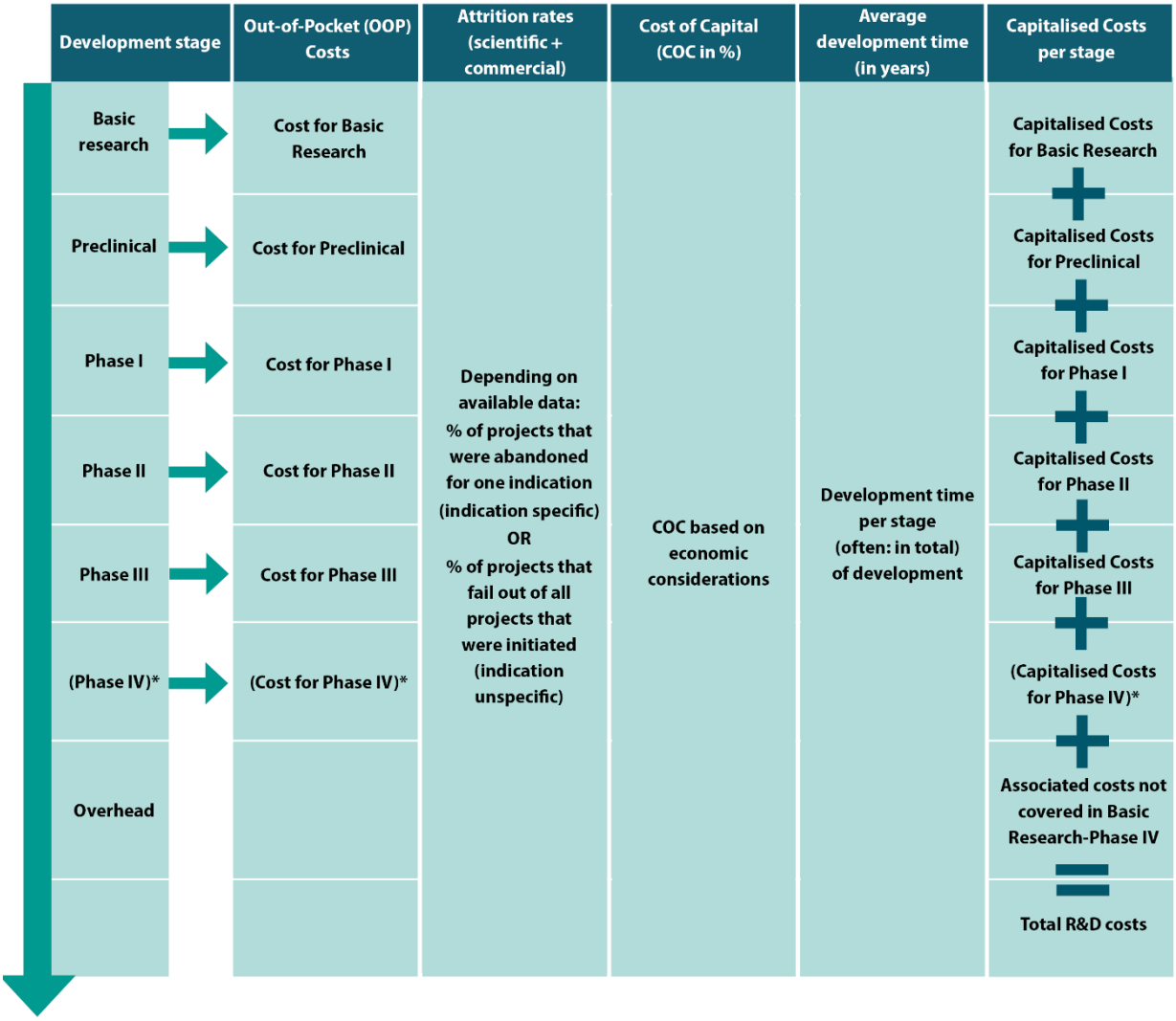

Figure 2.1-1: Calculations for pharmaceutical R&D cost estimations (inspired by Mestre-Ferrandiz et al. [1])

Based on the most recent systematic review on cost estimations for pharmaceutical R&D by Schlander et al. [45] and an updated search, we identified in total 24 studies on costs for R&D of medicines between 1979 and 2020. In recent years, several research institutes, scholars and governments have been interested in estimating the costs to bring a new medicine to the market. Already in 2011, a systematic review on this topic was conducted by Morgan et al. in 2011 [51], and updated in 2021 by Schlander et al. [45]. We identified two further publications, summing up to 24 included studies.

17 studies included (see Table C 1 in Appendices Chapter 2) give estimates for mixed therapeutic fields.

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2.1.1 R&D costs on mixed therapeutic fields

Study characteristics of publications

The earliest publication (1979) analysed a selected sample of medicines from 1963 to 1975 [52], and the most recent one (2022) analysed costs of drugs with aggregate data from 2001 to 2020 [26]. We visualized the drug inclusion periods in Figure 2.1 1 to investigate whether there are relevant gaps in the timeline of cost estimations. We found no relevant gaps from 1963-2020. The sample size (number of drugs analysed) is reported in all but three studies (see Table C 1 in Appendices Chapter 2), ranging between 8 (Gilbert 2003) [53] and 3,181 (Adams 2006) [54] drugs included in the analyses.

We classified the studies in four categories:

1 **Academic research** (no external funding, no interest groups): Wouters [5]
2 **Industry financed research** (research that received either partly or full funding from pharmaceutical companies or pharmaceutical interest groups): Hansen & Chien [52], Wiggins [55], DiMasi (Tufts Center for the Study of Drug Development's (CSDD)[1]: [28, 56-59]), Gilbert et al. (Windhover PharmaIntelligence[2]:[53]), Paul et al. (Lilly Research Laboratories (LRL)[3]: [60]), Mestre-Ferrandiz et al. (Office of Health Economics (OHE)[4]: [61]), Jayasundara et al. [39], Schuhmacher et al. [26]
3 **Governmental research** (funding received from governmental agencies): Adams & Brantner [54, 62],
4 **Not-for-profit research** (research that was conducted in a not-for-profit pharmaceutical development organization): DNDi [14], Young and Surrusco [63]

[1] Tufts Center for the Study of Drug Development's (CSDD) is funded in part by unrestricted grants from pharmaceutical and biotechnology.

[2] Windhover PharmaIntelligence is a consultancy providing business intelligence data to Pharma companies.

[3] Lilly Research Laboratories (LRL) is fully funded by Eli Lilly.

[4] This Office of Health Economics (OHE) project was partly funded by Astra Zeneca.

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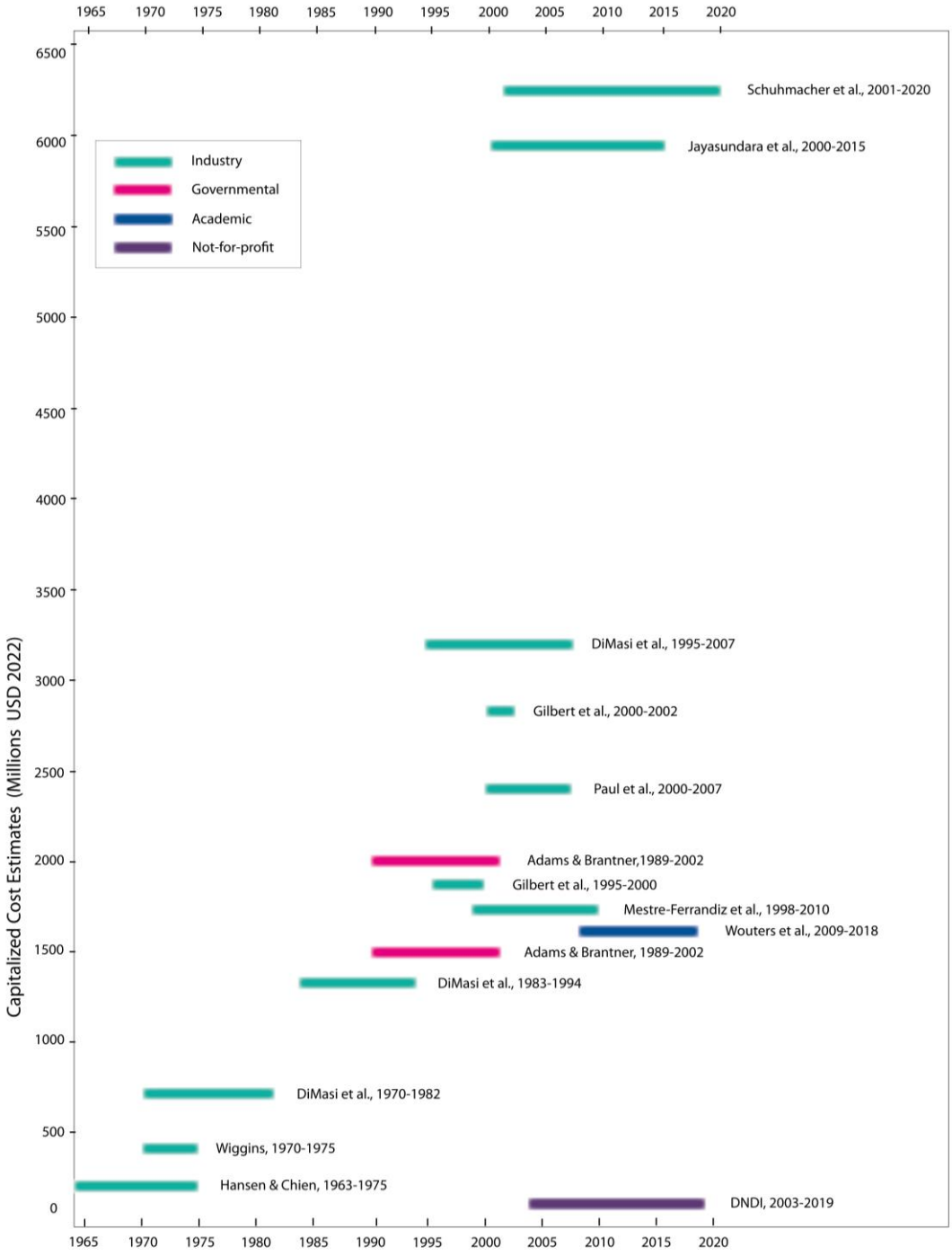

Figure 2.1-2: Analysed time-periods of the included studies (graph inspired by Mestre Ferrandiz et al. [48])

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Approaches for cost estimation in the selected studies

Methodologies to estimate average costs to bring one new drug to the market that start with total R&D spending of a company are faced with the challenge to attribute a specific amount of the firm's expenditures to preclinical spending [64]. The large ranges of cost estimates is the result of various data sources, data samples, and methodologies [64].

The studies included use different methodologies (see Table 2.1-2) To estimate cost estimates for mixed therapeutic areas (as seen in Figure 2.1-2). Cost estimates are either based on project-level data [14, 39, 52, 56, 58-61], on aggregate data [5, 26, 53] or on a combination of both [54, 62]. Project-level data is data on specific products under development gathered by surveying pharmaceutical firms. The reporting of project-level data can be either all associated costs accrued along the development of a product as many sums, or one total amount of costs associated with the development of one specific product. Aggregate data makes use of company-level data and reports on their R&D expenditure. When using aggregate data, the available data depends on the methodology used. When using data for the entire sector, per product R&D spending is estimated by examining the economic correlation between historical total research expenditure available in a database and new drug approval rates. When a database is used to calculate average costs, both failed and successful projects need to be included since not including failed projects would lower average costs.

When using project-level data selection bias may be an issue. This implies that the selection of which drugs that were developed may influence the reported average cost to bring one drug to the market. Selection bias refers to a distortion of data analyses where the chosen sample does not accurately represent the entire population of interest. This bias occurs when certain individuals or groups are either overrepresented or underrepresented in the sample, leading to skewed or misleading results. It can arise due to various factors such as non-random sampling, self-selection, or exclusion criteria. Detecting selection bias requires careful examination of the sampling methods employed and an understanding of the potential impact on the results. To control for selection bias DiMasi et al. [58, 59, 65] use random sampling of the data provided in their analysis. Mestre-Ferrandiz [61] use all data on drugs provided to them by industry and therefore, do not control for selection bias.

Origin of the data

The origin of the databases varies greatly (see Table 2.1-1). Data from confidential industry surveys were used most often [28, 52-54, 56, 58-62]. Publicly available databases such as clinicaltrials.gov [26, 39, 54, 62], industry-wide R&D cost reporting or periodic Securities and Exchange Commission (SEC)-reports [5] are alternative sources to confidential industry surveys to estimate costs of pharmaceutical R&D. TrialTrove and PharmaProjects [54, 62] was used to gather information on clinical trials, their duration and sample sizes. The most recent publication about costs of bringing one

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new drug to the market by Schuhmacher et al. [26] uses aggregate data of 16 big pharmaceutical companies. We asked the European Federation of Pharmaceutical Industries and Associations (EFPIA) if they provide their members with a standardized definition for their reporting on R&D, however they shared with us, that they do not provide a standardized method of reporting R&D expenditure which is in line with DiMasi et al.'s finding [59].

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Table 2.1-1: Methodology and origin of data for R&D cost estimations (mixed therapeutic fields)

Publishing Author(s)	Publication year	Type of data	Methodology	Details of data	Origin of data
Hansen & Chien [52]	1979	Project-level	Confidential surveys (of pharmaceutical companies)	Questionnaire sent to 25 US pharmaceutical companies, 14 completed questionnaires, data comprising of 10% of NCE tests 1963-1975. Exclusion of licensed-in products.	Industry
Wiggins	1987	Aggregate	Industry wide R&D costs, not project specific	Industry-wide R&D expenditure reporting	Industry
DiMasi et al. [56]	1991	Project-level	Confidential surveys (of pharmaceutical companies)	Survey sample of top 50 firms based on CSDD database of investigational drugs. Exclusion of licensed-in and co-developed products.	Industry
DiMasi et al. [58]	2003	Project-level	Confidential surveys (of pharmaceutical companies)	Survey conducted by the Tufts Center for the Study of Drug Development. 68 randomly selected drugs that obtained marketing approval from the FDA between 1983 and 1994.	Industry
Gilbert et al. [53]	2003	Aggregate	Modelling with confidential data	AI of the data presented in the study where conducted using the Bain drug economics model of 2003.	Industry (business consulting)
Adams & Brantner [54]	2006	Combination of project-level and aggregate	Based on Pharmaprojects database of unspecified drugs	All drugs that are included in the Pharmaprojects database that went into human clinical trial for the first time between 1989 and 2002 are included in the study. The database contains press releases, academic presentations, and other public information about drugs in development.	Governmental
Adams & Brantner [62]	2010	Combination project-level and aggregate	Based on Pharmaprojects database of unspecified drugs	Combined data from Standard Poor's CompuStat Industrial file and Global Vantage Industrial Commercial file. Identified drugs in development using the Pharmaprojects database. Exclusion of preclinical costs. Additionally, they synthesized information from different sources, such as research and development (R&D) expenditure reports, financial statements of pharmaceutical companies, and government databases.	Governmental
Paul et al. [60]	2010	Project-level	Confidential industry data	Data from 2000 to 2007 of the Pharmaceutical Benchmark Forum which includes 13 large pharmaceutical companies	Industry
Mestre-Ferrandiz et al.[61]	2012	Project-level	Confidential surveys (conducted by Centre for Medicines Research International)	Unpublished data from the Centre for Medicines Research International (CMRI) which gathered data from different pharmaceutical companies via confidential surveys of. The data on expenditure per stage of development comes from CMRI's 2002 Resource Metrics Pilot Programme under which 16 global pharmaceutical companies provided resource data at project level. Attrition rates come from CMRI's Industry Succes Rates 2003. Data on 97 projects is used for the estimates. Costs are included that occur between approval and first entering markets.	Industry
DiMasi et al. [59]	2016	Project-level	Confidential surveys (of pharmaceutical companies)	10 multinational firms of varying sizes provided data voluntarily via a confidential survey. Included were drugs that had their first human testing occurred between 1995 and 2007. DiMasi et al. used stratification to randomly select 106 drugs. Costs of basic research or non-compound specific R&D costs are not included in the study.	Industry
Jayasundara et al. [39]	2019	Project-level	Combination of several databases for cost estimations	Data was collected from public databases such as clinicaltrials.gov and Drugs@FDA website. Randomly selecting 100 orphan and 100 non-orphan drugs that received FDA approval between Jan 2000 and Dec 2015.	Industry
DNDi	2019	Project-level	Data from DNDi's own pharmaceutical R&D	Data from DNDi's past 15 years of pharmaceutical R&D. Data encompasses collaborations with other research institutes as well as DNDi's internal R&D data.	Not-for-profit
Wouters et al.[5]	2020	Aggregate	Data from quarterly and annual SEC-reports, ClinicalTrials.gov	Annual 10-K and quarterly 10-Q forms and data from ClinicalTrials.gov	Academic

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Schuhmacher et al. [26]	2023	Aggregate	Total R&D spending from 16 big pharmaceutical companies	R&D spending from 16 pharmaceutical companies collected from 2001-2020 and divided by the total number of FDA-approved drugs by those 16 companies	Industry

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Stage of start of cost estimates

As seen in the Appendix C most of the studies start the cost estimation at the discovery stage. Discovery costs are most often based on estimates only. Reasons given for the estimation instead of basing the costs on empirical data are the difficulty to estimate, not product specific expenses and a lack of data. In only seven of the included studies, the costs are reported distinct by stage [5, 56, 58-62]. Additionally, the complexity of drug discovery and clinical trials is not sufficiently reflected in most R&D cost estimates [45]. These issues arise where to account for compound-nonspecific or basic research that was used to create multiple drugs. It is unclear from the publications how compound-nonspecific research was accounted for.

Reported success rates (and attrition rates) in percentage

The success rates are reported in 13 of 17 studies and range from 7% [61] to 33% [39] or analogously attrition rates range from 93% to 67%. To understand the wide range, one must analyse the origin of the data of the studies as well as the methodologies used to calculate attrition rates. All of the studies use either aggregated or project-specific data. The calculation for attrition rates is the same for both aggregate and project-specific data, only the implications vary. Attrition rates per stage of development are calculated by dividing the number the projects that made it to the next stage of development by the total number of projects that entered that stage of development. Attrition rates for the entire process are calculated by dividing the drugs that received FDA/EMA approval by the total amounts of drugs included in the database of drugs in development.

None of the included studies differentiate between commercial or scientific attrition in their reporting.

Average capitalized cost estimate to bring one new drug to the market

Capitalized cost approximations encompass a broad range of expenditures, including direct costs like research staff, clinical trial expenses, and manufacturing costs, as well as indirect costs such as unsuccessful projects, overheads, and the opportunity cost of capital. The choice of cost of capital (COC) is a critical factor in cost estimation as it affects the final calculations and interpretations. Pharmaceutical companies weigh investment opportunities and evaluate the risks associated with drug development by considering the discount rate, which signifies their preferred rate of return or the cost of capital. [64].

A trend can be observed when looking at the capitalized cost estimates that analyze mixed therapeutic fields in Figure 2.1-2: Except for DNDi, the costs for pharmaceutical R&D have increased over time, despite controlling for inflation. The earliest publication reports the lowest cost estimates [52], while the most recent reports the highest [26].

The three most cited studies of the 17 studies of mixed therapeutic fields have Joseph A. DiMasi as the leading author, a researcher at the Tufts Center for the Study of Drug Development (funded by pharmaceutical companies). Those three studies were

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published in 1991 [56], one over a decade later in 2003 [58] and another in 2016 [59]. Each study builds upon the previous, and presents new, even higher average costs of R&D that cannot simply be explained by inflation alone. In the study of 1991, DiMasi estimates the capitalized out-of-pocket cost to the point of marketing approval at a 9% discount rate of a new chemical entity (NCE) being 594 million USD (in 2022 USD). In 2003, at a real discount rate of 11%, the estimation is 1368 million USD (in 2022 USD). The most recent study presents another cost jump to 3295 million USD (in 2022 USD) at a discount rate of 10.5%. When controlling for inflation, the estimates by DiMasi et al. from 1991 to 2003 increased by roughly 130% and from 2003 to 2016 again by roughly 141%. As seen in Table 2.1-2 estimates on average capitalized costs to bring one new drug to the market range from 594.11 million USD [56] to 3295.92 million USD [59] even though a similar methodology was used in each of the three studies.

Table 2.1-2: DiMasi' estimates of pharmaceutical R&D capitalized costs

Year the study was published	Cost estimates (in million USD)	Comparing to 2022 costs (in million USD)*	Price jump from previous estimation in %
1991 [56]	231 (in 1987 USD)	594.11	-
2003 [58]	802 (in 2000 USD)	1,368.00	130.26
2016 [59]	2558 (in 2013 USD)	3,295.92	140.93

** Figures converted using the US Gross Domestic Product deflator (Bureau of Economic Analysis).*

Relation between capitalized costs and out-of-pocket costs

Table 2.1-3 presents the 11 studies included that report both the out-of-pocket (OOP) as well as the capitalized costs and the respective costs of capital that were used to calculate the capitalized costs. As can be seen, there is no outlier in % of cost of capital. From 8% to 9% to 11% and then, most recent studies used 10.5%. However, the increase from the OOP costs to the capitalized costs has a large margin, ranging from 41.58% [39] to 180% [54] increase. It can be concluded that cost of capital is not the determining factor to explain the price jump from OOP costs to capitalized costs. When taking the reported average clinical development time in consideration no trend can be observed either. A problem arises when including the time of the R&D process: Included studies only analyse clinical development time and exclude basic research which can take decades.

To conclude, estimates to bring one new drug to the market range from 214.38 mil. USD (Hansen & Chien, 1979 [39]) to 6.160 billion USD (Schuhmacher et al., 2023 [18]). To understand why the results, have such a wide range, one must analyse where the data of the analysis comes from, the methodologies to estimate costs, as well as with what attrition rates are being calculated. All the analysed studies include attrition rates to calculate costs to bring one new drug to the market. The reported success rates range from 7 to 33%.

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Table 2.1-3: Studies that include out-of-pocket (OOP), cost of capital (COC) and capitalized costs for R&D for drug development (mixed therapeutic fields)

Publishing Author(s)	Publication year	Average out-of-pocket (OOP) costs estimated per successful drug (in mil. USD)*	Cost of capital (COC) (in %)	Average capitalized costs estimated per successful drug (in mil. USD)*	Increase from OOP to capitalized (in %)	Average Clinical Development time Phase I-III (in years)
Hansen & Chien [52]	1979	122.35	8%	214.38	75.22	4.58
Wiggins [55]	1987	151.50	8%	290.54	91.77	-
DiMasi et al. [56]	1991	231	9%	594.11	157.19	5.72
DiMasi et al. [58]	2003	687.41	11%	1,368.00	99.01	6.01
Adams & Brantner [54]	2006	526.85	11%	1,475.17	180.00	6.58
Adams & Brantner [62]	2010	810.88	11%	1,991.58	145.61	6.20
Paul et al. [60]	2010	1,201.41	11%	2,383.51	98.39	6.50
Mestre-Ferrandiz et al. [61]	2012	1,182.34	10.5%	1,980.65	67.52	5.90
DiMasi et al. [59]	2016	1,776.59	10.5%	3,295.92	85.52	6.73
Jayasundara et al. [39]	2019	Orphan: 208.54 Non-orphan: 365.57	10.5%	Orphan: 365.57 Non-orphan: 517.58	Oprhan: 75.30 Non-orphan: 41.58	-
Wouters et al.[5]	2020	-	10.5%	1,518.13	-	8.30
Schuhmacher et. al. [26]	2023	-	-	6,160.	-	-

**2022 prices adjusted for inflation using the U.S. Bureau of Labor Statistics inflation calculator*

2.1.2 R&D costs on specific therapeutic fields

Study characteristics of publications

Further 10 studies analyse costs for specific therapeutic fields (see also Table C 1 in Appendices Chapter 2), with an overlap of three studies [5, 65, 66] reporting on both mixed and specific therapeutic areas.

Methodology of the studies and Origin of the data

Eight studies [13, 28, 65-70] use project-level data while 2 use aggregate [5, 71] data (see Table 2.1-4). The methods used are the same as in the analyses on mixed therapeutic fields.

Stage of start of cost estimates

The stage of start of cost estimates are the same as in the analyses on mixed therapeutic fields: most of the studies start the cost estimation at the discovery stage.

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Table 2.1-4: Methodology and origin of data for R&D cost estimations (specific therapeutic fields)

Publishing Author(s)	Publication year	Type of data	Methodology	Details of data	Origin of data
DiMasi et al. [65]	1995	Project-level	Confidential surveys (of pharmaceutical companies)	Survey sample of drugs first tested in humans between 1970 and 1982.	Industry
Global Alliance for TB Drug Development* [13]	2001	Project-level	Based on experience of drug development within the organisation	Based on experience of drug development, estimates on costs of phases and secondary literature.	Not-for-profit
DiMasi et al. [66]	2004	Project.-level	Confidential surveys (of pharmaceutical companies)	Stratified random sample of 68 investigational drugs from 10 pharmaceutical companies that first entered clinical testing from 1983 to 1994.	Industry
DiMasi & Grabowski [28]	2007	Project-level	Confidential surveys (of pharmaceutical companies)	Data from the FDA, unpublished company surveys and publicly available commercial business intelligence database was used. The authors try to use a mix of confidential and public data to increase reliability of the data.	Industry
Chit et al. [67]	2014	Project-level	Publicly accessible clinical trial data, published literature and interviews with university based clinical researchers	Data from ClinicalTrials.gov on 39 seasonal influenza vaccines. Costs for clinical trials collected from university based clinical researchers and costs for preclinical development from secondary literature.	Industry
Falconi et al. [68]	2014	Project-level	Publicly accessible clinical trial data	Data from ClinicalTrials.gov on 676 clinical trials with 199 unique compounds that met the inclusion criteria on biomarkers and receptor targeted therapies	Academic
Sertkaya et al. [71]	2014	Aggregate	Data from three proprietary databases: • Medidata Grants Manager (PICAS database) • Medidata CRO Contractor (CROCAS database) • Medidata Insights	Combined the data from three proprietary databases on the negotiated contracts for studies funded by the global pharmaceutical industry. The combined dataset includes data from 2004 to 2021. The total number of contracts in the database is around 31.000.	Governmental
Prasad & Mailankody [69]	2017	Project-level	Data from US Securities and Exchange Commission's filings	Data on 10 fillings for cancer drugs from the US Securities and Exchange Commission were analysed. The 10 drugs included were approved by the FDA and received their approval between 2006 to 2015.	Academic
Årdal et al. [70]	2018	Project-level	Confidential surveys (of pharmaceutical companies)	25 out of 44 SMEs responded to a survey on expected pharmaceutical R&D costs, expected timelines and their business model.	Academic
Wouters et al. [5]	2020	Aggregate	Data from quarterly and annual SEC-reports, ClinicalTrials.gov	Annual 10-K and quarterly 10-Q forms and data from ClinicalTrials.gov	Academic

*Not-for-profit product development partnerships

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Reported success rates (and attrition rates) in percentage

Success rates for specific therapeutic fields range from 97% [5] to 61% [71] (attrition rate 3% to 39%). The lowest success rate is oncology, while the highest success rate is for vaccines.

Average capitalized cost estimate to bring one new drug to the market

Average capitalized cost estimates for specific therapeutic fields range from 183.75 [65] to 5,195.79 [5]. Cardiovascular therapeutic field has the lowest costs, while oncology the highest.

Relation between capitalized costs and out-of-pocket costs

Increases from the OOP to the capitalized cost estimates range from 25.8% to 247.5% (see Table 2.1-5), revealing a larger margin than the analysed studies for mixed therapeutic fields (41.58% and the highest is 180%).

Table 2.1-5: Studies that include out-of-pocket (OOP), cost of capital (COC) and capitalized costs for R&D for drug development (specific therapeutic fields)

Publishing Author(s)	Publication year	Average out-of-pocket (OOP) costs estimated per successful drug (in mil. USD)*	Cost of capital (COC) (in %)	Average capitalized costs estimated per successful drug (in mil. USD)*	Increase from OOP to capitalized (in %)	Average Clinical Development time Phase I-III (in years)
DiMasi et al. [65]	1995	185.75 (Non-steroidal anti-inflammatory) 116.09 (Cardiovascular) 281.77 (Anti-infective) 111.22 (Neuropharmacological)	9%	303.43 (Non-steroidal anti-inflammatory) 183.75 (Cardiovascular) 450.07 (Anti-infective) 192.11 (Neuropharmacological)	63.35 58.28 59.73 72.73	4.66
Global Alliance for TB Drug Development [13]	2001	60.85 (min) 65.97 (max)	-	125.17 (min) 189.42 (max)	105.70 187.13	6.58 9.30
DiMasi et al. [66]	2004	411.37 (Analgesic/anaesthetic) 592.70 (Anti-infective) 459.89 (Cardiovascular) 451.13 (Central nervous system)	11%	617.67 (Analgesic/anaesthetic) 810.37 (Anti-infective) 757.67 (Cardiovascular) 868.02 (Central nervous system)	50.15 36.73 64.75 92.41	3.87 4.21 5.0 7.71
DiMasi & Grabowski [28]	2007	828.98 (Oncology)	11%	1,829.60 (Oncology)	120.71	6.81
Chit et al. [67]	2014	80.31 (Seasonal influenza vaccine)	9%	279.09 ((Seasonal influenza vaccine)	247.52	7.33
Falconi et al. [68]	2014	-	11%	2,388.66 (Oncology)	-	11.5

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Sertkaya et al. [71]	2014	361.12 (Vaccines)	9%	-		6.7
Prasad & Mailankody [69]	2017	858.74 (Oncology)	7%	1,080.42 (Oncology)	25.82	7.3
Årdal et al. (min) [70] Årdal et al (max)	2018	-	-	-	-	1.5-6 (only Phase 1+2)
Wouters et al. [5]	2020	- - - -	10.5%	5,195.79 (Oncology) 1,665.82 (Alimentary tract and metabolism) 1,254.22 (Nervous system) 1,510.80 (Anti-infectives)	-	6.99 9.15 8.59 8.02

2.2 Results: Factors influencing differences in R&D Costs

In the following section, the RQ2 on the factors influencing the costs of R&D for pharmaceutical products is investigated. In addition to the findings from the literature review in the previous section, input from interviews was used to identify these factors that explain differences in pharmaceutical R&D cost estimates. We conducted additional hand searches, identifying 49 studies in total reporting on the following six factors.

Six factors were identified that will be elaborated on in the following chapter: type of drugs, self-originating vs licensed/ acquired drugs, compound screening, stage of clinical development, attrition rates, study design/ size of clinical trials, reported costs of clinical development phase I-III of pharmaceutical R&D.

2.2.1 Type of Drug: costs for orphan vs non-orphan

This chapter intends to analyse reasons why there is a difference in costs of orphan and non-orphan pharmaceutical R&D, as reported in Jayasundara et al. [39]. Clinical trials of orphan drugs can be smaller in-patient size in comparison to non-orphan. The development of orphan drugs intending to treat rare diseases or conditions, is often perceived to be less costly compared to the development of drugs for more common ailments. There are several reasons that contribute to this difference in cost:

Firstly, developing orphan drugs may require fewer and shorter clinical trials compared to drugs targeting more common conditions [39]. Since the patient population is smaller and regulatory data requirements are lower (many orphan drugs are approved based on Phase 2 studies [38]), it may be easier to recruit participants for clinical trials (due to the rarity of the disease many different sites may have to be coordinated which may be supported by public contribution like the coordination of European Reference Centres (ERN) for faster patient recruitment [72], leading to shorter enrolment periods

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and reduced costs associated with patient recruitment. The regulatory data requirement for orphan diseases is lower than for non-orphan diseases. Furthermore, the research and development of orphan drugs can benefit from existing scientific knowledge and advancements in related fields. In some cases, repurposing existing drugs or leveraging existing research can help expedite the development process and reduce associated costs.

Secondly, regulatory agencies such as the EMA often provide incentives and streamlined processes for the development and approval of orphan drugs [73]. Incentives, such as research grants, extended market exclusivity or tax credits aim to encourage pharmaceutical companies to invest in rare disease treatments. Furthermore, the EMA incentivises orphan drug R&D by reducing the regulatory fees [73, 74]. The availability of these incentives helps offset some of the costs associated with research, development, and clinical trials.

Additionally, the smaller patient population for orphan diseases means that the target market for these drugs is significantly smaller [38]. In many cases for non-orphan drugs to prove a better outcome over the standard of care huge patient populations in clinical trials are necessary. In a study by Moore et al. [75] the authors found that the highest-cost trials were those in which a new product was being developed that would compete with a well-established product. In those cases to prove superior benefits over the competitor a high number of patients in clinical trials is needed to achieve statistical power to document marginal benefits [75]. Developing drugs for larger patient populations involves extensive marketing efforts to reach a broad consumer base or to increase the market share, which incurs substantial expenses. In contrast, the target market for orphan drugs is smaller, reducing the need for extensive marketing and advertising campaigns (since there is less competition) [39].

However, it is important to note that while orphan drug development may generally be perceived as less costly, this is not always the case for every orphan drug. The cost of developing a drug depends on various factors, including the complexity of the disease, the required research and development activities, and the regulatory requirements.

2.2.2 Self-originating vs licensed/ acquired drugs

Self-originated drugs account for a decreasing share of novel drug R&D over time: from 2000 to 2011, one-third of drugs were licensed-in, and half had their development timelines cut short by a licensing agreement, a merger with a larger company, or a co-development agreement [76]. However, if earlier stages of research were funded by private companies, it may be difficult to follow expenditures after a product is bought by a new company, leading to studies for in-licensed pharmaceuticals to miss some costs [64].

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Studies by DiMasi et al. [56, 58, 59, 65] and Mestre-Ferrandiz [61] concentrate on the costs of pharmaceutical R&D only related to self-originating drugs, defining them as those developed entirely by a single company. Included in the definition are companies that were acquired by bigger companies during the development process of a drug but kept developing the drugs. Excluded are projects that were licensed in or where a company acquired a patent earlier than approval and subsequently developed till approval. The frequent practice of acquiring licenses or patents later in the R&D process challenges cost estimates for self-originating drugs as a definitive benchmark for all drugs. From 2000 to 2011, one-third of drugs were licensed-in, with half experiencing truncated development timelines due to licensing agreements, mergers, or co-development agreements [76]. This has prompted some to coin the term "Search & Development" for major pharmaceutical companies [40], emphasizing the evolving nature of industry practices.

Overall, available data indicates that compounds acquired through licensing demonstrate heightened rates of clinical success, attributed partly to pre-licensing screening processes [77]. Notably, during the pre-clinical phase, externally sourced projects exhibit a substantially higher likelihood of progressing to clinical testing compared to internal projects [49, 78, 79]. This trend aligns with the increasing prevalence of mergers and acquisitions involving Small and Medium-sized Enterprises (SMEs) and more streamlined parent companies [29]

For earlier time periods than DiMasi et al. [56], Gilbert et al. [53] examine disparities between self-originated and licensed-in pharmaceuticals. They state that although licensing-in has grown more popular, pricing rivalry for the licensing-in of compounds has intensified as a result. This led to higher prices for patents and licenses. They assert that from 1995 to 2000, the acquirer's estimated average return on investment for Phase III licensing-in fell from 12% to just under 6% [56]. According to DiMasi et al. [56], revenues from licensed-in drugs have been driven down in part by declining Phase III trial success rates. Contradictory, Nayak et al. [80] found that most licensed-in drugs have a lower failure rate and become “blockbuster” drugs that generate a large amount of the total revenue of pharmaceutical companies.

In general, the available data confirms that compounds obtained through licensing demonstrate elevated rates of clinical success. This can be attributed, at least in part, to a screening process that occurs prior to licensing as well as companies unlikely to license compounds that have a high chance of failing during clinical development [77]. Moreover, concerning the pre-clinical phase, the evidence suggests that projects obtained from external sources have a notably higher likelihood of progressing to clinical testing compared to internal projects [49, 78, 79]. This trend further exacerbates the trend towards mergers and acquisitions of SMEs and leaner parent companies [29].

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2.2.3 Compound screening

Potential strategies to reduce attrition by learning from molecule characteristics are analysed and discussed in Waring et al. [78]. By analysing successes and failures of AstraZeneca, GlaxoSmithKline, Pfizer, and Eli Lilly the authors conclude that properties of molecules can give an insight into whether or not a molecule will progress to the next phase in development. For example, the difference in lipophilicity between compounds failing or successfully progressing from phase I to II. In addition, the authors state that analysing the properties thoroughly can be a beneficial field of research that can support to reduce pharmaceutical attrition rates [78]. The number of small-molecule drug candidates failing due to poor pharmacokinetic profile can be reduced substantially [78]. Screening failures as the main cost drivers were also identified in a study on driving factors of clinical trials for "Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia" conducted by the Tufts Center for the Study of Drug Development [81].

2.2.4 Stage of clinical development (Phase I, Phase II, /III)

Most studies identified reporting costs on clinical trials in more detail did not include discovery/ preclinical costs: out of nine studies that published cost data on phase I-III studies, six did not cover discovery/ preclinical costs but rather estimated costs for discovery/ preclinical and included the estimated costs with Phase I costs. The range for discovery/preclinical costs (all in mil. USD) is 12.45 [14] – 513.39 [59]. The range for phase I trials is 3.35 [39] to 282.12 [61], for phase II trials 8.36 [39] to 378.35 [61] and for phase III trials 26.03 [71] to 304.93 [59] (see Table 2.2-1). We can see that the largest margin, both in total numbers as well as in relation to one another is in the discovery/preclinical stage.

Table 2.2-1: Out-of-pocket (OOP) mean development costs (in mil. 2022 USD)

Publishing Author(s)	Year of publication	Discovery/ Preclinical	Phase I	Phase II	Phase III	Total Phase - Phase I-III**
DiMasi et al. [56]	1991	-	5.20	10.41	32.53	48.14
DiMasi et al. [58]	2003	-	26.02	39.03	144.42	209.47
Paul et al. [60]	2010	-	20.82	54.64	205.56	279.72
Adams & Brantner [62]	2010	-	40.33	144.42	101.48	286.23
Mestre-Ferrandiz et al. [61]	2012	91.34	282.12	378.35	281.65	1,033.46
Sertkaya et al. [71]	2014	-	4.06	16.24	26.03	46.33
Jayasundara et al. [39]	2014	-	3.35	8.36	30.74	42.45
DiMasi et al. [59]	2016	513.39	30.21	69.96	304.93	918.49
DNDi* [14]	2019	12.45 - 24.91	4.98-7.48	-	37.38-56.06	54.81-88.44

**DNDi published their numbers in 2019 Euro- Firstly inflation adjusted to 2022 using the ECB's inflation adjustment and then adjusted to USD*

***The total sum may differ due to rounding*

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2.2.5 Attrition rates

Several factors contribute to the pharmaceutical industry's high attrition rates (failure). These include inadequate efficacy, safety concerns, lack of target validation, poor pharmacokinetic properties, and commercial considerations. Additionally, the complexity and costs of clinical trials, stringent regulatory requirements, and evolving scientific understanding of diseases and drug mechanisms further contribute to attrition. Understanding and reducing attrition rates are of top importance for pharmaceutical companies, as it can help minimize the financial risks associated with drug development. Efforts are being made to improve the drug discovery and development process through the use of advanced technologies, such as high-throughput screening, predictive modelling, and biomarkers, to enhance target identification, compound selection, and clinical trial design.

Many experts from industry and academia share the belief that the success rate of clinical drug development projects has declined in the past decade [49, 53]. In a study on success rates of clinical trials Wong et al. found in accordance to those reports, that the overall success rate for all drug development programs showed a decline from 11.2% in 2005 to 5.2% in 2013 [49] (see Figure 2.2-1). However, it is worth noting that this downward trend reversed after 2013. Numerous scholarly articles delve into the factors behind project failure and discontinuation. Table 2.2-2 shows attrition rates of 15 identified studies published between 1991 and 2018. None of the studies included differentiate between scientific attrition and commercial attrition in reporting. Earlier studies by DiMasi [57, 65]) categorize reasons for failure into three main groups: safety (e.g., "human toxicity" or "animal toxicity"), efficacy (e.g., "activity too weak" or "lack of efficacy"), and economics (e.g., "commercial market too limited", "insufficient return on investment" or "parallel development of a competitor's medicine"). These studies reveal a trend where economic factors progressively outweigh other reasons, and compounds failing due to economic, or efficacy concerns are more frequently terminated during later stages of clinical testing. In fact, economic considerations emerged as the primary cause for termination in advanced clinical research phases. A study by Kola & Landis [79] supports the finding that there is a trend towards commercial reasons for failure. They analysed pharmaceutical R&D from 1991-2000 and in that time period commercial reasons for attrition where below 10% in 1991 and roughly 20% in 2000 [79].

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Table 2.2-2: Reported attrition rates: phase I-III and cumulative probability

Source	Publication year	Phase 1	Phase 2	Phase 3	Cumulative probability of success (P1 to P3)	Origin of data*
DiMasi et al. [56]	1991	75%	44.2%	63.5%	21.1%	Industry
Gilbert et al [53] (1995-2000) (2000-2002)	2003	75% 69%	50% 56%	67% 40%	25.1% 15.5%	Industry (business consulting)
DiMasi et al. [58]	2003	71%	44.2%	68.5%	21.5%	Industry
Kola & Landis [79]	2004	60%	38%	55%	12.5%	Industry
Abrantes-Metz et al. [82]	2005	81%	57%	57%	26.8%	Governmental
Adams & Brantner [54]	2006	100%[5]	74%	46%	34.0%	Governmental
DiMasi et al. [83] (1993-2004) (1993-1998) (1999-2004)	2010	65% 67% 64%	40% 41% 39%	64% 63% 66%	16.6% 17.3% 16.5%	Industry
Paul et al. [60]	2010	54%	34%	70%	12.9%	Industry
Adams & Brantner [62]	2010	75%	48%	71%	25.6%	Governmental
Pammolli et al. [25][6]	2011	49%-68%	30-58%	50%-80%	7.4%-31.6%	Academic with industry grant
Hay et al. [47]	2014	10.4%	16.2%	50%	0.84%	Industry
DiMasi et al. [59]	2016	45.9%	43.5%	10.6%	2.11%	Industry
Thomas et al. [48]	2016	9.6%	15.3%	49.6%	0.73%	Industry
Wong et al. [49]	2018	13.8%	21%	59%	1.71%	Academic

**academic, academic financed by industry, industry, governmental origin*

[5] Data only includes drugs that passed Phase 1

[6] Not one average given but averages for different years between 1990 and 2004

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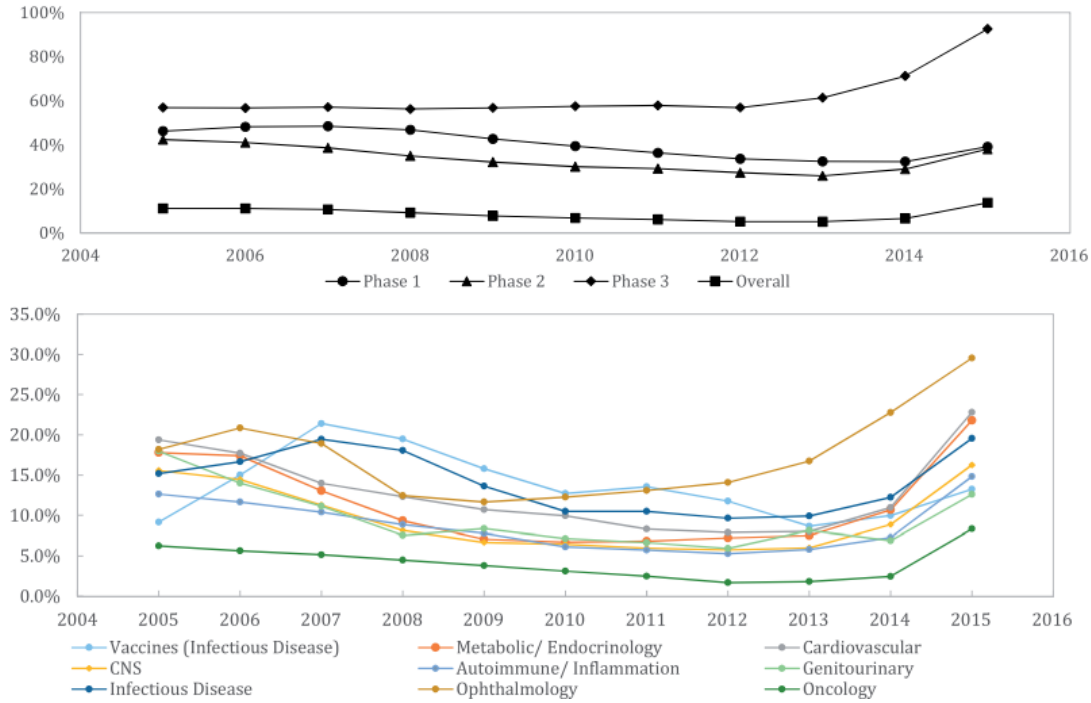

Figure 2.2-1: Graph on Attrition rates from Wong et al. [49]

2.2.6 Study designs and size of clinical trials

Per-patient costs are rarely reported, however costing tools before starting clinical trials include estimates for per patient costs for various activities (as seen in Appendices Chapter 2). We identified five publications on per- patient cost estimates for pharmaceutical R&D and received additional input from the interviews with representatives of Clinical Trial Coordination Centres and from DNDi, leading to seven per patient clinical trial costs. DNDi reported that they have compared their costs per-patient and found comparable7 (similar) to the costs per-patient of for-profit companies. The literature search found a lack of reporting on per-patient costs.

Clinical trials for pharmaceuticals involve a range of expenses linked to different phases of the trial, necessary for ensuring the safety and efficacy of drugs before public release. Common costs associated with pharmaceutical clinical trials are listed below [84, 85]:

Site Selection and Management: Identifying and setting up clinical trial sites, covering investigator site fees, staff training, and monitoring expenditures.

Patient Recruitment and Compensation: This includes expenses for advertising and other strategies to enrol eligible participants, as well as compensating them for their time and travel.

[7] No concrete data were shared in the interview.

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Clinical Trial Supplies: The costs of manufacturing or procuring the investigational drug and placebo, as well as expenses related to packaging, labelling, and distribution to trial sites.

Data Collection and Monitoring: Expenditures associated with data collection tools, electronic data capture systems, data management, and monitoring activities to ensure data quality and adherence to the trial protocol.

Clinical Personnel and Expertise: Salaries and fees for medical professionals, investigators, study coordinators, and other personnel involved in conducting the trial.

Safety Monitoring and Adverse Event Reporting: Costs related to monitoring participant safety during the trial and reporting any adverse events to regulatory authorities.

Quality Control and Quality Assurance: Expenses related to ensuring the integrity and reliability of trial data through rigorous quality control and assurance processes.

Statistical Analysis and Data Interpretation: The cost of statistical analysis of trial data and expert interpretation to draw meaningful conclusions.

Insurance and Indemnity: Insurance to protect against potential liabilities and indemnify participating sites must be acquired.

Overhead and Administrative Costs: General administrative expenses, office space, utilities, and other overhead costs related to running the clinical trial.

Monitoring Committee Costs: In case of a data monitoring committee overseeing the trial's progress and safety, their compensation and expenses are included.

Regulatory Costs: These charges are incurred during interactions with regulatory authorities, such as the FDA or EMA, for trial protocol review and approval.

The expenses associated with clinical trials have increased over time due to a surge in per-patient expenditures, an increase in the number of patients participating in these trials, and the growing complexity of the trials [81]. To manage these costs effectively, two potential strategies are emerging. First, there is a trend towards outsourcing trial management to specialized Clinical Research Organizations (CROs). Additionally, conducting certain clinical trials in developing countries but also emerging markets is also seen as a cost-containing measure [86]. A strategy that has been employed to reduce costs for clinical trials is the outsourcing of clinical trials, especially Phase II and onwards to developing countries [87, 88]. A shift towards India, China and Brazil for clinical trials can be observed [88]. The latter two are also seen as potential new markets, whereas India, due to its weaker patent protection laws and lower possible spending on pharmaceuticals not to the same extent. In 2007, for pivotal trials 11% of the patients came from Asia [89]. In a study from 2022 the authors found that 29% of clinical trials from 2014 to 2017 enrolled patients in lower middle income countries [90]

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In a study by Scannell et al. [27], the authors highlight an increase in the average number of patients per trial, partially driven by regulatory demands for more extensive data and an increased risk-averse approach by regulators. However, averages can be misleading since fewer patients are involved in clinical trials for orphan [75]. In an analysis of all drug approvals by the FDA from 2015-2016, the average patient enrolment was 488 [75]. However, three orphan drugs had fewer than 15 patients, whereas 16 non-orphan drugs had over 1000 patients in clinical trials each [91].

The complexity of clinical trials has grown due to both regulatory requirements and market demands. There is a shift towards more frequent testing of active compounds against placebos. Moreover, many public and private third-party payers now demand the inclusion of pharmacoeconomic and market-oriented variables in clinical studies to demonstrate cost-effectiveness. Based on a survey of pharmaceutical companies conducted by Mattison (Office of Health Economics) [92], development costs have increased due to these additional Health Technology Assessment (HTA) requirements. Roughly half of the surveyed companies believe that costs have risen by up to 10%, while others estimate increases of 10–25% or 25–50%.

Table 2.2-3: Costs per patient in clinical trials

Source	Publication year	Per patient costs*	Origin of data
Emanuel et al. [93]	2003	$ 9,692.61	Industry
Battelle (in cooperation with PHrMA) [94]	2013	$ 45,853.56	Industry (business consulting)
TEConomy (in cooperation with PHrMA) [95]	2017	$ 70,044.02 (Phase I) $ 164,084.75 (Phase II) $ 54,992.21 (Phase III) $ 245,035.28 (Phase IV)	Industry (business consulting)
Stergiopoulos et al. [81]	2018	$ 110,764.26 (only Phase III)	Industry
Moore et al. [91]	2020	$ 41.413[8]	Academic
Clinical Trial Coordination Center	2 interviews 2023	Average: € 11,000 Maximum: € 43,000	Academic
ECRIN	1 interview 2023	From € 5000 – 10,000	Non-profit

** 2022 prices adjusted for inflation using the U.S. Bureau of Labor Statistics inflation calculator*

In a study by Moore et al. [75] the authors found that the highest-cost trials were those in which a new product was being developed that would compete with a well-established product. In those cases to prove superior benefits over the competitor a high number of patients in clinical trials is needed to achieve statistical power to document small effects [75]. In a study by Emanuel et al. [93] comparing costs of clinical trials of government-sponsored and pharmaceutical industry-sponsored, the authors found that governmental-sponsored clinical trial take slightly more time on average (4012 to 3998 hours). Per patient costs for an industry-sponsored trial excluding overhead expenses were on average 9692.61 USD [93]. Costs per patient in clinical trials have a

[8] No information available on year for USD

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large range from 9692.61 [93] to 110.764 (for phase III) [81] as seen in Table 2.2-3. From the lowest to the highest costs per patient over an 11-fold increase can be observed.

2.3 Discussion

Determining the expenses involved in introducing a new medication to the market can differ substantially, depending on various elements such as the specific therapeutic indication, drug complexity, number of required clinical trials, their lengths of follow-up and duration of the development process. Due to the diverse nature of drug development programs and the confidential information held by pharmaceutical companies, it is a challenge to provide an exact assessment of the average capitalized costs.

2.3.1 Summary of findings and their interpretation

Capitalized cost approximations encompass a broad range of expenditures, including direct costs like research staff, clinical trial expenses, and manufacturing costs, as well as indirect costs such as unsuccessful projects, overheads, and the opportunity cost of capital. While all the 24 included studies analysed costs of bringing one new drug to the market, none of them reported public contributions at different stages of the drug development.

The discount rate reflects the preferred rate of return, or the cost of capital considered by pharmaceutical companies when evaluating investing and assessing the risks associated with drug development. It is worth noting that the selection of an appropriate discount rate involves subjective judgment and can vary among different organizations and analysts. The chosen discount rate significantly influences the estimated capitalized cost of pharmaceutical R&D, with higher COC leading to higher capitalized costs. When interpreting cost approximations, it is vital to consider the reasoning behind the selected discount rate, potential sensitivity analyses using different rates, and the assumptions and uncertainties associated with projecting future cash flows and outcomes in drug development [64].

Mainstream economic theories regard government funding as unproductive since it does not generate an expected return on investment [96]. The recommended discount rates of 3% and 7% by the US Office of Management and Budget for (unproductive) government spending are based on distinct theoretical principles [97, 98]: The 3% discount rate for federal spending approximates the historical cost of government borrowing, representing the full expense of government expenditure as written in OMB Circular No. A-94, "Guidelines and Discount Rates for Benefit-Cost Analysis of Federal Programs", or short: A-94 [98]. On the other hand, the 7% discount rate reflects the average productivity of private-sector investments and serves as a measure of the opportunity cost to the economy when public-sector spending crowds out private-

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sector investment [98]. Given evidence that funding from the National Institutes of Health (NIH) stimulates, rather than crowd-out private sector investment, it may be most in line with prevailing economic principles to estimate NIH investment using the 3% discount rate. Cooperations and knowledge exchange between the public and private are an ingredient factor of private sector productivity [99]. Public spending saves private companies millions in basic research. When comparing cost savings with the findings of DiMasi et al. [59] or Wouters et al. [5] on industry investment, it is suggested that the industry's R&D expenditures would more than double without the contributions from the public sector. Furthermore, this research acknowledges that economic efficiencies can arise through the transfer of knowledge or capabilities acquired from public-funded basic research to be utilized by multiple companies or products (see chapter 3 on public contribution). Such knowledge spillovers would decrease the estimated cost per approval attributed to the public sponsor.

Overall, both the use of aggregate data and the use of project-specific data brings challenges. The studies that use project-level data are faced with the challenge of how to account for compound-non-specific research that influenced the development of projects [64]. By selectively including or excluding certain compounds/ medicines, selection bias can unintentionally introduce systematic errors that compromise the validity and generalizability of the findings. As discussed in the section on the origin of data the studies used, many of the studies use confidential data of pharmaceutical companies. It stayed unclear if the participating pharmaceutical companies randomly picked R&D projects and shared data on them with the researchers or if specific projects were selected. The pharmaceutical companies could have shared data for the least expensive as well as for the most expensive drugs in development. Light and Lexchin [100] critique studies that try to estimate drug costs for using confidential data. The problem with confidential data is the lack of trust in the data as well as its replicability.

Only investigating the costs for self-originating compounds increases the variables that can be controlled for, but pharmaceutical companies often purchase licenses and buy patents. As a result of this trend, by only investigating self-originating compounds, a large number of drugs in development are being overlooked such as drugs that are the result of Public Private Development Partnerships. As a last point of concern in many different legislations, R&D expenses are deductible to incentivise high pharmaceutical activity [100]. Since the estimates in the analysed studies are pre-tax, the companies are incentivized to declare high R&D expenditures and a significant amount of resources "saved" by pharmaceutical companies is being neglected.

When analysing aggregate data of R&D spending of pharmaceutical companies, the issue may arise, to pinpoint when the development of a drug started. For example, U.S.

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Securities and Exchange Commission (SEC) reports9 include R&D spending as a whole for the last 3 years, however, drug development, as discussed by Wouters et al. [5] takes on average 8.3 years with large variance depending on the therapeutic field [45]. Consequently, in addition to aggregate data, researchers must analyse when the company first mentioned the generic name of the compound under development. Using this methodology excludes all early discovery (target-hit) or compound-nonspecific research, and these associated costs - originated in academic institutions - are neglected. Whether acquisition costs are included in the R&D calculations is opaque and can only be analysed case-by-case.

The issue of unaccounted costs of using scientific infrastructure that was paid for by the public is multifaceted:

- Scientific infrastructure often generates positive externalities, which are benefits that extend beyond the direct users and have broader societal impacts. These can include knowledge spillovers, advancements in technology or healthcare, and economic development. Quantifying and capturing the full value of these externalities can be challenging, resulting in unaccounted costs that are not fully reflected in the user fees or funding models [101].
- Publicly funded clinical infrastructure requires ongoing maintenance, upgrades, and operational costs to ensure its continued functioning and relevance. However, these costs may not always be adequately accounted for or covered by user fees (charges for the use of public infrastructure) or government subsidies. Insufficient funding for maintenance can lead to deteriorating infrastructure quality, reduced efficiency, and higher long-term costs.
- The opportunity cost of using publicly funded scientific and clinical infrastructure may not be explicitly considered. Opportunity cost refers to the potential alternative uses of resources, such as time, personnel, or equipment, if they were not dedicated to the (research and clinical) infrastructure. These costs can include missed research opportunities, delays in projects, or limited availability for other users or research purposes [101].
- There can be concerns regarding equitable access to publicly funded scientific infrastructure. Charges for the use of public infrastructure may be in place that can pose financial barriers for individuals or organizations, limiting their ability to benefit from the infrastructure. Therefore, unequal access can result in unaccounted costs and potential disparities in scientific advancement and innovation. Addressing the problem of unaccounted costs requires careful consideration and evaluation of the broader impacts and value generated by the scientific infrastructure. It may involve comprehensive cost-benefit analyses, assessing externalities, exploring alternative funding models, and ensuring

[9] The Securities and Exchange Commission (SEC) requires publicly traded companies to file periodic financial statements and sector specific data.

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adequate funding for maintenance and upgrades. Additionally, promoting transparency, accountability, and equitable access can help mitigate some of the challenges associated with unaccounted costs.

2.3.2 Limitations

This research has several limitations:

None of the calculations for the cost estimations of the analysed studies were reproduced to check the validity of the results. Many of the data sources that the researchers used, used either proprietary data sources or confidential data which made it impossible to validate the results. Therefore, we cannot guarantee that the presented results were calculated correctly.

Additionally, no critical appraisal and risk of bias assessment was conducted due to the heterogeneity of the studies.

The literature searches conducted were not systematic searches, but targeted hand-searches and screening of reference lists of authoring teams. Therefore, we could have missed additional information. Ideally, systematic review for each of the section and topics should have been conducted, esp. on the issues of influencing factors such as clinical trials costs, study design, compound screening and per phase costs.

The majority of information is available for the US-American context, not only because of regulatory requirements but also due to the language. In Europe, research often is conducted in native languages, which makes including these papers exceedingly difficult. We made the choice to only include research in English and German to avoid issues that may arise with translation.

However, we do not believe that any of the above limitations alter the general messages of the research results.

2.3.3 Conclusion

Measuring R&D activity of the pharmaceutical sector is challenging. Most detailed data on projects is confidential and aggregate data can be difficult to measure, considering there are no binding definitions for R&D. Therefore, many researchers have tried estimating R&D costs using either confidential data from companies directly or publicly accessible data or alternatively, a mixture of both. However, those methods pose challenges. Publicly accessible data might not be all encompassing while the use of proprietary databases and confidential data supplied by industry makes research to be non-replicable. The huge margins of the included studies prove that the lack of transparency leads to researchers working with different databases on the same topic come to vastly different cost estimates. One of the reasons being that even when the

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project related cost is specified there will be many cost components that are cross cutting along all projects and difficult to apportion to individual projects (overlapping or crosscutting). This shows the need of generating a standardised method of R&D cost reporting.

Out of 14 studies that analysed mixed therapeutic fields the top 5 highest cost estimates all had affiliations to industry or received funding from pharmaceutical companies. Because high R&D activity is rewarded with tax incentives it is in the interest of pharmaceutical companies to have researchers report high-cost estimates of bringing one new drug/medicine on the market. Non-affiliated researchers are unable to reproduce studies that use confidential data and therefore, cannot check the validity of the results.

We identified attrition rates, type of therapeutic field, clinical trial design, cost differences between acquired/ licensed drugs and self-originating, origin of data, affiliation of the researchers and compound screening to be the determining factors for differences in R&D cost estimates.

In conclusion, what the research shows is that for most of the R&D cost estimations in the literature the data used is not transparent and therefore the estimates cannot be replicated which reduces the quality and credibility of the figures provided. There is no standardized reporting of R&D activity, not even a standardized definition of R&D. Companies report annual R&D expenses but the money spent cannot be attributed to specific projects, neither can the expenses be disaggregated due to confidentiality. The public is forced to navigate through a labyrinth of research on the topic of cost estimates for drugs only to conclude that the research on the matter is very inconclusive. The estimates vary greatly and too many different interests are reflected in the cost estimates. Ultimately, without policies that force companies to be transparent about their R&D expenditures the public will not know if their contribution was large enough to play a relevant role in price negotiations.

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3 Public contributions to R&D of medical innovations

In contrast to chapter 2 dealing with R&D costs for the development of pharmaceuticals only, chapter 3 is covering the public contributions to all kind of medical innovations, pharmaceuticals as well as medical devices, in-vitro-diagnostics (IVD) and other health technologies.

The public contributions to the development of medical innovations (drugs, devices, in-vitro-diagnostics, digital technologies) have been discussed since several years inspired by M. Mazzucato´s book on "Public vs Private Sector Myth"s [1] and 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 sufficiently solid, even if most evidence was generated in the US. Media debate took up the increasingly strong data and accumulated on "the public pays twice" and, "risks are socialised and rewards are privatised" [1]. However, even with increasing evidence, corresponding public policies (such as conditionalities for approval and for price setting) are lacking. 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" in 2019 [8]. In April 2023 a proposal for a revision of the "Pharmaceutical Legislation"[10]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 [9] 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*" in relation to "*any activities for the research and development of the medical product*" covered by a national or centralised MA, irrespective of which legal entity has received the support.

The obligation is not restricted to only EU financial support, so MAHs will also need to consider any funding received from public authorities and publicly funded bodies located outside of the EU. The scope of the provision is very broad and covers direct funding for *any* R&D activities that relate to the development of the medicinal product. This reporting obligation could therefore include funding received during pre-clinical as well as clinical stages. However, the recitals to the Directive recognise that it will be difficult to identify indirect funding, such as tax

[10] consisting of a new Directive [9] (repealing and replacing Directive 2001/83/EC and Directive 2009/35/EC) and a new Regulation [10] (repealing and replacing Regulation (EC) No 726/2004 on the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency and No. 141/2000 on "orphan" medicinal products and incorporating relevant parts of the Paediatric Regulation (Regulation (EC) No 1901/2006)).

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advantages [11]. The "*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 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 [11]. However, no such obligations have been formulated yet for medical devices, digital technologies or in-vitro-diagnostics (IVD).

"R&D" comprises a wide range of activities and different aims starting with basic research aiming at mechanistic understanding of diseases, 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 the evidence about the efficacy and safety of that therapy that will support regulatory approval and health technology assessment (HTA). Securing intellectual property (IP) is quite different at each phase: pre-clinical knowledge (about the molecule or device) is protected by patent. Knowledge on the development (e.g. about manufacturing techniques) is protected sometimes by patent and sometimes by trade secrets. Clinical knowledge (after approval) is protected by market exclusivity and data protection rights.

It is the intention of the following paper to capture the categories one might need to think of, be it direct or indirect public contributions to R&D and 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. However, a comprehensive compendium of all public contributions is neither intended nor seems realistic, but a comprehensive system of categories is nevertheless aimed for – applicable to medicines, medical devices and other health technologies.

3.1 Results: Public contributions to R&D of (medicinal and other) products reported in the literature

To answer the research question (RQ3) which public contributions to R&D of medicines (and other products such as medical devices) a targeted hand search has been conducted. The research area of analysing public contributions to medicinal and medical product development has started to evolve about a bit more than a decade ago by several researchers and public institutions, and has gained speed in recent years, so far lacking a stringent methodology. They are based on either crude estimations across groups of products (mostly drugs)

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or on detailed analyses of on singular case studies of products (see details in Table A- 1 in the Appendices Chapter 3).

Study characteristics

Several data-analyses of large cohorts of FDA approved drugs reported in ten publications (two of them updated earlier analyses at different points in time (Stevens et al. 2011 [12] and 2023 [13] and Cleary et al. 2018 [14] and 2021 [15],[7]) or analysed subsamples (Nayak et al 2021 [16] of a larger dataset [6]) could be identified. Sampat et al. reported as early as 2011 on public contributions to 379 new molecular entities (NME) (approved 1988-2005) [17] and Nayak et al. 2021 on 248 (approved 2008-2017) [16]. Additional to these broad analyses across many different drug approvals and indications 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) [6, 16],[2, 18-23], the (US-) Institute for New Economic Thinking [7, 14, 15], authors from Columbia University [17, 24], US-authoring teams [12, 13] or Japan-based [25] from Technology Development, IP and Science Policy or from Advocacy Groups such as Treatment Action Group [26, 27] or UK-based Global Justice Now [28]. In Europe, only the Austrian Institute for Health Technology Assessment (AIHTA) [3, 4, 29] authored a few publications. None of the authoring researcher or teams declared to have a conflict of interest. All the research was financed by science grants of diverse public or charitable funds.

Results on public contributions to R&D reported in publications

Based on the datasets (some started as early as 1973 [12], [13] until 2019 [7]) across FDA approved drugs (NMEs) the analyses find that between 42% of all biologicals [16], half of all drugs approved [17, 25] or even >90% of drug target research [14] are associated with public sector institutions and/or their spin-offs. The association is even higher with drugs rewarded with "priority" or "expedited review": 64.5% [17] to 68% [6] indicating therapeutic importance. Between 9% of FDA- approved drugs hold public sector patent, even 17.4% for "priority" review candidates [17]. 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 [28] (see Table A- 1 in Appendices Chapter 3). Virtually all the important, innovative vaccines that have been introduced during the past 25 years have been created by public institutions [12]. Additional to the dominance of the indirect public sector effect over the direct effect (patents), the sales for these "priority review" drugs based on publicly

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funded R&D were far higher than for "standard review" drugs [17]. Most analyses focused on public contributions to basic research, however public contributions were found in at least one in four new drugs also in late stage development [6]. In Europe, 12.3% of all EC FP7-Health awards were related to the funding of late-stage clinical research, totaling € 686,871 million (mil). Pharmaceutical products and vaccines together accounted for 84% of these late-stage clinical development research awards and 70% of its funding [4].

Public funding amounts to $839 million (mil) (2018) [14] to $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 considering applications of basic research to multiple products. 2/3 of drugs and vaccines are discovered in the US and Canada, 1/3 in Europe (Germany, UK, Belgium, etc.), in the Asia-Pacific region (Australia, Japan) and Middle East (Israel) with on average $0.77 bil (Belgium), $0.55 bil (USA), $0.23 bil (UK), $0.14 bil (Germany) or $1.06 bil (Israel) academic expenditures per drug [13]. The top discovering public sector institutions were among other the NIH, Univ. of California, Emory University (USA), KU Leuven (Belgium), Hans Knöll Institute (Germany) and the Weizmann Institute of Science (Israel) [13].

One author concludes [7, 15] that spending from the NIH was not less than industry spending, with full costs of these investments calculated with comparable accounting.

Detailed analyses of development histories of products based on singular case studies strengthen the overall picture: Vokinger et al. focused on three highly expensive gene-therapies (Luxturna®, Zolgensma®, Carvykti®) [23] and CAR-T cell therapy [22]. The study showed 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. Roy described the drug history of Sofosbuvir (Sovaldi®) for patients with hepatitis C, indicating that public funding had a key role in developing and showcased the economic process (financialization) of buying academic knowledge and developing it with private equity resources to a profitable drug [30]. Barenie et al. identified 29 direct grants (US $7.7 mil) and 110 indirectly related awards (US $53.2 mil) granted to major academic institutions and companies engaged in the development of Sovaldi®. Schmidt et al. focused on paediatric orphan drugs (Spinraza®, Brineura® [29], Orfadin® [4]). The public/philanthropic contributions to funding of product-related research ranged between approximately €20 mil (Spinraza®) and €31 mil (Brineura®), however, the basic and translational research for Spinal Muscle Atrophy (SMA) totalled €165 mil and showed the role of philanthropic funding in the development of SMA-therapies [29]. Barenie et al. trace the history of the widely sold drugs Pregabalin (Lyrica®) [20] and *Buprenorphine (Subutex®)* in opioid use disorder, acute pain, and chronic pain [18]. They found numerous NIH

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awards related to pregabalin's development summing up to $13.8 mil and an estimated $62.3 mil in NIH awards for the development of *Buprenorphine*.

Others researched on the role of public R&D in the PARP-Inhibitor Olaparib (Lynparza®) in breast cancer [3], on Abiraterone (Zytiga®) in prostate cancer [31], Alemtuzumab (Lemtrada®) in Leukaemia, later Multiple Sclerosis, the tumor necrosis element (TNF) blocker Adalimumab (Humira®) in rheumatoid arthritis and other diseases, Infliximab (Remicade®) to treat a number of autoimmune diseases [28], Bedaquinile (Sirturo®) in tuberculosis [26] and many others compounds [5, 16]. Tessema investigated the HIV pre-expositions prophylaxis (PrEP) therapy Tenofovirdisoproxil (Truvada®) and counted a $143 mil public funding (inflation adjusted to 2022) [21]. Most recently, the public contributions to the development of mRNA vaccines have been discussed openly [2, 32, 33]: 34 NIH funded research grants that were directly related to mRNA covid-19 vaccines. These grants combined with other identified US government grants and contracts totaled $31.9 bil (€29.7 bil), of which $ 337 mil was invested pre-pandemic. Pre-pandemic, the NIH invested $116 mil (35%) in basic and translational science related to mRNA vaccine technology, and the Biomedical Advanced Research and Development Authority (BARDA) ($148 mil; 44%) and the Department of Defense ($72 mil; 21%) invested in vaccine development. After the pandemic started, $29.2 bil (92%) of US public funds purchased vaccines in risky Advanced Purchasing contracts (APC) including the acceptance of liability clauses, $2.2 bil (7%) supported clinical trials, and $108 mil (<1%) supported manufacturing plus basic and translational science [2].

However very few have researched yet on other technologies than drugs, such as biomarker and molecular diagnostic technologies as well as gene-panels [27]. 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 to also capture the public risk-investments: The hepatitis C vaccine received total European Community (FP7 and its predecessor, FP6) funding of €13,183,813 mil; total public and charitable research funding for this product development was estimated at €77,060,102 mil). The industry sponsor did not consider further development of this product viable; this now represents a public risk investment [4].

Sources used in published analyses

As sources for searches for public contributions, most authors searched in a key set of sources such as the FDA Database for information on approvals and information on type of review (priority, standard, etc.) and designation (orphan, etc.), the FDA´s Orange Book for patents, patent citation data, citation analyses on acknowledged funding and grants and employment information of authors and the NIH RePORTER for NIH funds per drug and per target. Most analyses so

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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 3.1-2).

Only a few authors (see Table 3.2-1) used additional sources on pharmacological and historical information on chemicals, drugs and biologicals (Merck Index or Therapeutic Target Db (TTD)) on drug development, clinical trials, safety, commercial deals and patents (AdisInsight) or on change of ownership (Technology Transfer Websites from universities on spin-out/offs, SEC-filings for royalty, mode of agreements such as licensing agreements or acquisitions and payments in FiercePharma, FierceBiotech, STAT Health). For public support to SME a range of sources, though mostly national, were searched, for information of public sponsorship of clinical trials two databases (ICTRP and ClinicalTrials.gov), but also requests to market authorization holder (MAH) as well as to investigating institutions were used. The least often a spotlight was put on the public contributions to market authorization and post-market launch, ev. because source are rare: National tax incentives, orphan drug incentives, tax deduction policies for donation programmes and post-launch data collections were either estimated or only mentioned.

Table 3.1-1: Sources to search for public contributions 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

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Public contributions considered in published analyses

The categories of public contributions (see Table 3.2-2) to drug (and other technologies) development considered in all identified analyses are supranational and national 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 or medium enterprises (SME) were mentioned, but less often considered in the actual data-analyses, since these grants to companies, but also provision of facilities/ infrastructure (often national or even regional data sources or lack of transparency) are not as easily available and accessible as research funds [34]. Ownership changes from academic institutions to SME and later multinational corporates were considered by Roy [30], Vokinger [23], Newham/ Vokinger [22]. Late stage development in form of public support for clinical research was considered in Nayak [6, 16] broadly and in Schipper et al. [34] in much detail, showcasing the multitude of sub-categories of funding and sources. Finally regulatory support in form of technical assistance for registration, methodological guidelines, but also the provision of priority reviews or vouchers are considered as a form of public investment due to their opportunity costs in Gotham [26, 27] only, as tax credits and deductions due to donations and post-launch data collections, often called real-world data for generating additional evidence, are considered.

Table 3.1-2: Categories of public contributions considered in published analyses

Public contribution by phase	Categories considered in literature
Basic & translational research	Basic and pre-clinical research support Translational or applied research support
Early stage research in SME Biotech Companies	Technology transfer and patent support Innovation support to SME and to projects for product development Public Venture Capital
Late stage development in Corporate Companies	Licensing, acquisitions, merging Trial support (supranational; national) by public sponsors
Market Authorization, PLEG	Regulatory support Tax credits and deductions RWE-data collections

To conclude, the research area of public contributions to health product is still in its infancy. However, it has gained increasingly interest and more analyses can be expected. For the next chapter we used the identified categories and searched in European sources for public information on contributions in these categories.

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3.2 Results: Categories of (direct and indirect) public contributions to R&D of (medicinal and other) products

To answer RQ4 the categories of public contributions to R&D of medicinal as well as medical devices and other health technologies – identified in the literature and in interviews - will be explored in the following sections of this chapter (see Table 3.3-1).

Table 3.2-1: Overview of categories of public contributions addressed in data collections

Public contribution by phase	Categories considered in literature	Addressed in
Basic, applied & translational research	Basic, applied and translational research support (incl 2 examples) Horizontal (pre-competitive) research support	3.3.1 3.3.2
Early stage research in SME and Biotech start-ups	Technology transfer support to university spin-out/offs Business support to SMEs and to innovative projects, Public Venture Capital	3.3.3 3.3.4
Late stage development in Corporate Companies	Changes in ownership: licensing, acquisitions, merging Late stage development in clinical trials	3.3.5 3.3.6
Market Authorization, PLEG	Regulatory support, Market Authorization Post Launch Evidence Generation (RWE-data collections)	3.3.7 3.3.8

PLEG-Post Launch evidence generation, RWE – real-world-evidence, SME – small and medium enterprise

3.2.1 Public contributions to basic, applied and translational research

According to OECD data, the OECD countries were spending 2.7 % of their gross domestic product (GDP) on R&D, with EU-27 spending only 2.2 % [35]. In absolute numbers R&D spendings sum-up to $470.73 bil (in EU-27), resp. $1,821.34 bil all OECD countries, of which two-thirds of expenditures is financed by business enterprises and one-third by the public/governmental institutions and from private not-for profit institutions (data from 2020: [36]).

In 2022, the total government budget allocations for R&D (GBARD[11]) across the EU stood at €117.4 bil, equivalent to 0.74% of GDP. This was a 5.4% increase compared with 2021 (€111.4 bil) and a 49.2% increase compared with 2012 (€78.7 bil) [38]: the biggest share of the GBARD, namely 35.5%, was directed to the general advancement of knowledge financed in a large majority by a public block grant known as public general university funds (GUF), 16.5% of the GBARD was earmarked for the general advancement of knowledge from other sources than GUF, followed by 10.2% to industrial production and technology, *8.3% to*

[11] GBARD covers not only government-financed R&D performed in government establishments but also government-financed R&D in the other three national sectors: business enterprise (BES), private non-profit (PNP), higher education (HES) as well as the rest of the world, including international organisations (§ 12.16, Frascati Manual, [37]).

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health and 5.9% to exploration and exploitation of space [38]. Health receives the fourth largest share of government R&D budget allocations.

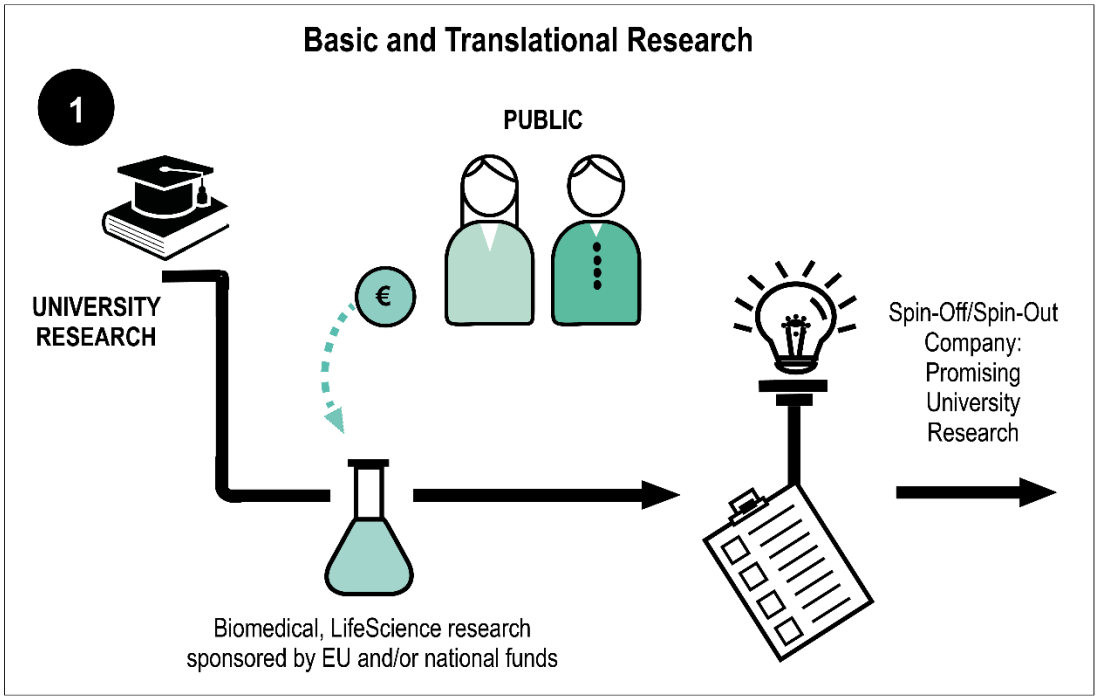

Figure 3.2-1 Public contribution to basic and translational research (inspired by [39])

To contrast: business enterprises expenditures on R&D (BERD) performed in the pharmaceutical industry is not reported cumulatively in OECD sources, but in EFPIA reports. For 2020: €39.66 bil expenditures on R&D in the region of Europe is reported [40]. However, due to a lack of a clear definition what is covered in Pharma R&D – one might assume that companies count as R&D all expenditures on activities for their products (direct such as clinical trials or indirect such as, manufacturing and distribution of the investigational drug) –, it is not possible to compare the public and private expenditures. Not surprisingly, most spendings (76%) of pharma-R&D happen in only a few countries: Germany (€7.8 bil), Switzerland (€7.4), UK (€5.65), Belgium (€4.96) and France (€4.5) [40]. MedTechEurope [41] does not report cumulative R&D spendings in Europe, publicly.

National expenditures on R&D for health research, life science and biotechnology are highly intransparent and not reported in a standardized and detailed manner (see Table A- 2 in Appendices Chapter 3). A review on public and philanthropic health research funding institutions, listing the 55 major funders, found that although large funding sums are provided (in 2010-2013, $37.1 bil of 10 top funders) there was neither a standardized classification system to report

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on funding (areas of funding, specificity on details, on outputs) nor a format of reporting [42]. However, the EC-grants (see also Table A- 6 in Appendices Chapter 3) are not only reported transparently, but also evaluated – even though with a certain delay of several years. Table 3.3-2 displays the funding of health projects within the last three research frameworks since 2007.

Table 3.2-2: EC R&D funding in health

R&D Programme	Overall budget in bil	Budget for Health in bil	Share In %
FP7 (2007-2013)	55	5.6	10.2
Horizon 2020 (2014-2020)	75	9.8	13.0
Horizon Europe (2021 – 2027)	97	8.3	8.6

Even if, overall data does not provide enough granularity to account for or estimate the public R&D contributions to medicinal or medical product discovery and development, this information helps to contextualize specific projects in a broader picture.

- Framework 7 (FP7, 2007-2013) had an overall budget of €55 bil, within the theme health FP7contributed with €5.6 bil to 1 008 projects in four areas (so-called pillars): 1. Biotechnology, generic tools and medical technologies for human health (174 projects, impact: 107 patents, 15 spin-off companies), 2. Translating research for human health (553 projects, impact: 126 patents, 19 spin-off companies), 3. Optimising delivery of health care to European citizens (139 projects, impact: publications only, 2 spin-off companies) 4. Other actions across the Health theme (121 projects, impact: 1 patent, 1 spin-off company) and Innovative Health Initiative (IMI1) (49 projects, impact: 1 patent, 16 spin-off companies [43]. (see in more detail: Table A- 4 to Table A- 5 in the Appendices Chapter 3). Patent filed derived virtually all from projects funded under pillar 1 and 2. Of all participants (n=12 599), 438 (3.5%) represented the European Federation of Pharmaceutical Industries and Associations (EFPIA), 505 other industries (4%) and 1 944 participants were SMEs (15.4%) [44].
- Horizon 2020 (2014-2020) was resourced with: €75 bil (€28.6 bil for societal challenges including health, demographic change and well-being with €7.3 bil [45], 6 571 projects (CORDIS) in health sciences with €9.8 bil EU contributions, areas of intervention: personalised medicine, innovative health and care industry, infectious diseases and improving global health, innovative health and care systems - integration of care, decoding the role of the environment, digital transformation in health and care and trusted digital solutions and cybersecurity in health and care [46]. Only in IMI2 (126 projects with an impact of 11 patents, spin-off companies not reported) were conducted. An evaluation will be published - according to the evaluator Prognos - in Q1/2024 [47].

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- Horizon Europe (2021 – 2027) is resourced with: €97 bil (€53.516 bil for global challenges and European industrial competitiveness including health with €8.246 bil [48], 988 projects so far (CORDIS) in health sciences with €2.367 bil EU contributions, areas of intervention: health throughout the life course, environmental and social health determinants, non-communicable and rare diseases, infectious diseases including poverty-related and neglected diseases, tools, technologies and digital solutions for health and care including personalised medicine, health care systems [49].

The attribution of public resources to the development of individual products can only be done on a case-by-case basis. This will be piloted in later stages of the project HI PRIX.

Two examples for disease-specific basic, applied and translational research

Most research on public contributions focus on NIH-support and very little is researched on EC R&D funds contributing to product development. While national expenditures are highly intransparent on details for expenditures for health (see Table A- 2 in Appendices Chapter 3), the EC RTD provides detailed reports on investments in R&D in Health and Biomedical Research. However, the attribution of these investments to the development of individual products can only be done for specific groups of products and will be explored in the exemplary case studies of orphan drugs and antibiotics. The following subsection will explore some of the project categories in more detail and will provide examples to illustrate the content of public contributions.

Example 1: Rare diseases and R&D for orphan drugs development

Despite the progress in quantity of rare disease drug development, the burden of rare diseases remains high. Treatment options are available only for around 5% [50]. According to a report from Technopolis (2019) [51], between 2007 and 2017, 131 medicines were approved as orphan medicinal drugs (OMP) for 107 rare diseases (actually 142, but 11 were withdrawn). 22 drugs were approved for two or more indications and for different periods of market exclusivity [51]. The proportion of supplemental indications rated as having high therapeutic value was substantially lower than for first indications [52]. 28% of all OMPs are oncology drugs (e.g. for Acute Myeloid Leukaemia/AML or gliomas), i.e. in indication areas where other therapeutic options were already available. The report found that the development of new OMPs had increasingly clustered around a limited number of therapeutic areas and indications, calling into question the incentives for the development of OMPs, since for the vast majority of rare diseases, no products have been developed [53].

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Due to the failure of the legislation to incentivize the needs-based development of OMPs, funding institutions in the US as well as in Europe have initiated extensive research programmes for rare diseases and granted clinical research grants for funding research on rare diseases:

- USA: The Office of Orphan Products Development (OOPD) of Food and Drug Administration (FDA) has awarded over 700 grants to conduct clinical trials of medical products for rare diseases since 1983, leading to over 70 marketing approvals. Many of those studies are for children, as young as newborns. Between fiscal years 2007—2011, OOPD funded 85 clinical trial grants. These grants spanned 18 therapeutic areas, including all pre-approval phases (Phases 1–3), and approximately 75% of the grants studied small molecule drugs. Nine (11%) product approvals (seven drugs and two devices) were at least partially supported by grants funded within this (narrow) 5-year timeframe. Four of the seven drugs approved were new molecular entities (NMEs) [54]. The FDA lists (2021) another 11 grants awarded to new clinical trial research, equalling more than $25 mil of funding for the next 2-4 years (see Table B- 1 and Table B- 2 in Appendices Chapter 3) [55]. Even though only snapshots on the public contributions to late-stage development of medicines for rare diseases are available, it is an additional proof of direct public spending.
- Looking at Europe, the EC RTD has launched a large "European Joint Programme on Rare Diseases (EJP RD, https://www.ejprarediseases.org/)" since 2007 with annual calls (14 calls 2007-2022, 194 funded projects) (see Table B- 3 and
- Table B- 4 in the Appendices Chapter 3). According to CORDIS (https://cordis.europa.eu/project/id/825575/reporting) the EJP RD consortia received €100.36 mil (only in 2019-2023) (of which the EU contribution was €55.07 mil; the rest is financed by national public R&D partners such as the Austrian Research Fund (FWF) or the German Research Fund (DFG).

Example 2: Antimicrobial resistance (AMR) and R&D for new antibiotics

Antimicrobial resistance is an urgent and growing global threat [56]. In 2017, the EC adopted the EU "One Health Action Plan against AMR" [57] as a framework to boost R&D on AMR, including research calls for the clinical management of AMR, new diagnostic and intervention tools, early signalling and assessing zoonotic threats and preventive vaccines [53]. A preceding review in 2016 [58] and several overviews of ongoing preclinical [59] and clinical developments [60] [61] [62] [63] found that there are 17 compounds in phase 3 trials (see Table B- 5 in Appendices Chapter 3) and further 82 in phase 1 or 2. Multilateral initiatives, such as …

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- the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR, https://www.jpiamr.eu/): The JPIAMR is comprised of 29 countries with the purpose of coordinating the national funding of its members towards specific AMR research projects. To date (2023), the initiative has funded projects for €141 mil. The funding is push-based[12] and is almost exclusively directed towards academic research of basic and preclinical science [58].
- the Global Antibiotic Research and Development Partnership (GARDP, https://gardp.org/): GARDP is a non-profit initiative that is jointly managed by the Drugs for Neglected Diseases Initiative (DNDi) and the WHO. The GARDP aims at accelerating antibiotic development and has four antibiotic treatments in its pipeline, in development with industrial partners. From 2016 to 2022, the total funding commitments and pledges to GARDP were €178 mil.
- the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X, https://carb-x.org/): CARB-X is a transatlantic public–private partnership that aims to accelerate basic science and preclinical R&D for a large portfolio of antibiotics, rapid diagnostic tools, and other antimicrobial products. CARB-X has a $398.2 mil invested until 2023 in 92 projects with funding support from BARDA, the US National Institute of Allergy and Infectious Diseases (NIAID), the UK's Wellcome Trust, GAMRIF, and the Bill & Melinda Gates Foundation. To date, 12 clinical trials have been conducted.
- the European and Developing Countries Clinical Trial Partnership (EDCTP): The EDCTP is a public–private partnership that brings together European countries, sub-Saharan African countries, and the pharmaceutical industry to facilitate clinical trials on new drugs for priority pathogens in antimicrobial resistance treating poverty-related communicable diseases in sub-Saharan Africa.
- In the EU DG-RTD has been a leader in initiating policy action to revitalize the antibiotic market [58] with the Innovative Medicine's Initiative (IMI, https://www.imi.europa.eu/), and the InnovFin Infectious Diseases Facility (InnovFin[13]; EU finance for innovators). Beyond these specific programmes, the EC provides funding support to numerous smaller R&D projects (see Table B- 7 in Appendices Chapter 3). Between 2007 and 2013, the DG-RTD gave €235.6 mil in direct funding for European antibiotics and diagnostics R&D projects, which were separate from the IMI and

[12] *Push incentives* aim to support innovation, R&D of new antibiotics from the early stages of basic science to clinical trials.

[13] H2020 Initiative of European Investment Fund (EIF) and European Investment Bank (EIB) to finance innovators.

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EDCTP. The IMI-New Drugs for Bad Bugs (ND4BB) programme is dedicated to the discovery and development of novel antibiotics for humans. Funding for the ND4BB programme is split between the EU and EFPIA and totals €700 mil (of which €427 mil are public contributions). There are seven core projects, which offer push-based support to most aspects of the antibiotic value chain: TRANSLOCATION and ENABLE assist early drug discovery, COMBACTE supports clinical development of antibiotics for Gram-positive bacteria, COMBACTE-CARE, COMBACTE-MAGNET and iABC facilitate clinical development of antibiotics for Gram-negative bacteria, and DRIVE-AB explores economic solutions to stimulating antibiotic R&D in a sustainable manner. DRIVE-AB's final report with recommendations was published in early 2018.

… have been formed to tackle the challenge of antimicrobial resistance [58]. The antibacterial drug discovery is mainly driven by academic research in cooperation with SME [64]. In 2015 60 SMEs were engaging in anti-bacterial drug R&D, of which more than half is concentrating entirely on antibiotics. The SMEs are more often engaged in the discovery and early research stages, larger companies step in later clinical development stages [64] (see Table B- 6 in Appendices Chapter 3).

3.2.2 Public contributions to horizontal (pre-competitive) research

Horizontal cooperation agreements between competitors to collaborate in certain areas, such as R&D, can be pre-competitive allowing companies to respond to increasing competitive pressure and changing market dynamics. They are used as a EC-policy tool to share risk, save costs, increase investments, pool know-how, and speed up innovation in Europe [65]. Horizontal "pre-competitive"[14] public contributions to product development are not at all or only rarely mentioned as public contributions to product development. In Europe the Innovative Medicines Initiative (IMI) is the most prominent example for extensive public contributions to drug development: IMI is intended as an initiative to increase the competitiveness of pharmaceutical research institutions in the European Union. IMI is the world's biggest Public-Private-Partnership (PPP) between the European Commission (EC) and pharma companies coordinated by the European Federation of Pharmaceutical Industries and Associations (EFPIA) aiming to speed up the development of medicines in Europe. The origins of the Innovative Medicines Initiative (IMI) lie in the European Technology Platform (ETP) on Innovative Medicines: ETPs were industry-led for a made up of private and public stakeholders. The Innovative Medicines Initiative (IMI, ….) and

[14] Pre-competitive is defined by conducting research jointly by usually competing companies for the purpose of developing new commercially applicable technologies.

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its successor Innovative Health Initiative (IHI) was founded as PPP between pharma-companies (IMI) and the EC, now encompassing also MedTech Companies to strengthen the respective industries in Europe (see Table 3.2-3).

Large companies that are members of the IHI industry partners contribute to the programme, primarily through 'in-kind' contributions (e.g. their researchers' time, laboratories, data, compounds), though they can also make cash contributions. At least 45% of each project's budget has to come from industry partner / contributing partner contributions, meaning that out of that 45%, for instance, 30% could correspond to the salaries of industry staff working on the project, 10% to trials, and 5% could be cash.

Table 3.2-3: Funding of public-private partnership (PPP) programmes

Name of Programme	Part of EC Research Programme	Funding in mil € (public contribution)
ETP-INNOMED, 2005-2009 (Innovative medicines for Europe)	FP6	18.5 (12)
IMI 1, 2008-2013 (Innovative Medicines Initiative)	FP7	2,000 (1,000)
IMI 2, 2014-2020 (Innovative Medicines Initiative)	Horizon 2020	3,276 (1,638)
IHI, 2021-2027 (Innovative Health Initiative)	Horizon Europe	2,400 (1,200)

- ETP-INNOMED (Innovative medicines for Europe, 2005-2009) was part of the 6th Research Framework Programme (FP6) on LifeSciences and had an overall budget of €18.5 mil, of which the public contribution by the EU was € 12 mil (https://cordis.europa.eu/project/rcn/78755/en). The individual projects targeted the four bottlenecks in the drug development process: Safety, Efficacy, Knowledge Management, Training and Education.
- IMI1 (Innovative Medicines Initiative, 2008-2013) was part of the 7th Research Framework Programme (FP7) with an overall budget of €2 bil: €1 bil came from the Health theme of the EU- FP7, €1 bil came from in-kind contributions of EFPIA companies (https://www.imi.europa.eu/about-imi/imi-funding-model).
- In IMI2 (2014-2020), the total budget was €3.276 bil, of which €1.638 bil came from the Health, Demographic Change and Wellbeing Societal Challenge of Horizon 2020, the EU's framework programme for research and innovation and €1.425 bil was committed to the programme by EFPIA companies (https://www.imi.europa.eu/about-imi/imi-funding-model).
- After extensive evaluation of the IMI-programmes [66] and criticism from several Public Health advocacy institutions such as Global Health Advocates and Corporate Europe Observatory [67], Prescrire [68] AIM

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(Healthcare and Social Benefits for all) and MN (Istituto de Ricerche Farmacologiche Mario Negri) [69] in 2021 the programme was revised and opened to a broader range of sectors from the medical technology, biotechnology, digital health and vaccine industries (COCIR, EFPIA (including Vaccines Europe), EuropaBio and MedTech Europe, https://www.ihi.europa.eu/about-ihi/imi-ihi). Criticism focused on the sole "agenda setting" and "governance" of the research programmes by industry and – accordingly – public investments in areas in which industry would have the need to invest anyhow [67].

- IHI (2021 – 2027) has a total budget of €2.4 bil, €1.2 bil comes from Horizon Europe, the EU's framework programme for research and innovation, €1 bil will come from the IHI industry partners, €200 mil will come from other life science industries or associations that decide to contribute to IHI as contributing partners.

IMI's Strategic Research Agenda (SRA), adopted in 2008 [70] for IMI1 and 2014 [71] for IMI2 is meant to be closely aligned with the World Health Organization's 2013 report on priority medicines for Europe [57], however poverty-related and neglected diseases are sparsely covered while cancer was and is still a major focus. The IMI1 and IMI2 programmes resulted in almost 200 projects covering a wide range of disease areas and addressing challenges across all areas of medical research and drug development (https://www.ihi.europa.eu/about-ihi/imi-ihi).

*Table 3.2-4: IMI 1+2 and IHI categories for projects (2008-2022) and public contributions per category**

IMI/ IHI Project Categories	Public Contributions in €
Target Identification, Drug Discovery, Drug Delivery	381,221,027
Tools for Predicting/ Monitoring Efficacy and/or Safety, as well as for Refining Disease Taxonomy/ Biomarker-Stratification	784,131,200
Clinical Trial Design, Real World Data and Evidence, Methods for Benefit-Risk Assessment and Regulatory and HTA Process	415,390,251
Conducting Clinical Trials	218,958,487
Big Data and Knowledge Management, Digital Health, Artificial Intelligence	452,495,335
Networks: Clinical Network and Patient Involvement in R&D, Education and Training	281,360,827
Sum	**2,533,557,127**

**all projects in the IMI/ IHI database were extracted, but – in case of multiple assignments to categories – were calculated only once.*

The six categories[15] of projects are described shortly in the following paragraphs:

1.) Public Contributions to *Target Identification, Drug Discovery and Drug Delivery*[16] : Target identification is the first step in drug discovery. It is the

[15] All projects in the IMI/ IHI database were extracted, but – in case of multiple assignments to categories by the respective researchers – the funding sums were calculated only once.

[16] Examples for the individual categories can be found in Appendix section B

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process of identifying the direct molecular targets involved in the pathogenesis of the disease. Target identification can be approached by computational methods, direct biochemical methods, and genetic interactions. The screening of as many candidates as possible is essential. For better understanding disease mechanisms, many research projects are studying the causes of diseases, such as genes that are mutated or molecular pathways involved in the disease´s biology (e.g. cancer). Once a new disease mechanism has been identified, the research focuses on the gene(s) or molecular pathways involved and identifies points where a drug could potentially stop the disease in its tracks by stopping the activity of a molecule in the body [72]. These drug targets can then be used to identify 'hits' – molecules that could interact with the drug targets. These 'hits' are then further studied and refined to create 'leads', molecules which could eventually become drugs [72] (see Table C - 1 in the Appendices Chapter 3).

A prominent (cross-indications) example is the "The European Lead Factory" (ELF) (funded 2013-2018 with €196 mil, of which nearly €80 Mil EUR are public contributions), which has created a collection of some 550,000 compounds (small molecules) from private and public sources (of which 200,000 were designed and synthesized de novo) [73]. A screening centre comparable to a library has been set up. First user reports show that drug discovery processes in the areas of cancer, metabolic disorders, neurodegenerative diseases or antimicrobial resistance etc. have been accelerated and delivered around 200 hit lists as starting point for new drug discovery programmes. Around 50 academic organisations and biotech companies have started to process from target identification to drug discovery programmes and lead optimization, with 2 actual drug candidates [73].
A follow-up project ESCulab (European Screening Centre: unique library for attractive biology) (funded 2018-2023 with €36.8 mil, of which €18.2 mil are public contributions) plans to run 185 new drug discovery projects during its lifetime. In the long term, the screening centre should become self-sustaining so that it can continue to provide these valuable services after the project has finished (https://www.imi.europa.eu/projects-results/project-factsheets/esculab).

2.) Public Contributions to the *Development of Tools for Predicting and Monitoring Efficacy and/or Safety, and for Identifying Biomarkers for Disease Stratification*: Throughout the earlier stages of drug development, a range of tests and tools to determine whether a potential drug will actually be effective and safe in humans are deployed. As testing humans is not feasible

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at this stage, research is relying on 'models' of the disease. These models can be samples of cells or tissues (these are known as 'in vitro' models), animals with the disease ('in vivo' models), or computer-based virtual models of the disease ('in silico' models) [72].

Several IMI-projects have developed such tools to ease the studying of diseases while reducing the use of animal research. In 2018, around 30 in vitro models, 300 in silico (computer-based) models, over 70 animal models and around 300 biomarkers are in development of which 130 have been validated in the meanwhile [74]. There is recognition that the way diseases are classified now needs to change [75]: the stratification of patients based on genetic and molecular causes of their disease increases the chance of treatments to be beneficial (see Table C - 2 in the Appendices Chapter 3).

3.) Public contributions to *Clinical Trial Design, Real World Data and Evidence, Methods for Benefit-Risk Assessment and for the Regulatory and HTA process*: During clinical trials, medicines are tested for the first time in humans (FIH), in healthy volunteers (to monitor whether the drug is safe, Phase 1 trials) and then in patients (to determine the dosage and according efficacy, Phase 2 trials) and finally in larger cohorts (to proof efficacy, Phase 3 trials). In recent years, "real world evidence (RWE)" is increasingly being used to evaluate drugs in the wider patient community: some IMI projects are investigating ways of improving the way clinical trials are run, so that they can generate reliable results in a faster mode. They are also setting up clinical networks that are already making it easier for trialists to rapidly identifying patients. A number of tools and processes developed by IMI-projects have been developed and are being reviewed by regulatory authorities such as the EMA and FDA. So far, many cohorts and registries [74, 75] were established and are running (see Table C - 3 in the Appendices Chapter 3).

4.) Public contributions to *Ecosystems and Networks: Clinical Network and Patient involvement in R&D, Education and training*: Clinical networks are essential for rapidly identify study centres and for recruiting patients for clinical trials. This is even more important in rare diseases investigating new treatments such as orphan drugs. Additional, in recent years patient involvement in the drug development as well as in the regulatory process and in health technology assessment (HTA) for reimbursement decisions have become a new endeavour, accelerated by the demand for patient-relevant outcomes in coverage decisions. IMI has invested in quite a few of such – research, clinical as well as patient – networks (see Table C - 4 in the Appendices Chapter 3).

5.) Public contributions to *Conducting Clinical Trials*: In areas like antimicrobial resistance, tuberculosis and Ebola, where there is a high level of market

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failure and a very clear and urgent medical and social need, IMI runs clinical trials of novel medicines, vaccines and radiotherapy. Several clinical trials and studies involving the COMBACTE networks are ongoing. These cover studies on the incidence, treatment and outcomes of certain types of infection, as well as clinical trials of novel anti-infectives [75]. (see Table C - 5 in the Appendices Chapter 3).

Public contributions to *Big Data and Knowledge Management, Digital Health, Artificial Intelligence*: Vast amounts of data are generated daily in healthcare. With the linkage of this data, new information and insights might be gathered – according to expectations - to further understand the causes and expressions of diseases that can support the development of new treatments. However, combining data from lots of different sources brings technical challenges (different file formats, different terminology, etc.) as well as legal and ethical challenges (depending on consent and permission of patients to use the data) [75]. Within IMI-projects methodologies are developed how to deal with these challenges (see Table C - 6 in the Appendices Chapter 3).

To conclude, the EC is investing in different horizontal activities that are easing the path to more efficient product development. Though conducted in Public-Private-Partnerships (PPP) these indirect public contributions seem as important as the direct funding is.

3.2.3 Technology transfer to university spin-off/ 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 the group of researchers with the intention to prove the concept in clinical research. Most medical universities command over "Technology Transfer" or "Patent Offices" to protect the intellectual property rights and universities are rewarded for granted patents and ranked according to the number of patent applications. As we move down the value chain from basic research to applied R&D, the public sector is either being reimbursed directly for their discovery (private buy-out of spin-offs) or retains some IP rights. At first glance, the net impact is therefore more of a financial benefit for the public R&D institution than costs. Therefore - in a second look - the total financial flows (revenues and costs) must be considered.

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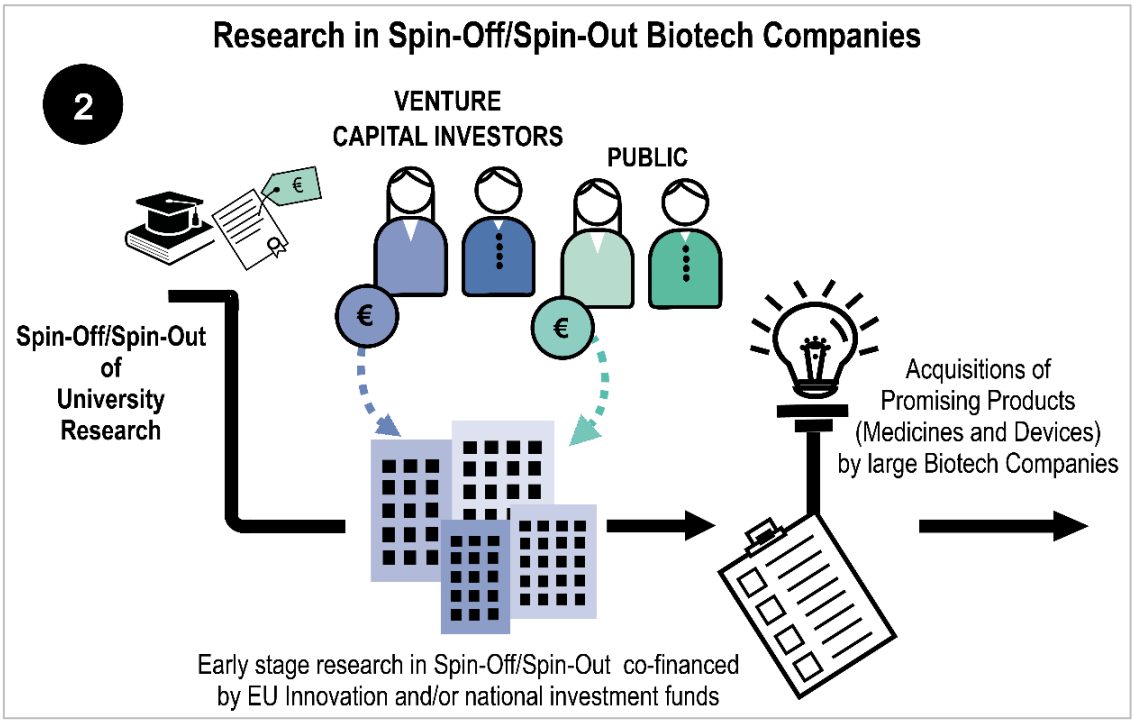

Figure 3.2-2 Public contribution to BioTech start-ups spin-off/spin-outs) (inspired by [39]

The role of patents and spin-out17-companies as indicators for economic exploitation of university research and as an important source of income for universities can also be observed by

- *Spin-off /out fellowships*, funding programmes incentivizing the development of business ideas for start-up companies; for example, this funding amounts to €15 mil p.a. and 500,000 for each innovation initiative at Medical Universities, provided by the Austrian Research Promotion Agency (FFG), followed by a risk capital fund set up by the Austrian Wirtschaftsservice Gesellschaft (aws) [76].
- *External investments and refunds* raised that channel back resources into university research: Oxford University is reporting on 15-20 new companies every year and over £2.5 bil income through its spin-outs since 2010 [77]. Berkeley College of Chemistry is reporting on a $100 mil only for one gene-therapy spin-out [78].

Since the small BioTech Start-Ups (Small and Medium Enterprises/ SMEs) are most 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, national business services in LifeScience clusters

[17] Spin-outs are typically owned and controlled by former employees of a university. In contrast, Spin-offs are a separate legal entity with different (albeit often overlapping) owners, outsourced by a larger corporation. These terms are often used interchangeable though well defined.

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provide support in founding a company with developing a business plan, assessment of the market or budgeting of resource needs for early-stage clinical trials, while R&D funds support the development of products. National funds (see Table A- 2 in Appendices Chapter 3) as well as European funds are granted for both categories of financial support.

Table 3.2-5: Good practice examples on transparent reporting of spin-outs/offs by technology transfer offices

Universities and Academic Centers: Reporting on Spin-Out/ Offs	
Oxford University/ UK	https://innovation.ox.ac.uk/portfolio/companies-formed/
University College of London/UK	https://www.uclb.com/portfolio/our-spinouts/
University of Dundee/ UK	https://www.dundee.ac.uk/life-sciences/start-ups
Aarhus University/ DK	https://international.au.dk/collaboration/technology-transfer/spin-outs
Leiden University/ NL/ NL	https://www.universiteitleiden.nl/en/science/science-based-business/careers/start-ups
Amsterdam University/NL	https://www.uva.nl/en/about-the-uva/organisation/faculties/faculty-of-science/valorisation/spin-offs/spin-offs.html
Radboud University Medical Center/ NL	https://www.radboudumc.nl/en/partners/spin-off-companies
Leuven University/ BE	https://lrd.kuleuven.be/en/spinoff/spin-off-companies
University of Zürich/ CH	https://www.innovation.uzh.ch/de/stories/allspinoffs-startups.html
University of California-San Francisco (UCSF)/ USA	https://innovation.ucsf.edu/featured-startups
And many more	

National analyses on spin-outs/ offs from public research institutions are rare (or written in national languages). A recent analysis from Germany [79] distinguishes between IP- or licence-based spin-offs that can be monitored with the awarded patents and knowledge-based spin-offs, based on expertise generated in public research institutions offering R&D-based services. Unfortunately, this German analysis is not reporting sector-specific data such as on health and biotechnology.

3.2.4 Business support to SME and to innovative projects, Public Venture Capital

The landscape of funding opportunities for start-ups and SMEs is vast, often organized for regions of the EU-member states or in national institutions. We provide only a few examples from Austria and Netherlands. Commonly, support is given on

- Funding for the phase before a life science company is set up is provided for the costs related to the scientific implementation and the economic application of a project. E.g. in Austria the maximum amount of this non-refundable financial support is €200,000 (aws LISA PreSeed: www.preseed.at).

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- The founding of a company needs not only know-how, but foremost capital. The starting phase of young companies is supported (in Austria) with up to €800,000, combined with tailored advice and support. Once the company is making profit or is sold, financial support must be refunded. Customary securities usually needed for bank loans are not necessary. However, the company must be partly and adequately funded through private capital (SeedFinancing/ AT: www.seedfinancing.at; NL: https://www.rvo.nl).
- Additional to the support of business activities, a wide range of contacts to other start-ups and to (international) investors, as well as established companies is supported with targeted networking activities and match-making or partnering services (incl. the organisation of specific targeted events; e.g.in AT: www.awsconnect.at (aws Connect).
- National public venture funds, such as the Dutch Venture Initiative (DVI, https://business.gov.nl/subsidy/dutch-venture-initiative/) – also called fund-to-funds – encourage a fund to invest in other funds with the objective to invest in fast-growing companies [34].

In the EC, the *European Innovation Council (EIC)* (see Table D- 1 in Appendices Chapter 3) was founded – after piloting – only recently in Horizon Europe[18] [80], incorporating existing instruments under the Horizon 2020 programme, in particular the SME instrument and Future & Emerging Technology (FET) programme, within a single work programme to provide direct support to innovators throughout Europe and to bridge the investment gap in early-stage innovation. The EIC is part of the 3 pillars of Horizon Europe [81], funding individuals and their research (mostly basic research), pre- defined research in clusters (Health, Climate, etc.) and bottom-up innovative projects. The general rule is, that innovations and projects in Technology Readiness Levels (TRL) 2 - technology concept is formulated – to TRL7 - technology prototype demonstration in operational environment is conducted - can be funded [82]. TRL 8 (finishing the product development) and TRL 9 (manufacturing and scaling up) are only supported with EC-resources in form of equity shares (the EC becomes shareholder and holds the right to vote, share profits and claim assets of a company) of up to 25% of SME-company shares. The funding of SME´s technology development projects can either be within consortia or for individual SMEs: within RIA (Research and Innovation Action, expected outcome TRL 2-6) or IA (Innovation Action, also 7-8) the SME is funded with 70% of their expenses. The EIC funds up to €2.5 mil for TRL 2-6, and up to 15 mil for TRL 6-8, but takes equity share of SME up to 25% (this is new Horizon Europe). These resources are

[18] In H2020 and previous programmes only SME-support in the form of grants were provided.

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managed by the European Innovation Fund (EIF, https://www.euinnovationfund.eu/).

The EIC has a budget of €10.1 bil to support innovations throughout the lifecycle from early stage research, to proof of concept, technology transfer, and the financing and scale up of start-ups and SMEs. Due to the novelty of this system for incentivizing innovation also in late development stages, there is no database for EIC projects in place, yet. However, the "Deep Tech Europe Report" provides some numbers from the EIC performance, focusing on results and impacts of its legacy programmes (SME Instrument and FET) The EIC pilot phase (2018-2020) resulted in 46 patent applications and 14 awarded patents and in over €5.3 bil raised in follow- up private investments (equity, debt, Mergers & Acquisitions/M&A, Initial Public Offering/IPOs).

- *EIC Pathfinder* projects are directed at entrepreneurial researchers from universities, research organisations, start-ups, high-tech SMEs or industrial stakeholders. Grants of up to €3 to 4 mil are provided for TRL 1-3.
- *EIC Transition* funds innovation activities that go beyond the experimental proof of principle to support the maturation and validation of a novel technology in a relevant application environment and the development of a business case and (business) model. Grants of up to €2.5 mil are available for TRL 5/6.
- The *EIC Accelerator* is supporting start-ups and SMEs to develop and scale up their innovations. Non-dilutive grants (without sharing equity) of up to €2.5 mil for TRL 5-8 activities are provided as "grant only" - for companies aiming to reach the TRL 8 at the end of the project and continue further development without the EIC support or as "grant first" - for companies reaching TRL 8 at the end of the project and possibility to apply for "dilutive equity"[19] to reach TRL 9. Direct investment is available as dilutive equity shares up to €15 mil, for market deployment (TRL 9), so-called «patient capital» principle with a 7-10 years perspective. "Blended finance" (a mix of non-dilutive grant for innovation activities (TRL 5-8) and dilutive equity for market deployment, (TRL 9)) or "Investment only" for mid caps (medium capitalized) companies and companies that have received a «grant only» is also a possibility provided. Additional tailor-made business coaching, a Corporate Partnership Programme, a Buyer Partnership Programme as well as an Investors Partnership Programme is offered [83, 84].
- Around 35% of all EIC activities are in the area of health and wellbeing: most of the funded companies are in only three industry sectors [83], of

[19] Equity dilution occurs when a company issues new shares to investors and with more shares in the hands of more people, each existing shareholder owns a smaller or diluted percentage of the company.

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which health is leading (1,262 companies funded), followed by energy (922 companies) and software (735 companies). Follow-up investments are also highest in these three sectors, again led by health, with 34% coming from corporates, either directly or from venture funds backed by corporates. Another 47% arise from venture capital. In 2020, 43 of those EIC-backed companies have been acquired by other corporates [83].

Additional to direct funding, the *European Innovation Ecosystems (EIE)* Initiative (https://eismea.ec.europa.eu/) provides networking and match-making events. The EIE is equipped with €155 mil for 2023/24 [85]. The *European Institute of Innovation & Technology (EIT)* was founded (in 2020) 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. The EIT holds a section on health (https://eit.europa.eu/), also complemented by national EIT Health institutions. In 2023, 20 SME-companies were selected for the EIT "Health Bridgehead" to support of "scaling-up" their enterprises so far. The selection was based on the criteria of innovativeness of solutions, business model, traction in the home market, and readiness to expand to other European markets [86]. In 2023, start-ups were supported with €4.19 mil (no data for 2022 available), in 2021, for €6.385 mil, € 3 mil through a "wild card" programme[20], 2020, €7 mil plus € 5.5 mil for rescue of 11 start-ups) by EIT programmes (see Table D- 2 in Appendices Chapter 3). The range of EIT programmes is broad and consists of a range of different categories of funding: Attract to invest: €25,000 + prizes of €20,000 or €15,000 or €10,000; Bridgehead: €25,000 (sponsored by Horizon2020 with €1 mil); Catapult: Prize of €30,000; DiGinnovation: up to €350,000; Drive: up to €50,000; Jumpstarter: Prize of €10,000; InnoStars Awards: €25,000 smart money or €4,000; Regional Innovation Scheme (RIS) Innovation Call: €75,000. The recipients of these grants are mostly SMEs in the field of MedTech and digital health technologies (see Table D- 2 in Appendices Chapter 3).

Additional to direct financial support of individual SME, the EC is providing assistance with targeted matchmaking, brokerage or partnering events and other services (provision of partnering database and market intelligence, legal advice, IPR expertise, finance and funding support) in *Enterprise Europe Network (EEN,* https://een.ec.europa.eu/about-enterprise-europe-network*)*. The intention of this programme is to support SME to grow Europe-wide and internationally. EEN works with an annual budget of € 63 mil and is complementing similar national initiatives in the LifeScience sector.

[20] Through the "Wild Card" Programme, EIT Health brings together the inventor with the right resources in an acceleration programme, for an early-stage start-up.

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At this stage also Venture Capital (VC)[21] comes into play. VC investors provide capital against shares of the start-up biotech SME. Despite a large private venture capital market exists, also governments are investing in risk finance of innovative SMEs to fill "funding gaps", esp. in innovation in specific targeted areas to capture public benefit [87, 88]. The European Investment Fund (EIF) is backing early-stage innovation specialists like e.g. BioGeneration Ventures (BCV) with funds. BCV, a leading early-stage VC in European biopharma, received € 140 mil investors money for a call BGV Fund IV in 2021, of which €30 mil (21.4%) came from the EIF [89] (see Table D- 3 in Appendices Chapter 3). If this investment with an expected return on investment (RoI) is risk-prone funding with public resources at opportunity costs or if the public is beneficiary of investments aiming at stimulating macroeconomically is debatable. However, the public contributions to innovations with risky investments is a but a not neglectable fact in the.

To conclude, the EC is investing in different activities to incentivize innovation in health (and other sectors). The high public spending on R&D are based on the assumption of macroeconomic effects of public R&D on the GDP [90] as well as on private R&D [83, 84] and accordingly on a return on investments with innovations. However, realistically it can be assumed that not all investments in supported projects will lead to market maturity and according refunding. For that reasons it must be stressed that also the public is spending as much on risky projects as private companies do.

3.2.5 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 re-investments from revenues [91]. EFPIA reports the allocations of the investments (based on a survey of members) with 14.9% for pre-clinical research, 44.1% for clinical research: 7.6% for phase 1, 9.3% for phase 2, 27.3% for phase 3 trials, 4.3% for approval, 11.5% for pharmacovigilance (phase IV studies) and 25.1% uncategorized [92]. Unfortunately, similar data is not available for the medical device industry. However, as reported in Chapter 2, the data cannot be verified independently since all publications reporting on industrial R&D are presented cumulatively, mostly dividing the R&D expenses by successful drug, lacking details on what falls under the definition of industrial R&D. A disaggregation of the data is not possible. Some authors and advocacy groups

[21] Invest Europe (formerly EVCA) defines **venture capital** as an "investment in unquoted companies by specialized VC firms." It is a subset of private equity, that is, equity investment in companies not listed on a stock market, as opposed to publicly traded companies.

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- such as Knowledge Ecology International (KEI, https://www.keionline.org/) - conduct detailed analyses of e.g. SEC (US Security and Exchange Commission) periodic data reports, tracking details on licensing agreements, acquisitions and expenses on clinical trials of individual companies regularly. KEI is in the role of a watchdog to monitor the compliance with the Bayh–Dole Act [93], a legislation permitting ownership of inventions arising from federal government-funded research but requiring the disclosure of the public funding.

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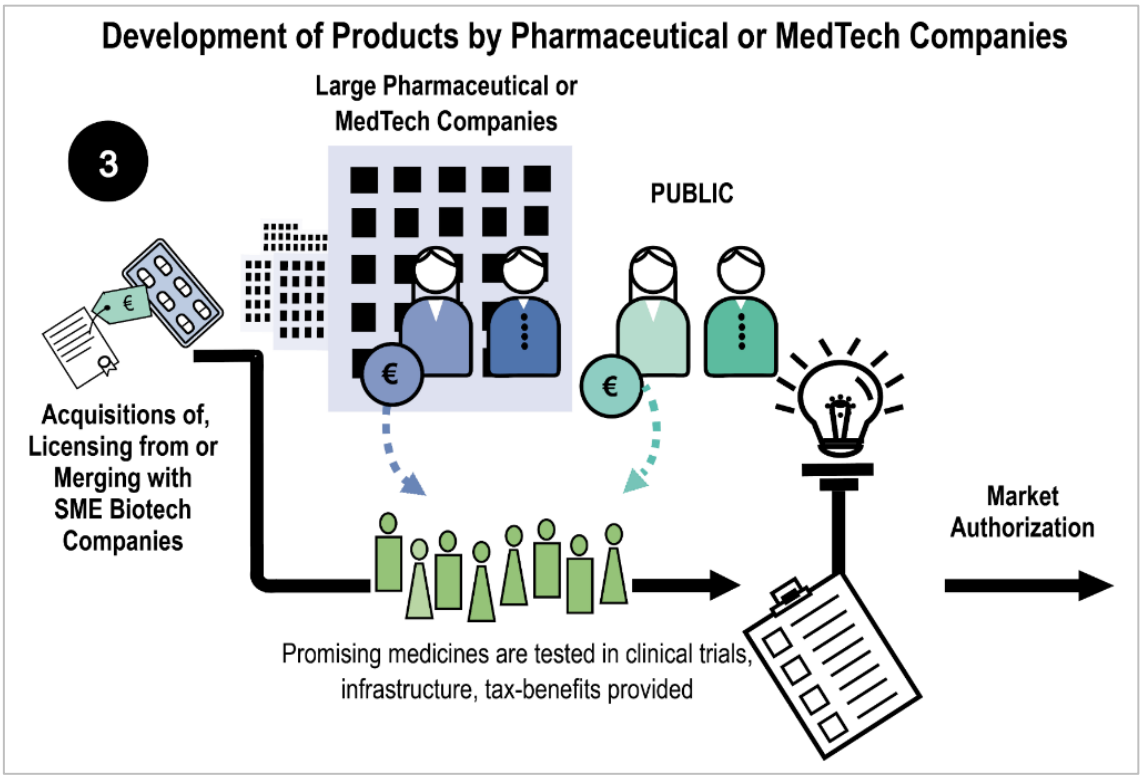

Figure 3.2-3: Public contribution to clinical development of products (inspired by [39])

As examples for the need for disaggregated data the currently approved Advanced Therapy Medicinal Products (ATMP, including CAR-T cell therapies and tissue-engineered products) are presented. So far (Sept 2023) there are 18 ATMP approved in Europe [94], and most of them also in the USA: As can be seen in Table D- 6 in Appendices Chapter 3, nearly all of them have their origin in public research institutions, the research funded by the public or by charities [95]. The change of ownership happens most often after milestones in product development have successfully been achieved.

The changes of ownership can happen via [22] [96, 97]:

- *Licensing Agreement* (LA): a LA is a contract between two parties that grants the licensee the ability to use the intellectual property (IP) owned by the licensor in return for compensation, such as royalties. An Exclusive License Agreement (ELA) ensures that no party other than the named licensee can exploit the relevant IP-rights. ATMP-examples are: CSL Behring reached an ELA with UniQure on Hemgenix® (list price: $ 3.3 mil, Estimates of global sales of $1.2 billion cumulatively through 2026) for patients with haemophilia B; Takeda entered into an ELA with TiGenix on Alofisel® (list price: $390,000) for patients with perianal fistulas in Crohn´s disease.

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- *Merger and Acquisition (M&A):* an acquisition, also known as take-over, entails one firm purchasing another outright. The acquired firm may retain its name and operate as a subsidiary of the acquirer or it may be incorporated into the acquiring firm. In contrast a merger combines two or more firms into one new legal entity, typically with a new name. ATMP-examples for M&A are: Bristol Myers Squibb (BMS) acquired Celgene with the CAR-T cell therapy Abcema® (list price: $419,500 and estimated $470-570 mil revenues in 2023) in patients with multiple myeloma; Gilead acquires Kite with the CAR-T cell therapy Tecartus® (list price: $373,000 and estimated $340 mil revenues in 2023) in patients with mantle cell lymphoma; Orchards Therapeutics acquired the GSK´s rare disease portfolio including Libmeldy® (list price: $3.8 mil) in early onset metachromatic leukodystrophy (MDL), etc.
- *Further types of deals are* partnerships and alliances, venture financing, asset transaction, debt offering and private equity deals [96].

The pattern of R&D for these most expensive therapies is almost always the same [6, 16, 22, 23]: ownership changes happen mostly after early phases of clinical research in humans and the pivotal trials are conducted thereafter by larger companies when they have secured their rights. Corporate companies monitor closely the promising developments in university research and their spin-outs/offs – supported by technology transfer offices –, in order to offer deals in time [34]. In diverse analyses of FDA/ 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% [16] of new approved biological drugs had evidence of public financial support for late stage development, the same holds for ATMPs (esp. CAR-T: [23, 98], SMA-therapies [29], orphan drugs [51, 54], oncology [99], etc.) (see also Table D- 6 in Appendices Chapter 3).

The methodologies used to reach at these conclusions are threefold.

1. Either patents or drug development histories on the origin of a single or a group of products are analysed in detail,
2. Or databases on public and charity contributions are analysed on their input to products,
3. Or - a rather new approach – the provenance of the highest-selling prescription medicines of individual companies´ products are scrutinized.

Some examples on patents analyses or drug development histories on the origin of a single or a group of products:

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- The University of Pennsylvania (UPenn, Principal Investigator (PI): C. June) has been working on T-cells for many years and in 2011 published an important paper using an anti-CD19 CAR T-cell therapy in CLL. In 2012, Novartis and UPenn agreed upon a deal for $20 mil towards a research center and Novartis gets exclusive worldwide rights to all CARs developed through the collaboration and to the CART 19, which is already in the clinic (NIH- grants of $30,335,306; 39 projects relating to CAR T between 1993 and 2016, only between 1993 to 2011: $16,330,088). In 2017, the 1st CAR T-cell therapy Kymriah® was approved and sold for a list price of $475,000 [98] and revenues went up from $500 to 500 mil per year [100].
- A summary of all 20 drug approvals (only between 2017-2022) of oncologic medicines originating from UPenn are reported by the Perelman School of Medicine (PSOM) and the Abramson Cancer Center (ACC) of the University of Pennsylvania [101].
- Kite (now a subsidiary of Gilead) relied in its R&D of CAR-T cell therapies on NCI CAR-T research. The Principal Investigator for the NCI on Kite's cooperative R&D agreement[22] (CRADA) 2012, St.A. Rosenberg, mentored Kite (mentioned as "Special Advisor" to Kite) and its CEO and co-Founder A. Belldegrun. Kite paid the NIH $3 mil annually for 3 CRADAs and 6 Exclusive License Agreements. The clinical evaluations on KTE-C19 cost $2.5 mil, but Kite reported $317 mil in R&D spending for CAR-T since 2012 and was selling the company for $11.9 bil to Gilead [98]. In 2017, the 2nd CAR T-cell therapy Yescarta® was approved and sold for a list price of $373,000 [98]. Yescarta® revenues increased to $337 mil in Q/4 2022 and $380 mil in Q2/2023, around 1.4 bil per year.
- The RANKL inhibitor denosumab (Prolia©, Xgeva©) inhibits bone resorption and is approved for the treatment of osteoporosis (Prolia©) and skeletal-related complications in adults with bone metastases due to solid tumours (Xgeva©). Denosumab was researched in the 1990s by J. Penninger's research group at the University of Toronto and subsequently in the 2000s at the Institute of Molecular Biotechnology (IMBA) of the Austrian Academy of Sciences (ÖAW) in Vienna. Amgen further developed the active substance and brought it as Prolia© in 2010, and as Xgeva© in 2011 to the market. In 2018, the EMA expanded the indication to patients experiencing an increase in bone mass as a result of a bone cortisone treatment. Prolia© is sold for a list price of $1,624.54 per injection every six

[22] CRADA is an agreement between a government agency and another government agency, a private company, non-profit, or university to work together on research and development.

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months; Xgeva© is sold for $3,156. In 2017, denosumab's 100,000 prescriptions generated social security costs of €28 mil [102, 103] in Austria.

Some example on analyses of databases on public and charity contributions:

- In August 2023, the NIH Reporter database (https://reporter.nih.gov/) shows 707 active NIH-funded projects on "chimeric antigen receptor" (funding amount $499,385,756), of which 293 are clinical trials (NIH funding: $283,547,455), mostly sponsored by the National Cancer Institute (NCI). Records dating back to 1993 report 1,564 clinical trials (NIH funding: $1,218,238,648) on CAR T cell therapies. Between 80% [104] and 91% (DeWilde 2017 in [98]) of all CAR-T celltherapy trials are sponsored by academic sponsors or – vice versa – only between 9% [98] and 20% [104] and by the pharmaceutical industry.
- While almost all analyses are conducted in the USA, very few come from Europe. A rare analysis of EC Framework 7 (FP 7) Health grants reported in the Cordis Db (https://cordis.europa.eu/) revealed that 12.3% (120/977) of all EC FP7-HEALTH awards are related to the funding of late-stage clinical research, totalling € 686,871,399 [4]. Pharmaceutical products and vaccines together accounted for 84% of these late-stage clinical development research awards and 70% of its funding. The hepatitis C vaccine research received total European Community (FP7 and its predecessor, EC Framework VI) funding of €13,183,813; total public and charitable research funding for this product development was estimated at € 77,060,102. However, the industry sponsor did not consider further development of this product viable; in contrast, FP7 funding for the late-stage development of Orfadin® for alkaptonuria formed the basis for market authorisation [4].
- Charities play an important role in research funding, especially in the USA and the UK, however their funding information is not easily searchable in one database, but in disease-specific sources [29, 99, 105]. For the UK it is reported that up to 14% of the total public funding that goes into medical R&D is invested by charities. [106]. For example, the Muscular Dystrophy Association (MDA) provided detailed information on the level of funding for projects they supported. 15 MDA funded specific projects totaling $3,768,516 and investment of $45 mil in SMA research are reported. According to its website, the Spinal Muscular Atrophy Foundation (SMA Foundation) has spent around $150 mil on basic, translational and clinical research since its inception in 2003. A total funding estimate – based on several databases - for SMA-therapies is around € 165 Mil for research into therapies. Only including projects named in the patents (or conducted by the same researchers named in the patents or named specifically in development documents), just over €20 mil of public or philanthropic

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money can be directly attributable to the development of Spinraza® [29]. The drug was further developed by Ionis Pharmaceuticals and marketed by Biogen with annual treatment costs of $750,000 for the first year of therapy and $375,000 for subsequent years.

Some examples on the provenance of the highest-selling prescription medicines of individual companies´ products:

- According to the 44 products listed in Pfizer's 2017 US annual report, only 10 (23%) of these are Pfizer's own developments; the rest, representing 86% of revenues totalling $37.6 bil, were acquired through takeovers or purchase of individual products. For example, the pneumococcal vaccine Prevnar 13, Pfizer's best-selling drug in 2017, was developed at Wyeth, which Pfizer acquired in 2009. Pfizer's palbociclib (Ibrance®), used to treat breast cancer, originated at Warner-Lambert and Onyx Pharmaceuticals. The 34 Pfizer products discovered by third parties accounted for 86% of the $37.6 bil in revenue its 44 leading products generated [107] (see Table D- 4 in Appendices Chapter 3).
- The situation is similar with Johnson & Johnson (J&J): Only two of J&J's 18 leading products (11%) were discovered in-house. J&J's highest-selling product, infliximab (Remicade®), is a monoclonal antibody that was synthesized by researchers at New York University in 1989 in collaboration with the biotechnology company Centocor. The 16 J&J products invented elsewhere accounted for 89% of the $31.4 bil that its 18 leading products generated [107] (see Table D- 5 Appendices Chapter 3).

The number of acquisitions in the pharmaceutical industry has been trending upwards [108, 109], with the largest deal of Amgen´s acquisition of Horizon Therapeutics (with a rare autoimmune and inflammatory disease portfolio) for $27.8 bil in 2022, followed by Pfizer acquiring Biohaven (with several migraine therapies) for $11.6 bil [97, 108]. In 2019 Bristol-Myers Squibb (BMS) acquired Celgene for $74 billion acquisition: the combined companies have nine products with more than $1 billion in annual sales. [110]. However, in 2023 BMS was accused of of defrauding investors by intentionally delaying drug approvals to avoid a $6.4 billion payout [111]. Medicine or portfolios are predominantly acquired when they have already proven to be effective in early stage trials [107]. With each change of ownership, the price of the company increases depending on the valuation of the product portfolios sold or bought. This process - called "financialization" - has been covered in many case studies [30, 112] and – it must be assumed due to the aggregated presentation of the R&D data – that the costs for M&A are covered under the industrial R&D expenses. A US Government Accountability Office report (GAO) [109] analyzed what large pharmaceutical companies spend most of their research expenditures on. The finding is consistent with EFPIA [92] self-reported data, showing that only 14.9% of

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industrial R&D is spent on preclinical studies — the basic and translational science that is the foundation for the discovery of innovative drugs. The reported total spendings on industrial R&D in Europe is €39.7 bil [92], of which 14.9% (€6 bil, own calculation) for preclinical research and 7.6% (€3 bil, own calculation) for early stage studies are only a fraction of the amount the European public spent to support the medical (basic, translational and precompetitive horizontal) research.

3.2.6 Public contribution to late stage development in clinical trials

Early stage (phase 1 and 1/2) as well as late stage clinical trials (phase 2, 2/3 and 3) are usually conduced in the setting they are meant to be delivered after market authorization, though under controlled conditions. The conduct of commercial clinical trials is often handled by Clinical Research Organizations (CRO). Since more than a decade university hospitals established their own departments, "clinical trial coordination centers", which support academic trialist with planning and implementation (e.g. with costing tools [113, 114]), while they also assist commercial trials in processing (recruiting, ethics committee´ vote, accounting of costs etc.) their trials.

For refunding the costs incurred during commercial trials the hospitals provide lists of prices for services delivered (staff cost, use of equipment, diagnostic monitoring, etc.) [115]. However, the commercial trialist is only paying for extra costs incurred and not for the costs of standard treatment. Whether the maintenance of the technical equipment is adequately covered, depends on the offer of the respective clinical trial coordination centers. The use and compensation of infrastructure is highly non-transparent, due to the competing interests of hospitals being rewarded for acquisition of clinical trials for academic as well as monetary reasons.
The average costs of clinical trials are estimated between $1.4 (pain and anesthesia) and $6.6 mil (immunomodulation) for Phase 1, between $7.0 (cardiovascular) and $19.6 mil (hematology) for Phase 2 and between $11.5 (dermatology) to $52.9 mil (pain and anesthesia) for Phase 3 trials, (data from 2004 – 2012) including estimated site overhead and monitoring costs of the sponsoring organization [116] . Across all study phases and excluding estimated site overhead costs and costs for sponsors to monitor the study, the top three cost drivers of clinical trial expenditures were clinical procedure costs (15%-22% of total), administrative staff costs (11%-29% of total), and site monitoring costs (9%-14% of total) [116]. Smaller trials (for orphan drugs) approved with only phase 2 evidence are far less expensive. As an example, Knowledge Ecology International (KEI) calculated the development costs of Nusinersen's pivotal trials (ten Phase 1-3 trials involving a total of 437 patients) at $ 17.8 mil. With a tax

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exemption of 50% due to orphan drug status, costs decreased to $ 8.9 mil and, after capitalizing the risk of failure, amounted to $ 35 mil only.

To conclude: while the public contributions to later stage development of products are less they still do exist. The coordination of 24 European Reference Networks (ERN) for rare diseases are essential public contributions for efficient recruiting, the advancement of methodologies in trial-designs, outcome measurement and validation for improving and the provision of well-equipped infrastructure for conducting clinical trials. Sponsors of late stage clinical trials will be explored in case-studies (on antibiotics or other medicines).

3.2.7 Public contributions to regulation and marketing authorization

Citizens, patients and clinicians expect regulators to provide an unbiased, rigorous and technically sound assessment of investigational therapies in a transparent manner. To advance methodologies for Marketing Authorization concepts for "regulatory science" have been developed to support regulatory assessments that inform not only Market Authorization Holders (MAH), but also HTA agencies supporting payers to make decisions on health care resources. Instruments have been developed for improving professional skills and capacity and for advancing methodologies for regulation. In 2011, the US Food and Drug Administration (FDA) has 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 [117]. Several years later in 2018 the European Medicines Agency (EMA) has launched its strategy for "Regulatory Science to 2025" [118], followed by a detailed list of "Regulatory Science – Research Needs" in 2021 [119].

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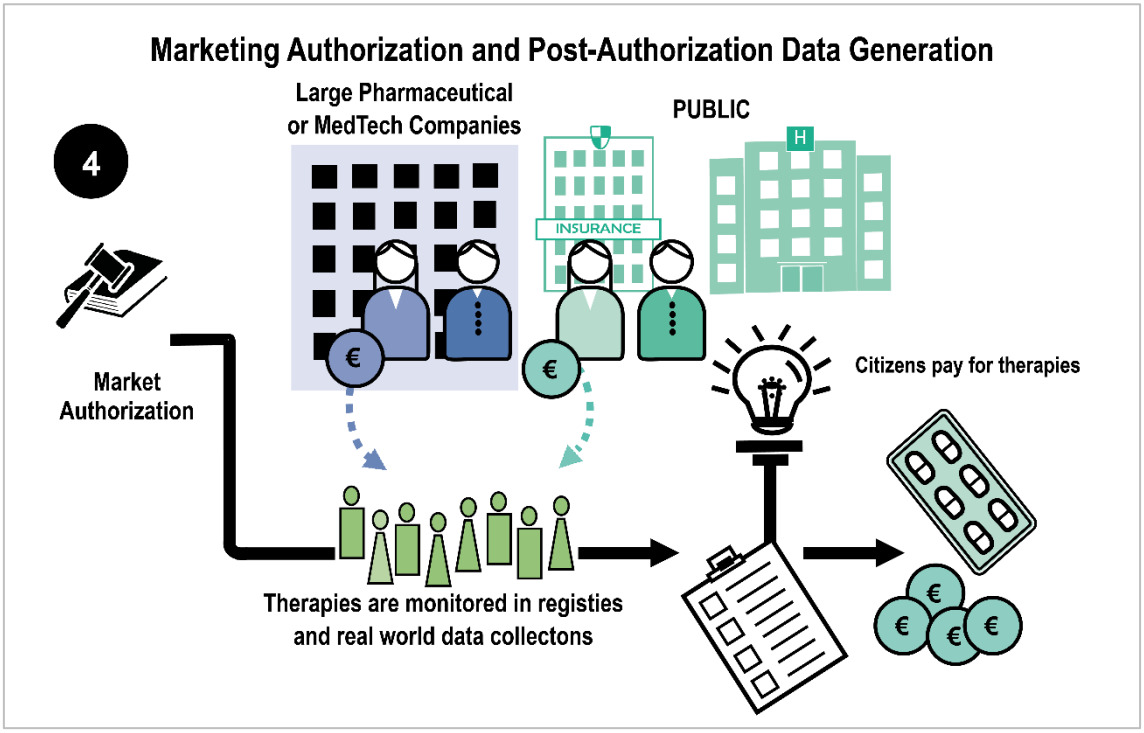

Figure 3.2-4: Marketing authorization and post-authorization data generation

All documents encompass the intentions of these plans and strategies, such as by

(1) enforcing regulators keeping up with the most recent science in order to enable high-quality and critical evaluations of the benefit-risk,
(2) advancing innovation in methods and standards for the evaluation of quality, safety, and efficacy of medicinal products throughout their product life cycle, and
(3) enabling innovation by a broad range of activities related to reaching out to stakeholders (i.e., patients and health care professionals) ensuring patient safety, safeguarding public health, and innovation.

The public contributions to Market Authorization are manifold. Though the regulators European Medicines Agency (EMA) and the Notified Bodies (NB) are primarily financed by private companies through fees, the public contribution is substantial [120]:

- For 2023, the total budget of the EMA amounts to €458 mil. Around 89.0% derives from fees and charges from industry, 10.9% from the European Union (EU) contribution for public-health issues and 0.1% from other sources. The public contribution is used for supporting advancement of regulatory methodologies, education and training as well as policies for orphan and paediatric medicines, advanced therapies (ATMPs) and SMEs.

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- While EMA coordinates the scientific evaluation of applications and related work with the national medicines regulatory authorities in the EU Member States, the national authorities conduct the assessment and are compensated for this work (involvement of staff members in scientific committees, working groups and other activities). However, the National Competent Authorities (NCA), have a remit far beyond contributions to market authorization (clinical trials of medicinal products and medical devices, pharmacovigilance and vigilance in the field of medical devices, and inspections), that is fully financed by the public.
- Next to approval activities, EMA is also developing scientific guidelines [121] and trainings. For building capacities training modules [122], workshops on e.g. patient registries [123] or on increasing use of real-world evidence, including registry data for regulatory purposes (e.g.[124]), and scientific events are publicly financed tasks of EMA [125] (see Table E- 1 on EMA reflection papers and guidances on novel methodologies for medicine development in Appendices Chapter 3).
- In recent years, health technology assessment (HTA) for pricing and reimbursement have become an ever more important role in providing Joint Scientific Consultation (JCA, formerly Early Dialogues/ ED), and Post-Launch Evidence Generation (PLEG). In contrast to EMA´s Scientific Advices, they were provided free of charge by the European Network of HTA (EUnetHTA) (see Table E- 2 in Appendices Chapter 3). Between 2017 and 2023 44 ED or JSC have been conducted by European Network for Health Technology Assessment (EUnetHTA) members summing up to € 2.86 mil.

Finally the public is not only providing support for orphan, paediatric medicines and ATMPs with scientific advices to optimise the generation of robust data, protocol assistance, accelerated approval via the PRIME (PRIority Medicines) Programme, but also numerous fee-reducing instruments are in place:

- Fee waiver: the application fee required for EMA review is waived for companies developing orphan drugs,
- Tax credits: the sponsor receives tax credit to offset R&D costs,
- Longer market exclusivity for orphan products and therefore higher prices for a longer period of time.

In the meanwhile, a large percentage of new medicines is approved as orphan drugs, a strategy known as "salami slicing" by dissecting broader diseases in subtypes (the slices). In 2022 23 orphan drugs were granted market authorization, often based on phase 2 pivotal trials [125], requiring Post-Launch Evidence Generation for decisions on reimbursement.

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3.2.8 Public contributions to post-launch evidence generation (real-world-data 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 for a generation of evidence after market-authorization has increased significantly by payer-institutions. For confirming the benefit-risk balance of a product, following a conditional approval based on early data (using surrogate endpoints) and short follow-up periods, the collection of evidence through real-life use to supplement clinical trial data has been supported by EC-grants as well as by national initiatives:

- ATMPs (cell- and gene-therapies) for life-threatening diseases raised expectations to be even curative. However, the evidence generation in order to conclude whether they can live-up to the expectations and promises is conducted in (partly) publicly sponsored patient and/or intervention registries as basis for outcome-based managed entry agreements. Data and governance concepts are developed in national HTA agencies [126, 127]. For example, the European Bone Marrow Transplantation (EBMT) CAR-T cell therapy registry (https://www.ebmt.org/registry/ebmt-car-t-data-collection-initiative) is working with a budget of € 12.7 mil, partly derived from public sources; the SMArtCARE registry is fully sponsored by the MAH of the three available therapies, however the study protocols and -plan for data collections accompanying the use of these therapies are conducted in public agencies [128, 129].
- The EC has launched several programmes to support the evidence generation: The EMA has established a coordination centre to provide real-world evidence on the performance of medicines called DARWIN EU (Data Analysis and Real World Interrogation Network, https://www.darwin-eu.org/), that will connect the European medicines regulatory network to the EC-initiated European Health Data Space (EHDS). In 2020 a Big Data Task Force was set to develop – among other activities – a framework for quality assured data collections across Europe [125].
- IMI/ IHI has contributed with € 415 mil public contributions to numerous projects on real world data and evidence generation (RWD, RWE, see Table C - 3 in Appendices Chapter 3) or with € 281 mil in establishing reference networks for a common understanding of how to diagnose and treat rare diseases and for faster patient recruitment and long-term monitoring through patient registries, for supporting partnerships and

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dialogues with patients as well as education and training; or even with setting up clinical trial networks (ECRIN/ European Clinical Research Infrastructure Network: https://ecrin.org/ https://www.ecraid.eu/, ECRAID/ European Clinical Research Alliance on Infectious Diseases: https://www.ecraid.eu/) for faster setting up of large EU-wide clinical trials.

- Within HTA-institutions the expenditures for a.) the preparation of the concept for the real-world-data collections, b.) the communication in advising the pharmaceutical company in the preparation of the study protocol and statistical analysis plan to be carried out by the company and c.) the Review of the study protocol and statistical analysis plan (usually by two reviewers) is estimated with 0.7[23] full-time-equivalents (FTE) per real-world-data collection.

3.3 Discussion

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 all too obvious. Aligned public policies enforcing transparency on R&D investments is key. But not only direct public contributions (leading to products) but also indirect (funding of basic research, methodology, tools and techniques) is thus an evidentiary necessity.

Public and private funding of the development of medicinal products are complementary ventures [130], sharing a division of work and both working with large amounts of risk capital. The complementary relationship between biomedical and health research and private pharmaceutical or biomedical R&D has been investigated in econometric models: a 1% increase in public sector expenditures is associated with a 0.81% increase in private sector expenditure [131]. Evidence from the UK suggests that every pound of public investment in R&D crowds in two pounds of private investment [132]. It can´t be denied that public R&D expenditures has macroeconomic effects on the GDP as one measure for flourishing economies as well as microeconomic effects on companies´ revenues [90, 133]. However, strategic aims of public R&D in health, lifescience and biotechnology must foremost serve public health interests, such as priorities for new health technologies meeting patients´ needs and only secondarily economic interests.

For companies, the return on investment (RoI) is expressed in profits, while for the public the return would be – at best – an increase in health, - at worst – paying twice. This publicly-induced increase in health is best observable when priority

[23] Personal communication with IQWiG.

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areas are defined (by the public) and targeted basic and translational research is publicly funded (HIV, Hep C) and further developed by commercial companies [17, 24] and marketed for reasonable prices. Value-based prices have been promoted in recent years by industry as a reaction to the debate, however the term is also criticized for demanding the maximum price payers would be willing-to-pay (disconnected from R&D) and for misusing the interpretation of "value": Currently, "value" in the context of healthcare is often discussed as aiming at increasing cost-effectiveness. This interpretation of "value" is often perceived as too narrow and the notion of "valueS-based healthcare" seems more suitable in conveying the guiding principles underlying solidarity-based healthcare systems [134].

When therapies are not available to those in need due to unaffordable prices, then this system of complementarity has failed. The EC has reacted on the ever more often expressed reproach [10, 135, 136] that the public pays twice for their medicines with the requirement for transparency in Article 57 of the proposed medicines Directive [9]. It is the intention of our research project to provide structured substance to this requirement on what kind of categories of public contributions one has to think of when asked for transparent information. There is a very strong argument that the public contributions to basic /translational science funded by taxpayers should be global public goods, and should be made freely available, because they generate spinoffs, positive externalities, and provide the impulse for private R&D.

3.3.1 Summary of findings

This research followed the methodology (see Figure 3-1) of dividing the development of products in stages and to search – supported by targeted interviews with experts in the field – for categories of public contributions. The literature and information analysis was based on secondary information (data collections of other authors) and own primary data collections (on detailed database extractions). We found eight categories (and many more sub-categories), but do not consider them as exhaustive. More research work has to be done.

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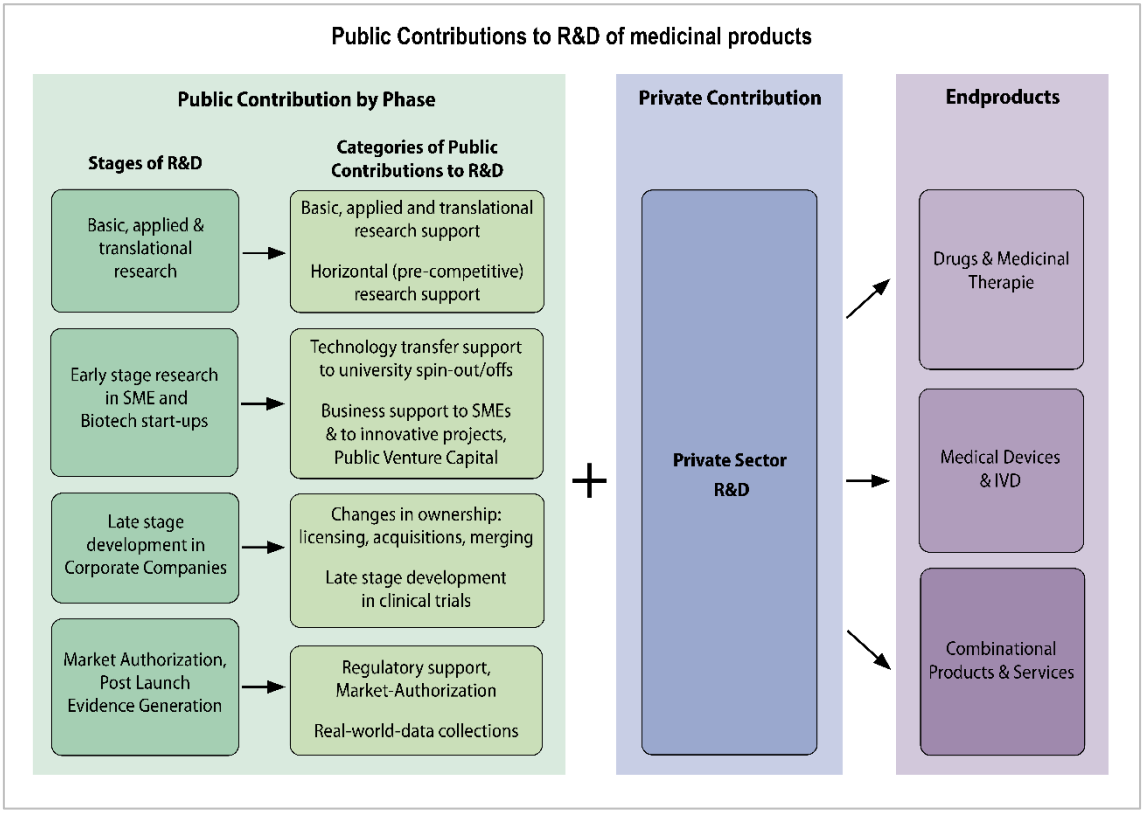

Figure 3.3-1: Model of analysis: public contributions to R&D of medicinal products

While EC is reporting their expenditures on R&D very transparently, national expenditures are not available in a structured format as much as commercial data on R&D spendings are not available in enough detail. Additionally, no definition on what is reported (and what is not allowed to be covered) as R&D spendings by companies is provided. No or unstandardized reporting of public fundings and their output (measured in KPIs) are part of the problem and hinder the disclosure of public contributions to R&D, for early as well as late-stage developments of health products. While the records for the most expensive drugs are broken annually, the public sector hasn´t had enough evidence to hold against: the direct and indirect public contributions to basic, applied and translational research, to horizontal contributions to knowledge on new methodologies for e.g. trial designs or stratification of diseases, but also on the true costs for clinical trials or factors influencing attrition rates.

However, the findings bear witness to how product development takes place: Research partnerships with public research organisations and small biotech start-ups are common. Major pharmaceutical companies are sending out 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. Research results are

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paid by pharmaceutical companies according to defined milestones (asset transfer agreements). The final approval and market introduction are then carried out by the global pharmaceutical companies.

3.3.2 Contextualization of findings and gap analysis

We have to accept that - if private sector investor capital is being provided as an input to the R&D system -, then a RoI will be the main motive, and that investment capital must be reimbursed to the investor, if the product is successful, along with some reward. That reimbursement can only be implemented as dividend, interest or buyback. The fundamental principle is clear, but perceptions differ about how much of the reward should go to investors. 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, an analysis on the contributions to innovation must not only count 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 in order to recruit and manage patients in clinical trials. The products (drugs, devices) are usually provided for "free", therefore representing a 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 of the actors, public sector and private. Consequently, only a mapping of all potential financial flows into the R&D ecosystem, out of it, and between stakeholders in innovation & R&D provides a full picture. This will be covered in the next steps of this research.

In the recent decades a mismatch of public health needed-driven products with large benefits and for-profit-driven products (e.g. in oncology) with marginal benefits [31, 42, 137] can be observed. The 2023 WHO-Report on "Health for all: Transforming Economies to Deliver What Matters"[138] argues for "an innovation ecosystem that prioritises the common good, ensuring equitable access to health innovation and that the design of innovation investments, policies, intellectual property rights and partnerships should recognise that innovation requires intelligence – from public and private sectors, and from multiple government departments and businesses. Innovation can be directed to tackle health challenges, and the partnerships required to solve these challenges can

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be designed to better share the risks and rewards of innovation, for example by making government funding conditional on affordable access and requiring profits to be shared or reinvested in R&D rather than used for shareholder buybacks" [139].

The complementarity of "intelligence from public and private sectors" is based on an implicit agreement (so called "social contract" [140]) 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) the corporate companies commit to bringing medicines to the market that address health needs in exchange for profits that compensate their investments [141]. 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 sector to complement each other in developing "public goods", that has worked well for long, seems "broken" or – on the contrary –, it is argued that the market is not broken, but rather it works *too* well. The incentives for orphan drugs are now so strong that it might be displacing investment capital from other therapeutic areas, that are likely to have a greater impact on public health. The many pull incentives for orphan drugs and rare diseases and the RoI for orphan drugs is now so high, that the attention 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 as well as increasing prices. Hence, it is important to develop a common conception of what is meant by "value" in therapeutic innovation and how it is measured and rewarded.

Alongside the escalating prices, the awareness of the problem has awakened: Nobel laureate Joseph Stiglitz warned already in 2020 that price policy could lead to an implosion of the entire pharmaceutical system. As an alternative, he proposes a much more active role for communities of states in drug development. Both, the Belgian HTA Institute KCE (Belgium Health Care Knowledge Center) 2016 [142] and the Dutch "Council for Public Health and Society" 2017 [143] concerned themselves with alternative models of drug development. One-off payments for genuine innovations could replace long patent terms. Submitting tenders for conducting clinical trials for new drugs with subsequent "generic" prices is also conceivable. The prices (cost plus) would have to include production costs, marketing expenditure, and profits, but the research effort would no longer be paid prescription by prescription. The first initiatives on patent pools and research platforms have shown that it is also possible to manufacture medicines outside the corporate world [144].

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Several recent US and European policy papers have started to propose national public pharmaceutical R&D institutions [145] and/ or public infrastructure [146] to counter the market failure or clinicians´ as well as regulatory initiatives have started to act based on existing regulatory frameworks such as "hospital exemptions" or "academic and non-profit development" [147] [94, 148, 149]. The UN High Level Panel on Access to Medicines has also called for the unbundling of the value chain of drug development and for decoupling R&D costs from the final price of health technologies in general [136]. A decoupling of the individual work stages has since long been executed as a de-risking strategy in the pharmaceutical industry but is not communicated. Questions remain whether the public sector have the mechanisms to measure and manage risk.

The purpose of increased transparency on financial contribution to (medical and medical) products' R&D is to take the public contributions into account when pricing a product and to increase the need of justification of very high prices. However, this work is just a stepping stone. Whatever method of accounting for the public contribution, the issue of the mergers' and acquisitions will pose very steep challenges: mergers and acquisitions complicate who ultimately has to discount from their rent extraction the public contributions, e.g., the company that initiated the innovation and cashed the rents selling before phase II and III (as an example) or the company that acquired the innovation at a price that did not discount the public contribution. These challenges are not unsurmountable but need to be considered in further analyses. Furthermore, exploration of policies for R&D investments strategies such as an option market [33] or a global R&D fund, paid for out of global revenues of the companies or policies enforcing disclosure of public funding and to monitor it is needed to support health policy.

Orphan drugs and antibiotics are two cases where the public contribution aims at fixing broken markets and at providing incentives. This is intentionally 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. However, the direction of R&D is not only determined by need and demand (incentives by payers and regulators for certain types of diseases and products), but equally by technical (supply-side) factors, such as progress in basic science: the decoding of the genome (around the turn of the century) led to applications (such as biomarkers) and spinoffs from those. Hence, who and how the public priorities are set, the governance and funding of basic science is of primary importance and underpins an argument that basic science should be a Global Public Good in the broadest, classic sense.

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3.3.3 Limitations

This research has several limitations:

- The major limitation to get a full picture is the lack of accessibility and availability of national sources providing data in enough detail or in a standardized format, esp. in Europe in the EU-27 countries. An obligation of structured and transparent reporting is needed. While the NIH RePORTER is easily searchable and provides the information in different formats, the Cordis Database is descriptive only. While US-located companies have to provide annual financial statements (SEC-reports), no such source is available in Europe.
- A lot of very well documented data and info of the public contribution to innovation and R&D, direct and indirect, is provided. However, the information is lacking linkages to product/projects in order to contextualize and relativise the public contributions and their impact. Since this was not within the scope of this part of the project, this will happen in the next step of the project, when the framework of categories is applied to case-studies.
- Another major limitation is, that some areas have not been covered by this research. What is lacking is information on taxes, esp. reduced taxes for commercial R&D, on national and regional support to companies to settle in a certain region, on overhead expenses for national and European services providing consultancy on EC-research funding and on innovation funding, on expenses for patenting (and public spending on over-patenting) etc.
- All aspects, such as skill development, academic education and training that are essential prerequisites for the settlement of companies in certain regions, is not touched at all, since these are public contributions, however not solely targeted at health innovations.
- Some public contributions were assigned – for pragmatic reasons - to one individual category (e.g. in horizontal contributions), and only mentioned in another (such as methodology advancement in collecting and handling real-world data). However, there is some overlap, what can be considered a limitation of the approach of categories.
- Furthermore, the information searched for and sought is not exhaustive and provides only examples. While a general impression can be given, a generalisation across all therapies, medicines and medical products is not easily possible. Especially, the areas of medical product development and of me-too drugs are under-researched.

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- Finally, we searched for and used only publications in English and German language.

3.3.4 Conclusion

The question is not so much why we need to consider the public contributions, but how to capture the substantial amounts of public funding from European as well as from US based (and further countries) public institution. Next to the legal ground laid by the Pharmaceutical Legislation (PL) the methods need to be further refined. The conditions attached to public R&D grants are not sufficient [150]. The proposal for the new PL plans transparency requirements on the reporting of direct public R&D received. However, – as was shown here – the indirect (e.g. horizontal) public contributions are as relevant as the direct ones. While showcasing the direct and indirect public contributions along the proposed categories seems easy in contrast to incorporating these figures into pricing. Therefore, we argue for a redesigning and updating the existing regulatory framework to make it more aligned with current challenges [151]. Furthermore, the conditions for transparency requirements are not yet in place to allow control and monitoring. Several policy options are proposed as conclusions of the paper:

- Standardized reporting of public and philanthropic R&D spendings, not only on the European level, but also for national funders, incl. their outputs (patents, spin-offs, …) and follow-up on KPIs, increase reporting granularity of data and projects´ outputs.
- Compulsory requirements of R&D reporting for industry with clearly defined in-/ and exclusion criteria for increase of comparability between Public and private of R&D expenditures, including detailed reporting of costs.
- Detailing contractual options for conditionalities and requirements attached to public support to research and further development of innovations (in academic research, in start-up, pin-out/spinoffs) such as to tie public investments to a "reasonable pricing clause", open access to intellectual property rights (IPR), profit-sharing or repayment of the initial investment or royalty payments to the public.
- Transparency on any changes of ownership from public to private and on the terms of these agreements ("conditionalities") on the reward the licensor for monitoring the relation between the profitability of the approved product and the return to the licensee.
- Exploitation of the national routine electronic health data sources and interoperability among sources (e.g hospital episode data, major clinical events, rehospitalizations, disease registries, linkage to death registration

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data, etc.) to conduct PLEG studies with full transparency and incorporation of this RWE data in models of prize-setting.

Finally, the role and willingness of political decision-makers to use the eventually established transparent information on public contributions, needs to be stressed. Otherwise, the transparency requirement clause will stay "dead paper" instead of advocating for a paradigm change.

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Appendices Chapter 2

Appendix A

Table A 1: Possible report on costs for clinical trials

Category	Amount	Cost per item	Sum
Subject compensation			
Subjects			
Screening Failures			
Drop Outs (50%)			
Compensation Schedule per Subject			
Screening (Visit 1)			
Day (Visit 2)			
Day (Visit X)			
Total costs per subject			
Lab costs			
Diverse material costs			
Disposable material			
Working hours			
Study nurse overall			
Physician overall			
Development of study documents (worksheets, source data, Recruitment, time schedule subject management)			
X h study nurse per subject preparing per subject/visit			
X h study nurse per subject/visit			
Screening hours			
X h study nurse per subject			
X h physician per subject			
Study Days			
Visit 1 study nurse X h			
Visit 1 Physician X h			
Visit X study nurse X h			
Visit X Physician X h			
Number of physicians per subject			
Start-up Fee (incl. protocol & contract review and initiation)			
Close out (including review of results and study report)			
Archiving			
Administration flat rate			
Overhead			
Total cost without overhead			
Total cost with overhead			

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Appendix B

Topic 1: Cost estimations

Q1: Do you have a costing tool for estimating the costs of clinical trials?

Q2: What factors are the reason for the immense cost differences between studies on estimations for pharmaceutical R&D?

Q3: What are the cost per patients in clinical trials? Are there differences between academic and commercial trials?

Q4: How can cost differences between commercial and academic studies be explained?

Q4: Do you include costs associated with basic research or compound-non-specific research in your cost reports for a specific new drug?

Topic 3: Attrition rates

Q1: Are you aware of a method to differentiate between scientific and commercial attrition of pharmaceutical R&D with publicly available data?

Q2: What are your estimations for attrition rates on basic research?

Topic 2: Public contributions to pharmaceutical R&D

Q1: When reporting on costs of product development, which categories of direct or indirect public contributions can be thought of?

Q2: How are costs of using public infrastructure in commercial studies reimbursed?

Q3: Are in-licensing and acquisitions counted as R&D costs?

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Appendix C

Table C 1: Publication on costs for pharmaceutical R&D: Mixed therapeutic and specific therapeutic fields

Publishing Author(s)	Publication year	Therapeutic class considered	Drug inclusion period	Sample number	Clinical approval success rate	Average capitalized costs estimated per successful drug (in Million USD)*	Origin of data	Accounting for failed clinical trials in cost estimation	Stage at which cost estimates start
Mixed therapeutic fields									
Hansen & Chien [52]	1979	Mixed	Selected sample of clinical trials 1963-1975	Not given	12%	214.38	Confidential surveys (of pharmaceutical companies)	Yes	Discovery
Wiggins [55]	1987	Mixed	Received FDA approval between 1970 and 1985	223	-	290.54	Industry wide R&D costs, not project specific	Yes	Discovery
DiMasi et al. [56]	1991	Mixed	Drugs developed between 1970 and 1982 (FDA approved and abandoned)	93	23%	520.31	Confidential surveys (of pharmaceutical companies)	Yes	Preclinical**
DiMasi et al. [65]	1995	Mixed	Drugs developed between 1970 and 1982	93	23%	541.19	Confidential surveys (of pharmaceutical companies)	Yes	Preclinical
Young and Surrusco [63]	2001	Mixed	Received FDA approval between 1990 and 1996	207	-	Only pre-capitalized estimated: Min.: 283.86 Max: 373.92	-	-	-
DiMasi et al. [58]	2003	Mixed	Drugs developed between 1983 and 1994 (FDA approved and abandoned)	68	22%	1,363.00	Confidential surveys (of pharmaceutical companies)	Yes	Discovery**
Gilbert et al. [53]	2003	Mixed	Pharmaceutical products that started clinical trials between 1995-2000	8 13	18% 14%	1,805.19 2,789.48	Modelling with confidential data	Yes	Discovery

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			between 2000-2002						
DiMasi et al. [66]	2004	Mixed	Drugs developed between 1983and 1994 (FDA approved and abandoned)	68	22%	767.54	Confidential surveys (of pharmaceutical companies)	Yes	Discovery
Adams & Brantner [54]	2006	Mixed	Drugs in development process from 1989-2002	3181	24%	1,424.74	Based on Pharmaprojects database of unspecified drugs	Yes	Preclinical**
Adams & Brantner [62]	2010	Mixed	Drugs in development process from 1989-2001	1684	24%	1,991.58	Based on Pharmaprojects database of unspecified drugs	Yes	Phase 1
Paul et al. [60]	2010	Mixed	Data from 2000 to 2007 of the Pharmaceutical Benchmark Forum	Not given	12%	2,383.51	Confidential industry data	Yes	Discovery
Mestre-Ferrandiz et al. [61]	2012	Mixed	Included if drug completed "Pre-first toxicity dose" interval between 1998-2002	77	7%	1,922.64	Confidential surveys (conducted by CMRI)	Yes	Discovery
DiMasi et al. [59]	2016	Mixed	Received FDA approval between 1995 and 2007	106	12%	3,153.78	Confidential surveys (of pharmaceutical companies)	Yes	Discovery
Jayasundara et al. [39]	2019	Mixed (orphan, non-orphan)	Received FDA approval between 2000 and 2015	100	Orphan: 33% Non-orphan: 10%	Orphan: 365.95 Non-orphan: 518.08	Combination of several databases for cost estimations	Yes	Phase 1
DNDi [14]	2019	Mixed (neglected diseases)	All drugs that were (co-)developed by DNDi (from 2004-2019)	-	-	5.07-40.55 million (new treatments that combine or repurpose existing drugs) 76.02-40.75 mil. (NCE)	Cost estimates based on their own previous experience with drug development. Transparent data on costs.	yes	Discovery
Wouters et al.[5]	2020	Mixed	Received FDA approval between 2009 and 2018	63	14%	1,518.13	Annual and quarterly SEC-reports and data from ClinicalTrials.gov	Yes	Phase 1

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Schuhmacher et al. [26]	2023	Mixed	All drugs that received FDA- approval by 16 pharmaceutical companies from 2001-2020	251	-	6.160	Total R&D spending from 16 big pharmaceutical companies	Yes	Discovery
Specific therapeutic fields									
DiMasi et al. [65]	1995	Non-steroidal anti inflammatory Cardiovascular Anti-infective Neuropharmacological	Any drugs between 1970-1982 that were available in the CSDD database	8 21 15 18	22% 26% 30% 20%	303.43 183.75 450.07 192.11	Confidential data from CSDD (Industry based) database	Yes	Discovery
Global Alliance for TB Drug Development [13]	2001	Tuberculosis	-	One hypothetical project	10%	191.06 (min) 395.31 (max)	Experience		Discovery
DiMasi et al. [66]	2004	Analgesic/anaesthetic Anti-infective Cardiovascular Central nervous system	Any drugs between 1983-1994 that were available in the CSDD database	10 9 12 13	25% 25% 18% 18%	617.67 810.37 757.67 868.02	Confidential data from CSDD Industry based) database	Yes	Discovery
DiMasi & Grabowski [28]	2007	Oncology	Drugs developed between 1990 and 2003 (FDA approved and abandoned projects)	17	30%	1,821.99	Confidential surveys (of pharmaceutical companies)	Yes	Discovery
Chit et al. [67]	2014	Seasonal influenza vaccines	2000-2011	39	20%	598.02		Yes	Estimated preclinical costs
Falconi et al. [68]	2014	Oncology (non–small-cell lung cancer)	Drugs under development from 1998 to 2012	199	11%	2,388.66	Publicly available resources on clinicaltrials.gov and other non-specified sources	Yes	Phase 1
Sertkaya et al. [71]	2014	Antibacterial drugs Vaccines	-	-	9% 39%	Only non-capitalized: 192.53 361.12	-	Yes	Preclinical
Prasad & Mailankody [69]	2017	Oncology	Received FDA approval between 2006 and 2015	10	-	1,080.42	US Securities and Exchange Commission filings	Yes	Estimated preclinical (2 years prior to

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									first mention in publication)
Årdal et al. (min) [70] Årdal et al (max)	2018	Antibiotics	- -	One hypothetical product	- -	-	Confidential data from industry surveys	-	-
Wouters et al. [5]	2020	Oncology Alimentary tract and metabolism Nervous system Antiinfectives for systemic use Dermatologicals Cardiovascular system Musculoskeletal system Blood and blood-forming organs Sensory organs	Received FDA approval between 2009 and 2018	20 15 8 5 4 3 3 2 2	3% 20% 15% 25% - - - - -	5,195.79 (Oncology) 1,665.82 (Alimentary tract and metabolism) 1,254.22 (Nervous system) 1,510.80 (Anti-infectives)) 2,328.94 (Dermatologicals) 1,343.08 (Cardiovascular system) 1,092.39 (Musculoskeletal system) 924.21 (Blood and blood-forming organs) 1,518.36 (Sensory organs)	Publicly available data from SEC-fillings	Yes	Phase 1

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Appendices Chapter 3

A: Funding of LifeScience

- A-1: Published data analyses on public contributions to R&D of drugs (and other technologies)
- A-2: National R&D Funding insitutions
- A-3: National (Biotechnology, LifeScience, Health) Innovation Support for Spin-Outs/ Offs and Start-ups
- A-4: EU Contribution and total project costs in FP7 Health
- A-5: EU Contribution to Patents (FP7 Health) -Number of patents by pillar and corresponding sub-activity
- A-6: Overview of EC-R&D Programmes

B: Public contributions to drug development (examples)

- B-1: Characteristics of Funded FDA Grants (2007—2011) for late stage clinical trials that Led to FDA Approvals
- B-2: FDA Research Grants for Product Development (Phase 1-3 trials)
- B-3: EC-Funds within the European Joint Programme on Rare Diseases (2007-2022)
- B-4: EC-funded projects on rare diseases with clinical trials
- B-5: Antibiotics currently in development (Phase 3)
- B-6: Actors in R&D of antibiotics
- B-7: EC-funded projects on antimicrobial resistance, drug development and clinical trials

C: Public contributions to…. (IMI/ IHI projects)

- C-1: Target Identification, Drug Discovery, Drug Delivery
- C-2: Development of tools for Predicting and Monitoring Efficacy and/or Safety, as well as for Refining Disease Taxonomy/ Biomarker-Stratification
- C-3: Clinical Trial Design, Real World Data and Evidence, Methods for Benefit-Risk Assessment and Regulatory and HTA Process
- C-4: Ecosystems and Networks: Clinical Networks and Patient Involvement in R&D, Education and Training
- C-5: Conducting Clinical Trials
- C-6: Big Data and Knowledge Management, Digital Health, Artificial Intelligence

D: Public Contributions to Spin-Off/ Spin-Out from academic R&D and acquisitions (overview and examples)

- D-1: European Innovation Council (EIC): Progrmmes and Funding 2021-2023

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- D-2: European Institute for Innovation and Technology (EIT) funded Health Products 2021-2023
- D-3: Good Practice Examples for transparent reporting on academic research spin-offs/ spin-outs in NL: BioGeneration Ventures (BGV): Examples from Portfolio BGV I
- D-4: Origins of drug products manufactured by Pfizer in 2017
- D-5: Origins of drug products manufactured by J&J in 2017
- D-6: Overview of EMA-approved ATMPs, acquisitions and licensing agreements in early research, later development

E: Public Contributions to Regulation and Marketing Authorization

- E-1: European Medicines Agency (EMA) reflection papers and guidances on novel methodologies for medicine development
- E-2: HTA-Joint Scientific Advice (JCS)/ Early Dialogue (ED) to Health Technology Developer (HTD)

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Appendix A

Funding of LifeScience

- A-1: Published data analyses on public contributions to R&D of drugs (and other technologies*)*
- A-2: National R&D Funding insitutions
- A-3: National (Biotechnology, LifeScience, Health) Innovation Support for Spin-Outs/ Offs and Start-ups
- A-4: EU Contribution and total project costs in FP7 Health
- A-5: EU Contribution to Patents (FP7 Health)
- A-6: Overview of EC-R&D Programmes

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Table A- 1: Published data analyses on public contributions to R&D of drugs (and other technologies)

Author/ Year	Data basis	Results: effects of public contributions	Sources used	Public contributions considered
		Across drug approvals		
Kneller 2010 [25]	252 FDA approved drugs (1988-2007)	The data indicate that drugs initially discovered in **biotechnology companies or universities** accounted for approximately **half of the scientifically innovative drugs approved**. Overall, of the 252 drugs studied, pharmaceutical companies were attributed 58%, biotechnology companies were attributed 18%, universities that transferred their discoveries to biotechnology companies 16%, and universities that transferred their discoveries to pharmaceutical companies ere attributed 8%. With regard to addressing unmet medical needs (priority review category), 46% were attributed to pharmaceutical companies, and 54% were attributed either to biotechnology companies or universities 30%.	Analysis of: FDA Database: for NME and information on priority review. Merck Index: on novelty of compounds. FDA Orange Book: Identification of patents from government or academic institutions. Citation data and employment information.	Basic research support Patents from public institutions Applied research in BioTech
Sampat/ Lichtenberg 2011 [17] Sampat 2011 [24]	379 FDA approved drugs (NMEs) (1988-2005)	**47.8% of drug approvals were associated with public sector institutions** (patents or publications); 9% hold a public sector patent. **64.5% "priority review**" vs. 36.2% "standard review" are associated with public sector patents or publications; **17.4%** vs 3.1% **hold a public sector patent**. Dominance of 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.	Analysis of: FDA Database: for NME and information on priority review or standard review. FDA Orange Book: Identification of patents from government or academic institutions. Citation data. Sales data.	Basic research support Patents from public institutions
Stevens et al 2011 [12] Stevens et al 2023 [13]	153 FDA approved drugs, vaccines, or new indications for existing drugs (only publicly discovered) (1973-2009) 364 FDA approved drugs, vaccines, or new indications for existing drugs (only publicly discovered) (1973-2016)	Total number of approvals of drugs, vaccines, or new indications for existing drugs was 1541, of which priority review was granted for 348 applications (22.6%). 153 products originated Public Sector Research. **Virtually all the important, innovative vaccines that have been introduced during the past 25 years have been created by public institutions**. Of the total approvals of new-drug applications, 483 (31.3%) were for NME, of which 64 (13.6%) originated in public institutions. 293 (incl. 153 above) drugs were discovered either wholly by a US public institutions or jointly by a US. and a non-US institutions. 119 drugs and vaccines were discovered outside the US. Of these, 71 were solely discovered outside the US, while 48 also involved intellectual property contributions by US public institutions. **2/3 of drugs and vaccines are discovered in the US and Canada**, 1/3 in Europe (Germany, UK, Belgium, etc.), in the Asia-Pacific region (Australia,	Analysis for drug discoveries by region: FDA Database: for information on approvals FDA Orange Book: Identification of patents from government or academic institutions. Database of Patent and Trademark Office. Annual licensing survey on technology transfer activities of academic institutions by Assoc. of University Technology Managers. SEC-filings. Additional in [13]: Reports of medical product manufacturers' payments to physicians and teaching hospitals under The Sunshine Act.	Basic research support Patents from public institutions Applied research Licensing/ technology transfers

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		Japan) and Middle East (Israel) with **on average $ 0.77 bil (Belgium), $ 0.55 bil (USA), $ 0.23 bil (UK), $ 0.14 bil (Germany) or $ 1.06 bil (Israel) academic expenditures per drug**.	Royality transactions by academic institutions [25]	
Cleary et al 2018 [14] Cleary et al 2023 [7] Cleary et al [15]	210 FDA approved drugs (NMEs) (2010-2016) 356 FDA approved drugs (NMEs) (2010 to 2019)	**NIH funding contributed to every one of the NMEs** approved from 2010–2016 and was focused primarily on the drug targets rather than on the NMEs themselves. There were 84 first-in-class products approved in this interval, associated with >$64 bil of NIH-funded projects. These data suggest that public-sector investment in research for each **first-in-class drug is as high as $839 mil**, with 89% of this cost associated with target research and 11% of the cost associated with the first-in-class compound or follow-on compounds. 20% of the NIH budget 2000–2016 contributed directly or indirectly to NMEs (approved 2010–2016). In 356 FDA approved drugs (2010 -2019), the **NIH spent $1.44 bil per approval** on basic or applied research for products with novel targets or **$599 mil per approval considering applications of basic research to multiple products.** Spending from the NIH was not less than industry spending, with full costs of these investments calculated with comparable accounting.	Analysis of: FDA Database: for NME and information on molecular targets Therapeutic Target Db (TTD) Citation data. NIH RePORTER:NIH funds per drug and per target.	Basic research support on biological targets Applied research on NMEs
Nayak et al 2019 [6] Nayak et al 2021 [16]	248 FDA approved drugs (NMEs) (2008-2017) 69 FDA FDA approved drugs (biological drugs only) (2008-2017)	The review of the patents associated with new drugs indicates that publicly supported research had a major role in the **late stage development** of **at least one in four new drugs**, either through direct funding of late stage research or through **spin-off companies** created from public sector research institutions. 19% of drug approvals were associated publicly supported R&D; 6% originated in companies spin-offs out from publicly supported research programmes. 68% expedited FDA approval of drug approvals were associated publicly supported R&D v 47%; 45% designated first-in-class v 26%: indicating therapeutic importance. **42%** of FDA approved **biological drugs had received financial support from public sector institutions or their spin-offs** for late-stage development support	Analysis of: FDA Database: for NME and information on approval pathway (priority review, standard review, etc.). FDA Orange Book: Identification of patents from government or academic institutions. Merck Index: assignment of originator. AdisInsight: for drug monographs on preclinical and clinical development, assignment of originator. Press releases, News, etc. Technology Transfer Websites, Start-up Spin-out/offs Citation data. SEC filings.	Basic research support Patents from public institutions Spin-outs/offs Licensing/ technology transfers Late stage development research support
Drug case studies (and of "other technologies")				
Global Justice Now 2017 [28]	Alemtuzumab/ Lemtrada® Adalimumab/ Humira® Infliximab/Remicade®	2/3 of all upfront R&D expenditures; 1/3 of all medicines originate in public sector research institutions	Estimations based on drug histories	Basic research support Licensing, acquisitions

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Roy 2017 [30]	Sofosbuvir/ Sovaldi®	Public funding had a key role in developing Sofosbuvir-based medicines, approved in late 2013. Roy 2017 showcases the **economic process (financialization) of buying academic knowledge and developing it** with private equity resources.	Detailed analyses of development history: Citation data. Legal data: Lexis Nexis Press releases, News: FiercePharma, FierceBiotech, STAT Health NIH RePORTER: NIH funds SEC-filings US Senate Finance Committee documents	Basic research support Applied research support Spin-outs/offs Licensing, acquisitions
Schipper et al 2019 [34]	Acalabrutinib/ Calquence® ATIR101 Pembrolizumab/ Keytruda® Lutetium (177Lu)-Oxodotreotid/ Lutathera®	The case study of Canquence shows the important role public funding plays in the start-up phase of a young biotech company. The **funding of infrastructure** by regional funders, the Ministry of Economic Affairs, and the Municipality, along with public financing through the **innovation credit**, and money from capital investors from the US, all played a vital role in the important **start-up phase of the company**. ATIR101 was developed by Screentec, a spin-off from the Leiden Academic Centre for Drug Research, later renamed to Kiadis. Like many Dutch start-up companies, benefited over the years from public and private investments. From 2001 – 2012, Kiadis used **public funds to help cover R&D costs**. According to Kiadis, the government **innovation credit** was used to help develop ATIR101222. Other funds used to develop ATIR101 came from financing rounds which included contributions from **government-banked investors** (LSP II B.V., Medsciences and the NOM). **Basic research** and **translational research** (known as pre-IND research) for 'immune checkpoint therapy' took place over many years at **publicly funded universities, at the Dutch Cancer Institute**, in the **Dutch Biotech company Organon**, the **Hubrecht Institute**, the US-based **Dana Farber Institut**e and the **Radboud University in Nijmegen**, among others. More than half of the Keytruda clinical trials in the US (69 per cent) and WHO (62 per cent) registries involve non-commercial funders initiating the trial, though this claim is refuted by MSD (MSD states that it has paid, or provided funding, e.g. MSD supplied the drugs for trials sponsored by public institutions). The drug's initial **discovery and its development** over many years started **at Erasmus MC hospital and Rotterdam Erasmus MC**. 2001, in **spin-out** from Rotterdam Erasmus MC was founded, biotech company **BioSynthema**, when it was awarded orphan designation	Detailed analyses of development histories: Dutch biomedical R&D institutions Dutch Innovation support EC-Funds: IMI, H2020 Dutch tax incentives Dutch public venture capital funds Dutch support to Biotech start-ups Dutch public venture funds.	Basic and pre-clinical research support Translational research support Late stage development (clinical trials) Financial support to spin-out/offs Provision of facilities/ infastructure Venture capital from public funds Public/private funds for early stage support to start-ups

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		status In September 2011, BioSynthema was transfered to Advanced Accelerator Applications, (**AAA),** which was acquired by **Novartis** in 2017.		
Schmidt et al 2020 [29] Schmidt et al 2021 [4] Schmidt et al. 2022 [3]	Nusinersen/ Spinraza®, Cerliponase alfa/ Brineura® Nitisinon/ Orfadin® HepC vaccine Olaparib/ Lynparza®	**Public/philanthropic contributions** to product-related research ranged between approximately € 20 mil (Spinraza®) and € 31 mil (Brineura®) Basic and translational research for SMA totalled € 165 mil. **Public and charitable research funding plays an essential role,** not just in **early stage basic research, but also in the late-stage clinical development** of products prior to market authorisation. In addition, it provides risk capital for failed products. **12.3% of all EC FP7-Health awards** 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. The hepatitis C vaccine received total EC funding of €13,183,813; total public and charitable research funding for this product development was estimated at € 77,060,102, however the industry sponsor did not consider further development viable; this now represents **public risk investment.** EC funding for the late-stage development and trials of Orfadin® for alkaptonuria formed the basis for market authorisation. **> 90% of pre-clinical projects received public or philanthropic funding.** public or philanthropic funding was declared by **23% of clinical trials**. Using information reported in the publications, £128 mil of public and philanthropic funding were identified. Hoewever, The Institute of Cancer Research (ICR) reported receiving 38 funding awards to support olaparib work for BRCA-mutant breast cancer totalling over £400 mil.	Detailed analyses of development histories: Therapeutic Target Db (TTD). FDA Orange Book: Identification of patents from government or academic institutions. Citation data. NIH RePORTER:NIH funds National research Funds: CIHR/ CA, NIGMS & NINDS/ US, BMBF/ GE, Charities, etc. SEC-filings Additional in [4] EC-funds: FP 7 Additional in [3] Request to ICR vis "freedom of information act"	Basic research support Applied research support Support for product development
Gotham et al 2020 [26] Gotham et al 2021 [27]	Bedaquinile/ Sirturo® GeneXpert molecular diagnostic technology	Public contributions through **clinical trials** funding were estimated at US$109–252 mil, tax credits at US$22–36 mil, tax deductions at US$8–27 mil, administration of a donation programme at US$5 mil, PRV revenues at US$300–400 mil. **Total public investments were US$455–747 mil and originator investments were US$90–240 mil** (if capitalized and risk-adjusted, US$647–1,201 mil and US$292–772 mil, respectively). GeneXpert diagnostic platform is an automated molecular diagnostic device that performs sample preparation and pathogen detection within a single cartridge-based assay. Due to these characteristics, the	Detailed analyses of funding and estimations: Clinical Trials: ClinicalTrials.gov Db Requests to study leads Request to MAH Orphan drug incentives: ODTC Donation programmes RWE-data collections Additional in [27]: SME-grants: Springboard grants	Late stage development research support SME-grants Priority Review Voucher Tax credits and deductions RWE (cohort studies) Technical assistance for registration, guidelines

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		platform is now widely used in low- and middle-income countries for diagnosis of diseases such as TB and HIV. Assays for SARSCoV-2 are also being rolled out. **Total public investments in the development of the GeneXpert technology were estimated to be $252 mil**, including >$11 mil in funding for work in public laboratories leading to the first commercial product, $56 mil in grants from NIH, $73 mil from other US government departments, $67 mil in R&D tax credits, $38 mil in funding from non-profit and philanthropic organizations, and $9.6 mil in small business 'springboard' grants.		
Barenie et al 2021 [152] Barenie et al 2021 [20] Barenie et al. 2021 [18]	Sofosbuvir/ Sovaldi® Pregabalin/ Lyrica® Buprenorphine/ Subutex®	29 research awards were identified that were directly (US$7.7 mil) and 110 that were indirectly (US$53.2 mil) related made to major academic institutions and companies engaged in the development of the drug. These findings indicate that public funding had a key role in developing sofosbuvir, with an **estimated US$60.9 mil provided in NIH funding**. Pregabalin was discovered largely on the basis of publicly funded research at Northwestern University; in 1990, it was licensed to Parke-Davis, which further developed it through its FDA approval in 2004. 6,438 core project awards and **37 NIH awards related to pregabalin's development were identified: 9 awards through 1990 ($3.3 mil) and 28 from 1991 through 2004 ($10.5 mil).** Over the course of nearly four decades, the active ingredient in buprenorphine was synthesized by a pharmaceutical manufacturer, but it was developed for opioid use disorder (OUD) primarily by investigators in government and academic centers, including a formal government-industry partnership for commercialization. 40 "highly related" ($39.9 mil) and 20 were "possibly related" ($22.4 mil) grants were identified. An **estimated $62.3 mil in NIH awards** to institutions and investigators **supported the development of buprenorphine as** a treatment for OUD.	Detailed analyses of development history and funding: FDA Orange Book: Identification of patents from government or academic institutions. Citation data. NIH RePORTER: NIH funds	Basic research support Applied research support Support for product development Licensing, acquisitions
Newham/Vokinger 2022 [22] Vokinger et al 2023 [23]	5 CAR-T cell therapies Voretigene neparvovec/ Luxturna®,	Paths of development from Phase 1 to Phase 3: research in academic settings to spin-offs or small biotech companies to late-stage acquisitions by large pharma companies. Same as above: pathways from academic settings to spin-offs or small biotech companies to late-stage acquisitions by large pharma companies.	Rough analyses of development histories Additional in [23]: Acquisition costs and payment arrangements	Ownership changes: Licensing, acquisitions and mergers

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	Onasemnogen-Abeparvovec/ Zolgensma®, Ciltacabtagene autoleucel/ Carvykti®			
Tessema et al. 2023 [21]	Tenofovirdisoproxil/ Truvada®	73 federal government awards to 11 researchers were identified as directly linked to the development and clinical testing of Truvada for prevention therapy, through which the **US government spent an estimated $143 mil**.	Detailed analyses of funding: FDA Database Citation data. NIH RePORTER: NIH funds	Basic research support Applied research support
Lalani et al 2023 [2]	Covid-19 vaccine mRNA	34 NIH funded research grants that were directly related to mRNA covid-19 vaccines were identified. These grants combined with other identified US **government grants and contracts totaled $31.9bil** (£26.3bil; €29.7bil), of which **$337m was invested pre-pandemic**. Pre-pandemic, the NIH invested $116m (35%) in basic and translational science related to mRNA vaccine technology, and the Biomedical Advanced Research and Development Authority (BARDA) ($148m; 44%) and the Department of Defense ($72m; 21%) invested in vaccine development. After the pandemic started, $29.2bil (92%) of US public funds purchased vaccines, $2.2bil (7%) **supported clinical trials, and $108m (<1%) supported manufacturing plus basic and translational science**.	Detailed analyses of funding: NIH RePORTER: NIH funds	Basic and translational science Late stage development and clinical trials Manufacturing

CAR-T - Chimeric antigen receptor T, FDA – Food and Drug Administration, NIH – National Institute of Health, NME – new molecular entity, PrEP -pre-expositions prophylaxis; R&D research and development, SMA - spinal muscular atrophy, TPP1 - tripeptidyl peptidase 1

Table A- 2: National R&D Funding institutions in Europe

Country	Funding agency	Website	Documents on funding amount	Notes
Austria	Austrian Science Fund (FWF)	https://www.fwf.ac.at/de/	FWF-Dashboard http://dashboard.fwf.ac.at/de/ 2021: Human Medicine, Health Sciences 49.072.293€ (grant amount)	Best database in terms of usability, filtering, etc.
Belgium	Research Foundation Flanders (FWO)	https://www.fwo.be/en/	Granted research projects, documents: https://www.fwo.be/en/news/results/research-projects-and-research-grants/ Database of financed research (no costs): https://www.fwo.be/en/financed-research/database-financed-research/	No filtering and total costs
	Fund for Scientific Research (FNRS)	https://www.frs-fnrs.be/en/	Annual report 2021: https://www.frs-fnrs.be/docs/RapportAnnuel_2021.pdf Public grants (total): 197.743.986€ (S. 14)	Documents in French only
Bulgaria	Bulgarian Academy of Science	https://www.bas.bg/?lang=en	n.a.	No relevant tasks identified

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Croatia	Croatian Science Foundation (HRZZ)	https://hrzz.hr/en/	https://hrzz.hr/en/funding-programmes/national-research-programmes/ Project database with complete dataset of funded projects: https://hrzz.hr/en/funding/project-database/ Annual report 2021: https://hrzz.hr/wp-content/uploads/godisnje-izvjesce-HRZZ-2021-ENG-web.pdf	
Cyprus	The Research Promotion Foundation (RPF)	https://www.research.org.cy/	Statistical data for RTDI: https://www.research.org.cy/en/strategic-planning/studies-and-statistical-data/#toggle-id-1-closed	Greek only
Czech Republic	Czech Health Research Council	https://www.azvcr.cz/	n.a.	Czech only
Denmark	Innovation Fund	https://innovationsfonden.dk/en	Investment overview (database): https://innovationsfonden.dk/en/investments/investments-overview Annual reports: https://innovationsfonden.dk/da/publikationer	Publications in Danish only
Estonia	Estonian Research Council (ETAg)	https://etag.ee/en/	Statistics on R&D funding in Estonia: https://www.etag.ee/en/activities/analysis/statistics-rd-funding-estonia/ (€ 211 Mil from public sector)	not specified by research area
France	Institut National de la Santé et de la Recherche Médicale (INSERM)	https://www.inserm.fr/	n.a.	no relevant tasks identified
	French National Research Agency (ANR)	https://anr.fr/en/	Database for funded projects: https://scanr.enseignementsup-recherche.gouv.fr/; Financed regions (with numbers): https://anr.fr/en/funded-projects-and-impact/data-analyses-and-impact-studies/	French only, not specified by research area
	ECRIN (European Clinical Research Infrastructure Network)	https://ecrin.org/	Funding information (combination of funding): https://ecrin.org/funding-multinational-clinical-trials Annual report 2021: https://ecrin.org/sites/default/files/2022-08/Ecrin-Annual_Report_2021_web.pdf 2021: ECRIN provided support to 39 clinical trials in different phases;	
Finland	The Academy of Finland (AKA)	https://www.aka.fi/en/	https://www.aka.fi/en/about-us/what-we-do/what-we-are/who-gets-the-funding/; 2021: €490 mil (total)	not specified by research area
Germany	Deutsche Forschungsgemeinschaft (DFG)	https://www.dfg.de/	Project database (no costs): https://gepris.dfg.de/gepris/programmlisten?language=de#PROGRAMM=Forschungsgruppen&VARIANTE=Klinische%20Forschungsgruppen Annual Report 2021: https://www.dfg.de/download/pdf/dfg_im_profil/geschaeftsstelle/publikationen/dfg_jb2021.pdf S.221: (2021: € 1322,6 mil. for Lifesciences)	
Greece	General Secretariat for Research and Technology (GSRT)	http://www.gsrt.gr/	https://gsri.gov.gr/en/programming-periods/	No details
	National Public Health Organization (NPHO)	https://eody.gov.gr/en/	n.a.	No relevant tasks identified
Hungary	Hungarian Academy of Science (HAS)	https://mta.hu/english	n.a.	No information found
	National Research, Development and Innovation Office (NKFIH)	https://nkfih.gov.hu/about-the-office	NRDI Fund: https://nkfih.gov.hu/english-2017/rdi-policy/management-of-the-nrdi; The NRDI Fund's 2021 programme strategy already included calls for proposals with a total budget of more than HUF 182 bil.	

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Ireland	Science Foundation Ireland (SFI)	https://www.sfi.ie/	Annual report 2021: https://www.sfi.ie/annual-report-2021/SFI-Annual-Report-2021.pdf	
	Health Research Board (HRB)	https://www.hrb.ie/	HRB is a State Agency under the DoH and supports/funds health and social care research and provide evidence to inform policy and practice. Annual budget of €45 mil, and investment portfolio of approximately €200 mil.	
Italy	National Institute of Health (ISS)	https://www.iss.it/web/iss-en	n.a.	No relevant tasks identified
	Fondazione Regionale per la Ricerca Biomedica (FRRB)	https://www.frrb.it/	Funded projects: 83; https://www.frrb.it/en/funded-projects	No reports, only individual projects with costs
Latvia	State Education Development Agency (VIAA)	https://www.viaa.gov.lv/	n.a.	No relevant tasks identified
	Latvian Academy of Sciences (LAS)	https://www.lza.lv/en/home	n.a.	No relevant tasks identified
Lithuania	Research Council of Lithuania (LSC/LMT/RCL)	https://www.lmt.lt/indexe.php	National programmes: https://www.lmt.lt/en/research-funding/national-programmes/2899	No costs displayed
Luxembourg	National Research Fund (FNR)	https://www.fnr.lu/	Annual reports: https://www.fnr.lu/news/fnr-publications/ Project finder: https://www.fnr.lu/project-finder/advanced-search/#results	French only
Malta	Malta Council for Science and Technology	https://mcst.gov.mt/	Funding: https://mcst.gov.mt/funding-opportunities/	No documents found
Netherlands	Netherlands Organization for Health Research and Development (ZonMw)	https://www.zonmw.nl/en/	n.a.	No documents found
	Netherlands Organisation for Scientific Research (NWO)	https://www.nwo.nl/en	Research programm database with costs and duration: https://www.nwo.nl/en/researchprogrammes Annual reports (no expenditures): https://www.nwo.nl/en/annual-report	No total costs
Norway	Norwegian Health Association (NHA)	https://folkehelseforeningen.no/	n.a.	Norwegian only
	The Research Council of Norway (RCN)	https://www.forskningsradet.no/en/	Investment plan for life sciences: https://www.forskningsradet.no/en/about-the-research-council/Portfolios/life-science/investment-plan-for-life-science/ The Research Council's Life Science portfolio is broad and encompasses many disciplines and topics that in 2022 have a value of approximately NOK 3.7 bil, including EU funding (excluding basic grants).	Documents only in norwegian
Poland	National Centre for Research and Development (NCBR)	https://www.gov.pl/web/ncbr-en	National programmes: https://www.gov.pl/web/ncbr-en/national-programmes; Annual report: https://www.gov.pl/attachment/567ea104-e7ed-4e8e-af29-ba5eb1fdd3a7 (National programmes: 411 400 000 PLN)	
	National Science Center (NCN)	https://www.ncn.gov.pl/en	Funded Life sciences projects (NZ): https://www.ncn.gov.pl/en/przyklady-projektow?field_konkurs_typ_target_id=All&field_projekt_grupa_nauk_target_id=471	No reports found
Portugal	Foundation for Science and Technology (FCT)	https://www.fct.pt/en/	Management documents: https://www.fct.pt/en/sobre/documentos-de-gestao/	Portuguese only
	Agency for Clinical Research and Biomedical Innovation (AICIB)	https://aicib.pt/	n.a.	No reports found
Romania	Autoritatea Naţională pentru Cercetare Ştiinţifică şi Inovare (ANCSI)	https://old.research.gov.ro/	Budget reports: https://old.research.gov.ro/ro/articol/2427/sistemul-de-cercetare-bugetul-cercetarii-executie	Romanian only

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	Executive Agency for Higher Education, Research, Development and Innovation Funding (UEFISCDI)	https://uefiscdi.gov.ro/	Activity reports: https://uefiscdi.gov.ro/rapoarte-de-activitate	Romanian only
Slovakia	Slovak Academy of Sciences (SAS)	https://www.sav.sk/?lang=en	Annual report: https://www.sav.sk/?lang=en&doc=docs-annual-sas 2021: Life, Chemical, Medical, and Environmental Sciences: 2,251,762€	
Slovenia	Slovenian Research Agency	http://www.arrs.si/en/opis-logotipa.asp	Facts and figures: https://www.arrs.si/en/analize/obseg01/ Annual report 2021: https://www.arrs.si/en/gradivo/dokum/inc/22/LP-ARRS-2021-ENG.pdf Sicris database of projects: http://www.sicris.si/public/jqm/cris.aspx?lang=eng&opdescr=prgSearch&opt=2&subopt=5 2021: Medical sciences (research programmes): 7,316,615€ (of 49,001,863€ in total)	
Spain	National Institute of Health Carlos III (ISCIII)	https://eng.isciii.es/	Finance reports https://eng.isciii.es/eng.isciii.es/InformacionCiudadanos/PortalTransparencia/IEPE/Paginas/Contratos.html	Spanish only
	The Foundation for the support of the Applied Scientific Research and Technology in Asturias (FICYT)	https://www.ficyt.es/index_uk.asp	Finance reports https://www.ficyt.es/portaltransp/Cuentas.asp	Spanish only
	FUNDACION PUBLICA ANDALUZA PROGRESO Y SALUD M.P. (FPS)	https://www.sspa.juntadeandalucia.es/fundacionprogresoysalud/es/	Finance reports https://www.sspa.juntadeandalucia.es/fundacionprogresoysalud/transparencia/pagina.php?secc=5&pag=documentos	Spanish only
Sweden	Swedish Research Council for Health, Working Life and Welfare (Forte)	https://forte.se/en/	Swecris – search for Swedish research projects: https://www.vr.se/english/swecris.html#/?funder=202100-5208&scb=3 2022: 1,6 bil SEK funding from VR in medical and health sciences Database for Swedish research projects with costs and durations	
	The Swedish Research Council (VR)	https://www.vr.se/english.html	Swedish Research Council, Report 2021: https://www.vr.se/download/18.7c48537717dc24f2564268cf/1643114120341/The_Swedish_Research_Barometer_2021_tg.pdf; https://www.vr.se/english/analysis/swedish-research-in-figures.html; In total, the VR allocates almost 8 bil SEK p.a. to research and research infrastructures.	No annual reports
UK	National Institute for Health Research (NIHR)	https://www.nihr.ac.uk/	Annual report 2022: https://www.nihr.ac.uk/documents/about-us/our-contribution-to-research/research-performance/NIHR-annual-report-21-22.pdf S. 28 - 31 (Research programmes total: £401.4 mil)	no filtering in terms of scientific field
	The Medical Research Council (MRC) of the United Kingdom	https://www.ukri.org/councils/mrc/	https://public.tableau.com/app/profile/uk.research.and.innovation.ukri./viz/UKRICompetitiveFundingDecisions2020-21/ Competitive Funding Decisions : https://www.ukri.org/what-we-offer/what-we-have-funded/mrc/; £289 mil funded (Last Update 10/2022)	no filtering in terms of scientific field
	The Chief Scientist Office (CSO) of the Scottish Government Health and Social Care Directorates	https://www.cso.scot.nhs.uk/	Funded research programmes (with costs): https://www.cso.scot.nhs.uk/funded-research/	No total costs, no filtering in terms of scientific field

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Table A- 3: National (Biotechnology, LifeScience, Health) Innovation Support for Spin-Outs/ Offs and Start-ups

Country	Funding agency	Website
Austria	Austrian Business Agency (ABA)	https://aba.gv.at/
	aws Life Science Austria (LISA)	https://www.aws.at/aws-lisa-life-science-austria/
	aws Best of Biotech	https://www.bestofbiotech.at/
Belgium	Flanders Innovation & Entrepreneurship (VLAIO)	https://www.vlaio.be/en
	Wallonia Export-Investment Agency (AWEX)	http://www.investinwallonia.be/home
Bulgaria	Bulgarian Small and Medium Enterprises Promotion Agency (BSMEPA)	https://egov.bg/wps/portal/en/egov/institutions/agencies/ag0032
	Ministry of Economy of the Republic of Bulgaria	https://www.mi.government.bg/en/
Croatia	Croatian Agency for SMEs, Innovation, and Investments (HAMAG-BICRO)	https://en.hamagbicro.hr
	Ministry of Economy and Sustainable Development	https://mingor.gov.hr
Cyprus	Research and Innovation Foundation (RIF)	https://www.research.org.cy/en/
	Deputy Ministry of Research, Innovation and Digital Policy	https://www.dmrid.gov.cy/dmrid/research.nsf/home_en/home_en?opendocument
Czech Republic	Technology Agency of the Czech Republic (TA CR)	https://www.tacr.cz/en/technology-agency-of-the-czech-republic/
	CzechInvest	https://www.czechinvest.org
Denmark	Danish Growth Fund (Vækstfonden)	https://www.eifo.dk/en/
	Scienceventures	https://scienceventures.dk/en/about-us/
Estonia	Enterprise Estonia (EAS)	https://eas.ee/en/#
France	Bpifrance	https://www.bpifrance.com
Finland	Business Finland	https://www.businessfinland.fi/en/for-finnish-customers/home
	Finnish Funding Agency for Technology and Innovation (Tekes)	https://helsinkibusinesshub.fi/tekes-the-finnish-funding-agency-for-technology-and-innovation/
Germany	High-Tech Gründerfonds (HTGF)	https://www.htgf.de/de/
	Fraunhofer Society (Fraunhofer-Gesellschaft)	https://www.fraunhofer.de
	Federal Ministry of Education and Research (BMBF)	https://www.bmbf.de/bmbf/en/home/home_node.html
Greece	National Documentation Centre (EKT)	https://www.ekt.gr/en/index
Hungary	Hungarian Investment Promotion Agency (HIPA)	https://hipa.hu
Ireland	Enterprise Ireland	https://www.enterprise-ireland.com/en/
Italy	Invitalia	https://www.invitalia.it
	Italian Ministry of Education, Universities and Research (MIUR)	https://www.miur.gov.it/english-corner
Latvia	Investment and Development Agency of Latvia (LIAA)	https://www.liaa.gov.lv/en?utm_source=https%3A%2F%2Fwww.google.com%2F
	Latvian Council of Science (LCS)	https://www.lzp.gov.lv/en/
Lithuania	Agency for Science, Innovation, and Technology (MITA)	https://mita.lrv.lt/en/
	Ministry of Economy and Innovation	https://eimin.lrv.lt/en/
Luxembourg	Luxembourg Ministry of the Economy	https://meco.gouvernement.lu/de.html
Malta	Malta Enterprise	https://www.maltaenterprise.com
Netherlands	Health~Holland	https://www.health-holland.com
	Netherlands Enterprise Agency (Rijksdienst voor Ondernemend Nederland, RVO)	https://english.rvo.nl
Norway	Innovation Norway	https://en.innovasjonnorge.no

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Country	Funding agency	Website
Poland	Polish Agency for Enterprise Development (PARP)	https://en.parp.gov.pl
Portugal	Portugal Ventures	https://www.portugalventures.pt/en/
Romania	Romanian Ministry of Research, Innovation and Digitalization (MIRID)	https://www.mcid.gov.ro
Slovakia	Slovak Agency for Research and Development (APVV)	https://www.apvv.sk/?lang=en
	Slovak Investment and Trade Development Agency (SARIO)	https://www.sario.sk/en
Slovenia	SPIRIT Slovenia, Public Agency	https://www.spiritslovenia.si
	Ministry of Economic Development and Technology	https://www.gov.si/en/state-authorities/ministries/ministry-of-the-economy-tourism-and-sport/about-the-ministry-of-economy-tourism-and-sport/industry-entrepreneurship-and-internationalisation-directorate/
Spain	CDTI (Centro para el Desarrollo Tecnológico Industrial)	https://www.cdti.es
	Spanish Ministry of Science and Innovation (Ministerio de Ciencia e Innovación)	https://www.ciencia.gob.es/en/Ministerio/Mision-y-organizacion.html
Sweden	Vinnova	https://www.vinnova.se/en/
UK	Innovate UK (part of UK Research and Innovation)	https://www.ukri.org/councils/innovate-uk/
	Biotechnology and Biological Sciences Research Council (BBSRC)	https://www.ukri.org/councils/bbsrc/

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Table A- 4: EU Contribution and total project costs in FP7 Health [44]

Pillar/activity/area	Total number of projects funded	Total EU contribution, € million	Average EU contribution per project, € million	Total project costs , € million	EU contribution as % of total costs
1.Biotechnology, generic tools and medical technologies for human health	**174**	**1 006**	**5.8**	**1 360**	**74%**
1.1. High-throughput research	28	158	5.6	213	74%
1.2. Detection, diagnosis and monitoring	55	272	5.0	369	74%
1.3. Predicting suitability, safety and efficacy of therapies	20	118	5.9	162	73%
1.4. Innovative therapeutic approaches and interventions	71	458	6.4	616	74%
2.Translating research for human health	**553**	**3 005**	**5.4**	**4 060**	**74%**
2.1. Integrating biological data and processes: large-scale data gathering, systems biology	86	648	7.5	880	74%
2.2. Research on the brain and related diseases, human development and ageing	89	518	5.8	711	73%
2.3. Translational research in major infectious diseases: to confront major threats to public health	162	764	4.7	1 030	74%
2.4. Translational research in other major diseases	216	1 074	5.0	1 440	75%
3.Optimising delivery of health care to European citizens	**139**	**399**	**2.9**	**509**	**78%**
3.1. Translating the results of clinical research outcome into clinical practice	34	107	3.1	138	77%
3.2. Quality, efficiency and solidarity of healthcare systems	36	99	2.8	128	78%
3.3. Enhanced health promotion and disease prevention	25	82	3.3	105	78%
3.4. Horizontal coordination and support actions across 'Optimising the delivery of health care to European citizens'	35	86	2.5	106	81%
3.5. Specific international cooperation actions for health system research	9	25	2.8	31	79%
4. Other actions across the Health theme	**121**	**289**	**2.4**	**393**	**73%**
4.1.Coordination and support actions across the theme	54	47	0.9	55	85%
4.2. Responding to EU policy needs	54	193	3.6	269	72%
4.3. Specific International Cooperation Actions (SICA)	13	49	3.8	69	71%
Other projects*	21	94	4.5	137	69%
IMI	**49**	**762**	**15.6**	**1 766**	**43%**
Total (with IMI)	**1 008 (1 057)**	**4 792 (5 554)**	**4.8 (5.3)**	**6 458 (8 224)**	**74% (68%)**

Source: analysis of CORDA data.

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Table A- 5: EU Contribution to Patents (FP7 Health) -Number of patents by pillar and corresponding sub-activity [44]

Pillar	Sub-activity	FP7 Health related patents only		Whole patent 'family'	
		No. of patents	Percentage share	No. of patents	Percentage share
1. Biotechnology, generic tools and medical technologies for human health		**107**	**45.73%**	**449**	**48.70%**
1.1 High-throughput research		45	19.23%	198	21.48%
1.2 Detection, diagnosis and monitoring		36	15.38%	142	15.40%
1.3 Predicting suitability, safety and efficacy of therapies		2	0.85%	5	0.54%
1.4 Innovative therapeutic approaches and interventions		24	10.26%	104	11.28%
2. Translating research for human health		**126**	**53.85%**	**469**	**50.87%**
2.1 Integrating biological data and processes: large-scale data gathering, systems biology		29	12.39%	129	13.99%
2.2 Research on the brain and related diseases, human development and ageing		18	7.69%	77	8.35%
2.3 Translational research in major infectious diseases: to confront major threats to public health		17	7.26%	55	5.97%
2.4 Translational research in other major diseases		62	26.50%	208	22.56%
4. Other actions across the Health theme		**1**	**0.43%**	**4**	**0.43%**
4.2 Responding to EU policy needs		1	0.43%	4	0.43%
Total		**234**	**100%**	**922**	**100%**
Source: patent analysis					

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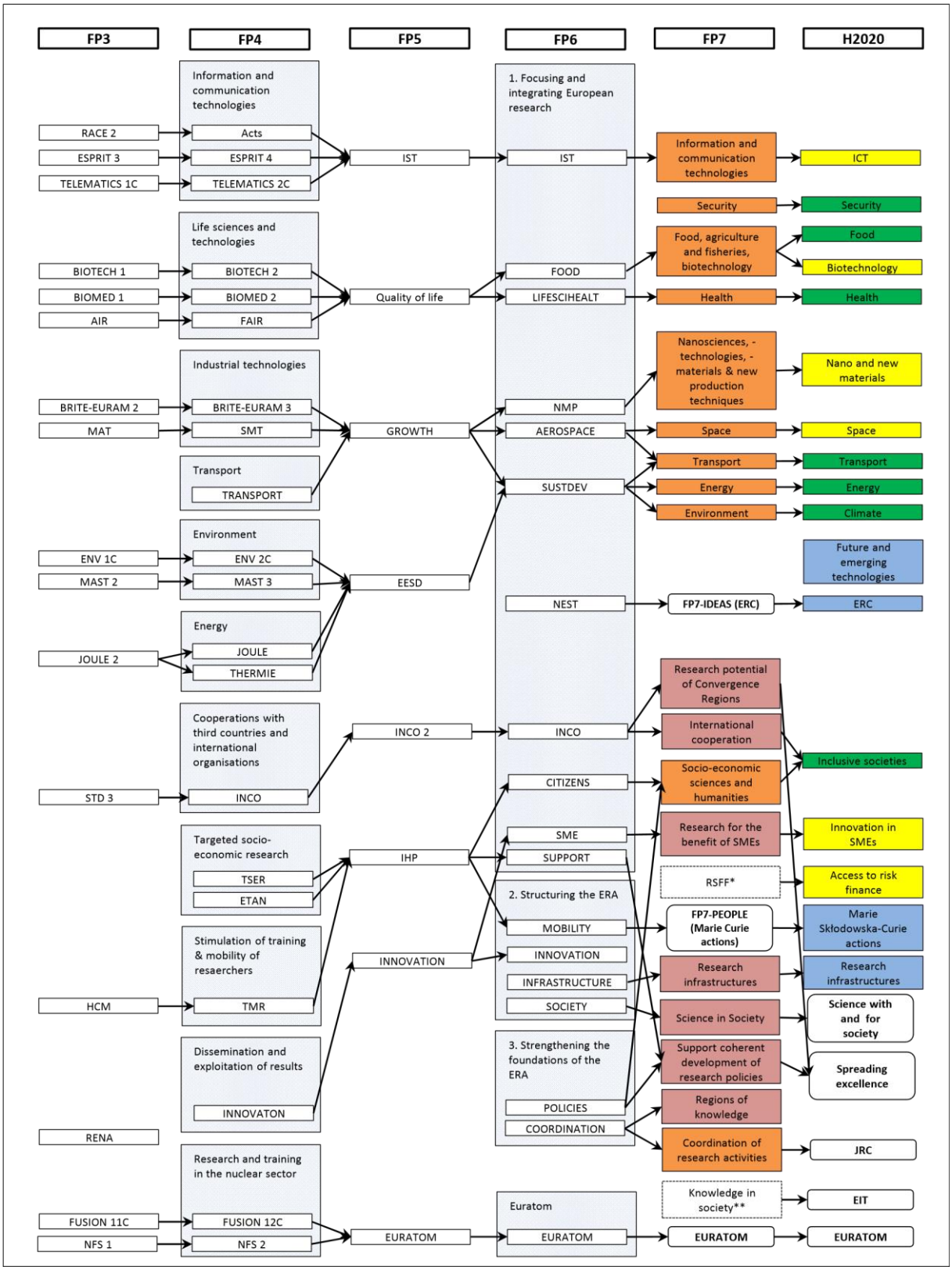
Table A- 6: Overview of EC-R&D Programmes [153]



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Appendix B

Public contributions to drug development (examples: Orphan Drugs & Antibiotics)

- B-1: Characteristics of Funded FDA Grants (2007—2011) for late stage clinical trials that Led to FDA Approvals
- B-2: FDA Research Grants for Product Development (Phase 1-3 trials)
- B-3: EC-Funds within the European Joint Programme on Rare Diseases (2007-2022)
- B-4: EC-funded projects on rare diseases with clinical trials
- B-5: Antibiotics currently in development or recently approved
- B-6: Actors in R&D of antibiotics
- B-7: EC-funded projects on antimicrobial resistance, drug development and clinical trials

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Table B- 1: Characteristics of Funded FDA Grants (2007—2011) for late stage clinical trials that Led to FDA Approvals, (N = 9) [54]

Year Approved (First Funded)	Generic (Trade Name) Manufacturer	Disease (Therapeutic Area)	Study Phase at Funding	PI Institution	Single or Multiple Study Sites
2012 (2007)	Ivacaftor (Kalydeco®), Vertex Pharmaceuticals	Cystic Fibrosis Subjects with G551D (Pulmonary)	Phase 2	Industry	Multiple- 8 sites
2013 (2008)	Topical nitrogen mustard, Mechlorethamine (Valchlor®), Helsinn Birex Pharma Ltd	Mycosis Fungoides (Oncology/Hematology)	Phase 2	Academic	Multiple- 2 sites
2015 (2011)	Asfotase alfa (Strensiq®), Alexion Pharma	Hypophosphatasia (Endocrinology)	Phase 2	Industry	Multiple- 7 sites
2015 (2008)	Parthyroid Hormone (Natpara®), Takeda Pharma	Hypoparathyroidism (Endocrinology)	Phase 3	Academic	Single
2015 (2007)	Sirolimus (Rapamune®), Wyeth	Lymphangioleiomyomatosis (Pulmonary)	Phase 3	Academic	Multiple- 8 sites
2016 (2011)	Cheatham Platinum Stent System™ NuMED, Inc.	Aortic Wall Injury Associated with Aortic Coarctation (Cardiovascular)	Phase 3	Academic	Multiple- 19 sites
2017 (2009)	EXCOR®Pediatric Ventricular Assist Device Berlin Heart GmbH	Bridge-to-Heart Transplantation in Children (Cardiovascular)	Phase 2	Academic	Multiple- 13 sites
2018 (2008)	Fish Oil Triglycerides (Omegaven®), FRESENIUS KABI	Reversal of Parenteral Nutrition-Associated Cholestasis (Gastrointestinal)	Phase 2	Academic	Single
2019 (2008)	Tafamidis meglumine/ Tafamidis free acid (Vyndaqel®/Vyndamax®), Pfizer	Familial Amyloid Polyneuropathy (Neurology)	Phase 3	Industry	Multiple- 8 sites

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Table B- 2: FDA Research Grants for Product Development (Phase 1-3 trials) (2021) [154]

Who	What	How much
Armgo Pharma, INC. (Ardsley, New York)	Phase 2 study of S48168 (ARM210) for the treatment of catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT1)	$1 mil over 2 years
Boston Children's Hospital (Boston, Massachusetts);	Phase 3 study of RELiZORB for the treatment of short bowel syndrome	$2.7 mil over 4 years
Castle Creek Biosciences, LLC (Exton, Pennsylvania)	Phase 3 study of FCX-007 (genetically modified autologous human dermal fibroblasts) for the treatment of recessive dystrophic epidermolysis bullosa	$1.8 mil over 4 years
Cincinnati Children's Hospital Medical Center (Cincinnati, Ohio)	Phase 2b study of sirolimus for the prevention of epilepsy in patients with tuberous sclerosis complex	$5 mil over 4 years
Cincinnati Children's Hospital Medical Center;	Phase 2 study of abatacept for the treatment of common variable immunodeficiency with interstitial lung disease (ABCVILD);	$3.1 mil over 4 years
Duke University (Durham, North Carolina)	Phase 2 study of peptide vaccine targeting CMV antigen for the treatment of newly diagnosed pediatric high-grade glioma and diffuse intrinsic pontine glioma and recurrent medulloblastoma	$1.8 mil over 4 years
Massachusetts General Hospital (Boston, Massachusetts)	Phase 2 study of oral cimetidine for the treatment of protoporphyrias	$1.6 mil over 4 years
Mayo Clinic Rochester (Rochester, Minnesota)	Phase 1 study of WSD0922-FU for the treatment of high-grade astrocytoma	$1 mil over 3 years
Mayo Clinic Rochester (Rochester, Minnesota)	Phase 2 study of intrathecally administered autologous mesenchymal stem cells for the treatment of multiple system atrophy	$3.2 mil over 4 years
Reveragen Biopharma, Inc.	Phase 2a study of vamorolone for the treatment of becker muscular dystrophy	$1.2 mil over 2 years
University of Florida (Gainesville, Florida)	Phase 2A trial of dichloroacetate for the treatment of glioblastoma multiforme	$2.5 mil over 4 years

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Table B- 3: EC-Funds within the European Joint Programme on Rare Diseases (EJP RD, https://www.ejprarediseases.org/) 2007-2022

Project Acronym	Title Link: https://www.ejprarediseases.org	Joint Transnational Call name	Year
COMPRare	Towards the most accurate diagnosis and monitoring of Complement-mediated rare kidney diseases	Development of new analytic tools and pathways to accelerate diagnosis and facilitate diagnostic monitoring of rare diseases	2022
UPS-NDDiag	Development of diagnostic solutions for neurodevelopmental disorders caused by ubiquitin-proteasome system dysfunction		2022
IMAGINER	Optical imaging as a diagnostic tool for monitoring brain function in X-linked rare disorders: from preclinical models to patients		2022
ProgerOmics	Identification of biomarkers to monitor the progression of Hutchinson-Gilford progeria syndrome		2022
PREDICT	Towards a PREcise DIagnosis in Ciliopathies		2022
EURONET- NF	European Network for improved molecular diagnostics of the Neurofibromatoses-schwannomatoses and related disorders		2022
GENOMIT	A multi-omics approach for diagnostics and monitoring of mitochondrial disorders		2022
Resolve 15q	Resolving complex outcomes in 15q13.3 copy number variants using emerging diagnostic and biomarker tools		2022
ODINO	Optimization of the diagnostic approach for inborn errors of immunity leading to hyper-inflammation		2022
PreDYT	PREdictive biomarkers in DYsTonia: defining the paradigm of monogenic dystonia to implement the diagnosis and prognosis of undiagnosed forms		2022
EUREKA	Bonding molecular genotyping and phenotyping to outcome measures in AL amyloidosis: A EUropean REgistry and sample sharing networK to promote the diagnosis and management of light chain Amyloidosis		2022
SPMH	Metabolic test in vivo for malignant hyperthermia		2022
SAPIENCE	Social and psychological long-term impact of NMDA receptor encephalitis	Social sciences and Humanities Research to improve health care implementation and everyday life of people living with a rare disease	2021
LIVES	Quality of life of patients living with vascular LIVEr diseaseS - Developing research on the social impact of rare diseases		2021
COCOS-IPF	Co-designing a Core Outcome Set for and with patients with Idiopathic Pulmonary Fibrosis (IPF)		2021
Q.RARE.LI	Improving health-related quality of life in patients with rare autoimmune liver diseases by structured peer-delivered support: a transnational effectiveness-implementation hybrid trial		2021
PAVE	Producing an Arthritis Value-Framework with Economic Evidence – Paving the Way for Rare Childhood Diseases		2021
BUILDCARE	Building Support for Children and Families Affected by Stroke		2021
GrowDMD	Growing into adulthood with Duchenne Muscular Dystrophy - comparing patient experiences and systems to optimize care		2021
BUR-EB e	Changes in the Socio-economic Burden of Epidermolysis Bullosa in Europ		2021
eCARE-22q11	Evaluating Parent Perceptions, Economic Burden, and the Impact of Online Coaching Interventions for Parents of Children Diagnosed with the 22q11 Deletion Syndrome		2021
NEUROREHAB	Impact of a neuro-cardiac rehabilitation programme on the quality of life of children, adolescents and young adults with rare congenital heart disease: the multicentre randomized controlled QUALI-NEUROREHAB trial		2021
PROFA	Patient-reported, health economic and psychosocial outcomes in Friedreich Ataxia		2021
SeeMyLife	Holistic mixed approaches to capture the real life of children with Rare Eye Diseases		2021
WilsonMed	Multimolecular targeting of copper overload in Wilson disease		2020
TREAT-SGS	Development and preclinical testing in human cell models and transgenic mice of a novel treatment for Schinzel-Giedion Syndrome		2020
CureMILS	A reprogramming-based strategy for drug repositioning in patients with mitochondrial DNA-associated Leigh syndrome		2020
TREATKCNQ	Targeted treatment for KCNQ related encephalopathies: retigabine analogues, repurposed drugs and allele specific knock down		2020
SCN1A-up!	Therapeutic strategies for Dravet syndrome: upregulation of endogenous SCN1A and modulation of remodeling		2020
CHARLIE	CHAnging Rare disorders of LysInE metabolism		2020
ProDGNE	Novel therapeutic approaches to target GNE Myopathy		2020
TreatRP	Translating cGMP analogues into a treatment for retinitis pigmentosa		2020

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MECPer-3D	Personalized MECP2 gene therapy using CRISPR/Cas9 technology coupled to AAV-mediated delivery in 3D cell culture and KI mice	Pre-Clinical Research to Develop Effective Therapies for Rare Diseases	2020
TC NER	Transcription stress Counteracted by Nutritional interventions of Exceptional importance for rare DNA Repair diseases		2020
TREAT-ARCA	Designing a toolbox of paradigmatic treatments for a targeted molecular medicine approach to autosomal-recessive ataxias		2020
ARMED	Antioxidant treatment as a novel therapeutic option for microvillus inclusion disease		2020
AAK-INSIGHT	Aniridia – Novel therapeutic tools to treat or prevent progressive cornea opacification		2020
DBAGenCure	Lentiviral-mediated gene therapy for Diamond Blackfan Anemia: Preclinical Safety and Efficacy Studies		2020
SILENCELQTS	SGK1 inhibition as a novel therapeutic approach in Long QT syndrome		2020
EpiThe4FSHD	Safety and efficacy of a possible epigenetic therapy for FSHD muscular dystrophy		2020
FANEDIT	Gene editing as a novel therapeutic strategy in Fanconi anemia		2020
GET-READY	Genetic therapy for EYS- and USH2A-associated retinal disease		2020
PREDACTING	Predicting the clinical outcome of non-muscle actinopathies	Research projects to accelerate diagnosis and/or explore disease progression and mechanisms of rare diseases	2019
FIGHT-CNNM2	For Improving diagnostics and Grasping the disease mechanisms of rare Hypomagnesemia in paTients with CNNM2 mutations		2019
MYOCITY	A multidimensional single-cell approach to understand muscle dystroph		2019
IDOLS-G	Improved diagnostic output in large sarcomeric genes		2019
EURDYSCOVER	Pathophysiology of dystonia - role of gene-environment interaction and common pathophysiological pathways		2019
GENOMIT	Mitochondrial Disorders: from a global registry to medical genomics, toward clinical trials		2019
LQTS-NEXT	To the NEXT level of risk prediction in patients with Long QT Syndrome		2019
ENISNIP	European Network on Inherited Sensory Neuropathies and Insensitivity to Pain		2019
PROSPAX	an integrated multimodal progression chart in spastic ataxias		2019
ASPECT-NMO	Measuring autoantigen-specific T cells as new diagnostic sensors and therapeutic targets in neuromyelitis optica		2019
FAIRVASC	FAIRVASC - building registry interoperability to inform clinical care		2019
NG4LEUKO	Exploring neuron-glia interactions in leukodystrophies using human iPSC-based models: implication for therapy		2019
PROGERIA	The rarest of the rare - exploring non-coding RNA in the disease pathogenesis of Hutchinson-Gilford progeria syndrome		2019
TARID	Thymic Abnormalities in Rare Immunological Diseases		2019
NSEURONET	European Network on Noonan syndrome and related disorders		2019
URGENT	Unveiling the Role of Glutamate in dopaminE traNspoTer deficiency syndrome		2019
SOLVE-RET	Solving missing heritability in inherited retinal diseases using integrated omics and gene editing in human cellular and animal models		2019
DEVDBA	Ontogeny as a critical determinant of DBA sensitivity in red blood cells		2019
ALEXANDER	The astrocyte nanofilament system in Alexander disease – from molecules to function, uncovering new leads for therapy		2019
RARE-ILD	Raising diagnostic accuracy and therapeutic perspectives in interstitial lung diseases		2019
RIBOEUROPE	The European Ribosomopathy Consortium		2019
PHYSPATH-KS	Understanding the pathophysiology of Keutel Syndrome: A path towards cure		2019
ReCognitiON	Recognition and Validation of Druggable Targets from the Response to Cognitive Behaviour Therapy in Myotonic Dystrophy type 1 patients	Research projects on hypothesis-driven use of multi-omic integrated	2018
INTEGRALS	INTEGRative multi-OMICs approaches on iPSC-derived 2D and 3D models to elucidate the role of immune and energy metabolism related genes/pathways in Amyotrophic Lateral Sclerosis		2018
MSA-omics	Multi-omics approach to predict therapeutic targets for multiple system atrophy		2018
IMPACT	Identification of converging Molecular Pathways Across Chromatinopathies as Targets for Therapy		2018
RAinRARE	Integrated analyses of retinoic acid signaling to understand and treat rare form of progressive motor impairment		2018
HETER-OMICS	Multi-OMICS interrogation of cerebral cortical malformations		2018
EUROGLYCAN	Towards a new era for the identification and characterisation of inborn errors of glycosylation		2018

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NARCOMICS	Deciphering the immunopathogenesis of type 1 nacolepsy with omics	approaches for discovery of diseases causes and/or functional validation in the context of rare diseases	2018
MAXOMOD	Multi-omic analysis of axono-synaptic degeneration in motoneuron disease		2018
LADOMICS	Multi-omics approaches for discovery of new disease mechanisms of LAD-I and LAD-III immunodeficiencies		2018
i-PAD	Integrative Multi-Omics Analysis of Primary Antibody Deficiency (PAD) Patients for Stratification		2018
REPETOMICS	Genomic Instability of Expanded Repeats in HD and ALS/FTD		2018
UltraAIE	Single cell-based ultra high-resolution characterization of intrathecal immunity in Autoimmune Encephalitis		2018
CureDravet	Curing Dravet Syndrome by Gene Therapy	Research projects for Innovative Therapeutic Approaches for Rare Diseases	2017
ERAAT	Enhancing Endoplasmic Reticulum Proteostasis to Rescue Alpha1 Antitrypsin Deficiency		2017
Cure-AID	IL-18 and MRP neutralization for the treatment of anti-IL-1-refractory autoinflammatory diseases		2017
SCA-CYP	Gene Therapy for Cerebellar Ataxias: restoring cholesterol metabolism by targeting brain cholesterol 24 hydroxylase (CYP46A1)		2017
EDSCIDPROG	Gene edited lymphoid progenitors for adoptive transfer as a treatment of primary immunodeficiency		2017
TREAT-HGPS	Exploring new therapeutic strategies in Hutchinson-Gilford progeria syndrome preclinical models		2017
TreatOPON	Preclinical Development of Treatments for OPA1-linked Optic Neuropathies		2017
TreatPolyQ	Allele-specific lowering of mutant polyQ proteins as treatment for Huntington disease, spinocerebellar ataxia type 3 and spinocerebellar ataxia type 7		2017
MuTaEB	Mutation-targeted gene and pharmacological therapies for dystrophic and junctional Epidermolysis Bullosa		2017
TREAT-MTMs	Novel therapies for neuromuscular diseases with altered phosphoinositide metabolism		2017
CALSER	The effect of CDNF in ALS and ER stress		2017
ReDox	Repurposing doxycycline in the treatment of AL amyloidosis	Proposals for new therapeutic uses of already existing molecules (repurposing) in rare diseases	2016
NICOFA	Nicotinamide for the treatment of Friedreich ataxia		2016
Dpem	Dimethylfumarate for the treatment of bullous pemphigoid		2016
HCQ4Surfdefect	Hydroxychloroquine (HCQ) in pediatric ILD		2016
ROPROP	Propranolol for preemptive treatment of threshold retinopathy of prematurity		2016
ROCK-ALS	Inhibition of Rho Kinase (ROCK) with Fasudil as disease-modifying treatment for ALS		2016
REALS	Repurposed Enoxacin for the treatment of patients with Amyotrophic Lateral Sclerosis		2016
TAMDMD	Tamoxifen in Duchenne muscular dystrophy – a randomised placebo controlled phase 2 trial		2016
INSTINCT	Induced pluripotent stem cells for identification of novel drug combinations targeting cystic fibrosis lung and liver disease	Research Projects on Rare Diseases	2015
SMART-HaemoCare	Small Antibody Fragment as Alternative Tools in Haemophilia Care		2015
NSEuroNet	European network on Noonan syndrome and related disorders		2015
PERescue	Translating Peroxisome Biogenesis Disorders: Identifying Pharmacological Therapies and Clinical Trial Endpoints		2015
Propekal5	Tracing the untackled facets of Peeling Skin Disease-Targeting epidermal proteolysis for treatment		2015
EuroCID	Non-SCID combined immunodeficiencies: a diagnostic and therapeutic challenge		2015
iNSC-WMD	Patient-Derived Glial Precursor Cell Therapy for Vanishing White Matter Disease		2015
Improve CPVT	Improving diagnosis and treatment of catecholaminergic polymorphic ventricular tachycardia: integrating clinical and basic science		2015
GENOMIT	Mitochondrial Disorders: from a genome-wide Registry to medical genomics, toward molecular mechanisms and new therapies		2015
INSAID	A comprehensive clinical and experimental approach to personalized molecular medicine in patients with defined and undefined autoinflammatory disorders		2015
EURO-CDG-2	A European research network directed towards improving diagnosis and treatment of inborn glycosylation disorders		2015
ERAdicatPH	Understanding primary hyperoxaluria type 1 towards the development of innovative therapeutic strategies.		2015

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KLKIN	Netherton Syndrome; From mechanism to therapies		2015
CoHEART	Improving Care for Cohesinopathies from heart phenotypes to novel therapies		2015
CMT-NRG	Modulation of Neuregulin signaling as an effective strategy to treat hereditary neuropathies (Charcot-Marie-Tooth disease)		2015
GETHERTHALPLUS	Novel Gene Therapy for Thalassemia: Pre-clinical Development and Assessment in Animal and Stem Cell Models		2015
PREPARE	Preparing for therapies in autosomal recessive ataxias		2015
Hipbi-RD	Harmonising phenomics information for a better interoperability in the RD field		2015
EuroDBA	Preclinical approaches towards therapeutic intervention for fragile X premutation carriers		2015
Treat-AID	New treatments for auto-inflammatory diseases	Development of Innovative Therapeutic Approaches for Rare Diseases	2014
Drug_FXSPreMut			2014
EBThera	Repurposing biomolecules for the treatment of epidermolysis bullosa		2014
RescueCFTR preclinic	Cysteamine for the treatment of cystic fibrosis: a translational research project		2014
CHAPRION	Pharmacological chaperones for genetic prion diseases		2014
EURO-CMC	Novel treatment strategies for autosomal dominant chronic mucocutaneous candidiasis		2014
TREAT-NEMMYOP	Fast Skeletal Troponin Activation for Restoring Muscle Strength in Mouse Models of Nemaline Myopathy: a Molecular, Cellular, Metabolic and Functional Assessment		2014
ARTEMIS	Targeting Alpha-Synuclein for Treating Multiple System Atrophy		2014
NTC study	Novel Therapies for Cystinosis		2014
CantuTreat	Sulfonylurea drugs to treat Cantú syndrome		2014
PrionImmunity	Immunotherapy of familial prion diseases		2014
CCMCURE	Cerebral Cavernous Malformations Pharmacological Supression Screen		2014
FaSMALS	Common Pathogenic Pathways and Therapeutics for SMA and ALS motoneuron diseases		2014
TheraLymph	Therapeutic approaches for treatment of hereditary lymphedema		2014
inter-FSHD-epigen	An international effort to understand FSHD muscular dystrophy epigenetics	Research Projects on Rare Diseases	2013
THYRONERVE	Allan-Herndon-Dudley Syndrome: Mechanisms of disease and therapeutic approaches in model organism		2013
OPTOREMODE	Retinitis Pigmentosa diagnosis and therapy: retinal remodeling and optogenetic reactivation of degenerated retina		2013
CLC & MLC	CLC chloride channels and Megalencephalic leukoencephalopathy: molecular mechanisms and therapeutics		2013
EUROMICRO	Primary monogenic microcephalies : from genetics to pathophysiology and the clinic		2013
SIRD	Stimulating Intrinsic Repair for DMD		2013
RNA-ALS	Dysregulation of RNA in the pathogenesis of ALS		2013
IIH-ECC	Idiopathic Infantile Hypercalcemia: European-Canadian Consortium		2013
ACAMIN	Autoantibodies to cell adhesion molecules in inflammatory neuropathies		2013
EUPLANE	EUropean PLAtelet NEtwork for studying physiopathology of two inherited thrombocytopenias, THC2 and MYH9-RD, characterized by genetic alterations of RUNX1-target genes		2013
GOSAMPAC	Genomics of cAMP signaling alterations in adrenal Cushing		2013
NEUROLIPID	Lipid metabolism in the pathogenesis of hereditary spastic paraplegia: genes, biomarkers, and models for therapy		2013
ALS-degeneration	The molecular basis for neurodegeneration and muscle atrophy in ALS		2012
COQ-iPSC	Coenzyme Q10 Deficiency Syndrome: Understanding the genotype-phenotype association and metabolic dysfunction through generation of induced pluripotent stem cells (iPSCs) from patient-specific uncorrected and genetically-corrected cells		2012
Cure-FXTAS	Experimental approaches towards therapeutic intervention for Fragile X-associated Tremor Ataxia Syndrome		2012

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EMINA-2	European Multidisciplinary Initiative on Neuroacanthocytosis – 2	Research Projects on Rare Diseases driven by Young Investigators	2012
Eur-USH	European young investigators network for Usher syndrome		2012
EuroDBA	European Diamond-Blackfan Anemia Consortium		2012
HEART DM	Exploring the mechanisms of heart dysfunctions in myotonic dystrophies		2012
PPPT-MJD	Towards the understanding of pathological protein processing and toxicity in Machado-Joseph Disease		2012
PYRAMID	Phenotype Research for ALS modifyer discovery		2012
SpliceEB	Splicing therapies for Dystrophic Epidermolysis Bullosa		2012
TARGET-CdLS	Targeting unknowns in causes and phenotypes of the Cornelia de Lange Syndrome		2012
CRANIRARE-2	An integrated clinical and scientific approach for craniofacial malformations	Research Projects on Rare Diseases	2011
EDEN	Eugène Devic European Network: establishment and use of an European database and biological bank for research and treatment in acute neuromyelitis optica and related disorders		2011
EURO-CDG	A European research network for a systematic approach to CDG and related diseases		2011
Euro-SCAR	Nosology and molecular diagnosis of the degenerative recessive ataxias		2011
GENOMIT	Mitochondrial Disorders – Connecting Biobanks, Empowering Genetic Diagnostics and Exploring Disease Models		2011
HEMO-iPS	Use of patient-specific induced pluripotent stem cells to improve diagnosisand treatment of hemophilia A		2011
IPF-AE	Acute Exacerbation of Idiopathic Pulmonary Fibrosis: Mechanism and Biomarkers		2011
MTMPathies2	MTM1 and MTMR2 myotubularins: biochemical activity and the regulation of membrane trafficking in health and disease		2011
Rare-G	The Epidermal Growth Factor System in Rare Glomerular Disease: From Molecular Mechanisms to Therapeutics		2011
SkinDev	In vitro and in vivo models of congenital rare skin diseases for molecular characterization and drug screening		2011
TRANSPOSMART	An innovating platform using transposon and S/MAR for von Willebrand disease gene therapy		2011
TUB-GENCODEV	Genetics of cortical gyral dysgenesis and pathophysiology of tubulin-related malformations of cortical development		2011
WHIM-Thernet	WHIM syndrome: Pathological basis and development of therapeutic molecules		2011
CAV-4-MPS	Understanding and treating neurodegeneration caused by mucopolysaccharidoses	Projects on Rare Diseases	2009
Cure-FXS	Targeting Rho-signalling, a new therapeutic avenue in fragile X syndrome		2009
EB	Identification of revertant mosaicism in epidermolysis bullosa and subsequently using the revertant keratinocytes in a pre-clinical mouse model suitable to test revertant cell therapy		2009
ELA2-CN	Congenital neutropenia with ELA-2 mutations (ELA2-CN): Identification of (epi)genetic co-factors and molecular pathways underlying clinical heterogeneity		2009
EMINA	European Multidisciplinary Initiative on Neuroacanthocytosis		2009
EuPAPNet	European pulmonary alveolar proteinosis network : molecular determinants of causes, variability and outcome		2009
EURO-CGD	Genetics and pathogenesis of chronic granulomatous disease and development of new gene transfer therapeutic approaches		2009
EuroGeBeta	European network on genetics, pathophysiology and translational research into rare pancreatic beta-cell insufficiency diseases		2009
GETHERTHAL	Improvements of vector technology and safety for the gene therapy of thalassemia		2009
HMA-IRON	Towards improved diagnosis and treatment of rare inherited microcytic hypochromic anemias related to iron metabolism		2009
MCL-Team	Megalencephalic leukoencephalopathy with subcortical cysts: from molecular basis to search for therapy		2009
NEMMYOP	Functional characterization of nemaline myopathy in a murine model with nebulin mutation: moving from basic understanding towards therapeutic interventions		2009
NEUTRO-NET	Inherited inhibition of inborn immunity – an integrated molecular genetic approach to discover novel human gene defects		2009
NsEuroNet	European network on noonan syndrome and related disorders		2009
RHORCOD	Comprehensive analysis of rod-cone photoreceptor degeneration associated with rhodopsin gene mutations		2009

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CRANIRARE	An integrated clinical and scientific approach for craniofacial malformations	Research Projects on Rare Diseases	2007
EUROBFNS	Benign Familial Neonatal Seizures (BFNS) as disease model for human idiopathic epilepsies: expansion of the genotype-phenotype correlations and insights into novel disease mechanisms		2007
Epinostics	"Autoimmune liver diseases" Epitope peptide mapping – The entry to novel and innovative diagnostic and therapeutic application		2007
EuroRETT	European Network on Rett Syndrome		2007
EUROSPA	European and Mediterranean network on spastic paraplegias		2007
HAE-III	Genetics, Pathophysiology, and Therapy of Hereditary Angioedema Type III		2007
HSCR	International Hirschsprung Disease Consortium		2007
Kindernet	International Kindler Syndrome Network		2007
MTMPathies	Myotubularinopathies: common molecular mechanism and tissue specificity		2007
OSTEOPETR	New Genes and Therapeutic Approaches to Osteopetrosis		2007
PodoNet	PodoNet: Consortium for Clinical, Genetic and Experimental Research into Hereditary Diseases of the Podocyte		2007
RISCA	Prospective study of individuals at risk for spinocerebellar ataxia type 1, type 2, type 3 and type 6 (SCA1, SC2, SCA3, SCA6)		2007
WHIMPath	Understanding the WHIM syndrome and search for new therapies: molecular analysis of CXCR4 functions in leukocyte trafficking and activation		2007

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Table B- 4: EC-funded projects on rare diseases with clinical trials (Cordis Db, https://cordis.europa.eu/de)

project/total cost – total costs per project (EU funding + other contributions) in €, project/ecMaxContribution – EU contribution per project in €

project/id	project/acronym	project/title	project/totalCost	project/ecMax Contribution
603160	ASTERIX	Advances in Small Trials dEsign for Regulatory Innovation and eXcellence	4,141,786	2,999,881
669026	BIORISE	Establishment of the Bioinformatics ERA Chair at the Cyprus Institute of Neurology and Genetics	2,526,162.50	2,273,546
666908	SCIDNET	DevelopIng Genetic medicines for Severe Combined Immunodeficiency (SCID)	7,474,316	6,926,313
667751	MYOCURE	Development of an innovative gene therapy platform to cure rare hereditary muscle disorders	5,998,937.50	5,998,937.50
743056	QRD	A uniQue platform enabling faster development of treatments for Rare Diseases	71,429	50,000
503246	ORPHANPLATFORM	Platform of information services for the coordination of rare disease research with various stakeholders from research, SMEs and patient organisations and the coordination of early clinical trials	474,992	400,000
602144	InSPiRe	Innovative methodology for small populations research	2,919,912.18	2,268,504.61
304999	MEUSIX	Clinical trial of gene therapy for MPS VI - a severe lysosomal storage disorder	7,876,955	5,995,041
BMH4983415	EURARENET	An European Network of Information Centres for Rare Diseases	0	0
602552	IDEAL	Integrated DEsign and AnaLysis of small population group trials	3,648,320.20	2958449
601573	SCOPE-DMD	Consortium for Products across Europe in Duchenne Muscular Dystrophy	21,358,069	5,999,210
297679	STEROLOSOME	Targeting common mechanisms of pathogenesis in diseases of sterol homeostasis associated with lysosome dysfunction; development of novel and rapidly translatable clinical therapies	200,371.80	200,371.80
305485	PREVENTROP	New approach to treatment of the blinding disease Retinopathy of Prematurity (ROP)	7,590,759.85	5,990,236
875615	MYODM-FSMP	New food for special medical purposes to nutritionally manage Myotonic Dystrophy type 1	71,429	50,000
242013	TREATRUSH	Fighting blindness of Usher syndrome: diagnosis, pathogenesis and retinal treatment (TreatRetUsher)	8,181,653.01	6,000,000
QLG1-CT-1999-00584	FRIEDREICH'S ATAXIA	Molecular and biochemical pathogenesis of friedreich's ataxia: search for treatments.	2,168,471	1,186,489
329284	WASHSCGENETHERAPY	Preclinical studies in mouse hematopoietic stem cells for gene therapy of Wiskott-Aldrich Syndrome	309,235.20	309,235.20
			75,012,799.24	**49,606,214.11**

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Table B- 5: Antibiotics in development (phase 3) [58] [59, 60] [61] [62] [63]

Product	Phase	Antibacterial class	Developer (MA holder)
Avibactam + Aztreonam (ATM-AVI, PF-06947387)	3	Novel non-β-lactam β-lactamase inhibitor	AbbVie/AstraZeneca/Pfizer
Bacteriophage	3	Bacteriophage	Tashkent Pediatric Medical Institute
BB128	MAA	Live biotherapeutic product	BiomeBank
Benapenem	2/3	β-lactam (carbapenem)	Sichuan Pharmaceutical
Durlobactam (ETX-2514) + sulbactam	3	DBO-BLI/PBP2 binder + β-lactam-BLI/PBP1,3 binder	Entasis
Enmetazobactam (AAI-101) + cefepime	3	BLI + β-lactam (cephalosporin)	Allecra Therapeutics
Epetraborole (BRII-658)	2/3	Oxaborole	AN2 Therapeutics
Exebacase (CF-301, Lysin CF-301)	3	Phage endolysin	Contrafect
Gepotidacin (GSK 2140944; GSK-2140944E)	3	Triazaacenaphthylene (topoisomerase inhibitor)	GSK
Nafithromycin (WCK-4873)	3	Macrolide	Wockhardt
Reltecimod (AB103)	Preregistration	Antagonist of superantigen exotoxins and CD28 T-cell	Atox Bio
Ridinilazole (SMT-19969)	3	Bis-benzimidazole	Summit Therapeutics
Solithromycin (T-4288, CEM-101, OP-1068)	NDA	Macrolide	iFUJIFILM Toyama Chemical
Sulopenem, Sulopenem etzadroxil/probenecid	NDA	β-lactam (penem)	Iterum
Taniborbactam (VNRX-5133) + cefepime	3	Boronate BLI + β-lactam (cephalosporin)	VenatoRx/GARDP
Tosatoxumab (AR-301)	3	Anti-S. aureus IgM monoclonal Ab	Aridis Pharmaceuticals, Inc.
Zoliflodacin (AZD-0914, ETX-0914)	3	Spiropyrimidenetrione Oral (topoisomeraseinhibitor)	Entasis/GARDP

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Table B- 6: Actors in R&D of antibiotics: "where is the innovation coming from" [64]

Ceftobiprole (Zevtera)	Roche *	Basilea (marketed in Europe)		
Dalbavancin (Xydalba)	Lepetit Research Center/Vicuron	Pfizer	Durata	Actavis
Oritavancin (Orbactive)	Eli Lilly *	Intermune	Targanta	The Medicine Company
Tedizolid (Sivextro)	Dong-A	Trius	Bayer/Cubist (Merck)	
Ceftolozane (+Tazobactam) (Zerbaxa)	Astellas*	Calixa	Cubist (Merck)	
(Ceftazidime+) Avibactam (Avycaz)	Sanofi *	Novexel	AstraZeneca-Forest/Actavis	
Omadacycline	Paratek	Novartis (colllab. discontinued)	Paratek	
Solithromycin, oral, iv-oral	Optimer	Cempra		
Delafloxacin, iv, oral	Wakunaga	Abbott	Wakunaga	Rib-X =Melinta Therapeutics
Eravacycline (TP-434)	Harvard University	Tetraphase		
Plazomicin	Isis	Achaogen		
Carbavance (+Meropenem)	??	Rempex	The Medicines Comp.	
Nemonoxacin (approved Taiwan)	TaiGen	Procter & Gamble	Warner Chilcott	TaiGen
Radezolid	Yale University	Rib-X =Melinta Therapeutics		
Lefamulin (BC-3781)	Sandoz/Novartis *	Nabriva	Forest/Actavis	Nabriva
Avarofloxacin (JNJ-Q2)	J&J (Janssen Pharm.) *	Furiex	Forest/Actavis	
Brilacidin (PMX-30063)	University of Pennsylvania	Polymedix	Cellceutix Corporation	
AFN-1252/Debio 1450	University of Toronto	Affinium	Debiopharm	
POL7080	University Zürich	Polyphor	Roche	

University/Small company
Larger company (>500 employees)
Global pharmaceutical corporation

* More than 10 years ago

The red arrows indicate the origin of a R&D program in a university/small company and/or the current late clinical development stage pursued in a small company.

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Table B- 7: EC-funded projects on antimicrobial resistance, drug development and clinical trials (Cordis Db)

project/id	project/acronym	project/title	project/totalCost	project/ecMaxContribution
765147	CARTNET	Combatting Antimicrobial Resistance Training Network	3,445,596.72	3,445,596.72
115618	DRIVE-AB	DRIVING RE-INVESTMENT IN R&D AND RESPONSIBLE ANTIBIOTIC USE	10,968,676	6,299,987
874735	VEO	Versatile Emerging infectious disease Observatory	18,118,385.70	18,118,385.70
826722	SIGNIA	SIGNIA: An innovative drug discovery platform for rapid identification and validation of antimicrobial applications in available pharmaceutical resources and drugs open for repurposing.	71,429	50,000
852985	SIMICA	Site-selective protein-modification chemistries for antibody-drug conjugates (ADCs)	800,000	800,000
303022	ICADIGE	The Integron Cassette Dynamics and the Integrase Gene Expression	193594.80	193594.80
966627	OMN6	A novel class of antibiotics to combat Antimicrobial Resistance	3,413,821	2,389,674.70
713482	ALERT	Local Training Network on Novel Tailor-Made Antimicrobials and Delivery Strategies From Synthesis towards Clinical Applications	3,976,320	1,988,160
115583	ENABLE	European Gram Negative Antibacterial Engine	100,832,798	58,900,000
706499	PACEMech	The structure and molecular mechanism of transport proteins within the PACE family of multidrug efflux pumps	195,454.80	195,454.80
101072632	BREAKthrough	Breaking the barrier - An integrated multidisciplinary approach to kill Gram-negative bacteria through existing antibiotics by making their outer membrane permeable	0	2,618,488.80
101073263	STOP SPREAD BAD BUGS	STOP SPREAD BAD BUGS: novel antimicrobial approaches to combat multidrug resistance in bacteria	0	4,060,348.83
101024300	COUNTERMAND	Small molecule inhibitors of bacterial communication - a new strategy for tackling antimicrobial resistance	196,590.72	196,590.72
843116	REBELLION	Light-REsponsive Nanomachines for Targeted Eradication of BactErial Pathogens in LocaLised InfectIONs	245,732.16	245,732.16
660668	ACT against AMR	Abyssomicin C Truncated derivatives against Antimicrobial Resistance	185,857.20	185,857.20
612338	DNA-TRAP	DNA-TRAP â€“ Delivery of Nucleic Acid-Based Therapeutics for the TReatment of Antibiotic-Resistant Pathogens	2,371,031	2,371,031
601725	NABARSI	New AntiBacterials with Inhibitory activity on Aminoacyl-tRNA Synthetases	5,372,277.01	4,102,157.50
289285	TRAIN-ASAP	Training and Research AImed at Novel Antibacterial Solutions in Animals and People	3,515,586.69	3,515,586.69
853989	ERA4TB	EUROPEAN REGIMEN ACCELERATOR FOR TUBERCULOSIS	207,963,891	89,815,600
853903	RespiriTB	Progress new assets (one pre-new molecular entity and one first-time-in-human start) for tuberculosis that act synergistically with bedaquiline, cytochrome bc or cytochrome bd inhibitors	9,962,900	6,840,000
853932	RespiriNTM	Progress novel assets (one FIH start) for non-tubercular mycobacteria that may act synergistically with bedaquiline and cytochrome bc drugs	8,060,640.75	5,687,983.75

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282512	R-GNOSIS	Resistance in Gram-Negative Organisms: Studying Intervention Strategies	15,654,161.20	11,999,999
268540	PBDR	The population biology of drug resistance: Key principles for a more sustainable use of drugs	2,272,403	2,272,403
867461	INFarm	A unique, interferon-based veterinary therapy to minimize antimicrobial overuse in cattle and tackle the societal global problem of antimicrobial resistance	71,429	50,000
899921	PureIgY	Towards the use of IgY antibodies as alternative therapeutics	0	150,000
101103053	eWHORM	Enabling the WHO-Roadmap 2030	7,967,127.50	7,967,127.50
947081	BRONCHOTHELIN	The first-in-class disease-modifying drug for chronic airway disorders	3,578,020	2,500,000
101107873	FungalHetEx	Heterologous expression of natural products from microbes living in a self-sustaining environment	0	254,330.40
812867	VitaminBlock	Development of antibacterial compounds that block essential transport function	150,000	150,000
101068156	BLISS	Beta-Lactamase Inhibitors Synthesised through in Situ click chemistry	0	188,590.08
101106871	The G-Q-reat ESKAPE	Druggability of G-quadruplexes, promising modulators for antimicrobial resistance	0	172,750.08
512099	PNEUMOPEP	New methods of treatment of antibiotic-resistant pneumococcal disease	1,702,800	1,500,000
223670	NABATIVI	Novel Approaches to Bacterial Target Identification, Validation and Inhibition	7,131,835.60	5,506,000
101039270	ERA-ARE	A new ERA for Environmental Risk Assessment: Chirality as a tool towards environmentally safe pharmaceuticals	1,499,950	1,499,950
115523	COMBACTE-NET	Combatting Bacterial Resistance in Europe	220,954,266	109,433,010
101007873	UNITE4TB	ACADEMIA AND INDUSTRY UNITED INNOVATION AND TREATMENT FOR TUBERCULOSIS	185,000,000	92,500,000
115737	COMBACTE-MAGNET	Combatting Bacterial Resistance in Europe - Molecules against Gram Negative Infections	168,658,666	75,340,000
847786	FAIR	FLAGELLIN AEROSOL THERAPY AS AN IMMUNOMODULATORY ADJUNCT TO THE ANTIBIOTIC TREATMENT OF DRUG-RESISTANT BACTERIAL PNEUMONIA	10,162,903.75	10,162,903.75
101080486	Vax2Muc	NEXT GENERATION VACCINES AGAINST GASTROINTESTINAL MUCOSAL PATHOGENS, USING HELICOBACTER PYLORI AS MODEL PATHOGEN	8,219,842.50	8219842.50
242146	NEOMERO	European multicenter network to evaluate pharmacokinetics, safety and efficacy of Meropenem in neonatal sepsis and meningitis	7,672,901.94	5,900,000
101080544	BAXERNA 2.0	Immunopeptidomics-based Development of Next-Generation Bacterial mRNA Vaccines	8,859,050	8,859,050
			1,029,445,939.04	**556,646,186.68**

project/total cost – total costs per project (EU funding + other contributions) in €, project/ecMaxContribution – EU contribution per project in €

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Appendix C

Public contributions to…. (IMI/ IHI projects)

- C-1: Target Identification, Drug Discovery, Drug Delivery
- C-2: Development of tools for Predicting and Monitoring Efficacy and/or Safety, as well as for Refining Disease Taxonomy/ Biomarker-Stratification
- C-3: Clinical Trial Design, Real World Data and Evidence, Methods for Benefit-Risk Assessment and Regulatory and HTA Process
- C-4: Ecosystems and Networks: Clinical Networks and Patient Involvement in R&D, Education and Training
- C-5: Conducting Clinical Trials
- C-6: Big Data and Knowledge Management, Digital Health, Artificial Intelligence

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Examples in category [72]: **Public Contributions to Target Identification, Drug Discovery and Drug Delivery**

- AETIONOMY discovered 180 putative disease mechanisms for Alzheimer's and Parkinson's diseases, of which 6 have been selected for further validation.
- ENABLE has identified a new way of targeting drug resistant bacteria. More broadly, the New Drugs for Bad Bugs (ND4BB) programme has delivered screening data on the antimicrobial activity and toxicity of several compounds.
- NEWMEDS developed three new methodologies for measuring neurotransmitters (the molecules that transmit nerve signals from one nerve cell to another) using positron emission tomography (PET).
- ULTRA-DD showed that a protein called PRMT5 could be a drug target for new treatments for glioblastoma, a highly aggressive type of brain tumour.
- ZAPI has identified vaccine candidates for a number of zoonoses (diseases that are transmitted to humans from animals), namely Rift Valley fever, Schmallenberg virus, and Middle East Respiratory Syndrome.

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Table C - 1: Public contributions to Target Identification, Drug Discovery, Drug Delivery

Project/ programme name	Description	IMI- Funding in €	Total in €
ADAPTED (2016-20)	Alzheimer's disease apolipoprotein pathology for treatment elucidation and development	3,510,000	6,796,740
AETIONOMY (2014-18)	Organising mechanistic knowledge about neurodegenerative diseases for the improvement of drug development and therapy	*	*
APPROACH (2015-21)	Applied public-private research enabling osteoarthritis clinical headway	7,500,000	17,961,492
CARE (2020-25)	Corona Accelerated R&D in Europe	36,559,186	75,906,676
COMPACT (2012-17)	Collaboration on the optimisation of macromolecular pharmaceutical access to cellular targets	10,184,909	29,983,730
EBOMAN (2014-17)	Manufacturing and development for rapid access Ebola vaccine	1,023,325	40,188,229
ELF (2013-2018)	European Lead Factory	79,999,157	196,578,615
ESCulab (2018-23)	European screening centre; unique library for attractive biology.	18,249,993	36,795,968
ENABLE (2014-21)	European Gram-negative Antibacterial Engine	58,900,000	100,713,372
EU-AIMS (2012-18)	European Autism Interventions - a Multicentre Study for Developing New Medications	20,490,981	37,480,613
AIMS2-Trials (2018-25)	Autism Innovative Medicine Studies – 2 – Trials	*	*
EUbOPEN (2020-25)	Enabling and unlocking biology in the OPEN	27,935,000	63,591,792
EUROPAIN (2009-15)	Understanding chronic pain and improving its treatment	*	*
iCONSENSUS (2018-22)	Integrated control and sensing platform for biopharmaceutical cultivation process high-throughput development and production	4,700,000	9,400,000
Immune-Image (2019-24)	Specific imaging of immune cell dynamics using novel tracer strategies	15,000,000	27,200,801
IMPRiND (2017-22)	Inhibiting misfolded protein propagation in neurodegenerative diseases	4,684,998	11,388,398
K4DD (2012-17)	Kinetics for Drug Discovery	8,286,930	20,860,250
MAD-CoV 2 (2020-24)	Modern approaches for developing antivirals against SARS-CoV 2	3,749,669	6,405,169
MELLODDY (2019-22)	Machine learning ledger orchestration for drug discovery	*	*
NEWMEDS (2009-15)	Novel methods leading to new medications in depression and schizophrenia	8,986,216	24,849,675
NGN-PET (2017-20)	Modelling neuron-glia networks into a drug discovery platform for pain efficacious treatments	1,500,000	3,050,000
Open PHACTS (2011-16)	The Open Pharmacological Concepts Triple Store	*	*
PD-MitoQUANT (2019-22)	A quantitative approach towards the characterisation of mitochondrial dysfunction in Parkinson's disease	*	*
PEVIA (-)	Pan Ebola vaccine innovative approach	6,189,570	17,731,398
PHAGO (2016-22)	Inflammation and AD: modulating microglia function - focussing on TREM2 and CD33	8,838,000	18,293,475
Pharma-Cog (2010-15)	Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in early clinical development	*	*
PRISM (2016-19)	Psychiatric Ratings using Intermediate Stratified Markers to facilitate the discovery and development of new treatments for social and cognitive deficits in AD, SZ, and MD	8,080,000	16,195,875
PRISM 2 (2021-24)	Psychiatric ratings using intermediate stratified markers 2	3,980,906	7,894,553
ReSOLUTE (2018-23)	Research empowerment on solute carriers	*	*
Resolution (2021-23)	Add medical genetic solutions to RESOLUTE (REsolution)	*	*
RespiriNTM 2019-25)	Progress novel assets (one FIH start) for non-tubercular mycobacteria that may act synergistically with bedaquiline and cytochrome bc drugs	5,687,984	8,060,641
SUMMIT (2009-15)	Surrogate markers for micro- and macro-vascular hard endpoints for innovative diabetes tools	*	*
TRANSLOCATION (2013-18)	Molecular basis of the bacterial cell wall permeability	15,984,203	29,754,154
ULTRA-DD (2015-20)	Unrestricted leveraging of targets for research advancement and drug discovery	21,200,000	51,058,785
ZAPI (2015-21)	Zoonotic anticipation and preparedness initiative	*	*

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Sum		**381,221,027**	**858,140,401**

** Project costs were - in case of multiple assignments to categories – calculated only once.*

Examples in category [72]: **Public Contributions to the Development of tools for Predicting and Monitoring Efficacy and/or Safety, as well as for Refining Disease Taxonomy/ Biomarker-Stratification**

- BTCure has defined new subsets of rheumatoid arthritis patients based on biomarkers analysed. This information is essential for improving clinical trials and moving towards more personalised treatments.
- eTOX drew on existing toxicity data to generate 200 'in silico' models for predicting the toxicity of medicines in the early stages of development. eTOX's toxicology database and models have been implemented in all 13 industry partners and used to predict the toxicity of drug candidate molecules.
- MIP-DILI developed a three-dimensional model of liver tissue that allows scientists to study how the liver works, and whether a drug is likely to harm the liver, among other things. These tools are supported by European and US regulators.
- ORBITO has designed a new tool based on an artificial membrane for predicting how a drug will be absorbed in the body. Several companies have successfully integrated ORBITO tools into their R&D routine.
- PREDECT developed the first animal model of a common form of breast cancer that faithfully replicates the human disease. Project partners are using the three-dimensional (3D) models of tumours in their research.
- SAFE-T developed biomarkers for the prediction, detection, and monitoring of drug-induced injuries to the kidney, liver, and vascular system; Companies are using the biomarkers to assess the safety of drugs in development.
- SUMMIT & DIRECT have identified a variant of a gene called SLC2A2 that affects how well a type 2 diabetes patient responds to the drug metformin.

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Table C - 2: Public contributions to Tools for Predicting/ Monitoring Efficacy and/or Safety, as well as for Refining Disease Taxonomy/ Biomarker-Stratification

Project/ programme name	Description	IMI- Funding in €	Total in €
3TR (2019-26)	Identification of the molecular mechanisms of non-response to treatments, relapses and remission in autoimmune, inflammatory, and allergic conditions	40,273,192	80,803,178
ABIRISK (2012-18)	Anti-Biopharmaceutical Immunization: Prediction and Analysis of Clinical Relevance to Minimize the Risk	18,170,217	32,851,056
ARDAT (2020-25)	Accelerating research & development for advanced therapies	11,773,000	25,490,492
BEAT-DKD (2016-23)	Biomarker enterprise to attack Diabetic kidney disease (DKD)	15,085,937	30,586,654
BIOMAP (2019-24)	Biomarkers in atopic dermatitis and psoriasis	10,500,000	21,953,309
BioVacSafe (2012-18)	Biomarkers for Enhanced Vaccine Immunosafety	17,408,770	30,931,370
BTCure (2011-17)	Insights into the causes and development of rheumatoid arthritis, earlier detection, prevention and inducing tolerance to RA	17,362,872	39,371,092
CANCER-ID (2015-19)	Cancer treatment and monitoring through identification of circulating tumour cells and tumour related nucleic acids in blood	6,620,000	21,250,040
CARDIATEAM (2019-24)	Cardiomyopathy in type 2 diabetes mellitus	6,700,000	12,906,217
COMBINE (2019-25)	Collaboration for prevention and treatment of MDR bacterial infections	8,000,000	25,460,100
ConcePTION (2019-24)	Building an ecosystem for better monitoring and communicating of medication safety in pregnancy and breastfeeding: validated and regulatory endorsed workflows for fast, optimised evidence generation	*	*
DDMoRe (2011-16)	Drug Disease Model Resources	*	*
DECISION (2020-24)	A minituarized disposable molecular diagnostics platform for combatting coronavirus infections	3,435,100	3,747,600
DIRECT (2012-19)	Diabetes research on patient stratification	21,388,643	46,484,127
DRIVE (2017-22)	Development of Robust and Innovative Vaccine Effectiveness	*	*
EBiSC (2014-17)	European Bank for induced pluripotent Stem Cells	21,840,380	34,327,858
EBiSC2 (2019-23)	EBiSC2 – A sustainable European bank for induced pluripotent stem cells	4,599,648	8,999,613
EBODAC (2014-20)	Communication strategy and tools for optimizing the impact of Ebola vaccination deployment	20,328,856	25,740,856
EbolaMoDRAD (2015-18)	Ebola virus: modern approaches for developing bedside rapid diagnostics	4,300,935	4,300,935
EMIF (2013-18)	European Medical Information Framework	*	*
EPND (2021-26)	European Platform for Neurodegenerative Diseases	*	*
ERA4TB (2020-25)	European regimen accelerator for tuberculosis	89,815,600	207,963,891
EQIPD (2017-21)	European Quality In Preclinical Data	4,495,523	9,360,692
eTOX (2019-16)	Integrating bioinformatics and chemoinformatics approaches for the development of Expert systems allowing the in silico prediction of toxicities	6,910,018	18,787,108
eTRANSAFE (2017-23)	Enhacing TRANslational SAFEty Assessment through Integrative Knowledge Management	*	*
EUROPAIN (2009-15)	Understanding chronic pain and improving its treatment	*	*
Filodiag 2015-17)	Ultra-fast molecular filovirus diagnostics	2,260,105	2,260,105
FLUCOP (2015-22)	Standardization and development of assays for assessment of influenza vaccines correlates of protection	6,100,000	13,833,121
Hypo-RESOLVE (2018-23)	Hypoglycaemia - REdefining SOLutions for better liVEs	13,450,057	26,774,582
IM2PACT (2019-24)	Investigating mechanisms and models predictive of accessibility of therapeutics (IM2PACT) into the brain	9,000,000	17,410,136
IMIDIA (2010-15)	Improving beta-cell function and identification of diagnostic biomarkers For treatment monitoring in diabetes	8,060,760	27,447,009
IMI-PainCare (2018-23)	Improving the care of patients suffering from acute or chronic pain	11,225,271	23,405,673
IMMUCAN (2019-25)	Integrated immunoprofiling of large adaptive cancer patients cohorts	17,830,000	35,779,304

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ImmUniverse (2020-24)	Better control and treatment of immune-mediated diseases by exploring the universe of microenvironment imposed tissue signatures and their correlates in liquid biopsies	15,500,000	31,110,000
imSAVAR (2019-25)	Immune safety avatar: nonclinical mimicking of the immune system effects of immunomodulatory therapies	10,999,316	21,750,812
Inno4Vac (2021-27)	Innovations to accelerate vaccine development and manufacture	*	*
ITCC-P4 (2017-23)	ITCC pediatric preclinical POC platform	7,370,000	19,930,473
K4DD (2012-17)	Kinetics for Drug Discovery	*	*
KRONO (2020-22)	Evaluation of a production ready portable, point-of-need platform (instrument and reagents), direct from nasal swab test for the molecular diagnostic detection of COVID-19 infection	784,470	1,819,964
LITMUS (2017-23)	Liver Investigation: Testing Marker Utility in Steatohepatitis	15,797,881	47,281,407
MACUSTAR (2017-24)	Intermediate AMD: development of novel clinical endpoints for clinical trials in patients with a regulatory and patient access intention	8,025,000	16,218,918
MARCAR (2010-15)	Biomarkers and molecular tumour classification for non-genotoxic carcinogenesis	6,049,578	13,110,690
MELLODDY (2019-22)	Machine learning ledger orchestration for drug discovery	*	*
MIP-DILI (2012-17)	Mechanism-Based Integrated Systems for the Prediction of Drug-Induced Liver Injury	15,335,538	32,319,866
MOBILISE-D (2019-24)	Connecting digital mobility assessment to clinical outcomes for regulatory and clinical endorsement	*	*
Mofina (2015-17)	Mobile Filovirus Nucleic Acid Test	1,162,622	4,398,252
NECESSITY (2019-24)	New clinical endpoints in primary Sjögren's syndrome: an interventional trial based on stratifying patients	8,200,000	15,820,020
NeuroDeRisk (2019-22)	Neurotoxicity de-risking in preclinical drug discovery	5,331,000	9,752,063
NEWMEDS (2009-15)	Novel methods leading to new medications in depression and schizophrenia	*	*
Onco Track (2011-16)	Methods for systematic next generation oncology biomarker development	16,757,282	31,080,319
ORBITO (2012-18)	Oral biopharmaceutics tools	8,975,392	25,274,674
PD-MitoQUANT (2019-22)	A quantitative approach towards the characterisation of mitochondrial dysfunction in Parkinson's disease	4,497,935	6,894,315
PERSIST-SEQ (2021-26)	Building a reproducible single-cell experimental workflow to capture tumour drug persistence	7,057,980	15,320,480
Pharma-Cog (2010-15)	Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in early clinical development	9,658,388	30,715,556
PREDICT (2011-16)	New models for preclinical evaluation of drug efficacy in common solid tumours	8,756,641	21,020,760
PRO-active (2009-16)	Physical Activity as a Crucial Patient Reported Outcome in COPD	6,767,597	15,635,822
PROTECT (2009-15)	Pharmacoepidemiological research on outcomes of therapeutics by a European consortium	11,009,715	28,617,382
Quic-Concept-(2011-18)	Quantative imaging in cancer: connecting cellular process with therapy	7,000,000	15,505,915
RAPID-COVID (2020-22)	Robust automation and point of care identification of COVID	2,832,585	2,832,585
RAPP-ID (2011-16)	Development of rapid point-of-care test platforms for infectious diseases	6,828,438	15,927,300
RealHOPE (2021-25)	Real world handling of protein drugs - exploration, evaluation and education	3,139,984	7,105,984
ReSOLUTE (2018-23)	Research empowerment on solute carriers	12,000,000	24,065,172
REsolution (2021-23)	Add medical genetic solutions to RESOLUTE (REsolution)	1,000,000	2,162,500
RTCure (2017-23)	Rheuma Tolerance for Cure	6,000,000	13,511,715
SAFE-T (2009-15)	Safer and Faster Evidence-based Translation	13,901,971	36,427,294
SPRINTT (2014-20)	Sarcopenia and physical frailty in older people: multi-component treatment strategies	23,999,439	56,128,596
STEMBANCC (2012-18)	Stem cells for biological assays of novel drugs and predictive toxicology	55,010,480	26,000,000
SUMMIT (2009-15)	Surrogate markers for micro- and macro-vascular hard endpoints for innovative diabetes tools	14,654,559	34,812,081
T2EVOLVE (2021-25)	Accelerating development and improving access to CAR and TCR-engineered T cell therapy	8,728,185	19,367,685

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TransBioLine (2019-24)	Translational Safety Biomarker Pipeline (TransBioLine): Enabling development and implementation of novel safety biomarkers in clinical trials and diagnosis of disease	13,999,998	27,982,744
TransQST (2017-22)	Translational quantitative systems toxicology to improve the understanding of the safety of medicines	8,000,000	18,132,874
TRISTAN (2017-23)	Imaging biomarkers (IBs) for safer drugs: validation of translational imaging methods in drug safety assessment	12,000,000	22,724,622
U-BIOPRED (2009-15)	Unbiased biomarkers for the prediction of respiratory disease outcomes	8,867,221	25,501,326
VHFMoDRAD (2019-23)	Viral haemorrhagic fever: modern approaches for developing bedside rapid diagnostics	3,316,013	5,050,013
VITAL (2019-23)	Vaccines and infectious diseases in the ageing population	5,499,882	12,427,217
VSV-EBOPLUS (2016-23)	Vaccine safety and immunogenicity signatures of human responses to VSV-ZEBOV	8,553,750	15,430,660
VSV-EBOVAC (2015-19)	Vaccine safety and immunogenicity signatures of human responses to VSV-ZEBOV	3,887,260	4,786,010
WEB-RADR (2014-17)	Recognising Adverse Drug Reactions	2,270,000	5,940,396
WEB-RADR 2 (2018-20)	Recognising Adverse Drug Reactions 2	1,168,750	2,140,980
Sum		**784,131,200**	**1,610,261,560**

** Project costs were - in case of multiple assignments to categories – calculated only once.*

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Examples in category [72]: **Public contributions to Clinical Trial Design, Real World Data and Evidence, Methods for Benefit-Risk Assessment and for the Regulatory and HTA process**

- EHR4CR has developed a platform that enables controlled access to hospitals' data for the preparation of clinical trials. The platform has demonstrated its usefulness in speeding up the recruitment of patients, while ensuring that patient privacy is respected.
- EPAD is currently recruiting the largest multicentre European deep phenotyped cohort (6 000 subjects) for preclinical Alzheimer's disease, including biosamples.
- iABC: Patient cohort databases European Bronchiectasis Registry, more than 8 000 patients from 25 countries enrolled.
- EUROPAIN's work on classifying patients by their sensitivity to pain contributed to EMA guidelines on the development of pain treatments.
- GETREAL developed new tools and resources for incorporating real world data (RWD) into drug development. GETREAL Initiative (a follow-up project) is to drive the adoption of these tools and so increase the quality of real-world evidence (RWE) generation in medicines development and regulatory /health technology assessment processes.
- PROactive's patient-reported outcomes on chronic obstructive pulmonary disease (COPD) are under review with the EMA. The tools are already being used by researchers from the project as well as at least one company from outside the project.
- PROTECT delivered a range of tools for regulators relating to the assessment of the benefits and risks of medicines.

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Table C - 3: Public contributions to Clinical Trial Design, Real World Data and Evidence, Methods for Benefit-Risk Assessment and Regulatory and HTA Process

Project/ programme name	Description	IMI-Funding in €	Total in €
ADAPT-SMART (2015-18)	Accelerated development of appropriate patient therapies: a sustainable, multi-stakeholder approach from research to treatment-outcomes	1,130,000	4,064,146
ADVANCE (2013-19)	Accelerated development of vaccine benefit-risk collaboration in Europe	4,999,811	11,344,500
AMYPAD (2016-22)	Amyloid imaging to prevent Alzheimer's disease	11,999,886	27,329,288
BEAMER (2021-26)	Behavioral and adherence model for improving quality, health outcomes and cost-effectiveness of healthcare	5,948,903	11,794,912
BigData@Heart (2017-23)	Big Data for Better Outcome (BD4BO) in Cardiovascular disease (CVD)	*	*
c4c (2018-24)	conect4children - Collaborative network for European clinical trials for children	*	*
CHEM21 (2012-17)	Chemical manufacturing methods for the 21st century pharmaceutical industries	9,829,638	26,710,806
COMBACTE-CDI (2017-21)	Combatting Bacterial Resistance in Europe - Clostridium Difficile Infections	2,312,305	4,179,307
COMBACTE-MAGNET (2015-22)	Combatting bacterial resistance in Europe - molecules against Gram negative infections	*	*
COMBACTE-NET (2013-23)	Combatting Bacterial Resistance in Europe	*	*
COMBINE (2019-25)	Collaboration for prevention and treatment of MDR bacterial infections	*	*
ConcePTION (2019-24)	Building an ecosystem for better monitoring and communicating of medication safety in pregnancy and breastfeeding: validated and regulatory endorsed workflows for fast, optimised evidence generation	15,299,991	28,782,491
DO->IT (2017-19)	Big data for better outcomes, policy innovation and healthcare system transformation	*	*
DRIVE (2017-22)	Development of Robust and Innovative Vaccine Effectiveness	8,999,813	9,999,938
DRIVE-AB (2014-17)	Driving re-investment in R&D and responsible antibiotic use	6,299,987	10,968,676
EBOVAC1 (2014-21)	Development of a prophylactic Ebola vaccine using an heterologous prime-boost regimen	*	*
EHDEN (2018-24)	European Health Data and Evidence Network	*	*
EHR4CR (2011-16)	Electronic Health Records Systems for Clinical Research	7,194,044	16,643,429
EPAD (2015-20)	European prevention of Alzheimer's dementia consortium	*	*
EU-AIMS (2012-18)	European Autism Interventions - a Multicentre Study for Developing New Medications	*	*
EU-PEARL (2019-23)	EU patient-centric clinical trial platform	12,004,953	25,655,311
EUROPAIN (2009-15)	Understanding chronic pain and improving its treatment	*	*
FACILITATE (2022-25)	Framework for clinical trial participants data reutilization for a fully transparent and ethical ecosystem	3,260,000	6,886,711
GETREAL (2013-17)	Incorporating real-life clinical data into drug development	8,000,000	16,952,280
GetReal Initiative (2018-21)	The GetReal Initiative	1,750,000	3,100,688
H2O (2020-25)	H2O Health outcomes observatory	10,476,687	21,978,937
HARMONY (2017-23)	Healthcare alliance for resourceful medicines offensive against neoplasms in hematology	20,200,000	42,137,217
HARMONY PLUS (2020-23)	Healthcare alliance for resourceful medicines offensive against neoplasms in hematology – PLUS	6,715,625	11,882,669
iABC (2015-23)	Inhaled antibiotics in bronchiectasis and cystic fibrosis	*	*
IDEA-FAST (2019-25)	Identifying digital endpoints to assess fatigue, sleep and activities in daily living in neurodegenerative disorders and immune-mediated inflammatory diseases	*	*
INNODIA (2015-23)	Translational approaches to disease modifying therapy of type 1 diabetes: an innovative approach towards understanding and arresting type 1 diabetes.	17,630,000	41,683,298
INNODIA HARVEST (2020-24)	Translational approaches to disease modifying therapy of type 1 diabetes - HARVESTing the fruits of INNODIA	*	*

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iPiE (2015-19)	Intelligent Assessment of Pharmaceuticals in the Environment	3,000,000	10,345,016
MOBILISE-D (2019-24)	Connecting digital mobility assessment to clinical outcomes for regulatory and clinical endorsement	25,395,897	49,911,564
NECESSITY (2019-24)	New clinical endpoints in primary Sjögren's syndrome: an interventional trial based on stratifying patients	*	*
NEWMEDS (2009-15)	Novel methods leading to new medications in depression and schizophrenia	*	*
NGN-PET (2017-20)	Modelling neuron-glia networks into a drug discovery platform for pain efficacious treatments	*	*
OPTIMA (2021-26)	Optimal treatment for patients with solid tumours in Europe through artificial intelligence	10,459,997	22,689,967
PARADIGM (2018-20)	Patients active in research and dialogues for an improved generation of medicines: advancing meaningful patient engagement in the life cycle of medicines for better health outcomes	4,498,931	9,127,316
Pharma-Cog (2010-15)	Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in early clinical develop.	*	*
PreDiCT-TB (2012-17)	Model-based preclinical development of anti-tuberculosis drug combinations	14,778,855	28,553,086
PREFER (2016-22)	Patient Preferences in benefit risk assessments during the drug life cycle	6,000,000	12,015,548
PREMIER (2020-26)	Prioritisation and risk evaluation of medicines in the environment	4,550,000	9,768,029
PRIMAVERA (2021-26)	Predicting the impact of monoclonal antibodies & vaccines on antimicrobial resistance	9,250,000	6,500,000
PROMISE (2021-24)	Preparing for RSV immunisation and surveillance in Europe	3,744,375	7,024,387
PROTECT (2009-15)	Pharmacoepidemiological research on outcomes of therapeutics by a European consortium	*	*
RESCEU (2017-22)	Respiratory syncytial virus consortium in Europe	14,498,125	25,453,316
RHAPSODY (2016-21)	Assessing risk and progression of prediabetes and type 2 diabetes to enable disease modification	8,130,000	18,691,126
ROADMAP (2016-18)	Real world outcomes across the AD spectrum for better care: multi-modal data access platform	3,998,250	8,210,381
SISAQOL-IMI (2021-24)	Establishing int. standards in the analysis of patient reported outcomes and HrQoL data in cancer clinical trials	2,281,840	5,944,755
SOPHIA (2020-25)	Stratification of obese phenotypes to optimize future obesity therapy	8,301,000	16,448,391
SUMMIT (2009-15)	Surrogate markers for micro- and macro-vascular hard endpoints for innovative diabetes tools	*	*
Trials@Home (2019-24)	Center of excellence – remote decentralised clinical trials	19,036,998	39,148,298
UNITE4TB (2021-28)	Academia and industry united innovation and treatment for tuberculosis	92,500,000	185,000,000
VAC2VAC (2016-22)	Vaccine lot to vaccine lot comparison by consistency testing	7,850,000	16,372,929
VALUE-Dx (2019-24)	The value of diagnostics to combat antimicrobial resistance by optimising antibiotic use	14,125,708	6,799,100
VITAL (2019-23)	Vaccines and infectious diseases in the ageing population	5,499,882	12,427,217
WEB-RADR (2014-17)	Recognising Adverse Drug Reactions	2,270,000	5,940,396
WEB-RADR 2 (2018-20)	WEB-RADR 2	1,168,750	2,140,980
Sum		**415,390,251**	**820,606,406**

** Project costs were - in case of multiple assignments to categories – calculated only once*

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Examples in category [72]: **Public contributions to Ecosystems and Networks: Clinical Network and Patient involvement in R&D, Education and training**

- COMBACTE group of projects is building a pan European antibacterial development networks and using them to run high-quality clinical studies addressing antimicrobial resistance.
    - The CLIN-Net hospital network includes over 800 hospitals in 42 countries in Europe. Capable of quickly and reliably recruiting, treating, monitoring and reporting data on the required numbers of patients in multinational, multicentre trials at all stages of clinical drug development.
    - EPI-Net harmonises and connects various European systems of disease surveillance. The aim is to increase our collective scientific knowledge about the distribution and determinants of serious bacterial infections in Europe.
    - LAB-Net maintains an extensive pan-European network of over 600 microbiology laboratories, with the overall objective to establish, train, and maintain a high-quality, geographically representative European laboratory network.
    - STAT-Net is a pan-European network of statistical experts from both
- EUPATI developed a programme on patient engagement in the drug development and regulatory process. The programme includes an in-depth training course (e.g. on clinical trial designs), an online toolbox, national platforms and wants to empower patients in expressing their needs and expectations.
- Diverse indications or patient-specific networks (EU-AIMS: network for autism spectrum disorder (ASD), INNODIA: trial network for type 1 diabetes, NEURONET: neurodegenerative research).
- The European Clinical Research Alliance on Infectious Diseases (ECRAID, https://www.ecraid.eu/about-us) is the successor of the European-funded projects COMBACTE and PREPARE. COMBACTE is part of the IMI-funded programme ND4BB (New Drugs for Bad Bugs) and focuses on improving the clinical development of antibiotics. PREPARE (the Platform for European Preparedness Against (Re-)emerging Epidemics) is a large scale European network, including 27 beneficiaries and is funded by the EU FP7 Programme. PREPARE started its activities in February already 2014.
- European Reference Networks (ERNs, https://www.erncare4ua.com/) are virtual networks across Europe (24 so far) aiming at improving care for patients with complex or rare diseases requiring highly specialized treatment by exchange of knowledge and collaborating [123]. ERNs were conceptualized and implemented through a Joint Action supported with EC-funds. The ERN initiative receives support from several EU funding programmes, including the Health Programme, the Connecting Europe Facility and Horizon Europe, but also national sources [155]. The European Rare Disease Research Coordination and Support Action (ERICA), in which all 24 European Reference Networks (ERNs) take part, aims at create a platform that integrates all

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ERNs research and innovation capacity. The European Rare Disease Registry Infrastructure (ERDRI, https://eu-rd-platform.jrc.ec.europa.eu/_en). This registry is also used for collecting safety data on drug-induced incidences (such as infections, neurological reactions etc.).

Table C - 4: Public contributions to Networks: Clinical Network and Patient involvement in R&D, Education and Training

Project/ programme name	Description	IMI- Funding in €	Total in €
c4c (2018-24)	conect4children - Collaborative network for European clinical trials for children	67,000,000	154,387,606
COMBACTE-CDI (2017-21)	Combatting Bacterial Resistance in Europe - Clostridium Difficile Infections	*	*
COMBACTE-MAGNET (2015-22)	Combatting bacterial resistance in Europe - molecules against Gram negative infections	*	*
COMBACTE-NET (2013-23)	Combatting Bacterial Resistance in Europe	109,433,010	212,598,841
EFOEUPATI (2018-20)	Ensuring the future of EUPATI beyond 2020	365,243	604,043
EMTRAIN (2009-16)	European Medicines Research Training Network	4,324,999	7,989,509
EPND (2021-26)	European Platform for Neurodegenerative Diseases	*	*
Eu2P (2009-16)	European programme in Pharmacovigilance and Pharmacoepidemiology	3,708,225	8,018,904
EUPATI (2012-17)	European Patients' Academy on Therapeutic Innovation	5,250,000	10,951,178
EU-PEARL (2019-23)	EU patient-centric clinical trial platform	*	*
FACILITATE (2022-25)	Framework for clinical trial participants data reutilization for a fully transparent and ethical ecosystem	*	*
H2O (2020-25)	H2O Health outcomes observatory	*	*
HIPPOCRATES (2021-26)	Health initiatives in psoriasis and psoriatic arthritis consortium European states	10,210,993	21,245,993
INNODIA (2015-23)	Translational approaches to disease modifying therapy of type 1 diabetes	*	*
MACUSTAR (2017-24)	Intermediate AMD: develop. of novel clinical endpoints for clinical trials in patients (regulatory and patient access intention	*	*
MOPEAD (2016-19)	Models of patient engagement for Alzheimer's disease	2,043,000	4,581,968
NEURONET (2019-22)	Efficiently networking European neurodegeneration research	1,199,125	2,353,125
PARADIGM (2018-20)	Patients active in research and dialogues for an improved generation of medicines: advancing meaningful patient engagement in the life cycle of medicines for better health outcomes	*	*
Pharmatrain (2009-14)	Pharmaceutical Medicine Training Programme	3,510,300	7,631,528
PREFER (2016-22)	Patient Preferences in benefit risk assessments during the drug life cycle	*	*
SafeSciMET (2010-2016)	European Modular Education and Training Programme in Safety Sciences for Medicines	2,374,904	5,982,957
SISAQOL-IMI (2021-24)	Establishing int. standards in the analysis of patient reported outcomes and HrQoL in cancer clinical trials	*	*
ZAPI (2015-21)	Zoonotic anticipation and preparedness initiative	9,538,688	19,646,794
Sum		**218,958,487**	**455,992,446**

** Project costs were - in case of multiple assignments to categories – calculated only once.*

Examples in category [72]: **Public contributions to Conducting Clinical Trials**

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- EURECA focuses on patients with serious carbapenem resistant infections and aims to learn how patients across Europe are currently treated and which patients respond well to which treatments.
- EBOVAC1 published data from a trial in the UK (87 participants) showing that the Janssen prime-boost Ebola vaccine regimen is safe, well tolerated, and induces durable immune responses. In total, 1 653 people have been enrolled in the EBOVAC1 and EBOVAC2 trials in Europe and Africa. An innovative community engagement strategy in Sierra Leone helped to ensure successful recruitment for the trial there.
- PROTECT-trial compares the results of proton therapy with radiotherapy for patients suffering from cancer of the oesophagus. The clinical trial will involve 400 patients in 9 countries.
- SAATELLITE is investigating a drug called MEDI4893. MEDI4893 targets a toxin produced by Staphylococcus aureus, a bacteria often associated with hospitalassociated infections and linked to resistance issues.
- UNITE4TB aims to accelerate and improve clinical trials of combinations of existing and new drugs, with the goal of developing new and highly active treatment regimens for TB, including drug-resistant TB.

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Table C - 5: Public contributions to Conducting Clinical Trials

Project/ programme name	Description	IMI- Funding in €	Total in €
AB-Direct (2019-23)	Antibiotic distribution and recovery in tissue	3,429,217	3,789,718
AIMS2-Trials (2018-25)	Autism Innovative Medicine Studies – 2 – Trials	54,999,999	115,441,584
CARE (2020-25)	Corona accelerated R&D in Europe	*	*
COMBACTE-CARE (2015-23)	Combatting Bacterial Resistance in Europe - Carbapenem Resistance	23,871,500	84,384,066
COMBACTE-MAGNET (2015-22)	Combatting bacterial resistance in Europe - molecules against Gram negative infections	46,725,530	89,630,943
EBOVAC1 (2014-21)	Development of a prophylactic Ebola vaccine using an heterologous prime-boost regimen	58,336,885	98.263.464
EBOVAC2 (2014-21)	Development of a prophylactic Ebola vaccine using an heterologous prime-boost regimen: phase II	22,790,820	50,710,893
EBOVAC3 (2018-24)	Bringing a prophylactic Ebola vaccine to licensure	29,402,656	50,979,890
EPAD (2015-20)	European prevention of Alzheimer's dementia consortium	25,880,000	58,986,698
GNA NOW (2019-25)	Novel Gram-negative antibiotic now	12,299,995	31,415,987
iABC (2015-23)	Inhaled antibiotics in bronchiectasis and cystic fibrosis	24,331,609	56,220,279
Impentri (2020-22)	Development of Impentri, an intravenous imatinib formulation for COVID-19 acute respiratory distress syndrome (ARDS)	3,662,963	3,985,732
INNODIA HARVEST (2020-24)	Translational approaches to disease modifying therapy of type 1 diabetes - HARVESTing the fruits of INNODIA	5,999,055	13,403,035
PD-MIND (2019-22)	Parkinson disease with mild cognition impairment treated with nicotinic agonist drug	999,698	2,131,609
PERISCOPE (2016-22)	PERtussIS COrrelates of Protection Europe	21,000,000	29,926,687
PRECISESADS (2014-19)	Molecular reclassification to find clinically useful biomarkers for systemic autoimmune diseases	9,999,323	23,098,292
PROTECT-trial (2021-27)	Proton versus photon therapy for esophageal cancer - a trimodality strategy	1,500,000	4,763,734
RespiriNTM (2019-25)	Progress novel assets (one FIH start) for non-tubercular mycobacteria that may act synergistically with bedaquiline and cytochrome bc drugs	*	*
RespiriTB (2019-25)	Progress new assets (one pre-NME and one FIH start) for tuberculosis that act synergistically with bedaquiline, cytochrome bc or cytochrome bd inhibitors	6,840,000	9,962,900
STOPFOP (2019-24)	Saracatinib trial to prevent FOP	999,710	1,999,712
TRIC-TB (2019-24)	Boosting Ethionamide efficacy and lowering the dose with a small molecule transcriptional modulators, to overcoming MDR-TB infections and define a new place for Ethionamide in 1st-line TB treatments	6,926,375	8,373,250
UNITE4TB (2021-28)	Academia and industry united innovation and treatment for tuberculosis	92,500,000	185,000,000
Sum		**452,495,335**	**922,468,473**

** Project costs were - in case of multiple assignments to categories – calculated only once.*

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Examples in category [72]: **Public contributions to Big Data and Knowledge Management, Digital Health, Artificial Intelligence**

- The BIGPICTURE has developed software tools to allow for the easy conversion of a range of existing whole slide image (WSI; glass slides are scanned to produce digital images) file formats to the digital imaging and communications in medicine (DICOM) standard: BIGPICTURE aims to generate a repository of 3 mil whole slide images (WSIs) for the development of AI algorithms and the acceleration of computational pathology.
- The EHDEN Real World Data Portal will offer findable, standardised data. The portal provides a one-stop-shop for study planning, data access, standardised analysis & reporting. It is currently populated with 160 mil patient records from 20 countries, and will grow to include the complete EHDEN network of ~830 mil patient records.
- EHR4CR has developed a platform that enables controlled access to hospitals' data for the preparation of clinical trials. The platform has demonstrated its usefulness in speeding up the recruitment of patients, while ensuring that patient privacy is respected.
- HARMONY and HARMONY PLUS focused on blood cancers, rganising datasets in the platform according to the observational medical outcomes partnership (OMOP) standard format for observational data, capable of admitting any information independently of its origin. HARMONY has expanded existing vocabularies, terminologies, and coding schemes. Approx. 150 000 patients' datasets had already been identified.
- Inno4Vac aims to harness advances in fields such as immunology, microbiology, systems biology, mathematical models, big data and artificial intelligence, and incorporate them into the vaccine industry.
- Open PHACTS created an online platform that links up diverse databases of informatirelating to medicines allowing quickly and easily access, query and analyse data from multiple sources.

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Table C - 6: Public contributions to Big Data and Knowledge Management, Digital Health, Artificial Intelligence

Project/ programme name	Description	IMI-Funding in €	Total in €
AETIONOMY (2014-18)	Organising mechanistic knowledge about neurodegenerative diseases for the improvement of drug development and therapy	7,993,234	17,812,216
BigData@Heart (2017-23)	Big Data for Better Outcome (BD4BO) in Cardiovascular disease (CVD)	9,664,970	19,449,972
BIGPICTURE (2021-27)	Central repository for digital pathology	32,319,825	70,081,907
ConcePTION (2019-24)	Building an ecosystem for better monitoring and communicating of medication safety in pregnancy and breastfeeding: validated and regulatory endorsed workflows for fast, optimised evidence generation	*	*
COVID-RED (2020-22)	COVID-19 infections - remote early detection	9,592,029	10,329,254
DDMoRe (2011-16)	Drug Disease Model Resources	10,399,426	23,063,274
DO->IT (2017-19)	Big data for better outcomes, policy innovation and healthcare system transformation	3,549,833	7,191,755
DRAGON (2020-23)	Rapid and secure AI imaging based diagnosis, stratification, follow-up, and preparedness for coronavirus pandemics	11,381,970	11,542,642
EHDEN (2018-24)	European Health Data and Evidence Network	14,105,750	30,188,808
EHR4CR (2011-16)	Electronic Health Records Systems for Clinical Research	*	*
EMIF (2013-18)	European Medical Information Framework	24,356,096	55,784,311
EPND (2021-26)	European Platform for Neurodegenerative Diseases	9,680,000	19,005,502
eTRANSAFE (2017-23)	Enhacing TRANslational SAFEty Assessment through Integrative Knowledge Management	20,000,000	40,882,350
eTRIKS (2012-18)	Delivering European Translational Information & Knowledge Management Services	10,309,818	24,244,741
FACILITATE (2022-25)	Framework for clinical trial participants data reutilization for a fully transparent and ethical ecosystem	*	*
FAIRplus (2019-22)	FAIRplus	3,996,150	7,827,194
Gravitate-Health (2020-25)	Empowering and equipping Europeans with health information for active personal health management and adherence to treatment	9,280,000	18,561,750
HARMONY (2017-23)	Healthcare alliance for resourceful medicines offensive against neoplasms in hematology	*	*
HARMONY PLUS (2020-23)	Healthcare alliance for resourceful medicines offensive against neoplasms in hematology – PLUS	*	*
IDEA-FAST (2019-25)	Identifying digital endpoints to assess fatigue, sleep and activities in daily living in neurodegenerative disorders and immune-mediated inflammatory diseases	20,997,523	40,949,634
Inno4Vac (2021-27)	Innovations to accelerate vaccine development and manufacture	18,600,000	39,342,552
MELLODDY (2019-22)	Machine learning ledger orchestration for drug discovery	8,000,000	18,635,465
MOBILISE-D (2019-24)	Connecting digital mobility assessment to clinical outcomes for regulatory and clinical endorsement	*	*
Open PHACTS (2011-16)	The Open Pharmacological Concepts Triple Store	11,466,433	20,782,066
PharmaLedger (2020-22)	Blockchain-based platform for the healthcare sector, using the supply chain, clinical trials, and health data as case studies	8,290,694	22,118,325
PIONEER (2018-23)	Prostate cancer diagnosis and treatment enhancement through the power of big data in Europe	6,000,000	13,549,160
RADAR-AD (2019-23)	Remote assessment of disease and relapse – Alzheimer's disease	4,999,757	7,659,120
RADAR-CNS (2016-22)	Remote Assessment of Disease and Relapse in Central Nervous System Disorders	11,000,000	25,712,111
ROADMAP (2016-18)	Real world outcomes across the AD spectrum for better care: multi-modal data access platform	*	*
Screen4Care (2021-26)	Shortening the path to rare disease diagnosis by using newborn genetic screening and digital technologies	11,938,569	25,423,569
Trials@Home (2019-24)	Center of excellence – remote decentralised clinical trials	*	*
WEB-RADR (2014-17)	Recognising Adverse Drug Reactions	2,270,000	5,940,396
WEB-RADR 2 (2018-20)	Recognising Adverse Drug Reactions 2	1,168,750	2,140,980
Sum		**281,360,827**	**578,219,054**

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Appendix D

Public Contributions to Spin-Off/ Spin-Out from academic R&D and acquisitions (overview and examples)

- D-1: European Innovation Council (EIC): Progrmmes and Funding 2021-2023
- D-2: European Institute for Innovation and Technology (EIT) funded Health Products 2021-2023
- D-3: Good Practice Examples for transparent reporting on academic research spin-offs/ spin-outs in NL: BioGeneration Ventures (BGV): Examples from Portfolio BGV I
- D-4: Origins of drug products manufactured by Pfizer in 2017
- D-5: Origins of drug products manufactured by J&J in 2017
- D-6: Overview of EMA-approved ATMPs, acquisitions and licensing agreements in early research, later development

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Table D- 1: European Innovation Council: Programme and Funding 2021-2023

	European Innovation Council	Funding in €
2021		**1.49 bil**
	EIC Pathfinder (across all topics)	300 mil
	EIC Pathfinder Open (across all topics)	168 mil
	EIC Pathfinder Challenges (5 pre-defined topics)	132 mil
	EIC Pathfinder Challenges (2 pre-defined topics health only)	52.8 mil
	• *Tools to measure & stimulate activity in brain tissue*	*26.4 mil*
	• *Emerging technologies in cell & gene therapy….*	*26.4 mil*
	EIC Transition (across all topics)	100.1 mil
	EIC Transition Open (across all topics)	59.6
	EIC Transition Challenges (2 pre-defined topics)	40.5
	EIC Transition Challenges (1 pre-defined topic health only)	20.25 mil
	• *Medical devices*	*20.25 mil*
	EIC Accelerator (across all topics)	1.09 bil
	EIC Accelerator Open (across all topics)	592.5 mil
	EIC Accelerator Challenges (2 pre-defined topics)	495.1 mil
	EIC Accelerator Challenges (1 pre-defined topic health only)	247.55 mil
	• *Strategic Health and Digital Technologies*	*247.55 mil*
2022		**1.7 bil**
	EIC Pathfinder (across all topics)	350 mil
	EIC Pathfinder Open (across all topics)	183 mil
	EIC Pathfinder Challenges (6 pre-defined topics)	167 mil
	EIC Pathfinder Challenges (2 pre-defined topics health only)	55.67 mil
	• *Cardiogenomics*	*27.83 mil*
	• *Towards the healthcare continuum: technologies to support a radical shift from episodic to continuous healthcare*	*27.83 mil*
	EIC Transition (across all topics)	131 mil
	EIC Transition Open (across all topics)	70.9 mil
	EIC Transition Challenges (3 pre-defined topics)	60.5 mil
	EIC Transition Challenges (1 pre-defined topic health only)	20.17 mil
	• *RNA-based therapies and diagnostics for complex or rare genetic diseases*	*20.17 mil*
	EIC Accelerator (across all topics)	1.16 bil
	EIC Accelerator Open (across all topics)	630.9 mil
	EIC Accelerator Challenges (2 pre-defined topics)	536.9 mil
	EIC Accelerator Challenges (1 pre-defined topic health only)	268.45 mil
	• *Technologies for Open Strategic Autonomy (Strategic healthcare technologies)*	*268.45 mil*
2023		**1.6 bil**
	EIC Pathfinder (across all topics)	**343 mil**
	EIC Pathfinder Open (across all topics)	179.5 mil
	EIC Pathfinder Challenges (5 pre-defined topics)	163.5 mil
	EIC Pathfinder Challenges (1 pre-defined topics health only)	32.7 mil
	• *Precision nutrition*	*32.7 mil*
	EIC Transition (across all topics)	128.3 mil
	EIC Transition Open (across all topics)	67.86 mil
	EIC Transition Challenges (3 pre-defined topics)	60.5 mil
	EIC Transition Challenges (1 pre-defined topic health only)	20 mil
	• *Full scale Micro-Nano-Bio devices for medical and medical research applications*	*20 mil*
	EIC Accelerator (across all topics)	1.13 bil
	EIC Accelerator Open (across all topics)	612.98 mil
	EIC Accelerator Challenges 2023 (pre-defined topics)	524.73 mil
	EIC Accelerator Challenges 2023 (2 pre-defined topics health only)	130 mil
	• *Novel biomarker-based assays to guide personalised cancer treatment*	*65 mil*
	• *Aerosol and surface decontamination for pandemic management*	*65 mil*

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Sources: EIC-WP2023-factsheet-main.pdf (Europa.eu), EIC-WP2022-factsheet-general.pdf (europa.eu), EIC-WP2021.pdf (europa.eu)

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Table D- 2: European Institute for Innovation and Technology (EIT) funded health products (https://eithealth.eu/)

Name of Product/ Origin of Country	Category of Health Product/ explanation	EIT Funding in € (category of funding)
2023		
Adiquit, CZ	Digital Health: a personalised, evidence-based online therapy that may help smoking patients meet the preoperative recommendations and, consequently, reduce the rate of cancellations in the ambulatory setting.	25,000 (BH) each
Aidx Medical BV, NL	BioTech: an automated diagnostic microscope for reliable and rapid detection of urinary tract infections using novel Artificial Intelligence (AI) algorithms. This proposed diagnostic technique is suitable for independent use by healthcare providers at the point-of-care.	
Antegenes, EE	MedTech, Estonia: a genetic tests to detect individual risks for the most common cancers worldwide, including breast, prostate, colorectal, and skin melanoma. Unlike traditional cancer screening programmes, which consider only age as a risk factor, Antegenes' tests are based on polygenic risk score technology, making them much more precise and efficient.	
DIVERSA Technologies, ES	BioTech: ready-to-use formulations for fast intracellular delivery of small molecules and complex macromolecules with high efficiency while boosting their therapeutic activity.	
Doctomatic, ES	Digital Health: a device and condition-agnostic AI-powered SaaS platform to monitor patients remotely. By downloading an app, patients can scan the results from any domestic medical device and automatically provide their doctors with the data.	
Envision medical, NL	MedTech: the Vascoscope system, a dedicated ultrasound to make vascular access simple to perform and easy to learn.	
Greenhabit BV, NL	Digital Health: a 12-weeks behavioural health treatment programme using AI to personalise treatment. This digital holistic intervention is evidence-based and educates patients to improve their quality of life.	
Health Force, AT	Digital Health: Developing an AI Assistant that can take care of everyday, time-consuming tasks to save hospital staff time. Currently, the AI Assistant is operating in the hospital back-office, where it will handle tasks such as managing supplies, creating and submitting medical bills, scheduling appointments and more.	
Heuristik, ES	Digital Health: 95% of identification errors happen because of the identification bracelets and the health cards in hospitals. To solve these daily problems, they developed a software solution combining fingerprints and artificial intelligence in order to identify and manage patients during the whole patient journey.	
HMG Systems Engineering, DE	Digital Health: The PGXperts System brings drug interactions and medication risks into genomics age by translating scientific knowledge on interactions, drug risk factors and pharmacogenetics into actionable results for medical professionals.	
Knopka, PL	MedTech: an advanced wireless nurse call system for patient care automation on hospital beds. The system helps nurses and doctors respond immediately by ensuring that medical staff arrives at a patient's bed within 3 minutes.	
Micro-Cosmos, NL	MedTech: help inpatients recover faster by providing a better healing environment in a mobile and easy way. Their domes reduce noise and light and thereby improve the sleep of patients.	
Morecognition, IT	Digital Health, Italy: Remo is a new, revolutionary digital treatment model based on a medical device that measures muscle activity, an APP and an AI. It allows patients to perform the exercises prescribed by the therapist at home, reducing the costs per session.	
OaCP, IE	BioTech: OACP saves lives by making crucial DNA tests for cancer and infections faster and more accessible.	
Osteobionix, ES	MedTech: for people who need extensive chest wall reconstruction are subject to impairment of physiologic breathing, discomfort, pain, deformity and severe risk of infection and re-intervention. oBreathe is a chest wall reconstruction implant developed with ITC and skilled thoracic surgeons, which allows for physiologic breathing and restores shape and function.	
Physikit, DE	Digital Health: Addresses the need for more accessible and convenient biosample testing solutions by providing e-health apps, telemedicine platforms, and hospitals with a simple and effective way to develop at-home sample collection programmes.	
sendance, AT	MedTech: developers of Smart orthopedic and other wearable devices face the problem that the design, production, and operation of such devices involve tedious, complex, and risky processes involving long timescales. With sendance, companies spend significantly less time and costs for the development of smart product design, enabling them to create innovative solutions that are easy to test and let companies focus on growing their business.	

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SpeakTX, EE	Digital Health: An online speech therapy platform that provides interactive exercises for children and adult patients, making speech therapy more accessible, effective and engaging.	
Stroke2Prevent, NL	MedTech: The use of traditional screening methods for the presence of atherosclerosis who are undergoing coronary artery bypass grafting or trans aortic valve replacement does not allow for full visualisation of the distal ascending aorta. This area can be fully visualised in real-time by TEE with the use of a fluid-filled catheter called A-View placed into the patients' trachea.	
Sympa Health, PL	Digital Health: A digital therapeutics application designed to provide personalised solutions for managing the symptoms of women's chronic conditions such as endometriosis and PCOS. Their app uses the latest developments in AI and personalised treatments to offer tailored treatment plans, real-time symptom tracking, and expert support to women.	
2022		
Medicud, IT	One in twenty patients undergoing surgery will suffer from Surgical Site Infection (SSI). Negative Pressure Wound Therapy (NPWT) has proven prophylactic efficacy. But use is limited due to unsuitable, expensive and unhandy current devices. Medicud aims to make NPWT the gold standard remedy for closed surgical incisions, such as caesarean sections, with its innovative, unmatchable and ultraportable device. The team has a working prototype and has filed four patents.	10,000 (ISA)
Sprin, HU	Inhaled drug delivery is impressive. The large surface area of the human lung, combined with its abundant blood supply, makes it one of the BEST routes for treating an array of disorders. The problem is that current inhaled delivery devices waste 50% of medication and, according to several studies, deliver less than a quarter of the active ingredient. Because of this, current devices cannot be used to deliver expensive or high-precision agents like insulin, antibiotics, gene therapy or replace injectables. The start-up team's solution is a pocket-sized smart nebuliser that helps to deliver precision medication in a safer, more effective, and pain-free way.	15,000 (ISA)
The IntraCross Catheter, GR	Peripheral Artery Disease (PAD) is a major chronic disease affecting mils worldwide and growing due to an ageing population. The team's technology addresses an unmet need for minimally invasive PAD procedures in roughly 30% of all chronic, severe arterial stenosis cases. They do this at a marginally higher cost than a conventional balloon catheter. This could mean 7.5bil euros in savings for the European healthcare system and reduced morbidity rates thanks to averted open bypass surgeries for roughly 300,000 patients.	25,000 (ISA)
deepeye, DE	deepeye stands out in the digital health category with its transformative AI-powered diagnostic solutions. By employing deep learning algorithms and computer vision technology, deepeye has developed a platform that accurately detects and analyses medical images, enabling earlier and more accurate diagnoses.	30,000 (HC) each
timeisbrain, ES	In the Medtech category, timeisbrain has captured the spotlight with its groundbreaking approach to revolutionising stroke care. By leveraging cutting-edge AI algorithms, timeisbrain has developed a state-of-the-art platform that enables real-time identification and assessment of stroke patients, ultimately leading to faster treatment decisions and improved patient outcomes.	
immunyx, US	immunyx takes center stage in the biotech category with its revolutionary immunotherapy advancements. Their innovative approach harnesses the power of the immune system to combat cancer and other challenging diseases. By developing personalised treatments tailored to each patient, immunyx is paving the way for more effective and targeted therapies, offering new hope to patients worldwide.	
Bonescreen, DE	Bonescreen, a team of five innovators, aims to translate two decades of research in medicine and AI into a medical software that would enable oncologists, radiologists, and patients to assess bone health. Their solution would produce automatically generated reports to help healthcare professionals identify the early signs of cancer at no extra cost to patients or healthcare providers.	1.5 M (WC) each
NIB biotec, IT	Italian venture, NIB biotec, is composed of four business professionals and scientists striving to develop a smart biosensor to diagnose prostate cancer. Using urinary molecules, the solution aims to make the diagnostic path of prostate cancer more efficient by minimising time in hospitals and decentralising exams. The team owns a patent that claims the use of a combination of urinary molecules as diagnostically and prognostically reliable biomarkers for prostate cancer.	
Amolab, IT	offers the first and patented technological solution for a safe, automatic and quantitative monitoring of childbirth/ labour.	
Ergotrics, BE	specialises in positioning patients with compressed air to provide better support without ergonomic burden for healthcare workers.	
Gaston Medical, NL	prevents dangerous or incorrect medication from being given to patients, by use of clinical decision support medical devices.	
Kids Speech Labs, IR	enables providers to identify the best approach to speech and language therapy at the earliest opportunity, supporting all stages of care from fully remote to hybrid.	
KWARTS, BE	helps life sciences companies improve HCP (healthcare professionals) relations using data-driven techniques.	
Medical Simulation Technologies, PL	is advancing medical simulators, by using the latest technologies in computer science and electronics.	

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Moona, FR	improves sleep for mils of people, using breakthrough technology and artificial intelligence (AI).	25,000 (BH) each
Tucuvi Care, ES	offers remote in-home patient care monitoring programmes through a CE-marked virtual care platform based on AI, voice technology and natural language processing (NLP).	
Cancer Center, PL	supports oncology diagnosis (pathology and radiology) to achieve a better and faster decision-making process using AI.	
Cardiolyse, FI	is addressing early cardiovascular disease detection/prevention through a post-discharge and chronic cardiovascular disease (CVD) patient monitoring platform.	
Deversify, SE	offers health tech solutions for increased individual health and wellbeing by providing a powerful tool through a combination of hardware, software, education, and research.	
Echolight, IT	provides a radiation-free solution for assessing the bone health status of lumbar vertebrae and femoral neck.	
Eodyne Systems, ES	develops and commercialises science-based, technological solutions for neurorehabilitation (medical process which aims to aid recovery from a nervous system injury).	
Exheus, ES	provides health intelligence reports that analyse the expression levels of the 22,000 genes of the genome through RNA sequencing and AI.	
GutyCare, FR	provides patients with a solution to improve their care and identify new predictive markers for digestive diseases.	
InukaCare, NL	helps you to prevent burnout, stress, dropouts and improve the overall wellbeing of your employees.	
Legit.Health, ES	is developing computer programmes powered by AI for the detection, measurement, and monitoring of visible diseases.	
Moveo, IT	self-powered, lightweight soft exoskeleton/exosuit that stores the energy generated by hip extensor muscles during walking and uses it to assist motion for patients with walking difficulties	
PHLECS, NL	has developed a unique technology platform that meets a large amount of needs in dermatology, in particular for the treatment of elderly itching and eczema.	
VR Medical, CZ	is creating rehabilitation programmes in virtual reality (physiotherapy, neurotherapy and occupational therapy applications) for a wide range of rehabilitation goals and diagnosis.	
Zendra, IR	provides turnkey digital health platforms, with the aim of helping with patient engagement and care optimisation	
Pae-IQ, ZA	provides telephone triage aimed at optimising health resource utilisation.	
2021		
Cibiltech, FR	develops digital solutions for predictive medicine in renal transplantation. Their AI-based algorithm helps nephrologists to better assess individual graft loss trajectory for each patient and to adjust treatment accordingly.	
Fizimed, FR	develops connected medical devices for women health. Emy is a connected medical device to strengthen pelvic floor at home to stop leaks associated with urinary incontinence.	
Flomics Biotech, ES	is developing a multi-purpose liquid biopsy capable of detecting multiple complex diseases from a standard blood sample even before the first symptoms appear.	
Japet Medical, FR	combines medical sciences and modern robotics in solutions for the health of peoples back. Its exoskeleton helps employees affected by back pain to recover and stay healthy at work.	
KIneto TECH REHAB SRL, RO	develops digital care programmes, for people with knee arthrosis and lower back pain. Based on two, simple to use, motion tracking sensors, patients receive a unique training session, in the comfort of their homes, monitored by a real physio and their orthopedic doctor.	
MRIguidance, NL	is a medical imaging software company combining a profound knowledge of MR physics with the newest deep learning techniques to visualise bone with MRI.	
MUNEVO, DE	aims to empower people with disabilities by using smart and innovative technologies. Munevo DRIVE is the first wheelchair control using smart glasses that allows user to control the wheelchair hands-free.	
Sinfonic Innovation Management Bt., HU	has created Babyndex, an app that can detect fertile saliva patterns in an ovulation microscope. It helps women to monitor their actual fertility even with irregular cycles.	
SmartSoft, BUL	is developing software products utilizing Optical Character Recognition, data capture, and image processing.	
STEMI Global, SK	is committed to the development of communication platform which assists healthcare professionals in managing emergency cases such as heart attack, stroke, trauma and recently COVID-19, by shortening the critical “time-to-treatment”.	
SuperSeton B.V., NL	is a CE class IIA Medical Device solution that prevents unnecessary irritation and discomfort for patients being treated for fistulas.	

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TheraPanacea, FR	is introducing cutting-edge technology in AI to disrupt cancer treatment with radiotherapy.	25,000 (BH) each
Think Biosolution, IR	is building chronic disease prevention platforms for assisted living and home health care agencies. Their Geriatric Care Platform helps long term facility nurse managers to monitor and triage patients.	
ZeClinics, ES	is a biotech company using zebrafish to accelerate drug discovery.	
AdEchoTech, FR	delivers expert diagnostic ultrasound imaging in real time to remote populations that need ultrasonography. This helps ensure the equitable provision of diagnostic services.	
ArthroSave, NL	offers a joint preserving surgical treatment for relatively young patients with knee osteoarthritis. The KneeReviver unloads the knee joint and allow for joint tissue repair, reducing pain and and improving mobility.	
Axomove, FR	is an e-health startup using a digital rehabilitation platform to allow practitioners to care for patients with physical conditions remotely.	
Biomedal S.L., ES	aims to be an international reference in innovative products and services for the diagnosis and monitoring of celiac disease and other chronic immune diseases as well as supporting the food industry in the identification of allergens and contaminants.	
Ergobyte Informatics S.A., ES	their RxReasoner service prevents prescribing errors by recommending suitable medications based on the patient's medical conditions and running drug-to-drug and drug-to-disease interaction checks.	
Eversens SL, ES	facilitates the diagnosis, personalized treatment selection and monitoring of asthma by providing useful information to enable patients to self-monitor their disease and help avoid attacks and unnecessary hospital visits.	
Healcloud, HU	provides enterprise software to hospitals, clinical research organizations, and pharmaceutical companies who would like to build virtual data networks that aggregate health Big Data with one tool to support clinical trials, observational studies and population health analytics.	
IDOVEN, ES	is redefining the way cardiac arrhythmias are diagnosed using artificial intelligence algorithms.	
Incepto Medical, FR	provides a single, secure, and integrated platform, which has its own and curated third-party AI apps for medical imaging that meet several different clinical needs, empowering doctors and radiologists to diagnose more precisely and faster.	
LS CancerDiag, FI	has developed DiagMMR®, an innovative screening service that reliably detects Lynch syndrome, the biggest single cause of hereditary cancers, in particular colorectal and endometrial cancer.	
Marsi-Bionics S.L., ES	is using deeptech to provide patients with a permanent and/or progressive gait-related disability with modular robotic exoskletons for rehabilitation treatments and activities of daily living.	
MJN Neuroserveis S.L., ES	has a wearable device that can alert patients before seizures occur by the continuous monitoring of brain signals.	
MOWOOT, ES	is treating intestinal transit disorders with a purely physical, non-drug, non-invasive solution.	
Parsek Information Technologies GmbH, AT	is using Vitaly Coordinated Care, a comprehensive, patient-centric solution, to offer care teams and patients 24/7 support, personalised to their health needs.	
Predilife, FR	has developed Mammorisk, a tool that uses AI to assess, from the age of 40, a women's risk of developing breast cancer, in order to promote early detection.	
PVR med d.o.o, SI	has developed a medical device for faster treatment and prevention of diabetic foot ulcers.	
Reactive Robotics, DE	has developed VEMO®, a robotic system for intensive care therapy. VEMO® provides very early mobilization for severely ill patients, allowing them to recover faster and free up ICU capacity.	
VItadio, CZ	provides a digital therapeutics platform that employs AI to deliver personalized digital care programmes and scalable support of own team of registered dietitians.	
naturalens, SE	A comfortable extended wear natural contact lens for managing myopia in dry eye patients. There is an urgent need for novel cost-effective and non-invasive approaches for management of myopia and dry eye to avoid visual impairment and blindness. Our solution, a bioengineered natural contact lens (NaturaLens), can help address this underserved need. Team NaturaLens is developing a Natural Contact Lens made from the same material as the human eye that can help manage myopia in dry eye patients.	1.5 M (WC)
PeriVision, CH	PeriVision, a MedTech spin-off from the ARTORG Center (AI in Medical Imaging lab) has won a prestigious European Wild Card in the 2021 challenge. A portable and AI-based perimetry device for 70% faster, patientfriendly and much more cost-efficient glaucoma patient monitor. PeriVision wants to reimagine glaucoma	

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	monitoring to benefit patients and doctors alike by offering a portable and AI-based perimetry device for 70% faster, patient-friendly and much more cost-efficient glaucoma patient monitoring.	
Confidence Socket, DE	Amparo, a German start-up that aims to revolutionise prosthetics with their 'Confidence Socket', has taken first place at the EIT Health-supported MedtecLIVE Pitch Contest by focusing on societal impact.	15,000 (MTL)
Methinks Stroke Suite, ES	Methinks Stroke Suite, is capable of assisting in stroke triage and providing decision support for life-saving treatment using non-contrast CT, with the potential to optimize stroke triage and reduce time to treatment. Methinks Stroke Suite is the first CE marked medical device that assists in finding large vessel occlusions (LVO) both hyperdense and not from NCCT and CTA. The software also has the ability to detect Intracerebral hemorrhages (ICH) on NCCT images.	5,000 (MTL)
Continuous "at home" monitoring for acute and chronic cardiorespiratory disease patients, GR	a wearable device allows monitoring of vital signs, paired with a customised physician-facing portal and a patient app, augmented with artificial intelligence.	75,000 (RIC 2021) each
CryoHolder, SI	a unique tool that enables quick, more efficient, and safe transfer of frozen cryovials. It can work with liquid nitrogen and also handle sterilisation in an autoclave at 121°C.	
ESAIA – Early Stage Ear Infection Assessment	a non-invasive medical device, called Otitest, evaluates the colour of the inner ear and eardrum, using an RGB sensor, for early-stage ear infection assessment.	
FRoom, SI	an all-in-one solution for home physiotherapy exercise programmes combining innovative technologies and expert design.	
Hermes, IT	a wearable device provides a near hermetic seal in an ergonomic system with battery operated filters, to give individual protection against exposure to contaminated droplets.	
Koatum, LV	a multiple-layer hybrid coating for medical implants with the ability of drug delivery. The three layers of the coating provide metal isolation, bioactive properties and delivery of a drug with antibacterial properties to promote the body's acceptance of the implant.	
Laboratory diagnostics from the patient's home with a doctor's remote consultation, SI	an online diagnostic platform for testing sexually transmitted infections allows patients to order the tests, take their own urine, swab or finger-prick sample, and send it in for analysis, followed by remote consultation if needed.	
Mindaux (MAX), PT	a digital therapeutics social platform to create healthier workplaces, using personalised electronic cognitive behavioural therapy.	
O2-CPAP add-on, LV	an add-on module for CPAP devices that helps patients with obstructive sleep apnoea (OSA) by controlling the oxygen concentration, enabling oxygen supplies to be adjusted while monitoring the patient.	
Remote monitoring of patients with cardiovascular diseases and SARS-CoV-2, SK	telemonitoring solution for patients with hypertension, dyslipidaemia, obesity, and/or high cardiovascular risk, and a SARS-CoV-2 positive test. The solution supports reduction of interventions or visits to the doctor.	
Stuey, HR	an assistive technology solution that helps people who stutter make phone calls with pre-recorded lines that are transmitted to the call with a high level of speech reality.	
Leuko, ES	Leuko is developing PointCheckTM, the first solution that enables at-home non-invasive white blood cell (WBC) monitoring.	30,000€ (HC) each
Ebenbuild, DE	By calculating regional distributions of mechanical quantities such as stresses and strains, Ebenbuild provides a novel computer-based imaging technique that makes ventilation therapy quantifiable for the first time. The scalable software solution can be used worldwide, regardless of the brand or manufacturer of the ventilator.	
SolasCure, UK	SolasCure is working on a novel way to treat chronic wounds with a new enzymatic debridement product. Maggots are nature's solution to removing dead tissue, by applying biochemical tools to digest wound debris. Using biomimicry, SolasCure is developing Aurase WoundGel, which contains an enzyme isolated and cloned from medical maggots. This hydrogel, still in the development phase, is expected to accelerate wound debridement.	
Advosense, DE	Advosense aims to transform incontinence management in healthcare settings by developing a next generation incontinence solution.	

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Arthex Biotech, ES	ARTHEx develops antisense RNA treatments for unmet genetic diseases. ARTHEx's first product in the pipeline is an oligonucleotide for the treatment of myotonic dystrophy.	50,000 (CA) each
Asthmaware, NL	Asthmaware develops a smart nightwear that monitors asthma symptoms in children and prevents asthma attacks. The product will offer continuous nocturnal monitoring to give the child, parents, and caregivers the information they need to keep asthma under control.	
Biel Glasses, ES	Biel Glasses uses 3D computer vision and augmented reality to create electronic glasses for people with poor vision. The glasses adapt the reality to each user's vision capacity detecting the relevant items (obstacles, objects and faces) and signaling them.	
DeepSpin, DE	DeepSpin's mission is to make MRI universally accessible by building portable, low-cost MRI devices based on proprietary novel NMR technology.	
Dermavision Solutions, ES	Dermavision aims to improve melanoma detection and decrease cost associated with the disease with an rapid acting autonomous device.	
DOTLUMEN, RO	Lumen creates glasses to aid navigation of the blind, aiming to replicate and build on the benefits of guide dogs.	
Evora Biosciences SAS, FR	Evora Biosciences develops a therapeutic treatment for complex digestive fistula, which do not respond to currently available treatments.	
Flowbone SA, CH	Flowbone offers a revolutionary treatment for hip fracture prevention. Their new generation biomaterial is injected into the bone under local anesthesia.	
Hephaï, FR	Hephaï develops an application to educate patients suffering from asthma, correcting their movements in real time while using their inhaler.	
Invivopower AB, SE	Invivopower aims to eliminate the need for heart transplants by providing a disruptive transcutaneous energy link which transfers energy wirelessly through the skin without penetrating the bacterial skin.	
Kyme NanoImaging srl, IT	Kyme NanoImaging has patented a nanotechnology platform to combine biomaterials with clinically used contrast agents to enhance the contrast capability and improve MRI diagnostics.	
neoMimix, IR	neoMimix has developed a novel microfluidics-based technology for the natural selection of sperm with better quality DNA within a human fertility clinic.	
Novus Diagnostics LTD, IR	Novus Diagnostics has developed SepTec, a next generation sepsis detection device that is making significant strides towards addressing the vital need for rapid and accurate sepsis diagnosis.	
Nursebeam OÜ, EE	Nursebeam has developed a health chatbot to make healthcare more accessible so that more people can instantly get health advice in their language and geography.	
Resitu AB, SE	ReSitu™ aims to revolutionise the biopsy market with a biopsy instrument that can remove a whole tumour without surgical intervention.	
Salvus Health BV, BE	Salvus Health aims to empower people to take control of their health and live healthier and more independent lives. They are creating a Point-of-Care platform integrating a range of medical devices (mhealth apps, consumer electronics and consumer tests) to make preventive healthcare and self-care more accessible and understandable.	
Serenno Medical, IL	Serenno Medical aims to reduce or even prevent ICU complications by monitoring ongoing Urine Output (UO) to catch Acute Kidney Injury (AKI) earlier, making it easier to prevent and treat affected patients.	
Sision Medical, IR	Sision Medical uses the latest advances in bioengineering and artificial intelligence to result in an entirely new treatment approach for chronic inflammatory endocrine conditions.	
SurgAR, FR	SurgAR (Surgical Augmented Reality), develops a real time augmented reality software based on artificial intelligence and computer vision to increase surgical procedures' effectiveness and efficiency.	
SYNDIAG S.R.L., IT	SynDiag develops AI based technology, called OvAI, to improve early diagnosis of ovarian cancer.	
ABANZA, ES	specialises in soft tissue repair by developing new surgical techniques, devices, and medical instruments.	25,000 (BH) each
AkknaTek, DE	provides innovative solutions for ophthalmology, with a focus on cataract surgery.	
BestHealth4U, PT	specialises in developing new and advanced material solutions for medical adhesives and skin-interacting medical devices.	
BeneTalk, GB	a digital speech therapy app helping people who stutter to communicate more comfortably.	
BioT:Connect, IL	a platform which helps connect medical devices to the cloud.	
Bitbrain, ES	provides high-tech electroencephalogram brain sensing devices and software solutions for human behaviour research, health and neurotechnology development.	
BV Medical Technologies, ES	develops healthcare products and methods to help better treat and diagnose conditions in the areas of otolaryngology, urology, paediatrics, and thoracic surgery.	

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DermaPurge, DE	develops, produces and markets specialised products to clean the skin from hazardous substances.	
Gripwise Tech, PT	gathers data to support frailty and sarcopenia assessments in a simple and effective workflow, aiming to maintain health and quality of life of the elderly.	
Healthy Mind, FR	a medical device that combines neuroscience, virtual reality, and medical hypnosis to reduce pain and anxiety.	
IKNOWHOW, GR	makes Evorad, a radiology information system and picture archiving and communications system that easily connects with hospital IT systems.	
I'm Fine, RO	a digital solution that provides psychological support and connects people to psychotherapists.	
KAMU Health, FI	develops digital therapeutics to help chronic respiratory patients manage their condition.	
HumanITcare, ES	a telemedicine platform powered by real-life data for remote home monitoring of patients with chronic diseases.	
Medicine Men, NL	develops a range of remote patient engagement mobile solutions to help improve the quality of life of chronically ill patients.	
Neolook, NL	offers augmented video services in neonatal intensive care units to support bonding and family ties, assist professional learning and advance medical understanding.	
N-Vibe, FR	develops haptic smart bands which vibrate to guide people with visual impairments, helping them to feel safer.	
PubGene, NO	uses data and AI technology to create personalised treatment option reports offering guidance to patients and clinicians.	
Parkinson Smartwatch, NL	is a smartwatch which helps people living with Parkinson´s manage their condition and treatment and supports them in their discussions with doctors.	
Sublimed, FR	develops drug-free treatment based on neurostimulation for relieving chronic pain.	
SurgiQ, IT	provides AI-based healthcare planning tools for hospitals, helping to reducing time spent scheduling activities, and increase resource utilisation.	
Tidewave, NO	removes the need for manual repositioning of patients. The Tidewave turning mattress is automating this procedure to prevent and treat pressure ulcers.	
Wellola, IR	an adaptable patient communications platform that plugs-in to hospital and clinic systems to give patients access to their healthcare information.	
Onward Assist, IN	aims to improve cancer treatment outcomes facilitating accurate and timely diagnosis and simplifying the process.	

Bridgehead (BH); Catalyst Award (CA); Health Catapult (HC); InnoStar Award (ISA); MedtecLIVE (MTL); RIS- Regional Innovation Scheme (RIS) Innovation Call (RIC); Wild Card (WC),

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Table D- 3: Good Practice Examples for transparent Reporting on academic research spin-offs/ spin-outs in NL: BioGeneration Ventures (BGV), Portfolio from BGV 1 https://biogenerationventures.com/en/portfolio/\ and acquisitions (own searches)

BioTech Company/ Location	Content of Research & Development (R&D): Product	Founder/ Co-Founder of company spin-out	Acquisitions
Netherlands			
Progentix Orthobiology/ Bilthoven/ NL spin-out from Twente Univ.	Biomaterials: synthetic bone substitutes designed to accelerate bone healing through a novel micro-structure	Joost de Bruijn, CEO of Progentix, *Professor of Regenerative Medicine and Entrepreneurship at Twente University*	**2009:** acquisition of Progentix's synthetic bone substitutes by Nuvasive for be $15 mil in cash, consisting of a $10 mil equity investment and a $5 mil loan to fund ongoing clinical and regulatory programmes. Upon reaching development milestones, NuVasive will buy the remaining equity of Progentix for $45 mil, with a further $25 mil in sales royalties possible. https://sciencebusiness.net/news/69788/Progentix-Orthobiology-secures-%2415M-from-commercialisation-partner
NovioGendix/NL spin-out from Radboud UMC, Nijmegen	Precision Diagnostics: new biomarker panel for the detection and management of prostate cancer and other cancers.	Jack Schalken, Co-Founder of NovioGendix, *Professor of urology at Radboud UMC*	**2010:** acquisition of the validated, non-invasive liquid biopsy test for prostate cancer by MDxHealth, for $8.8 mil total, incl. $5.1 mil in MDxHealth stock, $280,000 in cash, and up to an additional $3.3 mil in cash in future milestones. https://mdxhealth.com/press_release/mdxhealth-acquires-noviogendix-to-expand-uro-oncology-product-offering/
BioCeros/ Utrecht, NL spin-out from Utrecht University and/ or the University Medical Center Utrecht https://utrechtholdings.nl/spin-offs/	CMC services: cell line generation services related to the preclinical development of monoclonal antibodies and generation of GMP-ready protein producing cell lines.	Louis Boon, Founder and CFO *Emeritus Professor Faculty of Science and Engineering, Maastricht UMC*	**2015:** acquisition of BioCeros by EPIRUS Biopharmaceuticals for a total consideration of $14.1 mil in cash and stock payable in installments over a one-year period https://www.fiercebiotech.com/biotech/epirus-biopharmaceuticals-expands-biosimilar-pipeline-and-capabilities-through-acquisition **2016:** Polpharma Biologics acquired Dutch based Bioceros and their proprietary cell line development platform CHOBC®, as well as their comprehensive discovery, process development and analytical capabilities. https://www.businesswire.com/news/home/20200714005124/en/
Lanthio Pharma/ Groningen, NL Spin-out from Univ.of Groningen	Peptide technology: Lanthiopeptides, a new class of peptides with high target selectivity and improved "drug-like" properties.	Gert Moll, CEO, Founder and CSO of Lanthio Pharma *Professor Department of Molecular Genetics, GBB, University of Groningen*	**2015**: acquisition of Lanthio Pharma by MorphoSys for €20 mil ($22.5 mil), in a deal that adds to the buyer's portfolio Lanthio's pipeline of four preclinical drugs, led by a candidate for fibrotic diseases. https://www.genengnews.com/news/morphosys-acquires-lanthio-pharma/ https://www.fiercebiotech.com/financials/morphosys-swoops-for-lanthio-as-biotech-investment-plan-matures

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Table D- 4: Origins of drug products manufactured by Pfizer in 2017 [107]

Product	2017 Revenue	Key origins
Pneumococcal 13-valent Conjugate Vaccine (Prevnar 13)	$5.6 bil	Wyeth Pharmaceuticals, acquired by Pfizer in 2009
Pregabalin (Lyrica)	$5.1 bil	Northwestern University in the 1980s; later entered into a licensing agreement with Warner-Lambert, which was acquired by Pfizer in 2000
Palbociclib (Ibrance)	$3.1 bil	Warner-Lambert and Onyx Pharmaceuticals in the 1990s; Warner-Lambert was acquired by Pfizer in 2000
Apixaban (Eliquis)	$2.5 bil	DuPont Pharmaceuticals in 1995; acquired by Bristol-Myers Squibb in 2001; Bristol-Myers Squibb and Pfizer entered into an agreement to jointly develop apixaban in 2007
Etanercept (Enbrel)	$2.5 bil	Etanercept synthesized at Massachusetts General Hospital in the 1980s, with private funding from Hoechst AG; entered into a licensing agreement with Immunex Corporation in the late 1990s; Immunex entered into a co-promotion agreement with Wyeth-Ayerst Laboratories; Immunex was acquired by Amgen in 2002; Wyeth Pharmaceuticals was acquired by Pfizer in 2009. Since the expiration of the co-promotion agreement in 2013, Pfizer and Amgen have held marketing rights outside of and in the US and Canada, respectively
Atorvastatin (Lipitor)	$1.9 bil	Warner-Lambert in the 1980s, acquired by Pfizer in 2000
Tofacitinib (Xeljanz)	$1.3 bil	National Institutes of Health in the 1990s, which later entered into a collaboration with Pfizer
Sildenafil (Viagra)	$1.2 bil	Sandwich laboratories of Pfizer (U.K.) in the late 1980s; Pfizer scientists originally tested sildenafil as a treatment for angina, but during clinical trials in the 1990s, saw sildenafil's potential to treat erectile dysfunction; in the late 1990s and early 2000s, discovered evidence demonstrating sildenafil's potential to treat pulmonary hypertension
Sunitinib (Sutent)	$1.1 bil	Sugen, a biotechnology company founded by kinase researchers at New York University and the Max Planck Institute for Biochemistry; Sugen was acquired by Pharmacia & Upjohn in 1999; which was acquired by Pfizer in 2003
Varenicline (Chantix)	$997 mil	Pfizer in the 1990s
Conjugated estrogens (Premarin)	$977 mil	Ayerst, McKenna & Harrison and McGill University in the 1920s; Ayerst, McKenna & Harrison was acquired by American Home Products in 1943, which acquired Wyeth in 1931 and changed the company name to Wyeth in 2002; Wyeth was acquired by Pfizer in 2009
Amlodipine (Norvasc)	$926 mil	Pfizer in the 1980s
Celecoxib (Celebrex)	$775 mil	G.D. Searle in the 1990s, the pharmaceutical division of Monsanto Company, acquired by Pharmacia & Upjohn in 2000; Pharmacia was acquired by Pfizer in 2003
Coagulation factor IX recombinant, nonacog alfa (BeneFIX)	$604 mil	British Technology Group and Oxford University, which licensed Factor IX technology to Genetics Institute, a biotechnology company found by molecular biologists at Harvard University; the Genetics Institute was acquired by Wyeth in 1996; Wyeth was acquired by Pfizer in 2009
Crizotinib (Xalkori)	$594 mil	Sugen in 1996, a biotechnology company founded by kinase researchers at New York University and the Max Planck Institute for Biochemistry; Sugen was acquired by Pharmacia & Upjohn in 1999; Pharmacia was acquired by Pfizer in 2003
Enzalutamide (Xtandi)	$590 mil	University of California, Los Angeles, in the early 2000s, which later licensed the drug's patent to Medivation, which entered into a global agreement with Astellas to jointly commercialize enzalutamide in 2009; Medivation was acquired by Pfizer in 2016
Antihemophilic factor recombinant, moroctocog alfa (Refacto AF/Xyntha)	$551 mil	Dyax Corporation, which licensed phage display technology to Wyeth; Wyeth was acquired by Pfizer in 2009
Somatropin (Genotropin)	$532 mil	Genentech developed the first recombinant version of pituitary growth hormone, which had been used in treatment for many decades based on research at multiple academic centers. This version originated with Pharmacia Corporation, which was acquired by Pfizer in 2003.
Methylprednisolone (Medrol)	$483 mil mil	Pharmacia Corporation, which was acquired by Pfizer in 2003.
Sulbactam/cefoperazone (Sulperazon)	$471 mil	Pfizer in the 1970s

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Voriconazole (Vfend)	$421 mil	Pfizer in the 1980s
Infliximab (Inflectra/Remsima)	$419 mil	Pfizer manufactures follow-on biologics to Johnson & Johnson's infliximab (Remicade)
Axitinib (Inlyta)	$339 mil	Pfizer in the 2000s
Latanoprost (Xalatan/Xalacom)	$335 mil	Columbia University in the 1970s, which later entered into a collaboration with Pharmacia, which was acquired by Pfizer in 2003
Dalteparin (Fragmin)	$306 mil	Fresenius Kabi, a pharmaceutical company, in the 1970s, which later entered into a collaboration with Pharmacia, which was acquired by Pfizer in 2003
Desvenlafaxine (Pristiq)	$303 mil	Wyeth, acquired by Pfizer in 2009
Venlafaxine (Effexor)	$297 mil	Wyeth, acquired by Pfizer in 2009
Sertraline (Zoloft)	$291 mil	Pfizer in the 1970s
Epinephrine (EpiPen)	$290 mil	Epinephrine was first marketed in the early 1900s by Parke, Davis & Company, which was acquired by Warner-Lambert in 1970; Warner-Lambert was acquired by Pfizer in 2000. The device was invented in 1970s at Survival Technology, which became Meridian Medical Technologies in 1996; Meridian was acquired by King Pharmaceuticals, which was later acquired by Pfizer in 2010. Pfizer manufactures the EpiPen, which Mylan markets and distributes.
Linezolid (Zyvox)	$281 mil	DuPont in the 1980s, where oxazolidinones were first discovered; Pharmacia (formerly Pharmacia & Upjohn) in the 1990s, which was acquired by Pfizer in 2003
Azithromycin (Zithromax)	$270 mil	Pliva (now a subsidiary of Teva) in the 1970s, a pharmaceutical company, which later entered into a licensing agreement with Pfizer in 1986
Dibotermin alfa (BMP-2)	$261 mil	Genetics Institute, a biotechnology company found by molecular biologists at Harvard; Genetics Institute was acquired by Wyeth in 1996, which was acquired by Pfizer in 2009
Tigecycline (Tygacil)	$260 mil	Lederle Laboratories, the pharmaceutical division of American Cyanamid Company, which was later acquired by American Home Products in 1994, which acquired Wyeth in 1931 and changed the company name to Wyeth in 2002; Wyeth was acquired by Pfizer in 2009
Fesoterodine (Toviaz)	$257 mil	Schwarz BioSciences, a pharmaceutical company, which later licensed fesoterodine to Pfizer in 2006
Pegvisomant (Somavert)	$254 mil	Ohio University in the 1990s, where molecular biologists helped found Sensus Drug Development Corporation and used technology from Genentech; Sensus was acquired by Pharmacia in 2001, which was acquired by Pfizer in 2003
Sildenafil (Revatio)	$252 mil	See Viagra, above
Dexmedetomidine (Precedex)	$243 mil	Orion Pharma in the 1990s, a pharmaceutical manufacturing company which later licensed dexmedetomidine to Hospira, a spin-off of Abbott Laboratories; Hospira was acquired by Pfizer in 2015
Eletriptan (Relpax)	$236 mil	Pfizer
Bosutinib (Bosulif)	$233 mil	Wyeth, which was acquired by Pfizer in 2009
Alprazolam (Xanax)	$225 mil	Hoffman-La Roche in the 1950s, where the first benzodiazepines were discovered; Upjohn in the 1960s, which merged with Pharmacia Corporation in 1995; Pharmacia was acquired by Pfizer in 2003
Piperacillin; tazobactam (Zosyn/Tazocin)	$194 mil	SynPhar Laboratories, a joint venture between a scientist at the University of Alberta (Canada) and Taiho Pharmaceuticals; SynPhar licensed tazobactam/piperacillin to Wyeth, which was acquired by Pfizer in 2009
FSME-IMMUN/TicoVac	$134 mil	Hyland-Immuno in the 1980s, a division of Baxter International; Pfizer acquired Baxter's portfolio of marketed vaccines in 2014
Crisaborole (Eucrisa)</td	$67 mil	Anacor, a biopharmaceutical company founded by researchers at Stanford University and Penn State University; Anacor was acquired by Pfizer in 2016
Sildenafil	$56 mil	Pfizer manufactures a generic version of Viagra

** Origins listed for each drug based on methods described in article and do not exclude the possibility of contributions from other scientists or organizations.*

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Table D- 5: Origins of drug products manufactured by J&J in 2017 [107]*

Product	2017 Revenue	Key origins
Infliximab (Remicade)	$6.3 bil	Synthesized at New York University in the 1980s in collaboration with Centocor Ortho Biotech, which was acquired by J&J in 1999
Infliximab (Remicade)	$6.3 bil	Synthesized at New York University in the 1980s in collaboration with Centocor Ortho Biotech, which was acquired by J&J in 1999
Ustekinumab (Stelara)	$4.0 bil	Centocor, which licensed Medarex's UltiMAb technology to generate ustekinumab in 1997; Centocor was acquired by J&J in 1999
Paliperidone (Invega Sustenna/ Xeplion/ Trinza/ Trevicta)	$2.6 bil	J&J
Abiraterone (Zytiga)	$2.5 bil	UK Institute of Cancer Research in the 1990s, which later assigned rights for the development of abiraterone to British Technology Group International, which licensed abiraterone to Ortho Biotech Oncology Research & Development, a unit of Cougar Biotechnology, in 2004. Cougar was acquired by J&J in 2009
Rivaroxaban (Xarelto)	$2.5 bil	Bayer in the 1990s, which later entered into a collaboration with J&J to jointly develop rivaroxaban
Ibrutinib (Imbruvica)	$1.9 bil	Celera Genomics in 2005, a company founded by a geneticist as a unit of biotechnology company Applera. Pharmacyclis acquired some of Celera's drug discovery programmes, including ibrutinib, and entered into an agreement with J&J to jointly develop and market ibrutinib in 2011
Golimumab (Simponi/Simponi Aria)	$1.8 bil	Centocor, which licensed Medarex's UltiMAb technology to develop golimumab; Centocor was acquired by J&J in 1999
Darunavir (Prezista/Prezcobix/Rezolsta/Symtuza)	$1.8 bil	University of Illinois at Chicago, in collaboration with the National Institutes of Health and Purdue University, which later licensed darunavir to Tibotec, a pharmaceutical company founded by researchers at the Rega Institute for Medical Research, which was acquired by J&J in 2002
Daratumumab (Darzalex)	$1.2 bil	Genmab, a European spinoff of U.S.-based Medarex, in collaboration with the University Hospital in Utrecht; Genmab licensed daratumumab to J&J in 2012
Bortezomib (Velcade)	$1.1 bil	ProScript, originally founded as MyoGenics by scientists at Harvard; ProScript later collaborated with the National Cancer Institute to further develop the drug. ProScript merged with LeukoSite, which was acquired by Millennium Pharmaceuticals in 1999. Millennium was acquired by Takeda in 2008, which entered into a co-promotion agreement in J&J in 2010
Canagliflozin (Invokana/Invokamet)	$1.1 bil	Mitsubishi Tanabe Pharm, which later licensed canagliflozin to J&J
Epoetin alfa (Procrit/Eprex)	$972 mil	Amgen, which later assigned rights for non-dialysis indications in the U.S. and for all indications approved outside the U.S. to J&J
Risperidone (Risperdal Consta)	$805 mil	J&J in the 1980s
Methylphenidate (Concerta)	$791 mil	Ciba-Geigy in the 1940s. ALZA Corporation, which developed an alternative formulation of methylphenidate, was acquired by J&J in 2001
Rilpivirine (Edurant)	$714 mil	Tibotec, which was acquired by J&J in 2002
Macitentan (Opsumit)	$573 mil	Actelion in 2002, which was acquired by J&J in 2017
Bosentan (Tracleer)	$403 mil	Hoffman-La Roche, which later licensed bosentan to Actelion, which was acquired by J&J in 2017
Selexipag (Uptravi)	$263 mil	Nippon Shinyaku, which later entered into an agreement with Actelion to jointly develop selexipag in 2008, Actelion was acquired by J&J in 2017

** Origins listed for each drug based on methods described in article and do not exclude the possibility of contributions from other scientists or organizations.*

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Table D- 6: Overview of EMA-approved ATMPs, acquisitions and licensing agreements in early research and later development (IQWiG AMNOG appraisals: https://www.iqwig.de/ and Apoverlag: https://www.apoverlag.at/)

Active ingredient/ brand name/ Classification ATMP	Company/ Approval date/ Orphan status/ Indication	Clinical trials (Phase, n of pts. Status)	Sponsor of pivotal CTs, n of pts for Approval*	Origin, Acquisitions and Licensing Agreements**
Etranacogene Dezaparvovec/ Hemgenix® Gene therapy (AAV5 vector)	CSL Behring EMA: 20/02/2023 FDA: 22/11/2022 Orphan: Yes Haemophilia B	NCT03489291 (Phase 2b, 3 pts, ANR)*** NCT03569891 (Phase 3, 67 pts, ANR) NCT05962398 (Long-term FU, 56 pts, ANR)	CSL Behring 70 pts	**List price**: $3.3 mil **R&D** by St Jude Children's Research Hospital and Amsterdam Molecular Therapeutics (AMT) **2008**: Amsterdam Molecular Therapeutics (AMT), now UniQure, is a spin-out from the Amsterdam Academic Medical Centre, agreed a collaboration with St Jude Children's Research Hospital/USA to develop a gene therapy treatment for haemophilia B. **2020**: CSL Behring is reaching an **Exclusive Licence Agreement** from UniQure. to commercialize Etranacogene Dezaparvovec. UniQure received a $450 mil front cash payment from CSL Behring, alongside the potential to earn up to $1.6 bil in milestone payments. $300 mil of which are tied to regulatory events.
Tabelecleucel/ Ebvallo® Gene therapy (allogenic CAR-T)	Pierre Fabre EMA: 16/12/2022 FDA: - Orphan: Yes EBV-associated PTLD	NCT01430390 (Phase 1, 19 pts, ANR) NCT03769467 (Phase 1/2, 12 pts, Terminated) NCT04554914 (Phase 2, 190 pts, Recruiting) NCT03394365 (Phase 3, 66 pts, Recruiting) NCT02822495 (EAP, No longer available)	MSKCC Atara Biotherapeutics 43 pts.	**Estimated list price** between € 450 000 – €1.8 mil **R&D** by Memorial Sloan-Kettering Cancer Center (MSKCC) **2015**: Atara Biotherapeutics is reaching an **Exclusive Licence Agreement** from MSKCC for the **development** of EBV- specific T-cell therapies. **2021**: Atara receives an upfront payment of $45 mil, and up to approximately $ 320 mil in additional regulatory and sales milestone payments, plus significant double-digit tiered royalties as a percentage of net sales for the commercializing Tabelecleucel in Europe exclusive commercialization agreement for tabelecleucel (tab-cel®) with Pierre Fabre).
Valoctocogene Roxaparvovec/ Roctavian® Gene therapy (AAV5 vector)	BioMarin Europe EMA: 24/08/2022 FDA: 29/06/2023 Orphan: Yes Haemophilia A	NCT04684940 (Phase 1/2: 20 pts, Recruiting) NCT02576795 (Phase 1/2, 15 pts, ANR) NCT03520712 (Phase 1/2, 10 pts, Recruiting) NCT04323098 (Phase 3, 22 pts, ANR) NCT03370913 (Phase 3, 134 pts, ANR) NCT05768386 (Long-term FU, 172 pts, EbI)	BioMarin 149 Pts	**List price**: € 2 249 623 **R&D** by University College London (UCL)/ UK and St. Jude Children's Research Hospital/ US 2013: BioMarin has licensed a Factor VIII gene therapy programme for hemophilia A from University College London (UCL)/ UK and St. Jude Children's Research Hospital/ US to **develop** a gene therapy treatment for haemophilia A.

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Eladocagene Exuparvovec/ Upstaza® Gene therapy (AAV2 vector)	PTC Therapeutics EMA: 18/07/2022 FDA: - Orphan: Yes AADCD	AADC-CU/1601 (retrospective, compassionate use, 8 pts, Completed) – not registered NCT01395641 (Phase 1/2, 10 pts, Completed) NCT02926066 (Phase 2, 12 pts, Completed) NCT04903288 (Phase 2b, 12 pts, ANR)	National Taiwan Univ. Hospital 28 Pts. PTC Therapeutics	**List price**: € 3 500 000 **R&D** by National Taiwan University Hospital 2016: Agilis Biotherapeutics entered exclusive worldwide license agreement with National Taiwan University (NTU) 2018: PTC Therapeutics is paying $200 mil upfront to acquire Agilis Biotherapeutics. The deal gives PTC ownership of a gene therapy AADC deficiency.
Ciltacabtagene Autotemcel/ Carvykti® Gene therapy (autologous CAR-T)	Janssen EMA; 25/05/2022 FDA: 28/02/2022 Orphan: Yes Multiple myeloma	NCT03548207 (Phase 1b/2, 126 pts, Completed) NCT04133636 (Phase 2, 169 pts, ANR) NCT05347485 (Phase 2, 330 pts, Recruiting) NCT04181827 (Phase 3, 419 pts, ANR) NCT04923893 (Phase 3, 650 pts, Recruiting) NCT05201781 (Phase 4, 228 pts, Recruiting) NCT05346835 (EAP, Available)	Janssen 142 pts.	List price: € 420 000 **R&D**: University of Nanjing **2014**: Nanjing Legend Biotech **2015**: Legend Biotech/USA is founded by Nanjing Legend Biotech, China **2017**: Janssen (a Company of Johnson & Johnson) entered into a **License Agreement** with Legend Biotech to develop, manufacture and commercialize a chimeric antigen receptor (CAR) T-cell drug candidate LCAR-B38M. J&J paid $350 mil upfront for a global license. The deal positioned the companies to evenly split profits generated outside of China.
Lisocabtagene Maraleucel/ Breyanzi® Gene therapy (autologous CAR-T)	Bristol Myers Squibb EMA: 04/04/2022 FDA: 24/06/2022 Orphan: No DLBCL, PMBCL and FL3B	NCT02631044 (Phase 1, 385 pts, ANR) NCT03483103 (Phase 2, 74 pts, Completed) NCT03744676 (Phase 2, 41 pts, ANR) NCT04400591 (EAP, Available) NCT03484702 (Phase 2, 112 pts, ANR) NCT03575351 (Phase 3, 184 pts, ANR)	Juno Therapeutics Celgene 339 pts.	**List price**: € 345 000 **R&D**: Fred Hutchinson Cancer Center, Memorial Sloan Kettering Cancer Center (MSKCC) and Seattle Children's Research Institute **2013**: Juno Therapeutics, a spin-out of Fred Hutchinson Cancer Research Center; Seattle Children's; and Memorial Sloan Kettering Research Institute conducts early-stage **development** of CAR-T celltherapies. **2018**: Celgene acquires Juno Therapeutics for $9 bil. **2019**: Bristol Myers Squibb (BMS) is acquiring Celgene for $74 bil.
Idecabtagene Vicleucel/ Abecma® Gene therapy (autologous CAR-T)	Bristol Myers Squibb EMA: 18/08/2021 FDA: 26/03/2021 Orphan: Yes Multiple myeloma	NCT02658929 (Phase 1, 67 pts, Completed) NCT04196491 (Phase 1, 13 pts, ANR) NCT04855136 (Phase 1/2, 312 pts, ANR) NCT03361748 (Phase 2, 149 pts, ANR) NCT03601078 (Phase 2, 235 pts, Recruiting) NCT03651128 (Phase 3, 381 pts, ANR) NCT02786511 (Follow-Up, 50 pts, Completed) NCT04771078 (EAP, Available) NCT03274219 (Phase 1, 72 pts, ANR)	Celgene 207 pts. bluebird bio	**List price**: € 350 000 **R&D**: Genetix Pharmaceuticals **2010**: Rename of Genetix Pharmaceuticals in Bluebird Bio **2013**: Celgene announced a collaboration with bluebird bio **2015**: The collaboration was narrowed to cover only anti-BCMA treatments. **2018**: Celgene **exclusively licensed** ide-cel for $10 mil. They agreed to evenly split U.S. profits and costs for the treatment, with Celgene on the hook for up to $70 mil in milestone payments for ide-cel's first indication, as well as more milestones for a second indication. **2019**: BMS is acquiring Celgene for $74 bil. **2020**: With BMS´s CAR-T therapy under FDA review, bluebird bio is getting a $200 mil payout.

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Atidarsagene Autotemcel/ Libmeldy® Gene therapy (stem-cell based gene therapy)	Orchard Therapeutics EMA: 17/12/2020 FDA: - Orphan: Yes MDL	NCT01560182 (Phase 1/2, 20 pts, ANR) NCT03392987 (Phase 2, 10 pts, ANR) NCT04283227 (Phase 3, 6 pts, Recruiting)	Orchard Therapeutics 33 pts. Orchard Therapeutics& Ospedale San Raffaele	**List price**: € 2 875 000 **R&D:** San Raffaele University in Milan (Telethon Institute for Gene Therapy/SR-Tiget) **2010:** SR-Tiget signs strategic alliance with GlaxoSmithKline (GSK) to develop 7 gene-therapies for rare genetic diseases incl. a gene therapy for metachromatic leukodystrophy (MDL). **2018**: Orchard acquired GSK's rare disease gene therapy portfolio, in return for taking a 19.9% stake in the acquirer, as well as undisclosed milestone payments and royalties.
Brexucabtagene Autoleucel/ Tecartus® Gene therapy (autologous CAR-T)	Gilead (Kite) EMA: 14/12/2020 FDA: 01/10/2021 Orphan: Yes MCL	NCT03624036 (Phase 1, 125 pts, Terminated) NCT02614066 (Phase 1/ 2, 125 pts, ANR) NCT02625480 (Phase 1/2, 116 pts, Recruiting) NCT02601313 (Phase 2, 105 pts, ANR) NCT05537766 (Phase 2, 170 pts, Recruiting) NCT04880434 (Phase 2, 90 pts, ANR) NCT05776134 (EAP, 90 pts) NCT04162756 (EAP, 16 pts)	Kite (Gilead) 129 pts.	**List price**: € 360 000 **R&D:** Weizmann Institute and Tel Aviv Sourasky Medical Center **2012:** Cabaret Biotech, spin-out of Weizmann Institute **2013:** Kite is entering into **Licensing Agreement** with Cabaret Biotech for the development in preclinical and human clinical trials to obtain regulatory approval. **2017**: Kite is acquired by Gilead for $11.9 bil.
Onasemnogene Abeparvovec/ Zolgensma® Gene therapy	Novartis EMA: 18/05/2020 FDA: 24/05/2019 Orphan: Yes SMA 1	NCT02122952 (Phase 1, 15 pts, Completed) NCT03306277 (Phase 3, 22 pts, Completed) NCT03461289 (Phase 3, 33 pts, Completed) NCT03505099 (Phase 3, 30 pts, Completed) NCT03421977 (FU, 13 pts, ANR) NCT03955679 (EAP, Approved for marketing)	Novartis, 52 pts. United BioSource, AveXis	**List price**: € 2 314 550 **R&D:** Penn Medicine (University of Pennsylvania Health System and Penn's Raymond and Ruth Perelman School of Medicine) discovery of AAV-based platform Penn in the Wilson lab, AAV9 was the vector used in the Phase I SMA 1 clinical trial at Nationwide Children's Hospital. **2009**: RegenxBio, a clinical-stage biotechnology firm, secured exclusive rights to key IPR covering novel AAV vectors discovered at Penn in the Wilson lab. l for the approved therapy Zolgensma. **2014**: RegenxBio licensed the vector to AveXis. **2018**: Novartis acquires AveXis, acquired by for $8.7 bil.
Voretigene Neparvovec/ Luxturna® Gene therapy	Novartis EMA: 22/11/2018 FDA: 18/12/2017 Orphan: Yes RP and LCA	NCT01208389 (Phase 1/2, 12 pts, ANR) NCT00999609 (Phase 3, 31 pts, ANR) NCT03602820 (FU, 41 pts, ANR) NCT03597399 (Registry, 87 pts, ANR) NCT04516369 (Phase 3, 4 pts, ANR)	Spark Therapeutics 43 pts. Novartis	**List price**: € 830 000 **R&D**: University of Pennsylvania and Children's Hospital of Philadelphia (CHOP) **2013**: Spark Therapeutics is founded as a spin-out from CHOP **2018**: Novartis entered **Exclusive Licensing Agreement** with Spark Therapeutics. $105 mil upfront and another $65 mil in milestones based on European approval and sales.
Axicabtagene Ciloleucel/ Yescarta® Gene therapy (autologous CAR-T)	Gilead EMA: 23/08/2018 FDA: 18/10/2017 Orphan: Yes DLBCL and PMBCL	NCT02659943 (Phase 1, 27 pts, completed) NCT02348216 (Phase 1/2, 307 pts, ANR) NCT03105336 (Phase 2, 159 pts, ANR) NCT03391466 (Phase 3, 359 pts, ANR) NCT03153462 (EAP, Approved for marketing) NCT05776160 (EAP, Available)	NCI Kite (Gilead) Kite (Gilead) 125 pts	**List price**: € 282 000 **R&D:** Weizmann Institute and Tel Aviv Sourasky Medical Center **2012:** Cabaret Biotech, spin-out of Weizmann Institute **2013:** Kite is entering into **Licensing Agreement** with Cabaret Biotech for the development in preclinical and human clinical trials to obtain regulatory approval. **2017**: Kite is acquired by Gilead for $11.9 bil.

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Tisagene Lecleucel/ Kymriah® Gene therapy (autologous CAR-T)	Novartis EMA: 23/08/2018 FDA: 30/08/2017 Orphan: Yes ALL and DLBCL	NCT01626495 (Phase 1/2, 73 pts, Completed) NCT01029366 (Phase 1, 26 pts, Completed) NCT01747486 (Phase 2, 42 pts, Completed) NCT02228096 (Phase 2, 75 pts, Completed) NCT02435849 (Phase 2, 97 pts, Completed) NCT02445248 (Phase 2, 115 pts, Completed) NCT03570892 (Phase 3, 331 pts, ANR) NCT03123939 (Phase 3, 69 pts, Completed) NCT03601442 (MAP, available)	Univ.Pennsylvania Novartis 258 pts.	**List price**: € 380 800 **R&D**: University of Pennsylvania holds 428 patent rights on 54 separate CAR-T cell related inventions, 29 cell and gene therapy spin-out companies for the development of gene-therapies. **2012**: Univ. Pennsylvania enters **exclusive R&D Alliance** with Novartis
Darvadstrocel/ Alofisel® (allogeneic) Cell therapy	Takeda EMA: 23/03/2018 FDA: Orphan: Yes Perianal fistulas in CD	NCT01372969 (Phase 1/2, 24 pts, Completed) NCT01541579 (Phase 3, 278 pts. Completed) NCT04075825 (FU, Phase 3, 151 pts, ANR) NCT03706456 (Phase 3, 22 pts, Completed) NCT04701411 (Phase 3, 20 pts, Recruiting) NCT04118088 (Phase 4, 50 pts, Recruiting) NCT04971525 (5850 pts, ANR)	TiGenix Takeda 231 pts.	**List price**: € 60 000 **R&D**: TiGenix2016: Takeda and TiGenix enter into **Exclusive Licensing Agreement for Ex-US rights.** TiGenix will receive an upfront cash payment of €25 mil. TiGenix will be eligible to receive additional regulatory and sales milestone payments for up to a potential total of €355 mil and double digit royalties on net sales by Takeda. The first anticipated milestone payment is €15 mil upon obtaining the Marketing Authorization of Cx601 in the European Economic Area (EEA). In addition, Takeda will make an equity investment of €10 mil in the share capital of TiGenix within the next 12 months. 2018: Takeda Pharmaceutical has completed its purchase of all outstanding ordinary shares of for approximately $608.84m (€520m), representing €1.78 per share. 2018: Alofisel has been licensed from Belgium-based TiGenix to Takeda for the exclusive development and commercialization outside of the US. Milestone payments of €15 are agreed. Takeda has said it will review the manufacturing of Alofisel (darvadstrocel) if its €520m ($620m) bid for off-the-shelf stem cell developer TiGenix is successful.
Spheroids from autologous chondrocytes/ Spherox®/ Chondrosphere® Tissue-engineered product	Rejuvenate EMA: 10/07/2017 FDA: - Orphan: No Repair of certain cartilage defects	NCT01222559 (Phase 3, 102 pts, completed) NCT01225575 (Phase 2, 75 pts, completed)	CO.DON 282 pt.	**List price**: average cost of a course of treatment. £10,000 **R&D**: development of M-ACT therapy at diverse University clinics for Orthopaedics and Traumatology in Germany **1993**: CO.DON for R&D on tissue engineering s founded **2022**: Rejuvenate acquires CO.DON for €15 mil.

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Autologous CD34+ cells encoding ADA/ Strimvelis® Gene therapy	Orchard Therapeutics EMA: 26/05/2016 FDA: - Orphan: Yes ADA-SCID	NCT03232203 (16 pts, Completed) NCT04959890 (15 pts, ANR) NCT03478670 (Patient Registry, 50 pts, EbI)	Orchard Therapeutics 12 pts.	**List price**: € 594 000 **R&D:** San Raffaele University in Milan (Telethon Institute for Gene Therapy/SR-Tiget) **2010:** SR-Tiget signs strategic alliance with GlaxoSmithKline (GSK) to develop 7 gene-therapies for rare genetic diseases incl. a gene therapy for ADA-SCID immundeficiency.. **2016**: Orchard launched with $33 mil in series A money, two GSK alums among its founders and the hope to develop a drug to rival Strimvelis. Since then, the biotech reeled in another $110 mil in financing, which would carry its ADA-SCID candidate through late-phase development. It also has earlier-stage programmes aimed at immune deficiencies and metabolic diseases, including X-linked chronic granulomatous disease and Sanfilippo syndrome type A and type B. **2018**: Orchard acquired GSK's rare disease gene therapy portfolio, in return for taking a 19.9% stake in the acquirer, as well as undisclosed milestone payments and royalties. **2022**: the discontinuation of Strimvelis and investments in alternatives was announced.
Talimogene Laherparepvec/ Imlygic® Gene therapy (immunotherapy)	Amgen EMA: 16/12/2015 FDA: 08/10/2015 Orphan: No Melanoma	NCT02014441 (Phase 2, 61 pts, Completed) NCT02366195 (Phase 2, 112 pts, Completed) NCT02211131 (Phase 2, 150 pts, Completed) NCT02173171 (PR, 185 pts, Completed) NCT02147951 (EAP, No longer available) NCT02297529 (EAP, No longer available) NCT00289016 (Phase 2, 50 pts, Completed) NCT00769704 (Phase 3, 437 pts, Completed) NCT01368276 (Phase 3, 31 pts, Completed)	Amgen 466 pts. Biovex	**List price**: € 60 000 **R&D**: University College London **1999**: BioVex, spin-out of research group at University College London **2011**: Biovex is acquired by Amgen for $1 bil. Amgen is paying $425 mil upfront, with a further $575 mil to come on reaching some clinical and regulatory milestones. BioVex has become a wholly owned subsidiary of Amgen.
Living (corneal) tissue equivalent/ Holoclar® Tissue-engineered product	Holostem EMA: 17/02/2015 FDA: - Orphan: Yes LSCD	NCT03288844 (47 pts, Completed)	Holostem	**List price**: € 95 000 per eye **R&D**: University of Modena and Reggio Emilia **2008**: Holostem, a spin-out of University of Modena and Reggio Emilia is founded with the commercial support of Chiesi Pharmaceuticla Group **2022**: Holostem has to close after its main investor has withdrawn. Holostem's liquidation follows the recent announcement that the UK-US company Orchard is ending its investment in Strimvelis, another stem-cell based gene therapy.

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Appendix E

Public Contributions to Public Contributions to Regulation and Marketing Authorization

- E-1: European Medicines Agency (EMA) reflection papers and guidances on novel methodologies for medicine development
- E-2: HTA-Joint Scientific Advice (JCS)/ Early Dialogue (ED) to Health Technology Developer (HTD)

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Table E- 1: European Medicines Agency (EMA) reflection papers and guidances on novel methodologies for medicine development (excerpt) [156]

Title of methodological EMA guidance	Date published
GFR slope as a Validated Surrogate Endpoint for RCT in CKD	09/2023
Stride velocity 95th centile as primary endpoint in studies in ambulatory Duchenne Muscular Dystrophy studies	07/2023
iBox Scoring System as a secondary efficacy endpoint in clinical trials investigating novel immunosuppressive medicines in kidney transplant patients	12/2022
Use of Enroll-HD (a Huntington's disease patient registry) as a data source and infrastructure support for post-authorisation monitoring of medical products	07/2022
Prognostic Covariate Adjustment (PROCOVA™) as an Efficient Statistical Methodology intended to Improve the Efficiency of Phase 2 and 3 Clinical Trials by Using Trial Subjects' Predicted Control Outcomes (Prognostic Scores) in Linear Covariate Adjustment)	09/2022
Islet Autoantibodies (AAs) as Enrichment Biomarkers for Type 1 Diabetes (T1D) Prevention Clinical Trials	03/2022
IMI PREFER: Framework & Points to consider for method selection with methods for performing patient preference studies to inform regulatory & HTA body medical product decision-making	05/2022
Multiple sclerosis clinical outcome assessment (MSCOA)	03/2020
Treatment effect measures based on recurrent event endpoints that allow for efficient statistical analyses	04/2020
eSource Direct Data Capture (DDC)	07/2019
Stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device	04/2019
Cellular therapy module of the European Society for Blood & Marrow Transplantation (EBMT)	02/2019
The European Cystic Fibrosis Society Patient Registry (ECFSPR) and CF Pharmaco-epidemiology Studies	09/2018
Molecular neuroimaging of the dopamine transporter as biomarker to identify patients with early manifest Parkinsonism in Parkinson's disease	05/2018
Plasma fibrinogen as a prognostic biomarker (drug development tool) for all-cause mortality and COPD	04/2018
Proactive in chronic obstructive pulmonary disease (COPD)	04/2018
Paediatric ulcerative colitis activity index (PUCAI)	01/2016
Ingestible sensor system for medication adherence as biomarker for measuring patient adherence to medication in clinical trials	02/2016
Total kidney volume (TKV) as a prognostic biomarker for use in clinical trials evaluating patients with autosomal dominant polycystic kidney disease (ADPKD)	11/2015
Exacerbations of chronic pulmonary disease tool (EXACT), and EXACT-respiratory symptoms measure (E-RS) for evaluating treatment outcomes in clinical trials in COPD	04/2015
In-vitro hollow-fibre-system model of tuberculosis (HFS-TB)	01/2015
MCP-Mod as an efficient statistical methodology for model-based design and analysis of phase-II dose-finding studies under model uncertainty	01/2014
A novel data-driven model of disease progression and trial evaluation in mild and moderate Alzheimer's disease	09/2013
Alzheimer's disease novel methodologies / biomarkers for the use of cerebrospinal-fluid amyloid beta 1-42 and t-tau and / or positron-emission-tomography amyloid imaging (positive / negative) as biomarkers for enrichment, for use in regulatory clinical trials in mild and moderate Alzheimer's disease	02/2012
Low hippocampal volume (atrophy) by magnetic-resonance imaging for use in clinical trials for regulatory purpose in predementia stage of Alzheimer's disease	11/2011
Qualification opinion of novel methodologies in the predementia stage of Alzheimer's disease: cerebrospinal-fluid-related biomarkers for drugs affecting amyloid burden	04/2011
Alzheimer's disease novel methodologies / biomarkers for BMS-708163	02/2011
ILSI / HESI submission of novel renal biomarkers for toxicity	10/2010
Final conclusions on the pilot joint European Medicines Agency / Food and Drug Administration VXDS experience on qualification of nephrotoxicity biomarkers	01/2009

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Table E- 2: HTA-Joint Scientific Advice (JCS)/ Early Dialogue (ED) to Health Technology Developer (HTD) ([157] and personal communication with EUnetHTA)

Project	Time Period	Requested by HTDs	Completed	Cost per JSC	Comment	Public contribution
SEED	2013 - 2015	n.a.	11	Free of cost for HTD, No calculation available, Funding amount for SEED not available	the SEED project aimed to perform 10 Early Dialogues + some ED under JA 2	
JA 3	2017 - 2021	113	37	Free of cost for HTD, €54 732,00 - €65 132,00 (incl cost of secretariat + participation of 6 HTAb)	Cost calculation based on internal considerations of a financing mechanism	EUnetHTA 2017-2023: 44 JCA/ ED a 65 000 (all-in real costs) = € 2 860 000
EUnetHTA21	2021-2023	15	7	€ 69 120 for 6 – 8 JSCs (€ 8 640 € - €11 520 €/ per JSC calculated)	Service contract was limited to 6 – 8 Consultations, cost were completely underestimated	
G-BA	p.a. average	n.a.	Ca. 225	Fee-funded consultations, Depending on complexity: € 5000 – € 16 000	Around 30% - 50 % are early consultations, the rest is "presubmission" or interim re-consultation around 1 year before submitting a dossier.	

Joint Scientific Advice (JCS) = EMA + HTA, Early Dialogue (ED) = HTA only, HTD - Health Technology Developer, n.a. – not available

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