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# Assessing the Public and Philanthropic Financial Contribution to the Development of New Drugs: A Bibliographic Analysis

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**Abstract:** Background: There is wide debate on the cost of some pharmaceutical products and the impact this has on access to medicine. Little publicized knowledge on the public and philanthropic contribution to research and development costs exists so far. The objective of work reported here was to collect information on public contributions to research funding and thus contribute to the discussion on return on public investment. Methods: A multi-level search process was developed to search for public and philanthropic research funding based on 3 main steps: (1) identification of all generic and molecular names and terms, (2) systematic search for pre-marketing pathway information and related research funding, (3) systematic search for corresponding research funding amounts. Three Paediatric Orphan Drugs (Spinraza®, Brineura®, Crysvita®), which were approved by the European Medicines Agency (EMA) in 2017, were chosen to pilot the methods. Results: We estimated that public/philanthropic contributions to funding of product-related research ranged between approximately € 20 million (Spinraza®) and € 31 million (Brineura®). However, this is a very conservative estimate since pharmaceutical development calls upon basic research, which does not mention product-specific terms. For instance, for research into SMA as a whole, public and philanthropic research funding contributions totalling € 165 million were identified. Conclusions: Researching public and philanthropic R & D funding proved to be difficult and time consuming. Further piloting including the refinement and standardisation of the search strategy is underway.

**Keywords:** Pharmaceuticals, Funding, Pricing Policy, Return on Investment

## 1. Introduction

Up until recently the term "access to medicines" was mostly associated with discussions concerning the ability of developing countries to access cheaper, life-saving generic medicines to treat infectious diseases such as HIV and tuberculosis. However, the debate has now widened to include the prices of new active substances marketed in the USA and Europe, especially considering the degree to which publicly funded organizations, and charities fund basic and early research into drug therapies [1, 2]. An analysis by Global Justice Now reported it is estimated that the public pays for two-thirds of all upfront R&D drug costs and that around one-third of all medicines originate in research institutions in the public sector [3]. The discussion has therefore become one of a "public return on public investment" i.e. posing the question why there is no guarantee for taxpayers that their health system can access the medicine at an affordable price, and make use of the data and knowledge built up during the development cycle [3-5].

The US National Institute of Health (NIH) accounts for almost three-quarters of federal agency spending on biomedical R&D in the USA [6]. A review of the impact of publicly funded biomedical and health research found that (a) just over 10% of NMEs have an academic patent and (b) 48% of drug approvals over an almost 20 year period were associated with public sector patents or seminal publications [6]. Similarly, it was reported that in around 24% of new drugs approved by the FDA over a 10 year period, universities were involved in the first transfer to a pharmaceutical or

biotechnology company [7]. The involvement of public sector institutions may be even higher in the case of clinically important drugs likely to have a large impact on practice. Earlier analyses found that of 15 clinically important drugs, public sector research made key enabling discoveries for 11 of them [8]. More recent analyses of drug histories of highly expensive medicine such as Sofosbuvir for patients with hepatitis C [9] and CAR-T cell therapy [10] show these were financed and enabled by public grants. In a recent seminal piece of work, Cleary and co-authors sought to establish the contribution of NIH funding to published research associated with 210 new molecular entities [11]. Their results suggest an enormous spend of over $100 billion between 2000 and 2016 representing around 20% of the total NIH budget over this period [11]. Over 90% of the funding was on basic research related to the biological targets for drug action rather than the drugs themselves [11].

The focus of the present investigation was to identify the non-industry-financed component of R&D activities in early-stage research as well as early clinical trials undertaken up to the point of first market authorisation in the USA or EU using only bibliographic, publicly available sources. Our focus has therefore been on stage 6 "development of techniques or apparatuses for clinical use" as outlined in the six categories of research in clinical practice and health as conceptualised by Comroe and Drips in 1976 in [12] (see Table 1). Methods were developed in an iterative process, also in part following the exchange of ideas between international researchers in regular web conferences (see acknowledgement).

***Table 1.*** *Six categories of R&D for innovation (Comroe and Drips 1976 in [12]).*

| | |
|---|---|
| 1 | Basic research: unrelated to the solution of a clinical problem |
| 2 | Basic research: related to the solution of a clinical problem |
| 3 | Clinical oriented research not concerned with the basic biological, chemical or physical mechanism (e.g purely observational work or application of a procedure practiced in animals, to man) |
| 4 | Review and synthesis of published work |
| 5 | Developmental work/engineering to create improve or perfect apparatus or technique for research use |
| 6 | Developmental work/engineering to create improve or perfect apparatus or technique for clinical or other use |

# 2. Methods

### *2.1. Choice of Case Studies*

Case study products were chosen using the EMA list of new active substances in 2017 [13, 14]. In the first instance, paediatric-relevant products in the area of orphan medicine were chosen. 35 new active substances were recommended for approval by EMA in 2017, 13 of which were orphan products and four of these were declared by the EMA to be medicines for children representing an outstanding contribution to public health, three of which - Spinraza®, Brineura®, and Crysvita® - were selected for the analysis. Nusinersen (international nonproprietary name) is an antisense oligonucleotide therapy for treating children and adults with spinal muscular atrophy and is marketed internationally as Spinraza® by Biogen Idec Ltd. Cerliponase alfa (international nonproprietary name) is marketed internationally as Brineura® by the pharmaceutical company BioMarin International Ltd. Cerliponase alfa is an enzyme replacement therapy (ERT) that delivers TPP1 directly to the brain of children with neuronal ceroid lipofuscinosis (CLN2) disease and is approved to slow the loss of walking or crawling ability. Burosumab is marketed internationally as Crysvita® by the pharmaceutical company Kyowa Kirin Co. Ltd. Burosumab is a monoclonal antibody that blocks X-Linked hypophosphatemia (XLH) and is approved to treat children with the FGF23 disorder.

### *2.2. Inclusion and Exclusion Criteria; Extraction of Data*

All academic papers, grey literature and online information relating to the development of the drug in question that took place before the date of marketing authorization were considered relevant if there was any mention of public or philanthropic funding. Research activities generally continue beyond the date of market authorisation, however these activities cannot be attributed to development costs and hence were excluded. There was no restriction relating to the type of article (e.g. trial or review) or the quality of the publication. It was necessary to name a starting date from which to include funding so as not to apportion costs associated with basic research, which benefits all diagnostics and therapies in a particular disease area, to one specific pharmaceutical product. Therefore, for each case study product, we aimed to identify the time point at which researchers first described the gene or mechanism of action, which would form the basis of the therapeutical product. This was as follows for the products: the date when antisense oligonucleotides were identified (Spinraza®); the time point at which researchers first isolated TPP1 successfully to produce recombinant TPP1 in a cell culture system (Brineura®); the date at which the specific XLH gene was identified (Crysvita®). The following information was extracted from the identified funding organisations, where available: study title; date of funding; amount of funding; stage of development/content of project; lead institution; principal investigator; co-operating institutions.

### *2.3. Search Strategy*

A combination of search strategies was used in an iterative process to generate a picture of the product and the development path it underwent, including the role of key researchers. After obtaining background information on the drug in question from market authorisation agencies (FDA label via https://www.drugbank.ca/drugs/DB13173 and EMA label via https://www.ema.europa.eu/en/medicines/human/), all relevant product-related search terms were identified using the following databases: DrugBank, ChEMBL, Therapeutic Target Database (see Table 2).

***Table 2.*** *Databases for searches of drug-relevant information.*

| | |
|---|---|
| DrugBank https://www.drugbank.ca/ | This is a comprehensive source of bioinformatic and chemical information, combining detailed data on drugs (e.g. synonyms, chemical, pharmacological and pharmaceutical data) with detailed information on target connections (targets) e.g. sequence, structure, metabolic pathways. |
| ChEMBL https://www.ebi.ac.uk/chembl/ | Database of bioactive molecules with drug properties that includes synonyms, brand names, generic names and pre-commercial company names, as well as MeSH terms related to NCBI Query Translation. |
| Therapeutic Target Database (TTD) http://bidd.nus.edu.sg/group/cjttd/ | Database that provides information about known and researched therapeutic proteins and nucleic acid targets, the targeted disease, pathway information and the corresponding drugs for each of these targets. This database also contains links to relevant databases containing information on target function, sequence, 3D structure, ligand binding properties, enzyme nomenclature and drug structure, therapeutic class, clinical development status. |

Subsequent searches were conducted in databases/sources from which relevant institutions, researchers and projects could potentially be identified: Orphanet, google, FDA/EMA submissions, EDGAR Company Filings database for information of drug histories and milestones; trial registries for potentially relevant clinical studies (WHO, Clinical Trials. Gov, EudraCT); patent databases for information on intellectual property rights (USA: FDA Orange Book/ US PTO, worldwide: Espacenet patent database, Medicines Patent Pool, Pat-INFORMED, Canada: Health Canada Patent Database). The EDGAR Company Filings database was used to identify company records such as the 10-k report, which sometimes lists relevant patent numbers for products. The company websites (including online annual reports) of pharmaceutical companies marketing the products were searched for information on partner organizations in the public sector.

***Table 3.*** *Databases on Drug History, Trial and Patent information.*

| | |
|---|---|
| Drug histories | Orphanet (https://www.orpha.net)<br>Google search for review and timeline papers<br>FDA (https://www.fda.gov/home), EMA (https://www.ema.europa.eu/en) submissions<br>Pubmed https://www.ncbi.nlm.nih.gov/pubmed/<br>US Securities and Exchange Commission Filings https://www.sec.gov/edgar/searchedgar/companysearch.html |
| Trial Databases | WHO international trials registry: http://apps.who.int/trialsearch/<br>US-Clinical Trials. Gov: https://www.clinicaltrials.gov/ and EU clinical trials registry/EudraCT: https://www.clinicaltrialsregister.eu/ctr-search/search.<br>Also clinical study registries of relevant pharmaceutical companies: e.g. https://www.gsk-study register.com/ |
| Patent Databases | FDA orange book/ US PTO: https://www.accessdata.fda.gov/Scripts/cder/ob/index.cfm; https://www.uspto.gov/,<br>Health Canada Patent Database: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/patent-register.html<br>Espacenet patent database: https://worldwide.espacenet.com/,<br>Medicines Patent Pool Patent Search: https://www.medspal.org/,<br>Pat-informed (Patent Information Initiative for Medicines) database: https://www.wipo.int/pat-informed/en/, |

In addition, PubMed was searched using an ontology of drug names restricted to publications dated before the product was first marketed. An additional internet search was conducted to identify the names of relevant charities active in funding research in the relevant disease area. Where grant numbers or the names of funding organizations through any of the above sources were identified, the website of the appropriate funding organisation (such as NIH-RePORTER, CORDIS, Medical Research Council in the U.K., BMBF in Germany, Batten Disease Support and Research Organisation) were then searched for more detailed information on the funding in question. Where universities or other public sector organisations had been named in patents, their websites where searched for potential further information. Where the names of key researchers had been identified, an additional name search was conducted on the NIH-RePORTER database.

# 3. Results

### *3.1. Nusinersen/Spinraza®: Search Insights and Funding Results*

Particularly useful databases regarding the identification of projects researching SMA therapies was "Orphanet". Regarding funding information, the NIH (via the NIH-RePORTER) and the Canadian Institutes of Health Research as well as from the charity side, the Muscular Dystrophy Association (MDA), provided detailed information on the level for funding provided for projects they supported. The National Institute of Neurological Disorders and Stroke (NINDS) timeline document that detailed NINDS/NIH support for product development (identified through the google search) was a useful source. The 10-k report identified via the US Securities and Exchange Commission Filings was helpful in identifying patent numbers related to the product, which enabled further searching in the Orange Book and patent databases. Through Pubmed only 1 additional relevant project was identified that had not already been identified through other sources. The following funding sources and amounts were identified:

6 projects funded by Canadian Institute of Health Research for a total of Can $ 3,269,130.

3 National Institute of General Medical Sciences (NIGMS) or National Institute of Neurological Disorders and Stroke (NINDS) for a total of US $ 11,117,535 plus an additional 7 projects conducted by the 2 main researchers named in the patent projects for an additional $ 11,136,414.

E-Rare EU calls 1 project funded (amount not reported).

1 BMBF (German national funding programme) funded project € 387,854; 1 project was co-funded by the Deutsche Forschungsgesellschaft (no information on funding amount available).

Other national European funding bodies: Italian (Fondazione Telethon: 2 projects) and French (Association Française contre les Myopathies, the Actions Concertees-Science du Vivant, the Institut Electricite Sante, the Groupement de Recherches et d'Etudes sur les Genomes and the Programme Hospitalier de Recherche Clinique) national funding, although no funding amounts could be identified on the websites of these organisations.

Details could be found on 15 Muscular Dystrophy Association (MDA) funded projects totalling $ 3,768,516. On the MDA website it is claimed that MDA has invested more than $45 million in SMA research.

Families of SMA/Cure SMA (USA) was involved in supporting 4 projects and Kids' Cures in 1 project. Here the exact funding amount is unavailable. 1 project funded by Families of SMA amounted to $ 381,138.

It is stated in the Cure SMA annual report, that funding for research projects in 2018 totalled 5 million US $ (although only details on specific projects totalling 1 Million US $ could be identified).

SMA Europe lists a number of projects funded in this area before the date of market authorization (although there is no description of the projects, which makes an exact assignment to the medication impossible); these total just over € 3 Million.

According to its website, the Spinal Muscular Atrophy Foundation (SMA Foundation) has spent around $150 Million on basic, translational and clinical research since its inception in 2003.

*Nusinersen/Spinraza®: final figure*

Converting all monetary amounts into a common Euro currency leads to a total funding estimate of around € 165 Million for research into therapies for SMA. Taking a very conservative approach, i.e. just including projects named in the patents (or conducted by the same researchers named in the patents) or named specifically in development documents, around just over € 20 Million of public or philanthropic money can be directly attributable to Spinraza®.

### *3.2. Cerliponase Alpha/Brineura®: Search Insights and Funding Results*

The NINDS timeline document that detailed NINDS/NIH support for product development (identified through the google search) was again a useful source of project information. The search for information on public disclosures from patent documents identified several NIH projects, as did searching the NIH-RePORTER database for the names of key principal investigators. The information from charities regarding funding was however not as helpful as with the nusinersen case study; as a result we were unable to estimate the contribution from charitable organisations. The following funding sources and amounts were identified:

13 National Institute for Health (NIH) research projects were identified, for a total of US $ 28,775,650.

The US National Science Foundation funded a project to the amount of $ 94,931.

In terms of European national funding, one relevant project was identified as being funded by the Academy of Finland (€ 740,120) and 1 by the German Ministry for Education and Research (BMBF) (€ 390,457). For 2 BMBF-funded projects we could find no information on the funding amount.

The European Union Seventh Framework Programme (FP7/2007-2013) funded the DEM-Child project, which had an overall budget of € 3,971,420.

The Batten Disease Support and Research Association lists some information on projects and project fundings (but by no means all) on their website and in some annual reports. Here an amount of US $ 297,391 was identified that specifically went into the development of treatments for CLN2.

For the Neuronale Ceroid-Lipofuszinose (NCL) Stiftung, BDFA UK, Beyond Batten Disease Foundation, Charlotte & Gwenyth Gray Foundation, no projects or funding amounts could be identified for CNL2

*Cerliponase alpha/ Brineura®: final figure*

It was not possible to estimate a total CNL2 funding amount including charitable and philanthropic organisations as there was too little transparent information available online regarding charitable funding. Taking a very conservative approach, i.e. just including projects named in the patents (or conducted by the same researchers named in the patents) or named specifically in development documents, around just over 31 Million Euros can be directly attributable to Brineura® through public funding.

### *3.3. Burosumab/Crysvita®: Search Insights and Funding Results*

Information from PubMed regarding the development of animal models was the most informative method for this product. There were several references to Japanese national funding organizations in the development of the product, however these agencies do not routinely present information in English, which hinders an accurate assessment of the contribution to public funding of this product. Again, the information from charities regarding funding was very limited; as a result, we were unable to estimate the contribution from charitable organisations. The focus of this case study was more on basic research involved in the pre-development stage of this product; public funding estimates for this case study are therefore associated with the most uncertainty. The greatest contributor to this type of research was the NIH by far. The following funding sources and amounts were identified:

A total of 13 NIH projects for a total value of US $ 25,828,081.

Project funding by the Austrian Science Fund to the value of € 423,832.50 between 2011 and 2016 (identified via the pharmaceutical company's website).

Genome Canada and the Ontario Genomic Institute as well as the Canadian Institutes of Health Research, Centre for Modeling Human Disease grant were named, however no funding details could be found. A Canadian Institutes of

Health Research funded project was identified to the value of Can $ 709,152.

1 Patent and 3 PubMed publications referred to diverse projects that had received grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan and from the Ministry of Health, Labor and Welfare of Japan and Japan Society for the Promotion of Science. Also involved in funding was the Japan Foundation for Pediatric Research and a Grants-in-Aid for Scientific Research from the Japanese Society for the Promotion of Science. It was not however possible to ascertain funding amounts for these projects.

In terms of philanthropic contributions, the Ralph W & Grace M Showalter Research Trust Fund funded research work in this area.

Other funding organisations named in publications were the Indiana Genomics Initiative and the Indiana University School of Medicine. An American Heart Association Postdoctoral Fellowship was referred to, as was a European Society for Pediatric Endocrinology Research Fellowship. The National Kidney Foundation, the Swedish Research Council, the Swedish Society of Medicine and the Genzyme Renal Innovation Programme were all referred to in the publications and sources identified.

*Burosumab/ Crysvita®: final figure*

Converting all monetary amounts into a common Euro currency leads to a total funding estimate of around € 26.8 Million for research into therapy development related to Burosumab. The bulk of the known, specified funding was from the NIH; details into the often cited contribution of Japanese sources to product development could not be ascertained.

All available results are summarized in table 4.

***Table 4.*** *Public funding estimates for three drugs.*

| | Nusinersen | Cerliponase Alpha | Burosumab |
|---|---|---|---|
| Total estimated funding of research *into therapies* (public and philanthropic sources) | €165 Million | n. a. | n. a. |
| Conservative estimate specifically for product in question | €20 Million | €31 Million | €27 Million |

# 4. Conclusions

Although these were different products with different development paths and countries of origin, the results show surprising consistency regarding the likely conservative estimate of the contribution of international public funding, which we estimate lies between 20 and 30 Million Euros per product. This is in addition to the considerable amount of largely publicly-funded basic research, which has no specific product orientation but which product developers nevertheless base their work upon. The nature and extent of publicly-available information varies greatly and there is no systematic, standard way of reporting funding. This is particularly the case for charitable funding of research activities and for project funding from public authorities outside the US and European institutions. It is very difficult and time-consuming to try to piece the funding journey together, for this reason information on the experiences and results from other researchers are needed to find agreement on the best methods. A particular difficulty was found to be the delineation of research use: at which point can research funding be said to be associated wholly and exclusively with specific product development, as opposed to basic research about the disease and mechanisms of action (which may benefit several products or classes of products)? The principal investors in drug development differ at each stage. While basic discovery research is funded primarily by government and by philanthropic organisations, late-stage development is funded mainly by pharmaceutical companies or venture capitalists. The period between discovery and proof of concept is considered extremely risky and therefore has been difficult to fund.

The most recent publication of Cleary et al. [11] found that all 210 drugs approved in the USA between 2010 and 2016 benefitted from publicly-funded research, either directly or indirectly: NIH spending amounted to $ 12.5 billion for the 210 NMEs or just under 60 million € per new molecular entity (NME) or for first-in-class NMEs, 91 Million $ per drug. Our investigation aimed at a more focused approach to public R&D support for concrete products. Cleary´s data includes basic research and was not focused on specific products, whereas we selected three drugs and focused our analyses mainly on a late developmental stage. These investigations into public R&D complement each other as pieces of a large puzzle. We expect that more puzzle pieces with more detailed data will be published, especially given the global pressure for regulatory measures to safeguard “access to medicines” [18, 19] and the recent WHO-resolution on transparency in drug costs [20]. Requesting pharmaceutical companies to publish estimates of any public and philanthropic contributions to development (in relation to their own R&D spending) during price negotiations would be a good way forward.

We agree with others [15] that there is a need for more transparency about funding sources of health research globally, about the priorities of those funding sources and about the criteria for deciding upon priorities. A 2009 assessment of US biomedical research across therapeutic areas found the pharmaceutical industry led investments in neuroscience, cardiovascular, endocrine, gastrointestinal, respiratory and genitourinary research, while the NIH funded the majority of support for HIV/AIDS, infectious disease and oncology research [16, 17]. Data is often not available publicly or is reported in a haphazard and piecemeal fashion. Similar to standards of good practice for the reporting of clinical trials (CONSORT, STROBE, STARD etc.), standards for the transparent reporting of funding information are required.

The contribution of public and philanthropic funding to R&D activities is considerable but it is not always possible to quantify this contribution. We know that the contribution runs into tens of millions of Euros at least. This is a conservative estimate and does not include basic early research that does not mention product-related names.

More transparency and structured reporting is necessary to enable the clear quantification of the contribution of public funding to progress the debate on the price of pharmaceuticals and associated access to medicine.

There are several limitations of this analysis. Search strategies needed to be individualised for each product and there was no standardised reporting of funding amounts by funders, particularly by philanthropic organizations. There are tax concessions that pharmaceutical companies can take advantage of, particularly for orphan products, which were not included here, although they also represent public contributions to R&D costs. In terms of limitations, we have no estimate of the total R&D costs, including those incurred by the pharmaceutical companies, so we cannot estimate the proportion of total R&D costs borne by public or philanthropic organizations.

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