Overpriced

Drugs Developed with Dutch Public Funding

Irene Schipper & Esther de Haan & Roberta Cowan

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The Centre for Research on Multinational Corporations (SOMO) is a critical, independent, not-for-profit knowledge centre on multinationals. Since 1973 we have investigated multinational corporations and the impact of their activities on people and the environment. We provide custom-made services (research, consulting and training) to non-profit organisations and the public sector. We strengthen collaboration between civil society organisations through our worldwide network. In these three ways, we contribute to social, environmental and economic sustainability.

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Wemos is a Netherlands-based, internationally active lobby and advocacy organisation that advocates the right to health for all; access to health services and protection against threats to health. Since our foundation, 40 years ago, we analyse Dutch, European and global policies that affect health and propose relevant changes, targeting (inter)national policy-makers and politicians, and also reaching the broader public. We believe in using our knowledge base to build bridges, raise awareness of urgent health issues, and to strengthen the voices of partner organisations and those without easy access to healthcare.
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SOMO in collaboration with Wemos

Irene Schipper & Esther de Haan & Roberta Cowan

Amsterdam, May 2019
# Contents

1 Executive Summary ................................................................. 8  
  1.1 Key findings ................................................................................................ 9  
  1.2 Conclusions ................................................................................................. 10  
  1.3 Recommendations ......................................................................................... 11  

2 Introduction to the report ........................................................... 12  
  2.1 Background ................................................................................................. 12  
  2.2 Research objectives ....................................................................................... 15  
  2.3 Methodology ............................................................................................... 16  
  2.4 Outline of this report ..................................................................................... 17  
  2.5 Cooperation with Wemos ............................................................................ 18  

3 Trends in public funding for biomedical R&D ........................................ 19  
  3.1 Introduction ................................................................................................. 19  
  3.2 Basic or fundamental research phase ............................................................. 20  
  3.3 The role of academia in applied research ......................................................... 20  
  3.4 Empty pipelines of the large pharmaceutical companies .................................... 23  
  3.5 Cost of drug development ........................................................................... 26  

4 Public funding of biomedical R&D in the Netherlands ....................... 28  
  4.1 Introduction ................................................................................................ 28  
  4.2 Spending on biomedical R&D as reported by the Dutch Government ............... 29  
  4.3 Tax incentives ............................................................................................... 32  
  4.4 Public venture capital funds for the Dutch biotech sector ............................... 33  
    4.4.1 Overview of the Life Sciences & Health sector in figures ......................... 33  
  4.5 Financing instruments to support biotech start-ups ....................................... 37  
    4.5.1 Public venture funds ............................................................................... 38  
  4.6 Conditionalities attached to biomedical funding in the Netherlands ............. 43  
    4.7 Concluding remarks ............................................................................... 47  

5 Case study: Acerta Pharma’s Calquence (AstraZeneca) ..................... 48  
  5.1 The share of Dutch public funding in Acerta ................................................. 50  
    5.1.1 Pivot Park .............................................................................................. 50  
    5.1.2 Innovation Credit ............................................................................... 50  
    5.1.3 Brabant Development Agency (BOM) invests ......................................... 51  
    5.1.4 BioGeneration Ventures ..................................................................... 52  
    5.1.5 Financial history of Acerta Pharma ....................................................... 52  
  5.2 Concluding remarks ................................................................................... 53  

6 Case study: ATIR101 of Kiadis Pharma ............................................. 54  
  6.1 The development of Kiadis Pharma and ATIR101 .......................................... 54  
  6.2 Public investments in Kiadis ......................................................................... 56  
  6.3 Concluding remarks .................................................................................... 58
Glossary

Academic Start-ups (NL)
Start-ups based primarily on knowledge, research results, materials and/or intellectual property gained from scientific research carried out at Dutch universities, university medical centres (UMCs), and institutes at the Netherlands Organisation for Scientific Research (NWO), and the Royal Netherlands Academy for Arts and Sciences (KNAW).

Added Therapeutic Value (ATV)
Proven effects of a treatment on patient-relevant endpoints, a relevant level of effectiveness, and both in comparison with the best available treatment option.

Applied Research
The practical application of basic research with the purpose of drug discovery.

Basic Research
Also called fundamental research. Studying “the underlying mechanisms of disease and subsequently identify promising points of intervention”1. It is performed without specific applications in mind or product development.

Biomedical R&D
Research that looks at the causes, prevention and treatment of diseases. From basic research and applied research, to clinical research conducted to expand knowledge in the field of medicine.

Clinical Research
A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioural outcomes. (def. NIH)

Compulsory licensing
When a government allows someone else to produce a patented product or process without the consent of the patent owner, or plans to use the patent-protected invention itself. (def. WTO)

Drug Discovery
All scientific exploration leading up to the discovery of a candidate for clinical testing.

Drug Development
All scientific exploration of a candidate for clinical testing to prove its safety and efficacy in humans and its therapeutic benefit to patients.

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Fundamental Research
Also called basic research. Studying “the underlying mechanisms of disease and subsequently identify promising points of intervention”\(^2\). It is performed without specific applications in mind or product development.

License
A licence is an agreement between the owner of the intellectual property rights (the patent holder) and another party. It grants them permission to do something that would be an infringement of the rights without the licence.

New Drug Application (NDA)
The method in the US where drug sponsors formally propose that the US Food & Drug Administration (FDA) approve a new pharmaceutical for sale and marketing.

Non-exclusive license
A non-exclusive licence grants to the licensee the right to use the intellectual property, but means that the patent holder remains free to exploit the same intellectual property and to allow any number of other licensees to also exploit the same intellectual property.

Orphan Drugs
An orphan drug is a pharmaceutical agent that has been developed specifically to treat a rare medical condition, the condition itself being referred to as an orphan disease.

Patent
A title granted by public authorities that confers a temporary monopoly for the exploitation of an invention upon the person who reveals it, furnishes a sufficiently clear and full description of it, and claims this monopoly. (WHO def.)

Spin-off
The creation of a separate company from part of an existing firm. A spin-off is also a company whose business is based on products or technology initially developed in a parent company, university or research institution.

### Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AAA</td>
<td>Advanced Accelerator Applications (company)</td>
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<tr>
<td>ACM</td>
<td>Authority for Consumers &amp; Markets</td>
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<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
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<td>ATV</td>
<td>Added Therapeutic Value</td>
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<td>BMJ</td>
<td>British Medical Journal</td>
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<tr>
<td>BOM</td>
<td>Brabant Development Agency</td>
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<tr>
<td>CBG</td>
<td>Medicines Evaluation Board</td>
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<tr>
<td>CPMP</td>
<td>Committee for Proprietary Medical Products</td>
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<td>CRO</td>
<td>Contract Research Organisations</td>
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<tr>
<td>DIN</td>
<td>Drug Identification Number</td>
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<td>DVI</td>
<td>Dutch Venture Initiative</td>
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<tr>
<td>EAF</td>
<td>European Angels Fund</td>
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<tr>
<td>EC</td>
<td>European Commission</td>
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<tr>
<td>EFPIA</td>
<td>European Federation of Pharmaceutical Industries and Associations</td>
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<td>ERDF</td>
<td>European Regional Development Fund</td>
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<tr>
<td>EIB</td>
<td>European Investment Bank</td>
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<tr>
<td>EIF</td>
<td>European Investment Fund</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>EPAR</td>
<td>European Public Assessment Report</td>
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<td>EU</td>
<td>European Union</td>
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<tr>
<td>EZ</td>
<td>Ministry of Economic Affairs and Climate</td>
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<td>FDA</td>
<td>US Food &amp; Drug Administration</td>
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<td>FIGON</td>
<td>Federation Innovation Drug Research Netherlands</td>
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<tr>
<td>FP6</td>
<td>European Union’s Research and Innovation funding programme for 2002-2006</td>
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<td>FP7</td>
<td>European Union’s Research and Innovation funding programme for 2007-2013</td>
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<td>FPO</td>
<td>Follow-on Public Offering</td>
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<td>GSK</td>
<td>GlaxoSmithKline plc</td>
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<tr>
<td>GVS</td>
<td>Medicines Reimbursement System (geneesmiddelenvergoedingssysteem)</td>
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<tr>
<td>HTAs</td>
<td>Health Technology Assessments</td>
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<tr>
<td>HTS</td>
<td>High Throughput Screening</td>
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<tr>
<td>ICTRIP</td>
<td>International Clinical Trials Registry Platform of the WHO</td>
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<tr>
<td>IMI</td>
<td>Innovative Medicines Initiative</td>
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<tr>
<td>IND</td>
<td>Investigational New Drug</td>
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<tr>
<td>IPO</td>
<td>Initial Public Offering</td>
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<tr>
<td>KNAW</td>
<td>The Royal Netherlands Academy of Arts and Sciences</td>
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<tr>
<td>LSH</td>
<td>Life Sciences &amp; Health</td>
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<tr>
<td>MAA</td>
<td>Marketing Authorisation Approval</td>
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<tr>
<td>M&amp;A</td>
<td>Merger and Acquisitions</td>
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<tr>
<td>MSD</td>
<td>Merck Sharp &amp; Dohme Corp (known as Merck &amp; Co in the US and Canada)</td>
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<tr>
<td>NAS</td>
<td>New Active Substance</td>
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<td>NFIA</td>
<td>Netherlands Foreign Investment Agency</td>
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<td>NFU</td>
<td>The Netherlands Federation of University Medical Centres</td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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</table>
NKI  Dutch Cancer Institute
NL  The Netherlands
NME  New Molecular Entity
NOM  Investment and Development Agency for the Northern Netherlands
NWO  Netherlands Organisation for Scientific Research
NWO (TTW)  NWO Applied Technical Science (Toegepaste Technische Wetenschappen)
NZa  Dutch Healthcare Authority (Nederlandse Zorgauthoriteit)
OCW  Ministry of Education, Culture and Science
OECD  Organisation for Economic Cooperation and Development
PPPs  Public Private Partnerships
R&D  Research & Development
ROMs  Regional Development Agencies (Regionale Ontwikkelingsmaatschappijen)
RVO  Netherlands Enterprise Agency (Rijksdienst voor Ondernemend Nederland)
RVS  Netherlands Council for Public Health and Society
SMEs  Small and Medium Sized enterprises
SOMO  Centre for Research on Multinational Corporations
UK  United Kingdom
UMCs  University Medical Centres
US  United States of America
VU  Vrije Universiteit (Amsterdam)
VWS  Ministry of Health, Wellbeing and Sports
WBSO  R&D Tax Credit (Wet Bevordering Speur & Ontwikkelingswerk)
WHO  World Health Organisation
WGP  Medicine Prices Act (Wet Geneesmiddelenprijzen)
ZiN  National Healthcare Institute (Zorginstituut Nederland)
ZonMw  Netherlands Organisation for Health Research and Development
1 Executive Summary

The astronomical prices of new medicines make certain treatments increasingly inaccessible for patients as the medicines are unaffordable for national healthcare reimbursement systems, even in the Netherlands. There is growing awareness among EU governments¹, including the Dutch Government², that it is ultimately the tax payer that bears the costs of medicines, sometimes twice or thrice over, because of the public reimbursement system, and funding for academics institutes where basic research is conducted, tax incentives and grants made to stimulate innovative drug development, and public investments in spin-off companies from universities.

¹ Key note speech at the EU health conference under the Austrian Presidency of Council of the European Union titled "Matching Health Needs and Pharmaceutical Research – How to set the research agenda for public health", 25 September 2018, Vienna, Austria.
It is clearly problematic that so little data exists that details the exact amounts of public spending on the R&D of medicines and increasingly, Dutch Parliamentarians, political parties and civil society organisations are expressing an urgent need to map and measure the level of public investment in drug development.

This report tries to examine public funding in the Netherlands that is spent on, or invested in, the development of new medicines, using research from case studies of medicines that have been developed at least in part with Dutch public funding, in order to examine the possibility of attaching conditionalities to public funding of medical Research and Development.

1.1 Key findings

Dutch public funding into medicine development.
In 2017, according to figures provided by the Dutch Minister for Medical Care, approximately €780m of Dutch public funding was spent on biomedical R&D, with a further € 55m worth of funding coming from the EU. These amounts mainly refer to public funding of basic research (biomedical research performed without specific applications or product development).

This report shows that, in addition to funding basic research, there is also substantial Dutch public funding of applied research, drug development, clinical trials, as well as investments made in biotech companies via public-private partnerships, loans, tax breaks, and seed and/or venture capital schemes.

Public funding for medicine development through venture capital funds
Government funding of the early phase of drug development and preclinical testing – when the risk of failure is high and private investors are reluctant to commit their money – includes seed money, venture capital, loans and credits. In these cases, European, national, and regional government funding bodies in the Netherlands sometimes act as capital investors, using so-called revolving funds. As a consequence, the high risk is undertaken by the public, instead of the pharmaceutical companies.

Public costs of the growing role played by universities in applied research
Pharmaceutical companies are accessing external innovation by increasing cooperation with the academic world. Some pharmaceutical companies have even closed their traditional R&D sites to set up new facilities close to academic institutions. These new sites operate like head-hunters, identifying local academics, and university faculty, working on promising new biological medicines which pharmaceutical company could use in their own innovative drug-discovery programmes.

As the case studies in this report show, large pharmaceutical companies are also buying up small and medium sized biotech companies that have potentially promising medicines or therapies in development, to replace their own R&D into new medicines and boost their drug pipeline. These biotech companies often originate at universities.
Public funding of clinical trials
This report highlights findings that contradict the pharmaceutical industry’s mantra that it pays for all expensive clinical trials. Data from clinical trials databases for the cancer drug Keytruda, reveal more than half of Keytruda clinical trials around the world have been initiated by non-industry institutions and are at least partly funded by public institutions or non-commercial sponsors, including publicly financed medical or cancer institutes, and hospitals.

1.2 Conclusions

Lack of overview and transparency of public funding of biomedical R&D in the Netherlands
Because of a lack of overview on the amount of public money invested in public venture capital funds, tax incentives and the variety of financing schemes available to start-ups, along with a lack of information provided by public capital venture funds, there is no transparency on the total public funding of medicine development in the Netherlands.

Universities are increasingly working on applied research
The role played by universities and public research institutes in applied research continues to grow, because:
1 Large pharmaceutical companies are stepping away from playing a part in early drug development, preferring to leave this phase to universities and publicly funded research institutes;
2 The strategy of large pharmaceutical companies is gradually changing from ‘Research & Development’ to ‘Search & Development’, leading to increased cooperation with the academic world.

The public funding of biomedical R&D through seed and/or venture capital schemes does not necessarily yield public health benefits
Public funding of biomedical R&D through seed and/or venture capital schemes uses economic indicators, including financial return, economic growth, foreign investments, and job creation, to assess public return. However, there are currently no conditions on those investment schemes in place to safeguard a public return on the investments, including among other things, that medicines developed with this funding is affordable for the patients who need them.

There is lack of policy coherence
There is clear lack of policy coherence between publicly funding capital venture investments in drug development, along with the expected high return on such investments, and the government need to avoid high medicine prices.
The large pharmaceutical companies are profiting from the public spendings
What becomes clear from the case studies is that public funding in the Netherlands has been used to help develop medicines that are, or will be, sold at a very high price, making huge profits for the pharmaceutical companies that own the drug when it is brought to market. AstraZeneca, MSD, Novartis and their shareholders, are the beneficiaries of these profits whereas society, or tax payers specifically, receive little to no financial return on those public investments made throughout the R&D process, yet the public still must pay increasingly unaffordable prices for medicines.

Attaching conditionalities to public funding of biomedical R&D
Attaching conditionalities to public funding of biomedical R&D is still in its infancy in the Netherlands but the first steps are being taken to develop the principles of such conditions. It is important that the Dutch Government realized it is important to attach conditionalities to public funding of biomedical R&D.

1.3 Recommendations

Policy coherence
A more comprehensive approach towards public funding in medicine development could rebalance public health interests with economic policies. Existing frameworks, such as the Sustainable Development Goals (SDGs), could be used to analyze the social impact of public funding.

Transparency
The Ministries that channel biomedical R&D funding need to be more transparent about the nature and amounts of funding they provide, including more openness about the use of venture capital funds that invest public money.

Conditionalities
Attaching conditionalities to licenses developed with the help of public funding will result in better public return. It is recommended that the Dutch Government urgently pursues its commitment to attaching conditionalities to public funding of biomedical R&D.

It is also recommended that research is undertaken to investigate the possibility of introducing a European legislation that requires applicants for marketing approval to state whether any public funding contributed to the R&D of the medicine.
2 Introduction to the report

2.1 Background

The astronomical prices of new medicines make certain treatments increasingly inaccessible for patients as the medicines are unaffordable for national healthcare reimbursement systems, even in the Netherlands. There is substantial public funding available for new medicines and for start-up companies that develop new medicines. This report examines public funding in the Netherlands spent on the development of new medicines.

The Dutch Government sounded alarm bells in 2015 when it was predicted that a new lung cancer drug would cost around €200m per year for patients in the Netherlands, and that there would be more very expensive medicines on the market in the coming years. Given that the annual national expenditure on drugs administered in hospitals was €1.85bn, the realisation that one treatment alone might absorb 11 per cent of the available budget made the Dutch Government decide to stop automatically reimbursing new, expensive medicines. This decision was made on the basis that in the long term, given such expensive drugs, the Dutch Government could not guarantee its citizens access to affordable healthcare.3

Prices of medicines and availability

While high priced medicines are available for patients in the Netherlands, they challenge the boundaries of the health insurance system. It may be that, with more expensive medicines expected in the future — such as personalised medicines — this availability might come to an end. Already, there are medicines anticipated to be on the Dutch market in 2019, that are expected to cost millions of euros per treatment4.

In less wealthy countries, the availability of even average-priced medicines, is totally different. While deaths from cancer, for example, are slowly decreasing in wealthy countries, because of early detection and the availability of treatments, the situation is not the same for those living in low- and middle-income countries. According to the World Health Organisation (WHO), 80 per cent of children with cancer in high-income countries will be cured, but in low- and middle-income countries this figure drops to as low as 20 per cent, partly because of the high cost of treatment and medicines5.


The 2015 predictions came true. In 2016, the Dutch expenditure on medicines used in hospitals increased by eight per cent, and by nine per cent in 2017, totalling €2.1bn, with cancer medicines representing 44 per cent of the total amount. When combined with medicines dispensed from pharmacies (extra-mural), total Dutch expenditure on medicine was, in 2017, approximately €5bn.

In September 2018, Dutch newspapers reported that health insurance premiums were expected to rise in the coming years because of expensive new medicines. In 2018 the annual average premium per person was €1,308 but it is estimated that by 2021, this will have risen to €1,600.

Alarmed by the foreseen unaffordability of medicines, the former Dutch Minister of Health, Edith Schippers (2010-2017), prioritised the issue of high drug prices, and put it on the national and European agendas. During the Dutch Presidency of the Council of the EU (January – June 2016), cooperation among member states on medicine pricing and other policy measures to counter the trend of rising drug prices were discussed.

In an uncharacteristically fierce statement for government representatives, the Dutch Ministers of Foreign Trade and Development Cooperation and the Dutch Minister of Health wrote in the medical journal The Lancet in January 2017 that the current patent-based business model of drug development was ‘broken’ and emphasised the need for “full transparency on costs, prices, and who pays what beforehand”.

This government call for transparency has become more important following increasing awareness among the Dutch public of the significant amount of public funding given to new medicines. Public money pays for a substantial amount of basic research and, increasingly, applied research that contributes to breakthroughs in medicine development.

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6 Part of the increase can be explained by the growing number of patients treated with inpatient medicines.
8 The costs for extra-mural (pharmacy) expenditure was €2,985,740 million in 2017, this is exclusive of the pharmacists costs. When pharmacists service costs are included the amount is €4,576,386 million. The inpatient medicines (hospital medicines) was €2,078,273 million. GIPdatabank, <https://www.gipdatabank.nl/actueel> (28 December 2018).
The pharmaceutical industry claims that the research and development (R&D) costs for developing a drug are between US$2.2bn\textsuperscript{13} and 2.9bn\textsuperscript{14}. This high estimation is used, in part, by the industry to rationalise the high prices charged for certain medicines. Pharmaceutical companies do not disclose breakdowns in R&D or any insight into details of R&D costs of medicines brought onto the market.

There is growing awareness among EU governments\textsuperscript{15}, including the Dutch Government\textsuperscript{16}, that it is ultimately the tax payer that bears the R&D costs of medicines, sometimes twice or thrice over, because of the public reimbursement system, and funding for academics institutes where basic research is conducted, tax incentives and grants made to stimulate innovative drug development, and public investments in spin-off companies from universities.

No data exists in European countries on the exact amount of public funding spent on biomedical R&D. The Director General of the Austrian Federal Ministry of Health\textsuperscript{17} Clermens Martin Auer said in his opening speech at an EU Health Conference on the 25\textsuperscript{th} of September 2018 in Vienna that there is much more public money invested in drug development than we might think, but the problem is that we don’t know how much. He mentioned that according to the OECD roughly one third is public money but that we don’t have a clear picture.\textsuperscript{18}

Members of the Dutch Parliament, political parties, and civil society organisations and their networks have expressed the need to map and measure public investment in biomedical R&D; such data and information could also be used in price negotiations.

In January 2016, the Dutch Government, in an effort to prevent patients paying double for medicines, announced that, as part of its health policy, conditionalities would be attached to future public funding of drug development\textsuperscript{19}. On 7 February 2019 the Minister of Medical Care stated that the Netherlands Federation of University Medical Centres (NFU) had been asked to develop standards for socially responsible licensing, with emphasis on the transfer of knowledge between the public institute and the manufacturer.\textsuperscript{20}


\textsuperscript{15} Key note speech at the EU health conference under the Austrian Presidency of Council of the European Union titled “Matching Health Needs and Pharmaceutical Research – How to set the research agenda for public health”, 25 September 2018, Vienna, Austria.


\textsuperscript{17} In full the Ministry is called the Federal Ministry of Labour, Social Affairs, Health and Consumer Protection.

\textsuperscript{18} The EU health conference “Matching Health Needs and Pharmaceutical Research – How to set the research agenda for public health”, 25 September 2018, Vienna, Austria.


2.2 Research objectives

In this study, the Centre for Research on Multinational Corporations (SOMO) aims to shed light on direct and indirect Dutch public investment in the R&D of new medicines.

Research objectives for this study
1. Describe the Dutch system of public funding for medical R&D, and research figures for public funds invested in biomedical R&D;
2. Research case studies of medicines that have been developed at least in part with Dutch public funding to scrutinise the extent of public funding for biomedical R&D in the Netherlands;
3. Explore conditionalities and possibilities to attach conditionalities to public funding for biomedical R&D in the Netherlands.

Specific research questions
Specific research questions on the Dutch system of public funding for medical R&D, and research figures for public funds invested include:

☐ How is biomedical R&D publicly funded in the Netherlands?
☐ Which financial instruments, directly and indirectly, contribute to public funding for biomedical R&D? (including tax incentives, credits)
☐ How much does the Dutch government spend on medical R&D?
☐ What part of biomedical R&D, conducted in the Netherlands, is funded by European public funds?
☐ Does the Dutch Government include safeguards/conditionalities in its funding for medical R&D?

The case studies on high-priced medicines, or potentially high-priced medicines, aim to illustrate the extent of Dutch public funding in drug development, and provide concrete examples of medicines that have roots in the Netherlands, at Dutch universities, UMCs or Dutch companies.

Specific research questions for the case studies:

☐ What are the Dutch roots of the medication?
☐ What is the role and share of Dutch public funding in the R&D process of this medicine?
☐ What is the price level of the medication?

Specific research questions related to the attachment of conditionalities to public funding of biomedical R&D:

☐ What position does the Dutch Government take on conditionalities?
☐ What conditionalities currently exist internationally? Do the Dutch publicly funded research institutes involved in biomedical R&D have conditionalities?
2.3 Methodology

Research methodologies for this study include desk research, speaking to experts in non-governmental organisations (NGOs) and university networks with which SOMO has links, (including the Dutch Medicines Network,\textsuperscript{21} the European Alliance for Responsible R&D and Affordable Medicines, and the European Public Health Alliance (EPHA)), interviewing scientists involved in developing the drugs featured in the case studies, interviewing medical doctors involved in clinical trials, and reviewing regional development funds and case studies with the companies involved.

No public information is currently available on the exact amount and extent of Dutch public funding for biomedical R&D. The Minister of Medical Care was asked to provide such information to the Dutch House of Representatives at the General Meeting on Medicines (Algemeen Overleg) on 22 November 2017. The Minister, Bruno Bruins, did provide this information but almost a year later (‘Kamerbrief’, 8 October 2018)\textsuperscript{22}, and some of the budgets presented were annual budgets, while others covered longer periods. For the purposes of this research, SOMO converted the budgets into annual amounts, allowing for a very rough estimation of total public funding in 2017\textsuperscript{23}.

The information on the Keytruda clinical trials came mainly from the U.S. trial registry ‘Clinicaltrials.gov’ and the WHO trial registry ‘WHO ICTRP’. Datasets from both registries were downloaded into excel formats. The EU Clinical Trials Register names both the sponsor of the trial and the source of the ‘monetary or material support for the clinical trial’ but does not identify the kind of support. The US clinical trial register names the sponsor and the ‘collaborator’ (similar to the source of the ‘monetary or material support’ identified in the EU registry). SOMO also contacted principal investigators involved in clinical trials with Keytruda in the Netherlands.

SOMO’s research methodology includes a ‘right to reply’ policy. Companies cited in the case studies were invited to review a draft of the part of the report that related to them and were given the opportunity to provide comments and make corrections. The following companies responded: AstraZeneca, Kiadis Pharma, Dezima Pharma, MSD and Novartis. In addition, the Brabant Development Agency (BOM) and the Investment Development Agency for the Northern Netherlands (NOM) were asked to review parts of the report. The NOM declined to review the report\textsuperscript{24}.

\textsuperscript{21} Members of this network include License to Heal, Universities Allied for Essential Medicines (UAM) in the Netherlands, Wemos, Health Action International, various charity organisations/funds for specific diseases.
\textsuperscript{23} For example, a fund dispersed over a period of 5 years was divided by five to get a yearly amount, however these are only approximations since in practice items are not always divided equally over the years and there will be some variation about the starting time of the grants
\textsuperscript{24} Phone call following up on review request with Mrs. Wouterse, Investment Manager at NOM, on 15 April, 2018.
2.4 Outline of this report

Chapter 3 describes the trends in public funding of R&D in medicines, and notes the main players active in the different phases of research. It looks into the gradual shift of R&D away from large pharmaceutical companies towards small and middlesized companies and/or academic institutions, and outlines current discourse about the costs of medicine development.

Chapter 4 focuses on the public funding of biomedical R&D in the Netherlands and estimates funding levels. This chapter provides an overview of the ‘traditional streams’ of public funding for biomedical R&D in the Netherlands based on official data provided by the Dutch Minister for Medical Care. It also describes the role played by public venture capital funds – also called revolving funds – in supporting Dutch biotech start-up companies, and outlines the Government’s position on attaching conditionalities to public funding for biomedical R&D.

Chapter 5 is a case study of the drug Calquence, made by Acerta Pharma, a biotech company from the Province of Brabant. It examines how public venture capital funds – including the regional development agency the BOM – were invested in Acerta during its start-up phase, and how other forms of public funding were also used to support this small biotech company in developing a cancer medication.

Chapter 6 includes the case study on ATIR101 made by Kiadis Pharma, a Dutch biotech company. Kiadis Pharma received funding via a venture capital fund belonging to a regional development agency the NOM as well as from other public financing schemes.

Chapter 7 is the Keytruda case study, a cancer medication developed by Merck & Co. (MSD). Keytruda’s origins can be traced back to fundamental and pre-clinical research in publicly funded institutions, including universities. The case study also shows how public funding provided during the clinical phase of the drug development, can be substantial.

Chapter 8 is a case study on the drug Lutathera, a cancer medicine now owned by Novartis but originally developed by researchers at the Dutch Erasmus Medical Centre in Rotterdam. Before being bought by Novartis, the drug was made in hospitals; since Novartis began producing Lutathera in January 2018, its price has reportedly increased five-fold.

The report finishes with conclusions and recommendations.
2.5 Cooperation with Wemos

From 2006, SOMO has worked closely with Wemos on research projects related to the pharmaceutical sector. Wemos is an independent Dutch global health lobby and advocacy organisation, which advocates access to health for everyone everywhere, and aims to improve public health worldwide. This research project is jointly set up and follows the usual division of tasks between SOMO and Wemos, with SOMO being responsible for the research and Wemos for the lobby and advocacy activities.

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3 Trends in public funding for biomedical R&D

3.1 Introduction

This chapter looks into the gradual shift of R&D away from large pharmaceutical companies to small and middle sized companies and/or academic institutions.

Fundamental research, which is the basis for drug development, is primarily undertaken by academic and public-sector researchers\(^{26}\). Companies play a more active role in applied research which results in drug discovery and further drug development.

This chapter elaborates on the applied research phase of drug development which has seen an increase in public funding. For an overview of the phases in drug development, see Table 1.

This chapter also describes the current discourse about the R&D costs needed to develop a new medicine. There is much disagreement about the different methods used to calculate R&D costs.

<table>
<thead>
<tr>
<th>Phase of drug development</th>
<th>Description</th>
<th>Timelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic research (also called fundamental research)</td>
<td>Studying “the underlying mechanisms of disease and subsequently identify promising points of intervention”(^{27}). It is performed without specific applications in mind or product development.</td>
<td>3 months to 30 years</td>
</tr>
<tr>
<td>Applied research (drug discovery and early drug development)</td>
<td>Practical application of basic research with the purpose of drug discovery. Includes target identification, hit to lead identification using compound screening processes and lead optimization.</td>
<td>4.5 years</td>
</tr>
<tr>
<td>Preclinical testing</td>
<td>Testing the identified molecule in animals and other biosystems (e.g. cell lines, tissue cultures) for efficacy, toxicity and pharmacokinetic profile</td>
<td>1 year</td>
</tr>
<tr>
<td>Investigational New Drug (IND) filing (FDA) or Investigational Medicinal Product Dossier (EMA)</td>
<td>Drug developers must submit an application to FDA or EMA before beginning clinical research.</td>
<td></td>
</tr>
<tr>
<td>Clinical Trials Phase I</td>
<td>Safety testing done on 20-100 healthy people</td>
<td>1–2 years</td>
</tr>
<tr>
<td>Clinical Trials Phase II</td>
<td>Testing of drug on 100-300 patients to assess efficacy</td>
<td>1-2 years</td>
</tr>
<tr>
<td>Clinical Trials Phase III</td>
<td>Testing of drug on 300-3000 patients to assess efficacy, effectiveness and safety</td>
<td>1-4 years</td>
</tr>
<tr>
<td>NDA or MAA (FDA/EMA)</td>
<td>Application for new drug approval or marketing authorization application</td>
<td>18 months</td>
</tr>
</tbody>
</table>

Table 1 Overview of the phases in drug development, including timeline

\(^{26}\) Research in the public sector is carried out in a wide range of establishments that include those run by government departments and agencies, nationalised health services, and independent research institutes that work on a not-for-profit basis.

Timelines
Different sources indicate that R&D (across all therapeutic areas) can take an average of 14 years, following the basic research stage. Discovery research lasts about 4.5 years; preclinical testing continues for approximately 1 year; the three clinical trial phases can take 3 to 8 years in total, and the phase from submission to launch requires up to another 18 months. Data analyses done by Deloitte indicates that the clinical testing phase takes longer, apart from those drugs with Fast Track, Breakthrough, Orphan or Priority Review designations. According to Deloitte the average time for the clinical trial phase has increased from 6.1 years (2015) to 6.6 years (2018) across all therapeutic areas. Oncology trials alone take an average of 9.4 years.

3.2 Basic or fundamental research phase
Basic research involves studying the underlying mechanisms of a disease and identifying promising points of intervention.

A Johns Hopkins University School of Medicine Study confirmed that almost all medicine is developed on the back of basic research conducted by publicly funded research institutes. The study found that of the 210 drugs approved by the Food and Drug Administration (FDA) from 2010-2016, all had benefited from government funding, with 90 per cent of the drugs associated with government funding at the fundamental research stage.

3.3 The role of academia in applied research
As described in Table 1, applied research is the practical application of basic research with the purpose of drug discovery. This chapter describes how universities and public sector research institutes play an active role in the applied-research phase of medicine development.

In 2011, Ashley Stevens et al. published an analysis of US academic and public sector research contributions to biomedical R&D. It analysed all 1541 FDA drug approvals from 1990 to 2007, and concluded that in 143 cases (9.3 per cent) the US academic and public sector had participated in the applied research phase. Any intellectual property created during this phase – a patent or patent application, for example – had subsequently been transferred to a company.

31 Applied research is the practical application of basic research with the purpose of drug discovery. Closely related is the term “translational research”.
A similar examination, excluding older data, was undertaken by Robert Kneller. He analysed drugs approved by the FDA over ten years (1998-2007), looking to those drugs approved under New Drug Applications (NDAs), New Molecular Entities (NME) and Biologics License Applications (BLAs). Of the 252 drug approvals in total, he found that in the case of 60 approvals (24 per cent) the organisation that had discovered the drug was either an academic or not-for-profit research organisation. In two-thirds of those 60 approvals, the first transfer of the license was to a biotech company. In the remaining third, the first transfer was to a pharmaceutical company.

Given that approximately 60 per cent of the drug approvals that originated from a public research institute were given priority review status by the FDA, both studies concluded that academic and public sector research institutes are more likely to discover drugs with significant clinical and therapeutic effects.

A report looking at the origins of new drugs in Europe also came to similar conclusions. Researchers affiliated with the EMA looked at all 94 approved marketing authorisation applications (MAAs) in Europe for medicinal products containing a new active substance (NAS) between 2010 and 2012. Of the 94 MAA holders, 87 per cent were large pharmaceutical companies (59 per cent) or intermediate-sized pharmaceutical companies (28 per cent) while 13 per cent were small and middle sized entities (SMEs). But when the products were tracked back to the original patent registration, or the ‘patent originator’, large or intermediate-sized pharmaceutical companies accounted for only 49 per cent of the products (large, 28 per cent; intermediate-sized, 21 per cent), SMEs for 27 per cent, and academic/public bodies/Public Private Partnerships (PPPs) 17 per cent. The original patents from private–private collaborations accounted for 7 per cent (see also Graphic 1).

The report revealed that none of the academic/public bodies, and/or PPPs identified as originators, kept the product on to the stage of marketing authorisation. Of all the products, 81 per cent were out-licensed to large or intermediate-sized companies, with the remainder out-licensed to SMEs.

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34 In this study, the origins of the drugs analysed were determined by identifying the inventors in the key patents and their places of employment at the time of the discovery. Kneller, R., “The importance of new companies for drug discovery: origins of a decade of new drugs”, Nat Rev Drug Discov. 2010 November, <https://www.ncbi.nlm.nih.gov/pubmed/21031002> (13 November 2018).


36 Of the 348 priority reviews in the period 1990-2007, 66 (19.0%) resulted from public sector research institutes. Viewed from another perspective, 46.2% of new-drug applications from public sector research institutes received priority reviews, as compared with 20.0% of applications that were based purely on private-sector research.


38 The researchers took the EU criteria for categorizing SMEs: headcount less than 250, and not more than €50 million in turnover or €43 million on the balance sheet. However, they didn’t make the difference between large and intermediate sized companies clear. “Intermediate sized companies” is not a standard classification.

The shift to biological medicines

The increased role of publicly funded research institutes in applied research can also be looked at coinciding with the transition from classic small molecule medicines to biological medicines. Biological medicines are drugs made from complex molecules, such as enzymes or antibodies, and manufactured in a complex process that uses living micro-organisms, plants, or animal cells. In the biological drug development process, a biotech company often interacts with universities during all development steps through to the regulatory phase of the process. Because small biotech companies usually do not have all the necessary specialised knowledge and facilities in-house, they depend on universities who do have the relevant expertise and facilities, such as specialised animal models, access to patients, gene therapy production facilities.

Graphic 1 Originator and the marketing authorization holder for all 94 approved new medicines by the EMA between 2010-2012

On the basis of these studies it can be concluded that academic and public sector research plays a vital role in the development of medicines with a priority review status or containing a new active substance, while large and intermediate sized companies are almost exclusively in charge of the commercialisation of new drugs. The SMEs, academic and public sector research institutes – including PPPs – are therefore very important in filling the pipelines of large and intermediate sized companies.

The research also indicates that the role of public research institutes is becoming increasingly important at the applied research phase, as more large pharmaceutical companies seek to work with them in collaboration, or outsource the work to them. Possible reasons for the growing role of academia in applied research include the weak pipelines of large pharmaceutical companies, the shift from medicines made of small molecules to biologics and the strategies of large pharmaceutical companies to outsource their R&D activities.

3.4 Empty pipelines of the large pharmaceutical companies

Over the past decade the pharma industry has not had much success in getting approval for new molecular entities produced from in-house R&D. According to a Deloitte report published in 2018, based on data from 12 large biopharma companies, R&D returns are expected to continue declining in the coming years due to the empty late-stage drug pipelines.

In an effort to compensate for their weak pipelines, large pharmaceutical companies try to access external innovation by either buying up small and medium sized biotechnology companies that have promising medicines or therapies in development, or by increasing their cooperation with the academic world. The industry’s shift to increasingly collaborate with academia’ has resulted in publicly-funded universities playing a larger role in applied research for drug discovery, and the expansion of publicly-funded drug development programmes. GlaxoSmithKline (GSK), for example, ‘has decentralised half of its R&D spending into the hands of academics and biotech companies’ through a GSK programme called Discovery Partnerships with Academia (DPAc), see Graphic 2.

Additionally, MSD announced a US$1.25bn cut for in-house R&D in 2014 in order to establish new headhunter centres in Boston, San Francisco, London and Shanghai. From these bases, a network of scouts look for innovative drug discovery programmes and promising new biology being undertaken by local academics and faculties. Other pharma companies, such as Pfizer, Johnson & Johnson, GlaxoSmithKline and Bayer, have already established such centres in the same areas.

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Also, publicly funded projects exist to link pharmaceutical companies to academic and public institutes. Literature shows, for example, that large pharmaceuticals are increasingly outsourcing screening for molecules to academic and institutional libraries:

- The European Lead Factory platform provides a compound library and the opportunity to screen the compounds to find small molecules. It is managed by an international consortium of 30 partners funded under the European Innovative Medicines Initiative (IMI/FP7). The total project budget is approximately €196m.

- The Centre for Open Innovation in LEAD Discovery, (COILED 2016-2020), is co-financed by Operational Programme East. It is a collaborative drug discovery initiative that aims to bring together academic, biomedical research with industry standards on drug discovery to speed up and valorise innovation. The project is lead by Radboud University but other organisations involved include the Pivot Park Screening Centre, Inntrest, BioAxis Research and Pansynt. Of the project’s total budget of € 4.453m, over 78 per cent of the money comes from public

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51 Total project budget is around €196 million, with €80 million from the European Commission and €91 million of “in kind” contributions from participating members of the European Federation of Pharmaceutical Industries and Associations (EFPIA). A further €25 million comes from non-EFPIA participants under which VU University Amsterdam, Lygature (formerly known as TI Pharma and funded by the Dutch government), Rijksuniversiteit Groningen, Radboud University Nijmegen, Leiden University Medical Center, and Leiden University. Pivot Park Screening Centre (Oss) is the central screening site for the European Lead Factory.


funds. The project was established in recognition that worldwide, “the pharmaceutical industry has been retracting from the early stages of drug discovery. In particular, for the identification of lead compounds, ensuing optimisation and selection of drug candidates, which form the basis for new innovative therapies.”

Critics say that projects such as COILED allow large pharmaceutical companies to outsource risks for failures in R&D, save R&D costs, and increase their flexibility while benefiting from public funding.

It is realistic to assume that public investment in the early phase of drug development will continue to increase, at least for the near future. Several pharmaceutical companies have closed their traditional R&D sites and opened new ones in close proximity to academic institutions. ‘Research & Development’ in large pharmaceutical companies is gradually changing into a strategy of ‘Search & Development’.

Profitable pharmaceutical companies

Pharmaceutical companies are some of the most profitable companies in the world, even more profitable than technology and on par with banking, according to a BBC report and Forbes, which lists biotech companies, generic pharmaceutical companies and major pharma companies in the top ten most profitable industries.

By revenue and profit the Swiss Novartis (2018 Novartis reported 12.6 billion dollars profit on 53 billion dollars in revenue) and the American Merck (2018 Merck & Co reported 6.2 billion dollars profit on 42 billion dollars in revenue) and the British AstraZeneca (2018 AstraZeneca reported 2.2 billion dollars profit on 22 billion dollars in revenue) are in the top 10 of the richest pharma companies.

60 Datawrapper, “The world’s 100 largest pharmaceutical companies”, no date, <https://www.datawrapper.de/_/3qmPfl/> (16 April 2019).
61 All financials taken from ThomsonReuters Eikon database on 16 April 2019.
3.5 Cost of drug development

The estimated cost for developing a drug does not include the cost for basic research, though this is fundamental to drug discovery. Such research can take from three months to 30 years to complete, though an accurate timescale and estimation of cost is hard to calculate as several strands of research stretching back over many years may be pulled together.62

There are extensive debates around the costs of bringing a new drug to market and the estimated figures on the cost of drug development vary greatly mostly due to disagreements about marketing costs and other hidden costs, including how to calculate the financing costs, or interest on capital invested in the long R&D process. Pharmaceutical companies also talk about the cost of failure, since some products do not make it to market.

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The most quoted (and also contested) estimation of R&D costs by the pharmaceutical industry is US$ 2.8 bn for each new drug.63 This figure comes from a report by the Tufts Centre for the Study of Drug Development, led by Dr. Joseph DiMasi, and is based on unpublished and internal data provided for the study by 10 pharmaceutical companies, though none of this data is disclosed in the study. The figure for the “financing cost” (the interest on money (capital) tied up during the lengthy R&D process) is contentious since DeMasi uses interest rates as high as 11.5 per cent in his calculations which significantly raises his estimated total cost of drug development, and raises capital costs upwards of US$ 1.16bn, or around half of the estimated total cost of developing one drug.64

Another study by Gupta Strategists found R&D costs for a new molecular entity (NME) amounted to an average of US$ 2.5bn in 2017. These costs included out-of-pocket success (7 per cent), out-of-pocket failure (40 per cent) and capital costs (53 per cent). Gupta also concluded that R&D costs differ substantially between different therapeutic areas.65

A study in the Journal of the American Medical Association (JAMA), estimated much lower R&D costs, partly because the researchers used a lower interest rate (companies reported interest rates between one and seven per cent, so the authors used the highest amount, or seven per cent). Analysing publicly available Security and Exchange Commission (SEC) filings for 10 start-up companies with a single approved product, the JAMA study reported the average cost of developing a cancer drug was US$ 648m (€ 540m), significantly lower than the Tufts Centre estimation. The drugs in the JAMA study were, like the Tufts study, successful commercial drugs and reaped revenues post approval ranging from US$ 2bn to 22.3bn per drug.66

Calculating the cost of capital is a controversial subject. It can be influenced by investors’ expectations and the associated risk of investment, along with arbitrary interest rates, which can inflate the estimated cost of producing drugs. Given the long R&D process, the effect of including capital costs can be significant and will increase with every additional year.

64 C.Cookson, “Studies fuel criticism of high drug development costs,” FT, 6 April 2015, <https://www.ft.com/content/6a57fcd4-bdcd-11e4-8cf3-00144feab7de> (15 February 2019).
4 Public funding of biomedical R&D in the Netherlands

4.1 Introduction

The countries that have the highest public funding of biomedical R&D include the US and the UK. In the US alone, taxpayers fund US$37bn (€32.6bn) a year of expenditure on R&D, channelled through the National Institutes of Health (NIH). The UK government spent GB£ 2.3 bn (€2.6bn) on health R&D in 2015 alone.

This chapter will first look at the ‘traditional streams’ of public funding for biomedical R&D in the Netherlands based on official data provided in a letter from the Dutch Minister for Medical Care Bruno Bruins to the House of Representatives (‘Kamerbrief’, 8 October 2018). The letter was a response to a request from the House of Representatives in November 2017 for more insight into the public financing of medicine development. In the letter the Minister explains that Dutch public funding of medicine development takes place through various streams that fall under the responsibility of four different ministries:

- The Ministry of Education, Culture and Science (OCW) funds fundamental research at universities and institutes of the Royal Netherlands Academy of Arts and Sciences;
- The Ministry of Health, Welfare and Sports (VWS) funds research conducted by medical centres at universities;
- Ministry of Economic Affairs and Climate (EZK) finances public-private partnerships, the Netherlands Organisation for Applied Scientific Research (TNO) and companies;
- Ministry of Foreign Affairs (BZ) finances R&D into diseases that affect poorer populations.

In addition, the European Commission finances the development of medicines in the Netherlands through Horizon 2020 and Innovative Medicines Initiative (IMI), a public-private partnership.

In the second part of this chapter, SOMO reports on the additional streams of funding not reported in the Minister’s letter, particularly public venture capital funds – also known as revolving funds –

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68 StopAids, Global Justice Now, October 2017, “Pills and profits: How drug companies make a killing out of public research”. Their source was the Office for National Statistics. UK government expenditure on science, engineering and technology, 2017.
70 This request was done during the “Algemeen Overleg geneesmiddelenbeleid van 22 november 2017”.
which are used to support Dutch biotech start-up companies. With these funds the Government
does not give one-off subsidies or grants, but acts as a capital investor in new companies.

In the third part of this chapter, SOMO looks at the existing and possible conditionalities attached
to public funding. In his 2018 letter, the Minister of Medical Care concluded that the amount of
Dutch public funding for biomedical research is substantial, and conditionalities should be attached
to any patent licenses developed with such funding, if these medicines are to remain affordable.72

4.2 Spending on biomedical R&D as reported by the Dutch Government

The overview of public funding of biomedical R&D, given by the Minster in his 2018 letter, is imprecise
and, because of the differing lead-times of the various subsidies and grants, provides no information
on the total amount spent. A rough estimation of the amounts spent annually is available in Table 2.

Table 2 Overview of Dutch public funding of biomedical R&D in the Netherlands73

<table>
<thead>
<tr>
<th>Ministry and provider</th>
<th>Amount as provided in the Minister's Letter in millions</th>
<th>Amounts converted by SOMO into a yearly contribution for 2017 in millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ministry of OCW</td>
<td>€ 657 (2017)</td>
<td>€ 427 (~65%)</td>
</tr>
<tr>
<td>Ministry OCW</td>
<td>€ 7.5m yearly, of which between 30 and 40 per cent goes to biomedical R&amp;D.</td>
<td>€ 2.6 (~35%)</td>
</tr>
</tbody>
</table>

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72 Rijksoverheid, Ministry VWS, “Kamerbrief over inzicht in collectieve middelen voor medicijnontwikkeling”, 8 October 2018,
https://www.rijksoverheid.nl/documenten/kamerstukken/2018/10/08/kamerbrief-over-inzicht-in-collectieve-middelen-voor-
medicijnontwikkeling> (8 January 2019).

73 The information provided by the Minister, has been summarized in a table, with estimates made for yearly contributions.
This means for example, a fund dispersed over a period of 5 years was divided by five to get a yearly amount. Explanations
are included in the table.

74 Ministerie van Financien, “IBO Universitair Medische Centra”, Inspectie der Rijksfinanciën, March 2012,
https://www.rijksoverheid.nl/documenten/kamerstukken/2018/10/08/kamerbrief-over-inzicht-in-collectieve-middelen-voor-
medicijnontwikkeling> (8 January 2019).

75 In the letter of Minister Bruins the project amount is given with the period indication “in 2016 and 2017”, SOMO understands
this as one amount for two years. Therefore we have split the amount in two to make it a funding for the year 2017.
<table>
<thead>
<tr>
<th>Ministry and provider</th>
<th>Amount as provided in the Minister’s Letter in millions</th>
<th>Amounts converted by SOMO into a yearly contribution for 2017 in millions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VWS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ministry of VWS</td>
<td><strong>€ 670</strong> (2017)</td>
<td>€134 (~20%)</td>
</tr>
<tr>
<td>Ministry of VWS</td>
<td>Development of antibiotics Netherlands Anti-biotic</td>
<td>€1.8</td>
</tr>
<tr>
<td>Ministry of VWS</td>
<td>Development Partnership, total of €1.8m of which 0.5 is</td>
<td>€0.5</td>
</tr>
<tr>
<td>Ministry of VWS</td>
<td>spent on drug development.</td>
<td></td>
</tr>
<tr>
<td>Ministry of VWS</td>
<td>Contribution VWS to NWO-TTW NACTAR anti-biotics</td>
<td>€4.85</td>
</tr>
<tr>
<td>Ministry of VWS</td>
<td>development €4.85m.</td>
<td></td>
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<tr>
<td>Ministry of VWS</td>
<td>Annual VWS-contribution to the Global Antibiotic</td>
<td>€2.5</td>
</tr>
<tr>
<td>Ministry of VWS</td>
<td>Research &amp; Development partnership (GARDP).</td>
<td></td>
</tr>
<tr>
<td>Ministry of VWS</td>
<td>Annual VWS-contribution aan Project Directie AvL (PD Alt)</td>
<td>€7.5</td>
</tr>
<tr>
<td>Ministry of VWS</td>
<td>for development of vaccines.</td>
<td></td>
</tr>
<tr>
<td>Ministry of VWS</td>
<td>Contribution VWS to Project Directie AvL (PD Alt)</td>
<td>€7.1 (2016 and 2017)</td>
</tr>
<tr>
<td>Ministry of VWS</td>
<td>for RSV-vaccin €4.3m in 2016 and €2.8m in 2017.</td>
<td>€2.8</td>
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<tr>
<td>Ministry of VWS</td>
<td>Annual VWS-contribution to the Global Antibiotic</td>
<td>€17</td>
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<tr>
<td>Ministry of VWS</td>
<td>Research &amp; Development partnership (GARDP).</td>
<td></td>
</tr>
<tr>
<td>Ministry of VWS</td>
<td>Translational Research for drug development €6.27m in</td>
<td>€6.27 (2016-2017)</td>
</tr>
<tr>
<td>Ministry of VWS</td>
<td>Basic biomedical research in 2016 and 2017.</td>
<td>€4.35 (2016-2017)</td>
</tr>
<tr>
<td>Ministry of VWS</td>
<td>Contribution to Joint Programming Initiative on</td>
<td>€0.6 (2016-2017)</td>
</tr>
<tr>
<td>Ministry of VWS</td>
<td>Antimicrobial Resistance.</td>
<td></td>
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<tr>
<td><strong>EZK</strong></td>
<td></td>
<td></td>
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<tr>
<td>EZK</td>
<td>Top Sector Life Sciences &amp; Health (LSH)/Health Holland76</td>
<td>€25 (2013-2017)</td>
</tr>
<tr>
<td>EZK</td>
<td>for Public Private Partnerships, contribution of €25m,</td>
<td></td>
</tr>
<tr>
<td>EZK (RVO)</td>
<td>of which €18m for drug development and €7m for basic</td>
<td>€5</td>
</tr>
<tr>
<td>EZK (RVO)</td>
<td>biomedical research.</td>
<td></td>
</tr>
<tr>
<td>EZK (RVO)</td>
<td>companies to develop drugs (in principle a revolving</td>
<td></td>
</tr>
<tr>
<td>EZK (RVO)</td>
<td>fund), supplied by Rijksdienst voor Ondernemend Nederland (RVO). The 2017 data is based on the RVO database anf projects approved in 2017. See footnote for update 2018.77</td>
<td>€2778</td>
</tr>
<tr>
<td>EZK (RVO)</td>
<td>WBSSO - Wet Bevordering Speur en Ontwikkelingswerk, a</td>
<td>€107 (2017)</td>
</tr>
<tr>
<td>EZK (RVO)</td>
<td>fiscal inventive for innovative R&amp;D. In 2017, €107m was</td>
<td></td>
</tr>
<tr>
<td></td>
<td>paid out to pharmaceutical companies, mainly SMEs.</td>
<td></td>
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</tbody>
</table>

76 Health~Holland is the Top Sector LSH’s communication channel.

77 In 2018, the total budget for innovation credit was approximately €70 million: €30 million for clinical development projects (maximum €5M per project) and €40 million for technical development projects (maximum €10M per project). Depending on enterprise size, loans range between a minimum of €37,500 and a maximum of €10 million (interest rate 7 to 10%). For 2019, the budget will be €60 million: €30 million for clinical development and €40 million for technical development projects, RVO, subsidies, <https://www.rvo.nl/subsidies-regelingen/innovatiekrediet> (24 January 2019).

78 This amount is calculated by SOMO on the basis of the RVO database that includes all projects receiving funding though Innovatiekrediet. All projects of 2017 that received funding for drug development or therapies were selected, the selection was done by checking the project description, <https://www.rvo.nl/subsidies-regelingen/projecten?query-content=innovatiekrediet&f%5B0%5D=subsidies%3A4018&f%5B1%5D=jaar%3A2017&page=2> (23 April 2019).
<table>
<thead>
<tr>
<th>Ministry and provider</th>
<th>Amount as provided in the Minister’s Letter in millions</th>
<th>Amounts converted by SOMO into a yearly contribution for 2017 in millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>EZK</td>
<td>€4</td>
<td>€4</td>
</tr>
<tr>
<td>EZK, VWS and OCW via ZonMW</td>
<td>€33.5 (2017-2021)</td>
<td>€6.7</td>
</tr>
<tr>
<td>BZ</td>
<td>76.3m (2015-2020)</td>
<td>€15.2 (= 1/5)</td>
</tr>
<tr>
<td>EC</td>
<td>€225.5 (2008-2018)</td>
<td>€22.5 (= 1/10)</td>
</tr>
<tr>
<td>EC</td>
<td>€158.3 (2014-2018)</td>
<td>€32 (= 1/5)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>€837.25</strong></td>
<td></td>
</tr>
</tbody>
</table>

Source: Dutch Ministry of Health; Compilation by SOMO with the amounts based on the data provided by Minister of Health in October 2018.

Based on the information provided by the Minister in his 2018 letter, it appears that approximately €783m of Dutch public funding was spent on biomedical R&D in 2017. When EC funding is also included, the total figure for expenditure is approximately €837m.

This picture however is incomplete as the overview does not include all funding schemes from Dutch Ministries including from the Ministry of Economic Affairs such as seed capital and venture capital, tax incentives and schemes such as the Mibiton Scheme.

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4.3 Tax incentives

The Netherlands has several tax incentives in place to promote R&D, including general corporate and specific tax incentives that not only reduce R&D costs but also lower a company’s taxable base. According to the Minister, as described in Table 2, in 2017, €107m tax was reduced for pharmaceutical companies through the Wet Bevordering Speur- & Ontwikkelingswerk or WBSO (Act for the Stimulation of Research & Development), mainly to SMEs.

**WBSO**

The WBSO is a tax credit that allows companies to lower the wage costs for R&D, along with other R&D costs such as expenditure on prototypes or research equipment. Clinical trial staff costs, and other costs related to clinical trials, are also eligible for tax credits.

In 2018, the WBSO’s total budget was €1.163bn (this was for all sectors). For 2019, the WBSO’s budget has been increased to €1.205bn.

Companies may be entitled to as much as a 32 per cent reduction (40 per cent for start-ups) on the first €350,000 of R&D wage costs and other R&D-related expenses, and a 16 per cent reduction for costs over €350,000.

**Innovation Box**

The Innovation box, or Innovatiebox, was introduced to promote innovative research by offering special tax breaks. All profits produced by innovative activities are placed in this ‘fiscal box’, but it was not included in the Minister’s 2018 letter since it does not directly finance R&D. The Innovation Box does, however, finance R&D-based companies that profit from their innovations, many of which also receive public funding.

Under the Innovation Box initiative, companies can benefit from a seven per cent effective tax rate (rather than the usual corporate rate of 20 – 25 per cent) on income generated from (R&D) patented and unpatented intangible assets. Innovations or patents linked to the R&D tax credit are eligible for the Innovation Box.

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86 This was 5% until 2017.
4.4 Public venture capital funds for the Dutch biotech sector

The Dutch Government financially supports innovative biotech start-ups and biomedical R&D through public capital investment funds or other revolving funds. The Life Sciences & Health (LSH) sector is promoted by the Dutch Government as a leading sector of the Netherlands, crucial for national economic growth, new businesses, new employment opportunities and, on the international stage, promotes Dutch innovation and the knowledge-based economy. The biotech sector, which includes hundreds of small and medium sized companies – often spin-offs from universities – is seen as providing future prosperity for the Dutch knowledge economy and is, therefore, supported by the Government, financially and practically (by offering facilities, for example).

The Province of Brabant’s development agency, BOM, often cites its Acerta Pharma and Bionovion investments as evidence of the success of regional revolving funds. BOM’s original investments in these local biotechnology companies were not publically disclosed but are thought to be less than €10m. Both companies were sold in 2015. According to its 2015 annual report, BOM earned €64m in returns when it sold its shares in Acerta Pharma and Bionovion.

4.4.1 Overview of the Life Sciences & Health sector in figures

In its 2016 sector brochure, Life Sciences 2030, HollandBio (the Dutch biotechnology industry association) promotes national business opportunities, highlights existing achievements and outlines its ambitions for the future.

In 2015, according to HollandBio, there were 667 companies working in the Dutch biotech sector, double the amount of companies a decade earlier in 2005, all of which are involved in R&D.87 Around a third of the companies are very small (1-10 employees), and the remainder are medium sized (75-130 employees). A total of 24,000 people were employed by the sector in 2015, with HollandBio predicting that, by 2030, there would be more than 1200 companies working in the Dutch life science and health sector, employing approximately 60,000 workers.88

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Innovative products developed by the Dutch biotech sector and promoted by HollandBio include Keytruda (developed in Oss, MSD), Glybera (first gene therapy on the Western market by uniQure), Daratumumab (developed in Utrecht by Genmab as a treatment for bone marrow cancer), MammaPrint (cancer diagnostics by Agendia, spin-off Dutch Cancer Institute NKI-AVL), RAPLIXA (developed in Leiden by Profibrix) and Ruconest (developed in Leiden by Pharming). In 2019, the rheumatism drug Filgotinib, developed by the Dutch-Belgium company Galapagos, is expected to be available on the market.89

Credit: CCO MaxPixel.freegreatpicture.com

Table 3 illustrates the high level of investments in Dutch biotech companies in 2015, one of the most successful financial years for the companies, according to HollandBio.

In 2015, total investments in the sector90 (also Annex I) amounted to €4.3bn. The same year, the sector had 322 medicinal or diagnostic pipeline products, of which 124 were in the clinical testing phase.

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Table 3 Successful financial deals in the Dutch biotech sector in 2015

<table>
<thead>
<tr>
<th>Dutch Biotech</th>
<th>Partner</th>
<th>Type of deal in 2015</th>
<th>Private investments in € million</th>
<th>Potential value in $ million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acerta Pharma</td>
<td>Venture Capital (May)</td>
<td>335</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acerta Pharma</td>
<td>AstraZeneca</td>
<td>M&amp;A (December)</td>
<td>2,300</td>
<td>7000</td>
</tr>
<tr>
<td>AM-Pharma</td>
<td>Pfizer</td>
<td>M&amp;A (May)</td>
<td>78</td>
<td>600</td>
</tr>
<tr>
<td>BioNivon</td>
<td>Aduro</td>
<td>M&amp;A (September)</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Dezima Pharma</td>
<td>Amgen</td>
<td>M&amp;A (September)</td>
<td>268</td>
<td>1550*</td>
</tr>
<tr>
<td>Galapagos</td>
<td>IPO (May)</td>
<td></td>
<td>279</td>
<td>318</td>
</tr>
<tr>
<td>Galapagos</td>
<td>Gilead</td>
<td>Licensing⁹¹ (December)</td>
<td>668</td>
<td>2075</td>
</tr>
<tr>
<td>Kiadis Pharma</td>
<td>IPO Euronext, (July)</td>
<td></td>
<td>32.7</td>
<td></td>
</tr>
<tr>
<td>Merus</td>
<td>Venture Capital (August)</td>
<td>73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>uniQure</td>
<td>BMS</td>
<td>Licensing (april)</td>
<td>46.3</td>
<td>2307</td>
</tr>
<tr>
<td>uniQure</td>
<td>FPO⁹² (april)</td>
<td></td>
<td>88.5</td>
<td></td>
</tr>
<tr>
<td>uniQure</td>
<td>BMS</td>
<td>Milestones (August)</td>
<td>80.3</td>
<td></td>
</tr>
</tbody>
</table>

Source: data is retrieved from HollandBIO, publication “Life Sciences 2030”.

To help promote the Netherlands as a place to set up biotech companies, HollandBio extols the benefits of government-backed funding opportunities – such as the financing of various stages of drug development and research – which are available to SMEs. The industry association explains that when drug development is still so far from the market, and the risk in the short and medium term of failure is simply too large for private investors to withstand, only the government or a non-profit organisation can, and will, provide finance.⁹³ It highlights how seed money, loans and credits provided by the Dutch Government, at the early stages of drug development and pre-clinical testing, can later be matched by financing from the private sector. The industry promotional material goes on to explain that when a drug reaches the clinical trial phase, the private sector becomes involved through licencing deals, IPOs, and venture capital as well as through mergers and acquisitions (M&As).⁹⁴

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⁹¹ A licensing deal is [...] in this case Galapagos has signed a license agreement with Gilead for the further development and marketing of filgotinib. Gilead has paid Galapagos €300 m in front, this money is secured. Besides this amount Gilead has invested 425 million dollars by buying (new) shares up the company in return for 14.75 percent ownership in Galapagos.

⁹² A follow-on public offer (FPO) is a stock issue of additional shares made by a company that is already publicly listed and has gone through the IPO process.


4.5 Financing instruments to support biotech start-ups

PharmInvest Holland estimates that, in 2017, approximately €4bn was invested into 411 Dutch companies. These investments included venture capital injections into fast-growing start-ups mainly working in the fields of life sciences and ICT – and private equity investments into more mature companies. It is currently unknown how much of the €4bn went exclusively towards drug development or how much came from public or government sources.

While the Dutch Government does finance capital venture funds and initiatives that support innovation and start-up companies in the life sciences sector, there are so many schemes in existence, that it is beyond the scope of this report to give a complete overview, however, a selection of some initiatives and funds are outlined in this chapter.

This part of the report focuses mainly on public venture funds.

Other funds are also available which support spin-off companies from universities and help start-up companies with facilities, initial concept development, and market access. These include:

- **Mibiton Foundation.** This fund invests in the Dutch life sciences infrastructure and finances (pre) starters that are spin-off companies from Dutch knowledge institutes (such as universities). Many Dutch biotechs – such as Kiadis, Merus, and Prosensa (now Biomarin) – use the facilities funded by Mibiton. Between 1994 and early 2017, 83 facilities were funded in the Netherlands by the Mibiton Foundation, a total investment during that period of €30.6m, of which €22.3m were eventually repaid. The Ministry of EZK co-finances Mibiton.

- **MIT - SME Innovation Stimulation (MKB Innovatiestimulering Topsectoren (MIT)).** This fund offers SME entrepreneurs additional funding for innovative R&D activities within the top Dutch sectors, including LSH. Of its €51m expenditure in 2017, €6m were spent on companies in the LSH sector. The funding partly comes from national and regional instruments.

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95 PharmInvestHolland is a public-private initiative that focuses on enhancing the business and R&D climate for biopharmaceutical companies in the Netherlands and the earlier availability of medicines for patients. PharmInvestHolland is powered by the American Chamber of Commerce, Dutch Association Innovative Medicines, Health+Holland, HollandBIO, Lygature, Ministry of Economic Affairs and Climate Policy, Netherlands Foreign Investment Agency, VNO-NCW, <https://www.health-holland.com/biopharma_bidbook_2018_2/65/#zoom=z> (19 January 2019).


97 There is a startup Box that contains various government schemes for financing. This tool helps startups to find the scheme that best suits the startup. The tool is still under construction, <https://english.rvo.nl/topics/innovation/startup-box-funding-innovative-starters> (19 January 2019).


4.5.1 Public venture funds

The Dutch Government finances venture funds which provide capital to biotech start-ups. In this overview, the report will focus on the provinces’s regional development funds, and the venture capital funds financed by the Dutch Government/Ministry of Economic Affairs (EZ). The European Commission also funds Dutch biotech companies through venture capital funds.

The Seed Capital programme

Some of the most important venture capital instruments of the Dutch Government are the Seed Capital Funds. From 2005 to 2015, the Seed Capital programme contributed more than €200m to 55 public investment funds. This money was subsequently invested in approximately 300 innovative start-up companies, including many biotech companies. For a list of these funds see Annexe II of this report.

The Ministry of Economic Affairs believes that the Seed Capital programme fills a finance gap as commercial banks hardly ever issue loans to start-up companies. The Seed Capital Schemes are “a special type of private equity fund specifically intended for innovative start-ups where private investors provide half the capital required and the Ministry of Economic Affairs matches this investment.” By contributing to the Seed Capital programme, the Government hopes to encourage private venture capitalists to also invest in the start-ups.

Examples of seed funds include; BioGeneration Ventures III (€12m, of which the Ministry of EZ invested €6m), Health Innovation Fund III (€12m, of which the Ministry of EZ invested €6m). Several of these venture capital funds did invest in Dutch biotech companies featured in this report, such as Biogeneration Ventures II B.V (€8m, of which the Ministry of EZ invested €4m), which invested in Acerta Pharma and Kiadis. Medsciences Seed Fund B.V. (€8m, of which the Ministry of EZ invested €4m) also invested in Kiadis.

National Public Venture funds

The Dutch Venture Initiative DVI-I was launched in 2013; DVI-II launched in 2016. These investment initiatives, called ‘fund-to-funds’, encourage a fund to invest in other types of funds with the objective of financing fast-growing and innovative Dutch companies. Both DVI-I and DVI-II began via the European Investment Fund (EIF), PPM Oost, the Dutch Ministry of Economic Affairs and, in the case of DVI-I, the BOM. It is reported that the BOM invested approximately €5m into DVI-I,

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106 Participatienaatschappij Oost Nederland, a regional venture capital company which is part of the East Netherlands Development Agency “Oost NV”, (19 January 2019).
Following the success of DVI-I, the €200m DVI-II was launched, with life sciences one of four sectors targeted for investment.

Box 1 Dezima Pharma funded by the Dutch Venture Initiative (DVI)

Despite stopping development of its cholesterol drug, Dezima is nevertheless considered a success story for publicly financed Dutch biotech companies. It has a prominent spot in the RVO brochure about the Seed Capital programme. Both Forbion Capital Partners and BioGenerations Ventures have invested in Dezima Pharma.

BioGenerations Ventures is a seed venture capital fund and receives public funding through the Seed Capital Programme of the Ministry of Economic Affairs (EZ). Dezima also received public funding through the Innovation Credit programme of EZ (Innovatiekrediet).

Forbion is a venture capital fund, investing in life sciences, the pharmaceutical sector and medical devices. Forbion’s capital comes from the European Investment Fund (EIF), via the European Recovery Programme (ERP), the LfA-EIF Facility and Dutch Venture Initiatives. Forbion also has a joint venture with BioGeneration Ventures.

Dezima started in 2012 with the development of ta-8995, a promising medicine intended to reduce the production of cholesterol (a CETP inhibitor). The company was taken over by Amgen in 2015. In a deal that could have potentially been worth US$1.6bn (€1.4bn), US$300m were to be received immediately with the remainder in milestone payments. Within weeks of the deal, doubts surfaced about the CETP inhibitor and in October 2017 Amgen reported that it was no longer investing in the development of ta-8995. Amgen was not the only company to discontinue development of a CETP inhibitor at that time. Pharma giants Pfizer, Roche and Merck also stopped developing CETP inhibitors.

112 Biotech financial reports, January 2018, Northsea Therapeutics secures (euro) 25 million funding.
113 Forbion raises 270M, EU-focused life science fund, Global Data Point, July 12, 2018.
Box 1 Dezima Pharma funded by the Dutch Venture Initiative (DVI)
It is still unclear as to whether development of the drug was halted because it was deemed unprofitable or because it was thought to be ineffective. The public funders that financed the start-up had no influence on the decision to stop development of the drug, even if they would think the medicine still had promise. In this case, the public money invested may well have created profits – when the company was taken over – but in the end, did not produce a medicine.

There are still some who believe that a successful medicine can be produced by developing CETP inhibitors. DalCor is currently conducting a phase-III trial on its CEPT-inhibitor, Dalcetrapib.\(^{117}\)

Regional Public Venture Capital
Regional development organisations (ROMs) have venture capital funds that occasionally become shareholders in regional operating companies. In 2017, ROMs invested €89m across 140 companies.\(^{118}\)

**Regional development organisations**
- Dutch Investment and Development Agency for the Northern Netherlands (NOM)
- Oost NL (formerly PPM Oost)
- Brabant Development Agency (BOM)
- Limburg Development and Investment Company (LIOF)
- InnovationQuarter (includes the funds IQCapital\(^{119}\), UNIIQ\(^{120}\) and ENERGIIQ.)

As well as the regional development organisation’s venture capital funds, there are other venture funds that support startups with a regional focus. The regional development organisations are involved in some of these, for example RedMedTech II venture fund (Province of Gelderland), promoted by Health Valley Nederland, Radboudumc, Saxion and Oost NL.\(^{121}\)

The European Regional Development Fund (ERDF) contributes to several of the regional development programmes in the Netherlands. These programmes are intended to boost the region’s potential for Research and Innovation (R&I), a key priority of the programme.

\(^{117}\) DalCor, Pioneering precision medicine for cardiovascular Disease, [https://www.dalcorpharma.com/about/about-dalcor/](https://www.dalcorpharma.com/about/about-dalcor/) and Fouzia Laghrissi-Thode, Enrollment for phase 3 trial of dalcetrapib completed, Healia, 17 December, 2018, [https://www.healia.com/cardiology/chd-prevention/news/online/%7Be56e34a5-98b3-4dc0-bf61-ac04e06f6c2d%7D/enrollment-for-phase-3-trial-of-dalcetrapib-completed](https://www.healia.com/cardiology/chd-prevention/news/online/%7Be56e34a5-98b3-4dc0-bf61-ac04e06f6c2d%7D/enrollment-for-phase-3-trial-of-dalcetrapib-completed) (24 April 2019).


\(^{119}\) The fund IQ capital consists of EC-subsidie €14,300,000, public cofinancing €3,000,000 (these two amounts together – 17,300,000 – are also called the contribution of “Kansen voor West”) and private cofinancing of €33,840,000. Europa om de hoek, “IQ: fondsuitbreiding innovation quarter fonds”, no date, [https://www.europaomdehoek.nl/projecten/ qe-fondsuitbreiding-innovationquarter-fonds](https://www.europaomdehoek.nl/projecten/qe-fondsuitbreiding-innovationquarter-fonds) (24 April 2019).


Dutch Investment and Development Agency for the Northern Netherlands (NOM)

The NOM N.V is a Dutch Government investment and development agency in the Netherlands focusing particularly on the northern provinces. It provides financing and business development to small and medium-sized companies in the region, and to companies the NOM is trying to recruit to the region. The NOM’s purpose, according to its website, is to support the regional economy through developing long-term business relationships with companies that demonstrate innovation and are likely to succeed in the northern Netherlands.

NOM financing is provided through share capital, loans, or a combination of both, and comes from NOM’s revolving €90m fund. NOM finances start-ups and companies with growth potential. NOM makes a financial commitment for a set period of time, after which its shares are sold and the loan repaid. NOM invested in Kiadis (see Chapter 6).

Brabant Development Agency (BOM)

BOM was founded in 1983 by the Province of Brabant and the Ministry of Economic Affairs, to accelerate economic growth in the province. BOM invests in scalable start-ups, and companies that have both growth potential and a strong link to Brabant. BOM’s sector focus includes agrofood, life sciences and medical technology, and the Agency stresses the importance of making a social and economic impact on the region.

In an interview, the BOM stated that because it has Non-Disclosure Agreements (NDAs) with the companies it invests in, it cannot publically disclose details of those investments — including the amount — and can only confirm that any investments it makes have both social and economic objectives. BOM is technically a not-for-profit public entity, and focuses on economic growth, job creation, finding solutions for social issues, and increasing the region’s competitiveness.

The BOM invested in Acerta (see Chapter 5).

127 Interview with Bram van den Hoogen, BOM, on January 18, 2019 and email from Bram van den Hoogen, BOM, on January 22, 2019 (on file with SOMO).
Venture capital funds of the European Commission (EC)

Although many venture capital funds are funded by the EC, this report will not provide an overview of all these EU funds, but will instead focus on the major fund relevant to the report’s objectives, which is “InnovFin – EU Finance for Innovators”.

In June 2014, the European Investment Fund (EIF) and the European Investment Bank Group (EIB) launched a new fund belonging to a new generation of EU financial instruments: venture capital and private equity interventions. The fund, “InnovFin – EU Finance for Innovators”, aims to provide access to equity for high-growth and innovative SMEs, and is part of the EU research programme 2014-2020.

The EIF and EIB have provided ‘InnovFin’ with more than €24bn of financing for research and innovation, undertaken by small, medium and large companies. This finance is expected to support up to €50bn of final research and innovation investments. The following stream of equity funds are part of ‘InnovFin’:

1. InnovFin Equity
2. InnovFin Technology Transfer
3. InnovFin Business Angels
4. InnovFin Fund of Funds

As part of InnovFin Equity, the EIF targets investments in around 45 funds, enabling €4-5bn to be invested in enterprises located, or active, in the EU and Horizon 2020 Associated Countries. The EIF provides equity investments and co-investments in companies in their pre-seed, seed, and start-up phases, which operate in innovative sectors covered by Horizon 2020, including life sciences, clean energy and high-tech.

In addition, and specific to the Netherlands, the EIF currently manages and deploys three programmes on behalf of the Dutch Ministry of Economic Affairs:

- The Dutch Venture Initiatives. (DVI I and DVI II);

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131 Iceland, Norway Albania, Bosnia and Herzegovina, the former Yugoslav Republic of Macedonia, Montenegro, Serbia, Turkey, Israel, Moldova, Switzerland, Faroe Islands, Ukraine, Tunisia, Georgia and Armenia.
**European Angels Fund Netherlands.** The Business Angels co-investment programme, the European Angels Fund (EAF), has a current budget of €320m. Of this, more than €200m are already committed to some 80 selected Business Angels who have a portfolio of more than 340 SMEs co-investments. EAF is an €45m initiative funded by the Dutch Venture Initiative (“DVI”).

**The Dutch Growth Co-Investment Programme** will be the third initiative undertaken, through the Netherlands Investment Agency (NIA), by the EIF and the Dutch Ministry of Economic Affairs. The EIF and the NIA will each invest €50m.133

See Annex III for the Dutch Venture Initiatives I and II and Annex IV for a list of capital venture funds active in the Netherlands and included in the EIF’s portfolio for the Dutch Growth Co-Investment Programme.

### 4.6 Conditionalities attached to biomedical funding in the Netherlands

In January 2016, the Dutch Government announced134 that, as part of its health policy, conditionalities would be attached to future public funding of drug development. Updating the policy in November 2017, the Minister informed the House of Representatives135 that these conditions would include open access to publications and research data, and measures to prevent citizens paying double the necessary amount for medicines. In October 2017, the Minister pointed out that conditionalities for open access research data are included in the ZonMw subsidy conditions, and conditionalities to prevent the public paying double for drugs are in the strategic plan of the Oncode Institute, the new joint venture for cancer research. In addition, the Dutch Government has initiated a process to formulate principles for ‘Socially Responsible Licensing’ with the Netherlands Federation of University Medical Centres (NFU) taking the lead in overseeing this process.136

**Conditionalities nationally**

SOMO also explored conditionalities of Dutch publicly funded research institutes involved in biomedical R&D.

**The UMCs**

Because University Medical Centres (UMCs) conduct a proportion of biomedical R&D, they could play an important role in Socially Responsible Licensing to secure public benefits from publicly

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funded biomedical R&D. In Europe, 17 per cent of all new approved drugs originate from, and are patented by, academic institutes. In the US, the figure is 24 per cent (Chapter 3). 137

Valorisation of scientific knowledge is regarded as a socially desirable development. The Dutch Government has used the following definition, since 2009, for valorisation: “Valorisation is the process of creating value from knowledge by making knowledge suitable and/or available for economic and/or societal use and translating that knowledge into competitive* products, services, processes and entrepreneurial activity. (Ministry of Education, Culture and Science/OCW).” The word ‘competitive’ were removed from the definition in 2011. 138

**NFU**
The standard manner of commercialising knowledge or inventions, (valorisation) is by creating a company, a patent, or a license. In 2009, the NFU published the framework document “Naar een goede waarde (Towards Fair Value)” in which the UMCs formulated conditions for careful and fair valorisation. 139 This framework is not binding on the UMCs, but any contracts for valorisation are expected to be made with reference to the framework. The core elements of this framework are the following:

- The institute where the knowledge was generated will own the patent, and the inventors (not their superiors) will be cited on the patent.

- When a patent/IP is licensed to a commercial company, the patent remains the property of the institute but the commercial party has the right to use the knowledge.

- It is recommended that agreements are made regarding royalties and that there be a yearly contribution towards the cost of maintaining the patent.

- Wherever possible, non-exclusive licenses are preferred. If a company has not used the patent within 1-2 years it should be possible to dissolve the license agreement. It should also be possible to retrieve the licence if a company goes bankrupt or is the subject of a takeover. 140

- When licensing to a commercial party is not possible because the knowledge needs to be further developed, the UMCs may facilitate a spin-off for this development, and either transfer the patent to the spin-off or license it. If the patent is licenced it avoids the possibility of it being resold thereby losing control of the IP and royalties. 141


Aidsfonds
The Aidsfonds also finances drug development and has formulated the following conditions to secure public benefit:

- ‘The Partner undertakes that the generation of income and/or the exploitation of a right for which a patent has been obtained or applied for, will be consistent with the goals of the Aidsfonds.’
- ‘The Partner agrees to undertake any activities related to, or beneficial to, the Project, including the application of a patent or the use of an awarded patent, in a manner which serves the general welfare and includes timely access to affordable medicines. The Partner agrees to include this obligation in any agreements it enters into with third parties related to the Results of the Project in the form of a perpetual clause (kettingbeding’).  

It is notable that Aidsfonds included the terms ‘access’ and ‘affordable’ in their conditions.

ZonMw
In its open-access policy, the Netherlands Organisation for Health Research and Development, ZonMw, attempts to ensure that the results of publicly financed projects are freely available to be shared and reused. In the document ‘General Terms and Conditions Governing Grants of ZonMw’, ZonMw confirms its open-access policy by prohibiting projects from keeping knowledge and information confidential, ‘unless there are weighty interests involved (such as privacy or an application for a patent) that make it necessary to keep information confidential on a temporary basis’.

ZonMw’s conditions also state: ‘The results of the projects that are financed in whole or in part by ZonMw are intended to benefit Dutch society as a whole’.  

But the allowance for knowledge to remain confidential for privacy reasons or in case of a patent creates a big loophole.

NWO TTW
The NWO guidelines oblige the license partner to ensure it makes an effort to commercialise or apply the license, and to report on these efforts.  

Conditionalities of funders internationally
SOMO explored how different public and philanthropic research funders and universities around the world, secure public benefits from publicly funded drug development. Some of the core elements and themes that arose, and are consistent and relevant for socially responsible licensing, include:

- Ensuring a meaningful health impact for society;
- Ensuring innovation and further development of the invention;
- Ensuring the right of continuing use of the knowledge that is licensed for own research goals and educational purposes;
- Ensuring knowledge sharing, sharing research findings though open access;
- Ensuring populations in need have access to end products;
- Ensuring affordability related to the pricing of the medication;
- Ensuring availability and production of the product.

Socially responsible licensing should transfer non-exclusive licenses only, keeping the option to revoke a license available on the grounds of attached conditionalities such as those listed above.

Conditionalities by public venture funds
Managers at several venture capital funds were asked by a Dutch journalist about the desirability and possibility of attaching conditionalities to the investment regarding accessibility and affordability of the medicines produced. The journalist reported that Mr. Sander Slootweg, Managing Partner at Forbion (DVI I and in EIF portfolio), stated that it was not the task of venture funds to interfere with the price. “We will never say you can buy this innovation from us, but then you have to put it on the market cheaply. That obviously will have a negative effect on the price. We are a commercial party, so we simply have to realise the maximum return for our investors”. Mr de Vries from the Erasmus Biomedical Fund indicated in the same article that the companies they invest in are too far removed from the final market or that there are other companies between them and the market.

Sources include:
- Websites of Medical research Councils such as the UK MRC, NHMRC (Australia), UK National Institute for Health research (NIHR), the Wellcome Trust, Drugs for Neglected Diseases initiative (DNDi), the Canadian Institutes of Health Reaserch (CIHR), US National Institutes of Health (US NIH).
4.7 Concluding remarks

R&D funding used to develop medicine comes from both the private and public sectors. It is generally understood that public funding for medicine development is primarily available at the basic and early stages of the research process. The data on public funding provided by the Dutch Minister in his letter to the House of Representatives, primarily concerns basic research.

Public funding for applied research, or the stage following basic or fundamental research, (where drugs are discovered and early drugs are developed and a market authorisation application is made) is, according to the Minister’s letter, very limited in the Netherlands. In 2017, based on information provided by the Dutch Minister for Medical Care, the Dutch Government provided approximately €783m of funding, and €55m also came from EU-funding sources.

However, when the number of other schemes available for start-ups – such as public venture capital funds and tax incentives – are taken into account, it becomes apparent that a substantial amount of public money is invested in biotech firms also working on applied research.

Given the substantial amount of public funding for biomedical R&D, the Government has announced its commitment to attaching conditionalities to such funding. Groundwork being conducted on national and international levels by, for example, the NFU, the Aidsfonds, the UCL Institute for Innovation and Public Purpose, could be used as a reference point.

Credit: CCO Belova50 at pixabay.jpg

5 Case study: Acerta Pharma’s Calquence (AstraZeneca)

In this chapter the biotechnology company Acerta Pharma is used as a case study to highlight the influence of public funding on biomedical R&D and its possible impact on medicine prices, as well as to show the lack of transparency in government funding.

Acerta Pharma developed the drug Calquence, (acalabrutinib) to treat a type of lymphoid cancer known as mantle cell lymphoma. In October 2017, the drug was approved by the FDA148 and currently retails in the US for approximately US$15,000 per month.149 It is unclear when Calquence will be approved by the European Medicines Agency (EMA). According to an AstraZeneca spokesperson, the firm does not expect EMA approval for its first indication before 2020,150 and there is no record yet that AstraZeneca has filed for EMA approval.151

Acerta Pharma has operations in Oss in the Netherlands, and in San Francisco in the USA. Dutchmen Allard Kaptein and Tjeerd Barf started the company Covalution Pharma after MSD closed down its Dutch research department in Oss (formerly Organon) in 2011, at a time when job cuts in Organon were rife. When he was working at Organon, Kaptein was interested in the development of so-called covalent inhibitor drugs, a new method in medicine development, at that time. One of Covalution Pharma’s earliest investors, Edward van Wezel from BioGeneration Ventures, saw the potential of Kaptein and Barf’s startup business, and helped them negotiate a deal with MSD to purchase the necessary licenses. In 2013, Kaptein and Barf joined forces with American scientists who had published promising data using covalent technology, to set up Acerta Pharma.152

BioGeneration Ventures and the BOM (Brabant Development Agency)153 were capital investors from the time the company was set up. The development of Calquence (acalabrutinib) progressed quite quickly and by 2015, AstraZeneca had bought a 55 per cent stake in Acerta Pharma for an initial price of US$2.5bn, with an agreement that a further US$1.5bn would be paid once the drug was approved by the FDA. It was also agreed that AstraZeneca would have the option of buying the remaining 45 per cent of the company for US$3bn.

149 Information has been taken from the following website: https://www.drugs.com/price-guide/calquence> (4 April 2019).
150 Email of Ad Antonisse, Director Market Access & External Affairs of AstraZeneca BV in the Netherlands, February 13, 2019 (on file with SOMO).
151 Phone calls with the EMA and Acerta on the 24th of January and AstraZeneca on the 25th of January did not provide any lead to when Calquence will be put forward to the EMA
Box 3 What is Calquence?

Calquence, (acalabrutinib), targets and helps block a protein, called BTKi or Bruton tyrosine kinase inhibitor, that contributes to cancer cell growth. In the Orange Book, which is patent information for the FDA, four patents are listed under Calquence product information. The first patent on kinase inhibitors was patented in 2003. The second and third patents are registered by MSD and the inventors who worked with Tjeerd Barf (eight inventors in total). The last patent is registered by Acerta Pharma, and also lists Tjeerd Barf as one of the inventors.

Calquence was approved in the US using the Accelerated Approval pathway, a way of getting a medicine approved faster than normal, when there is “unmet medical need and a drug is shown to have certain effects that are reasonably likely to predict a clinical benefit to patients.” The FDA approval was based on data from a trial that included 124 patients with mantle cell lymphoma who had received at least one prior treatment. Of these patients, 81 percent experienced “complete or partial shrinkage of their tumors after treatment”. The approval process was accelerated and the drug was granted “Priority review” and “Breakthrough therapy” designations as well as “Orphan drug” designation (which gives further incentives for development of medicines that treat rare diseases). On 21 March 2016, Calquence was also granted an orphan designation by the EMA Committee for Orphan Medicinal Products, for chronic lymphocytic leukaemia/small lymphocytic lymphoma, mantle cell lymphoma and lymphoplasmacytic lymphoma. However at the time of writing this report, a request for Calquence’s approval does not yet appear to have been filed at the EMA.
5.1 The share of Dutch public funding in Acerta

The public funding for Acerta’s development of Calquence came in at least three forms: provision of facilities, venture capital from public funds, and public/private funds. These three forms of public support are examined below.

5.1.1 Pivot Park

Acerta Pharma has operations in Oss in the Netherlands and in San Francisco in the USA. The Oss location is at Pivot Park, a breeding ground for new biotech firms. The former premises of Organon, it was taken over by Schering-Plough in November 2007, who then merged with MSD in 2009. MSD closed down the former Organon operation in 2010. It sold its properties and laboratories in Oss for the symbolic amount of €1, effectively an in-kind donation to the community of Oss of €30m. This €30m gift was matched by Dutch government agencies: the Ministry of Economic Affairs, the BOM and the municipality of Oss, to develop Pivot Park. Pivot Park also received a €13.9m loan from the Province of North-Brabant at the beginning of 2017, with the province itself having to take out loan insurance for €3.5m. The Municipality of Oss also committed to invest €25,000 per year, for a period of eight years, to advertise Pivot Park as well as an investment of €93,000 per year (for 11 years) to stimulate the “Life Science Climate” in Oss. According to an email sent by the BOM to SOMO, there are now 550 people working at Pivot Park and it is the fastest growing campus in the Netherlands.

5.1.2 Innovation Credit

In 2013, Acerta received a €2.7m innovation credit from the Dutch Government. According to the Rijksdienst voor Ondernemend Nederland (Netherlands Enterprise Agency), this credit was provided to support the “development of promising and challenging innovations with excellent marketing prospects”, such as technological or clinical developments. The interest rate on credit provided for clinical development projects is usually 10 per cent. This loan including interest has been paid back by Acerta.
5.1.3 Brabant Development Agency (BOM) invests

The BOM was one of Acerta Pharma’s first funders in 2013. When AstraZeneca bought 55 per cent of Acerta Pharma’s shares in 2015, the BOM sold its shares in the company. Although the amount of BOM’s 2013 investment and the 2015 share value were not publically disclosed, the Agency reported in its 2015 annual report, a €64m return on investments, from selling its stakes in two biotechnology companies, one of which was Acerta.172

As a revolving fund, it re-invested the profits it made from selling the Acerta shares into other regional investments, which in turn supports Brabant’s economy. When asked about its influence as a shareholder on how a company prices its medicine, BOM stated that its influence is almost non-existent, primarily because by the time a company has been sold BOM’s investment has been seriously watered down. It does, however, perceive that it has a substantial impact during the initial phase. This is true in the case of Acerta since without BOM’s investment, CalQUENCE might never have been developed.173

172 Bionovion was sold for €29m, Acerta for up to $7bn with a guaranteed payment of $2.5bn.
173 Interview with spokesperson Bram van den Hoogen, BOM, on January 18, 2019 and email from Bram van den Hoogen, BOM, on January 22, 2019 (on file with SOMO).
BOM takes several factors into account when investing in a biotech company including the potential target group for the medicine, unmet needs, seriousness of the disease, and the medicine’s potential impact. BOM said it expected a substantial number of patients would experience improvement in their quality of life as a result of Acerta’s medicine.¹⁷⁴

### 5.1.4 BioGeneration Ventures

Along with BOM, BioGeneration Ventures (BGV) was one of the initial investors in Acerta in 2013 (and also in Dezima, see box in Chapter 4) and ranks the sale of its shares in Acerta Pharma – an initial guaranteed payment of US$2.5bn and a possible final total of US$7bn – as one of its most successful investments. The sale of Acerta Pharma’s shares was the largest exit ever of a privately held European biotech company.¹⁷⁵

BGV¹⁷⁶ invests both public and private money. The private money comes from private equity managers, private funds, pension funds and academic institutions (Leiden University). The public funds come from sources such as regional development funds (BOM and Topfonds Gelderland) as well as the European Investment Fund.¹⁷⁷ BGV has three funds, and invested in Acerta through BGV Fund II, which is co-sponsored by BioGeneration Ventures B.V. and Forbion Capital Partners.¹⁷⁸ BGV Fund II also received a loan from the Ministry of Economic Affairs.¹⁷⁹

### 5.1.5 Financial history of Acerta Pharma

According to Acerta Pharma’s annual accounts, the company started in 2012 with modest capital of €18,000. In 2013 it received a €2.7m innovation credit from the Ministry of Economic Affairs as

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¹⁷⁴ Interview with spokesperson Bram van den Hoogen, BOM, on January 18, 2019 and email from Bram van den Hoogen, BOM, on January 22, 2019 (on file with SOMO).
¹⁷⁷ The European Investment Fund manages and invests through InnovFin Equity (part of InnovFin – EU finance for Innovators, an initiative launched by the European Commission and the EIB Group in the framework of Horizon 2020 backed up by the European Fund for Strategic Investments (EFSI)) set up under the Investment Plan for Europe) which focuses on enterprises in innovative sectors.
well as funding from the BOM and BioGeneration Ventures. Capital investors from the United States also invested in the company for the following two years.\textsuperscript{180} By mid 2015 new investments in the company amounted to approximately US$ 387m. At the end of 2015, even after selling 55 per cent of its shares, Acerta still had a very healthy balance of 260.1 million dollars. In terms of employees, the company started out with the equivalent of eight full time members of staff in 2013, increasing to 10 members of staff in 2014, then to 155 staff in 2015. The money spent on R&D increased from US$ 55.7m in 2014 to US$ 170.1m in 2015, mainly because of money spent on clinical trials.

5.2 Concluding remarks

The case study of Acerta and Canquence shows the important role public funding plays in the start-up phase of a young biotech company. The funding of Pivot Park, by the BOM, the Ministry of Economic Affairs, and the Municipality, along with public financing through the innovation credit, the BOM and BioGeneration Ventures, and money from capital investors from the US, all played a vital role in the important start-up phase of the company.

Because public funds often take the financial risk in a company at a phase in which private capital is hesitant to invest, they are immensely valuable to innovative biotech start-ups. Though the initial investment by a public venture fund might be small, it not only directly finances the company, it also helps attract private capital. With Acerta, the public investments were small compared to those made later by venture capital funds and large pharmaceutical companies. The BOM refers, in its 2015 annual report, to a multiplier, (the amount of money from other sources that every euro invested by the BOM attracts). In 2014 and 2015 the BOM reported that its multiplier was more than five (every euro invested by the BOM was matched by more than five euros from others).\textsuperscript{181}

BOM, an early stage funder, financed by the Ministry of Economic Affairs and the Province of North-Brabant, states that it cannot impose any conditionalities on the development of medicines apart from the investment must ultimately have an economic and social impact. Both the BOM and BioGeneration Ventures, declined to disclose information on the amount of money invested in Acerta Pharma.

Critics of the deal argue that the BOM pursues economic gains at the cost of societal gains, as the multi-billion dollar deal for Acerta Pharma was based on the assumption that the cancer medicine it developed would be sold at a high price and, indeed, Calquence currently retails in the US for around US$ 15,000 for a month’s worth of treatment.\textsuperscript{182}

\textsuperscript{180} Thieu Vaassen, “In 5 jaar van start-up naar miljarenbedrijf”, het Financieel Dagblad, 16 augustus 2018; BOM jaarverslag 2015, 17 mei 2016; annual accounts Acerta 2014 and 2015; email correspondence with Ad Antonisse, Director Market Access & External Affairs AstraZeneca BV, on February 13 and 25, 2019 (on file with SOMO).

\textsuperscript{181} Information has been taken from the following website: <https://www.drugs.com/price-guide/calquence> (4 April 2019).

\textsuperscript{182} Information has been taken from the following website: <https://www.drugs.com/price-guide/calquence> (4 April 2019).
6 Case study: ATIR101 of Kiadis Pharma

Kiadis Pharma N.V. is a Dutch biopharmaceutical company with its headquarters in Amsterdam, the Netherlands. This case study outlines the history of the company and identifies Dutch public investment in Kiadis Pharma B.V.

The main product produced by Kiadis is ATIR101 (Allodepleted T-cell Immunotherapeutics), a cell-based medicine designed to make bone marrow transplants for patients with blood cancer or inherited blood disorders, safer and more effective. ATIR101, which is currently in Phase III\textsuperscript{183} clinical trials in Europe and North America, helps patients receive stem cell transplants from healthy donors – including family members – who are not a perfect match.

The medicine was awarded orphan drug designation in both the US and Europe, and Kiadis expects marketing authorisation to be granted by the EMA in the first half of 2019, after which it will be launched commercially.\textsuperscript{184}

The Dutch newspaper, het Financieel Dagblad, reported that the former CEO of Kiadis, Manfred Rüdiger, said in 2016 that he expected ATIR101 to cost approximately €100,000. And, in 2017, het Financieel Dagblad reported that the then new CEO of Kiadis, Arthur Lahr said ATIR101 had ‘blockbuster potential’.\textsuperscript{185} The newspaper took this to mean that the medicine would bring in an annual turnover of over a billion euros.\textsuperscript{186} In the Dutch Horizonscan of the National Healthcare Institute, it is estimated that, once on the market, the price of ATIR101 will be €175,000 - 200,000 per patient, per year.\textsuperscript{187}

6.1 The development of Kiadis Pharma and ATIR101

In 1997 Screentec was set up, a spin-off from the Leiden Academic Centre for Drug Research (LACDR).\textsuperscript{188} Screentec focused on high-resolution screening, a technology being used to speed up

\textsuperscript{185} Amy Sullivan, Senior Vice President of Corporate Affairs Kiadis, mentions in the review of this chapter that Artur Lahr has mentioned that the market has blockbuster quality, not the product. Email to SOMO on February 14, 2019. On file with SOMO.
\textsuperscript{187} Zorginstituut Nederland, Horizon Scan geneesmiddelen”, no date, <https://www.horizonscangeneesmiddelen.nl/> (4 April 2019).
the discovery of new pharmaceuticals. In 2002, Screentec changed its name to Kiadis BV and, in 2003, acquired a company called Selact (a spin-off from the University of Groningen).

In 2006, Kiadis bought the Canadian firm, Celmed Biosciences Inc. This purchase proved crucial for Kiadis as it included the patent that would lead to the development of ATIR101. Denis-Claude Roy, a Canadian doctor and one of the patent holders for ATIR101, had been working on a technique related to bone marrow transplantation since 2002, at both Celmed Biosciences and the Maisonneuve-Rosemont Hospital in Montreal. A year after Kiadis bought Celmed BioSciences, it announced that ATIR101 had been granted orphan drug designation by the FDA. In 2007 Kiadis moved its headquarters from the provincial town of Groningen to Amsterdam, and focused only on developing ATIR101 and other products that could be developed using the Theralux Platform, the technology pioneered by Roy. Kiadis has the exclusive license to use this Theralux Platform – the basis for the development of ATIR101 – on the condition that it develops and commercialises other products using the technology. The University of Montreal receives royalties from the revenues.

In later years, however, according to Kiadis’ 2015 prospectus, the company’s operations were financed by the issuance and sale of equity, and from loans and grants. From 2012 – 2015, this financing amounted to €20.2m, and in 2015, Kiadis Pharma became a listed company on the Euronext stock market. An initial public offering (IPO) raised €32.7m when it listed around 2.5 million shares for €12.50 each.

Before the IPO in 2015, according to media reports, Kiadis raised approximately €55m via venture capital investment from Dutch Life Science Partners and Dutch MedSciences, as well as from the British Draper Esprit, the American Alta Partners, the Belgium Quest for Growth, and the regional NOM.200

Operating data
Kiadis’ operating expenses in 2017 were €16.1m, an increase of €4.7m on the previous year. Of this, €11.2m were spent on R&D (compared to €8.2m in 2016), and €4.9m were spent on general administrative costs. The number of staff employed by Kiadis also increased from 39 at year-end 2016, to 61 by the end of 2017. Other increased costs were either related to the start-up costs for the ATIR101 Phase III trial in 2017, or increased consultancy expenses related to the Marketing Authorization Application submission.

In 2017, the company became in-house manufacturers of ATIR101 when they entered into a lease agreement for a manufacturing facility in Amsterdam, suited to producing the drug. The facility included process development and quality control laboratories, as well as the Kiadis Pharma headquarters.201

6.2 Public investments in Kiadis

By piecing together publically available sources, it appears that Kiadis, like many Dutch start-up companies, benefited over the years from public and private investments. The firm had several times raised capital from investor consortiums before launching its IPO in 2015.202

It is difficult to estimate and quantify the amount of government investment Kiadis received indirectly via public-private schemes, or directly through the NOM (a 100 per cent government financed fund), as consortium investments are not broken down per investor.

Kiadis’ prospectus states, however, that in June 2015, the company owed the Dutch Ministry of Economic Affairs €7.3m from two outstanding loans including the government Loan I (RVO NL) and Government Loan II (RVO NL).203 According to the firm’s 2017 annual report, these loans, which had been issued to stimulate innovation, were fully paid off by August 2017.204

Some of the Dutch Government-linked investments in Kiadis, compiled from publically available sources including media, government and the company’s reports, include:

Screentec\textsuperscript{205} (formerly Kiadis) and the Amsterdam Vrije Universiteit awarded a million guilder subsidy in 2001 from the Ministry of Economic Affairs;\textsuperscript{206}

Screentec\textsuperscript{207} (formerly Kiadis) benefited from a half a million euro investment from the Ministry of Economic Affairs’ Mibiton Foundation (Material Infrastructure Biotechnology Netherlands) between 2000 and 2004 for a laboratory shared between five companies;\textsuperscript{208}

Kiadis: a €2.8m investment loan from RVO Nederlands, part of the Ministry of Economic Affairs, between 2009 and 2011;\textsuperscript{209}

Kiadis: €3m as Dutch Government Innovation Credit from AgentschapNL, part of the Ministry of Economic Affairs, in 2013;\textsuperscript{210, 211}

Kiadis: €2.2m Dutch Innovation Credit from RVO Nederland, part of the Ministry of Economic Affairs, in 2012 and 2014;\textsuperscript{212}

Kiadis’s 2015 prospectus reports the following organisations as institutional investors in the company. These organisations are also public/private partnership schemes and receive investment/funding from the Dutch or European Government;

- **Dutch Life Science Partners**, or LSP Management Group, is an Amsterdam-based private equity and venture capital firm which focuses on healthcare start-up companies in Europe and in North America. It is also a Kiadis shareholder. In June 2015, two LSP units, including Life Science Partners BV (15.5 per cent) and Life Science Partners II BV (11.6 per cent)\textsuperscript{213} were Kiadis shareholders. Together, their holding amounted to 27.10 per cent, a little less than the 29.8 per cent stake held by DFJ Esprit.\textsuperscript{214} The Life Sciences Partners II B.V. is a capital venture fund co-financed

\textsuperscript{205} Amy Sullivan, Senior Vice President of Corporate Affairs Kiadis mentions in the review of this chapter, in an email to SOMO on February 14, 2019 which is on file with SOMO: “There have been no advances of therapeutics from Screentec or Selact and all products and technologies of Screentec or Selact that benefited from this government subsidy or other funding failed.”


\textsuperscript{207} Amy Sullivan, Senior Vice President of Corporate Affairs Kiadis mentions in the review of this chapter, in an email to SOMO on February 14, 2019 which is on file with SOMO: “There have been no advances of therapeutics from Screentec or Selact and all products and technologies of Screentec or Selact that benefited from this government subsidy or other funding failed.”


by the European Investment Fund (EIF). Life Sciences Partners II B.V. is included in the EIF’s portfolio for the Dutch Growth Co-Investment Programme, and the Dutch Venture Initiative I and II. (See annex III and IV).

- Lendilis Holding B.V. was Kiadis’ second biggest shareholder (19.1 per cent) as reported in the 2015 prospectus, and works as a pooling entity on behalf of Life Science partners BV, Life Science Partners II BV, MedSciences Capital II BV, Proventures I BV, and LSP Management Group.  

- Dutch Investment and Development Agency for the Northern Netherlands, also known as the NOM N.V, bought shares in Kiadis in 2004 when the company still had its headquarters in Groningen. NOM also invested during consortium financing rounds in 2007 and in 2012. In 2015, NOM had a four per cent equity stake in Kiadis according to the company prospectus.

### 6.3 Concluding remarks

The fundamental research for ATIR101 took place within public institutes and universities, linking its development to public money. As patent holder, the University of Montreal, has attached one condition to the license; that the company is obliged to further develop and commercialise products based on the patent in order to keep the licence. The University of Montreal receives five per cent of royalties.

From 2001 – 2012, Kiadis used public money to help cover R&D costs.

According to Kiadis, the government innovation credit was used to help develop ATIR101. 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).

There is a lack of transparency from both Kiadis and the NOM, about the amount of government-backed investment the company has received. The same is true about the amount of profit made on the investments. Given the role that public support – both financial and intellectual – have played in the development of ATIR101, there will be a great deal of interest when the drug reaches market as to how it is priced.

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217 Het Parool, 18 juni 2015, “Kiadis : Amsterdams medicijnbédrijf wordt beursgenoteerd”.
222 Amy Sullivan, Senior Vice President of Corporate Affairs Kiadis. Email to SOMO on February 14, 2019 (on file with SOMO).
7 Case study: MSD’s Keytruda

7.1 Introduction

This chapter explains Keytruda’s development history and its connection to the Netherlands. Keytruda’s development follows the traditional R&D path: basic research took place over many years at publicly funded universities, corporate researchers with ties to the academy then conducted translational research, drug discovery and development; the clinical trial phases followed. From the clinical trials databases it appears that more than half of all the Keytruda clinical trials have been initiated or sponsored, and partly funded by public institutions. This claim is refuted by Merck & Co, the company that owns Keytruda (known as MSD outside North America). MSD states that it has paid, or provided funding, for almost all the Keytruda clinical trials and provided links to five published articles, as examples for this report, from clinical trials that acknowledge that MSD supplied the drugs for trials sponsored by public institutions.223

Keytruda is a blockbuster drug and is, by far, Merck’s most important and most profitable product currently on the market. Keytruda alone reported $7.2 billion in Merck’s 2018 sales, up 88% from sales of $3.4 billion in 2017. In 2018 Keytruda was responsible for 17% of Merck’s $43 billion in sales, which analysts and investors expect will continue to rise into the future due to Keytruda’s prospects for winning approvals for increasingly more indications.224

7.2 Keytruda’s Dutch roots

Keytruda is a new type of cancer treatment, known as an immune checkpoint inhibitor. Unlike traditional cancer treatments such as radiotherapy or chemotherapy, Keytruda does not directly attack the cancer itself but instead helps the patient’s own immune system do so. This new class of drug is called PD-1 or PD-L1 inhibitor, which means that the drug “block(s) a mechanism tumours use to evade detection from cancer-fighting cells.”225

223 R. Kastelein, Associate VP Immunology & Immuno-Oncology Early Development & Discovery Sciences, Merck & Co, Palo Alto, USA, 14-02-19, interview with author.
It was while working at the Dutch pharmaceutical company Organon, that Dutch scientists discovered the checkpoint inhibitor pembrolizumab, which became the commercial drug Keytruda. Dr Andrea van Elsas is one of a handful of Dutch scientists involved in the discovery and development of this new class of drugs. Following a PhD at the University of Leiden on immunology and melanoma, he conducted post-doctoral research at UC Berkeley before returning to the Netherlands to undertake research at the Dutch Cancer Institute.

Van Elsas spent three years combining work at the Dutch Cancer Institute, with post-doctoral immuno-oncology research at UC Berkeley (in Nobel Laureate James Allison’s laboratory) which led to him being named as a co-inventor on the original patents for the first commercial checkpoint inhibitor drug, ipilimumab or Bristol-Myers Squibb’s Yervoy. In 1999, he moved to the Dutch pharma company Organon to work in target discovery and validation, immunology, and facilitate research collaboration between academia and biotech. “As [Organon] Director of Tumour Immunology, Van Elsas ran the immune oncology portfolio including the programme that later produced pembrolizumab.”

Other Dutch scientists formerly at Organon, including Hans van Eenennaam (University of Nijmegen) and John Dulos (Utrecht University), who also contributed to the discovery of Keytruda and are named as inventors on the drug’s key patents. Cooperation between universities, publicly funded research institutes and the pharmaceutical industry, particularly in the field of pre-clinical oncology drug discovery, was then, as it is now, promoted by the Dutch Government through the Royal

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228 Van Elsas is a co-inventor on the original patents that formed the basis for developing ipilimumab, (Bristol-Meyers Squibb’s Yervoy) the first checkpoint inhibitor approved by the FDA in 2011 for the treatment of melanoma, and directed Organon research lab focused on the immune oncology portfolio program which became pembrolizumab. (Merck & Co’s Keytruda)
Netherlands Academy of Arts & Sciences (KNAW).236 According to David Nicholson237, formerly from Organon, “We worked a lot with the Dutch Cancer Institute, NK238 and the Hubrecht Lab239, partly through personal contacts and also through collaborative research projects.”240

After the PD-1 molecule was selected, Organon collaborated with academics including in the US-based Dana Farber Institute (Dr Hodi)241 and the Radboud University in Nijmegen.242 MDS’s Kastelein243, confirmed this collaboration but said244 Organon paid for the data supplied by Radboud University.245

7.3 The historical timeline of Keytruda

Organon’s PD-1 antibody programme began in the Netherlands in 2003 and became part of a portfolio set up to support Organon’s core objectives, which at the time included autoimmune disease research, ahead of moving part of the lab to Cambridge MA in mid-2005.246 The Organon PD-1 lab, set up in the USA, conducted research with the biotechnology firm Medarex,247 (Nobel Laureate James Allison was working with Medarex to monitor clinical trials of the portfolio he had licenced to the firm).248 In early clinical trials, Medarex’s product showed promise in treating melanoma and, in 2009, was bought by Bristol-Myers Squibb (BMS) for US$2.4bn249. Subsequently, Yervoy was developed and, in 2011, became the first checkpoint inhibitor on the market; an achievement for which Dutchman, van Elsas, must also take credit250.

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240 D. Nicholson, former Organon EVP, Organon, Oss, The Netherlands, 8 November 2018, interview by SOMO.
244 Without providing evidence.
245 R.Kastelein, Associate VP Immunology & Immuno-Oncology Early Development & Discovery Sciences, Merck & Co, Palo Alto, USA, 14-02-19, interview with SOMO.
250 Andrea van Elsas is a co-inventor on an original Ipilimumab patent. See <https://www.aduro.com/about/leadership/> (3 December 2018).
Under Van Elsas’ direction, Organon scientists shifted the focus of the PD-1 programme to oncology from autoimmune disease. “With my academic history in anti-CTLA4251 (even though clinically, cancer immunotherapy was still highly controversial at the time) and with a growing appreciation for the portfolio’s potential in oncology, we had enough reasons to pivot to oncology,”252 Van Elsas said in an article about Keytruda.

Preclinical PD-1 research continued at Organon but following two rounds of acquisitions: Schering-Plough in 2007; and MSD in 2009, the priorities for the programme shifted. Management at MSD reportedly had no interest in the “checkpoint inhibitor” research and, while Schering-Plough was merging into MSD, instructed the lab to ditch the entire body of work, deeming it unimportant and worth a “negligible” amount. As a result the PD-1 molecule was effectively put up for sale by being placed on an out-licence list253 even though Dutch scientists had been working on the molecule since 2003, six years at Organon.254

It was only in 2010 after the New England Journal of Medicine published the results of a successful Phase III melanoma study with Ipilimumab255, that MSD understood that its drug could also be a potential cancer game-changer. By that time, however, it was five years behind the market leader.256 MSD urgently revised the PD-1 research and, after four years of clinical trials and a new breakthrough designation programme, pembrolizumab went to market faster than expected.257 Pembrolizumab became an example for the new FDA programme designed to expedite the review of drugs intended to treat serious conditions.258

On 4 September 2014, Keytruda received both FDA accelerated approval as a therapy for advanced melanoma and breakthrough therapy designation from the FDA for patients with advanced non-small cell lung cancer.259 In July 2015, Keytruda got marketing authorisation in Europe for melanoma.

251 Post-doctorate at UC Berkeley with Allison, research at the Dutch cancer institute and a PhD in antigens in melanoma; co-inventor in original patent that formed the basis for Yervoy.
254 And possible in collaboration with academia, as Van Elsas states on his CV.
Hodgkins Disease and non-small cell lung cancer. Keytruda is currently approved to treat a broad range of cancers, and the expectation is that it will be approved for more indications in the future.

The promising impact of checkpoint inhibitors, the exclusivities they are awarded and the faster drug approval process have made pharma companies wake up to their blockbuster potential. And though it was BMS’ Yervoy that became the first checkpoint inhibitor to be approved (in 2011), it is MSD’s Keytruda that has reportedly had more commercial success.

Keytruda is MSD’s most successful drug, and has become the primary driver of Merck’s growth, having fetched $7.2 billion in 2018 sales alone, up 88 per cent from $3.4 billion in 2017. Since Merck brought Keytruda to market, Merck’s share price has shot up more than 50 per cent, valuing the company in April 2019 at more than 200 billion dollars.

7.4 Public investment in basic and pre-clinical research

It has not been possible to quantify the amount of public investment that contributed to developing Keytruda or this new class of cancer treatments as the academic research was conducted over decades, in the US, the Netherlands, Japan and elsewhere. In 2018, however, the Nobel Prize for Medicine was awarded to academics for research that played a fundamental part in the development of drugs such as Keytruda. The Nobel Prize was specifically awarded for the pre-IND, or Investigational New Drug, demonstrating the link between research and a commercially successful drug.

There are investigations however that show this connection including the US-based study, Cleary et al, that traced the financing grants of all FDA approved drugs between 2010 and 2016. The findings show that all the drugs had received public funding, demonstrating both the magnitude of public

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sector financial support for fundamental research, and the scale of basic research necessary to bring a novel product to market.\textsuperscript{269}

Given that there is no disclosure of public funding for scientific research in Europe, and that those scientists that did respond to requests for information were unable to supply the information, there is no way of estimating how much public investment went into Keytruda. It is also unclear what time frame should be used to measure costs as contributing research took place over many years, at universities around the world, including those in the US, Japan and the Netherlands. However problematic, these are also some of the reasons that estimations for the total cost of developing a new pharmaceutical drug do not include the costs for the basic research.\textsuperscript{270}

### 7.5 Public investment in the clinical trial phase of Keytruda

Data examined from Keytruda clinical trials, including those registered in the U.S. National Library of Medicine’s data set,\textsuperscript{271} the World Health Organisation’s registry,\textsuperscript{272} and the EU Clinical Trials Register,\textsuperscript{273} reveal some information about funding for clinical trials. The data shows that the pharma industry has not financed the entire clinical trial process and that, in fact, 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. (see Table 4 below) Initiating or sponsoring a trial can mean financing all or part of the trial, but primarily it means leading the trial and being responsible for conceiving it, conducting it and finalizing it.

MSD refutes this claim and says trials led or sponsored by non-commercial or public institutes do not always report the funding or financial support they have received from MSD. “For several trials listed as non-industry funded, MSD provides pembrolizumab and additional trial funding,” MSD said in statement,\textsuperscript{274} adding, “Nearly all clinical trials for Pembrolizumab were financed by the private sector,” MSD said in a separate statement.\textsuperscript{275}

Estimating the cost of the trials, assessing a trial’s significance are or tallying up the number of participants in each trial have not been considerations in this report. The clinical registry data was only used in this case study to compare the number of trials initiated by commercial (industry) and non commercial (public health) trial sponsors.

\textsuperscript{273} EU Clinical Trials Register, website, <https://www.clinicaltrialsregister.eu> (4 January 2019).
\textsuperscript{274} MSD written statement provided to SOMO on 12 March 2019 (on file with SOMO).
\textsuperscript{275} MSD written statement provided to SOMO on 22 February 2019 (on file with SOMO).
There are more than 800 Keytruda clinical trials registered worldwide. On 22 November 2018, the US clinical trial registry included 930 clinical trials with search terms such as pembrolizumab or Keytruda or lambrolizumab or MK-3475. However, 67 of these trials were suspended, terminated or withdrawn and therefore excluded from the analyses, leaving a remainder of 863. These remaining trials were either recruiting, active, completed, enrolling by invitation, or the status was unknown. The majority of the trials took place in the US, with many also in Europe and China.

It is worth noting that the US and WHO datasets cover trials taking place worldwide, including those conducted in Europe, while the EU registry only includes information on trials that take place in Europe. The WHO and US registries therefore are comparable, but the EU registry should be considered separately.

Definitions of funder, sponsor, collaborator in clinical trials

All three registries report that the trial sponsor is in charge of the clinical trial, and probably finances all, or part of, the costs. However, as laid out in the definitions below, the trial sponsor may, or may not, pay all the costs.

According to the US Government Clinical Trials register a clinical trial “sponsor” is the organisation or individual who initiates the study, and has authority and control over it. A “collaborator” is an organisation or individual, other than the sponsor, that provides support to the clinical study, perhaps funding, design, implementation, data analysis, or reporting. The US Government adds that although sponsors and collaborators can be trial funders, funding comes from four different sources. These are; the U.S. National Institutes of Health (government); other U.S. Federal agencies (for example, Food and Drug Administration, Centers for Disease Control and Prevention, or U.S. Department of Veterans Affairs); Industry (for example: pharmaceutical and device companies) and others (including individuals, universities, and community-based organisations).

According to the EU and WHO Clinical Trials register, a “sponsor” or a “primary sponsor” is an individual, company, institution, or organisation, responsible for the initiation, management, and/or financing of a clinical trial.
Table 4 Data Clinical trials Keytruda (pembrolizumab)

<table>
<thead>
<tr>
<th>Clinical trial register</th>
<th>Total in register</th>
<th>MSD or Merck as lead sponsor</th>
<th>Other companies as lead sponsor and MSD as collaborator</th>
<th>Other companies as lead sponsor and no MSD as collaborator</th>
<th>Public research institutes as lead sponsor and MSD as collaborator</th>
<th>Public Research Institutes as lead sponsor without mentioning MSD as collaborator</th>
<th>Public research institutes as lead sponsor and NIH mentioned as (co) funder</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Clinicaltrials.gov*</td>
<td>863</td>
<td>105 (12%)</td>
<td>159 (18%)</td>
<td>279 (32%)</td>
<td>192 (22%)</td>
<td>128 (15%)</td>
<td></td>
</tr>
<tr>
<td>WHO Register ICTRP</td>
<td>853</td>
<td>137 (16%)</td>
<td>61 (7%)</td>
<td>125 (15%)</td>
<td>233 (27%)</td>
<td>298 (35%)</td>
<td>n.a.</td>
</tr>
<tr>
<td>EU-register</td>
<td>152</td>
<td>60 (39%)</td>
<td>n.a.</td>
<td>48 (32%)</td>
<td>n.a.</td>
<td>44 (29%)</td>
<td></td>
</tr>
</tbody>
</table>

7.5.1 Results of the data analyses

There have been approximately 860 clinical trials worldwide that have included Keytruda. The total number of trial participants included, or targeted to be included, is almost 128,000, according to the WHO register.284

Though MSD told SOMO it financially supported all or nearly all non-commercial Keytruda clinical trials, the databases show that the majority of Keytruda trials are initiated, or sponsored, and therefore in practice led by, public research institutes.285

The US governmental clinical trial database reveals that MSD has been the lead sponsor (without other collaborators) on 12 per cent of Keytruda clinical trials (105 trials of 863) (see A). The WHO registry shows that 16 per cent of Keytruda trials have MSD as the lead sponsor without other collaborators. The US government and WHO datasets demonstrate that, on average, 14 per cent, of Keytruda trials are fully paid for by MSD.

The smaller data set from the European registry of trials, shows that 39 per cent of Keytruda trials (60 out of 152), have MSD as the lead sponsor, without other collaborators.

Data from the US and WHO registers show that between 18 and 22 per cent of all clinical trials that included Keytruda were initiated by private companies other than MSD (see B and BB), when public institutions were not registered as collaborators. Many of these trials are combination trials with other

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285 MSD written statement provided to SOMO on 22 February 2019.
drugs. Given that the lead sponsors are from the private sector, and public institutes are not registered as collaborators, it appears that these trials are also funded by the pharmaceutical industry.

According to the data registries, between 27 and 32 per cent of trials where MSD is registered as a collaborator are sponsored by a public research institute – including hospitals, medical and cancer centres. In these trials, the public institute pays for at least part of the trial – possibly staff and facilities – and it is thought that MSD supports the trial through activities related to funding, design, implementation, material support, data analysis, or reporting. The data registries do not supply information on the kind of support provided by MSD.

Trials sponsored by a public institute (see D, E), where no private companies are registered as collaborators, appear to be paid for entirely by the lead sponsor, or public research institute/hospital. Such trials amount to 35 - 37 per cent of all Keytruda clinical trials worldwide, or 320 trials.

There are more than 300 trials listed in the US dataset registered as not having industry support. MSD says that it provided the drug for “several” trials listed in the US clinical trials registry categorized as non-industry funded and backed up this statement by providing SOMO a list of five publications from five separate clinical trials, each of which acknowledge MSD provided the drug for the trial.286

However, even when MSD provides or donates Keytruda for trials led and/or sponsored by a public institute, the public institute must still pay for everything else including planning, recruiting, operationalising, researching and reporting on the trial.

Only 30 per cent of trials in the US registry, and 38 per cent of those in the WHO registry, name a pharmaceutical company (such as MSD) as the lead sponsor. The remaining 70 per cent of Keytruda clinical trials registered in the US databank and the 62 per cent in the WHO databank, name a public research institution as the lead sponsor. According to the registries, more than half of all Keytruda clinical trials (599 out of 860) are initiated or led by public research institutes and, therefore appear, to be funded, in total or in part, by public or state-funded institutions.

MSD refutes the method of comparing the number of industry vs non-industry sponsored trials and says that based on the numbers of patients taking part in the Keytruda trials (as reported in the clinicaltrial.gov dataset), MSD reckons 78 per cent of Keytruda clinical trial patients would have participated in industry-funded trials.287 Even when using MSD’s preferred method288, 22 per cent of patients must, therefore, be participating in non-industry funded trials, or trials sponsored and paid for by the public sector.

In the Netherlands, according to the EU clinical trials registry, at least 35 Keytruda clinical trials are taking place, or have taken place, in Dutch hospitals. Most of these trials are sponsored by MSD, with seven reportedly sponsored by Dutch public medical research centres or hospitals, including

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286 MSD document sent to SOMO on 12 March 2019.
287 MSD email sent to SOMO on 15 April 2019.
288 Which SOMO did not try to replicate.
the Dutch Cancer Institute, the VU Medical Centre, the Erasmus MC Cancer Institute and the Antonie van Leeuwenhoek Ziekenhuis.289

7.6 Keytruda’s high price

At a cost of US$ 150,000 (€ 100,000) per year, Keytruda is an expensive drug. Because of this, in April 2017, at the behest of the Dutch Government, the medicine was placed ‘on hold’ or in the Dutch ‘sluice’ (pakketsluis) in an effort to control state expenditure. During this time, the National Healthcare Institute assessed the added therapeutic value (ATV) of Keytruda.

After the Dutch Minister of Health negotiated with MSD to lower the price of Keytruda, it was included in the Dutch reimbursement scheme from 1 July 2017 onwards for all current and future indications. A Dutch government website reports that Keytruda costs € 40,000 - 60,000 per patient, per year290. It is recommended in an FDA data sheet on prescribing Keytruda that, for most cancers including melanoma, gastric and cervical, the appropriate dosage is 200mg every three weeks “until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.”291

7.7 Concluding remarks

Fundamental research & preclinical trials

The 2018 Nobel Prize in Medicine was awarded to two academic292 scientists for discoveries293 that ultimately spearheaded a blockbuster multibillion-dollar pharmaceutical market for new cancer medicines, including Keytruda. By programming the immune system to attack cancer cells through ‘immune checkpoint therapy’, their discoveries have radically changed the way some cancers are treated.”294

The two Nobel Laureates and their students (including Dutch students and scientists in the Netherlands) conducted their basic research over decades in universities and public research

institutes. Their work furthered fundamental and preclinical research in universities, public cancer institutes and pharma companies that was taking place between the Organon scientists and, the Dutch Cancer Institute, the Hubrecht Institute, the US-based Dana Farber Institute and the Radboud University in Nijmegen, among others. This research – known as pre-IND research – led to the discovery of drugs such as Keytruda, that now underpin ‘immune checkpoint therapy’, a new approach used to treat cancer.

Post IND & Clinical Trials

Analysis of clinical trials, using raw data from the registries, shows that the majority of Keytruda clinical trials worldwide (62-69 per cent) have been sponsored, paid for in part or in total, by public research institutions, or non-commercial sponsors, including public cancer institutes and hospitals.

This finding sheds new light on the pharmaceutical industry’s mantra that it pays for the clinical trials. According to the datasets, more than one third of all Keytruda clinical trials worldwide (35-37 per cent), are entirely financed by public or state-funded institutions.

MSD refutes this data and insists that it supplied the drugs for almost all trials, providing, as evidence for its claims, a list of five post-trial publications that acknowledge MSD supplied the drugs for specific trials. If this is the case, and MSD did supply drugs for trial, it still means that public institutes are providing and paying for the staff, facilities and expertise needed to conduct more than half the clinical trials in the registries.

Credit: CC2.0 Pixabay


296 D. Nicholson, former Organon EVP, Organon Oss, The Netherlands, 8 November 2018, interview with SOMO.


298 Email from MSD (on file with SOMO).
Case study: Lutathera of Novartis

This chapter summarises research conducted by Dutch journalist Lucien Hordijk’s into the history of the development of a cancer drug. The research was reported in an article written by Hordijk entitled “Reconstructing Lutetium Octreotate,” published in the Dutch Medical Journal NTVH, or Nederlands Tijdschrift voor Geneeskunde.

The article sparked controversy in the Netherlands, because it reported that Swiss pharma giant Novartis who owned the rare cancer medicine Lutathera, raised the price of the drug more than five times above what it previously cost. Hordijk reported that before Novartis owned the drug – which targets neuroendocrine (hormonal) tumours – Dutch hospitals made the treatment in-house, at a cost of approximately €4,000 per infusion, and he reported that Novartis now charges approximately €23,000 per infusion. Treatment consists of four infusions.

In response to this news report, a Novartis spokerson said, “Novartis has not raised the price of any product. The price of Lutathera has to date, not been set in the Netherlands [and] pricing discussions are with the insurance conglomerate are ongoing.”

Novartis also disputes the premis of Hordijk’s article, or that that it acquired a PPRT previously made by Dutch hositals, and states that Novartis developed and obtained FDA and EMA approval for its own ready-to-use PPRT Lutathera. Novartis also states patients never lost access to tretament.

Hordijk reconstructed the history of the drug’s initial discovery by Dutch physicians in an academic setting and its development over many years, from when it was awarded orphan designation status by the EMA, through its production at Dutch hospitals, up to its acquisition by Novartis. Hordijk’s article was published in early January 2019. It prompted a concerned reaction in the media from Dutch politicians, health advocates, and health insurers.

302 R.Levine, Head of Communications & Patient Advocacy, Novartis, email, 8 April 2019 (on file with SOMO).
303 Peptide Receptor Radionuclide Therapy.
304 R.Levine, Head of Communications & Patient Advocacy, Novartis, email, 8 April 2019. On file with SOMO.
305 Orphan medicines benefit from ten years of market exclusivity once they receive a marketing authorisation in the European Union (EU). This measure is intended to encourage the development of medicines for rare diseases, by protecting them from competition from similar medicines with similar indications, which cannot be marketed during the exclusivity period. <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/orphan-medicines/market-exclusivity-orphan-medicines> (12 January 2019).
The Dutch Minister for Health used the press to reprimand Novartis for increasing the price of the rare cancer drug. There were similar strong reactions from the insurance industry. Dutch insurer VGZ, for example, said it could not explain “that cancer patients no longer have access to a medication developed by the hospital because it has become unaffordable through the intervention of a pharmaceutical company that has contributed nothing to the development of the medicine.” 307

The following is a summary of Hordijk’s January 9, 2019 report, with a small number of additional sources. Hordijk reviewed this text and added some extra context.

8.1 The development history

In the mid-1980s, endocrinologist and Professor of Nuclear Medicine, Dr Eric Krenning,308 employed by the Erasmus MC309 hospital since 1973, began developing a foundation for a precision neuroendocrine tumour (NETs) treatment. In 1992, he treated a NET-patient with a radioactive protein for the first time and though the treatment showed positive signs, it did not work to the extent Krenning had hoped. In fact, it would take years to identify a better protein for treatment and to reduce side-effects. In 2001, six doctors from the Rotterdam Erasmus MC – including Krenning, and several nuclear researchers – created a biotechnology company named BioSynthema. According to Hordijk, doctors -, other than Krenning, – had a minimal stake in the firm (no larger than one per cent each), while Krenning’s stake was 23.39 per cent. The Erasmus MC hospital did not have a stake in the business and in 2005 and 2007, BioSynthema announced exclusive license agreements with the hospital.310

Hordijk reported that the third version of the drug was invented ‘outside the walls’ of Erasmus MC. Krenning is named as an inventor on some of the drug’s patents. Neither Erasmus MC nor the other doctors, are named on any of the patents.

According to the EMA, on January 31 2008, the first orphan designation was granted to BioSynthema Global Operations BV, the Netherlands, for Lutetium used in the treatment of gastro-entero-pancreatic neuroendocrine tumours. In September 2011, this was transferred to Advanced Accelerator Applications, or AAA.311 If orphan drug approval pre-dates EMA market approval, then orphan drug designation takes effect the moment the drug is approved for commercial use.

The owners of BioSynthema sold their shares in the company to the French pharmaceutical firm AAA in 2010. This sale, according to Hordijk, provided the financing needed for the Phase III clinical trials, the last research phase necessary to bring the drug to market. Hordijk confirmed that AAA valued

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309 Formerly known as "Rotterdamse Dijkzigt"-hospital.
BioSynthema at €10.07m. It paid €9.7m in AAA stock and the rest in cash, in instalments, or over time based on performance milestones.\textsuperscript{312} BioSynthema shareholders who had traded their shares for AAA shares received some cash after each of three performance milestones. The drug itself was renamed ‘Lutathera’.\textsuperscript{313}

Clinical trial results published in September 2015 demonstrated that Lutathera was five-times more effective than existing medications.

In July 2017, the EMA renewed the drugs’ orphan status in the EU for a further ten years.\textsuperscript{314} In September 2017, Lutathera gained market approval by the EMA\textsuperscript{315}, and by October 2017, Novartis had offered AAA shareholders €3.3bn (US$3.9bn) for the company.\textsuperscript{316} Less than a week after Novartis finalised the AAA acquisition in January 2018, the FDA approved Lutathera for the US market.\textsuperscript{317}

Novartis bought AAA for its prize possession, Lutathera, a drug approved by the EMA and the FDA, with an orphan drug designation, and guaranteed market exclusivity for at least ten years in Europe and up to seven years in the US.

Hordijk reports that not only is Krenning’s stake in AAA now worth at least €12m, he also has the right to receive royalties for ten years. According to the AAA prospectus filed at the US Securities and Exchange Commission, Erasmus MC is entitled to up to €2m in royalties, for the right to use certain of its data relating to the drug.\textsuperscript{318} Hordijk also reported that Novartis has guaranteed the Erasmus MC hospital that it can buy Lutathera for the lowest price in Europe.

\textsuperscript{312} Form F1, Advanced Accelerator Applications SA, 17 November 2014, <https://www.sec.gov/Archives/edgar/data/1611787/000157104914006490/t1401878-f1.htm> SEC (7 March 2019).

\textsuperscript{313} Novartis spokesperson R. Levine said in an email on 8 April 2019, that Lutathera is the registered and approved product produced as a ready-to-use formulation, one file with SOMO.


\textsuperscript{318} Form F1, Advanced Accelerator Applications SA, <https://www.sec.gov/Archives/edgar/data/1611787/000157104914006490/t1401878-f1.htm> SEC (7 March 2019).
8.2 Price

Since owning Lutathera, Novartis has increased the price of the drug five-fold. Hospitals in the Netherlands previously made the treatment in-house, for about €4,000 per infusion but now Novartis asks approximately €23,000 per infusion. A treatment usually consists of four infusions. One of the roles of Dutch Horizonscan, a government funded research group, and part of the Dutch Ministry of Health’s Zorginstituut, is to forecast prices for new and innovative medicines. On 12 June 2018, it reported that, in the US, the cost of the treatment per dose is US$47,500, a total of US$190,000 per treatment. Based on the number of patients and cost per patient, Horizonscan forecast that, in the Netherlands, the expected total cost of treatment will be approximately €37m. Separate market reports, including those in trade publications, predict Lutathera sales could bring in around €1.75 - 2.0 bn in annual sales for Novartis.

On the Novartis website, the company state: ‘Lutathera’s price is carefully determined, and based on, among other things, the investments made to get the medicine registered; to make it available worldwide; and the benefit the treatment offers to patients.’

8.3 Public investment in Lutetium Oxodotretotide

Lutetium Oxodotretotide, or Lu 177 dotatate, would not have been developed without the Erasmus MC hospital. Erasmus MC was instrumental in all phases of research and development including the clinical trials, since doctors working at the hospital conducted most of the research into this medicine. Phases I and II of the clinical trials were targeted studies conducted on Dutch patients.

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319 As previously stated, Novartis disputes this and states that it has not raised the price of any product in an email by R.Levine on 8 April, 2019 (on file with SOMO).
via Erasmus MC. Phase III\textsuperscript{326} study, Netter-1, was open, randomised and included Dutch and other European patients.\textsuperscript{327}

According to medical publications, of the 1,214 NET patients treated and examined, almost half saw their tumours appear to shrink and most lived 4 - 6 years after receiving NET treatment.\textsuperscript{328}

8.4 Pharmaceutical Compounding

Health insurers in the Netherlands want Dutch hospitals to continue with the pharmaceutical compounding of Lutetium Oxodotreotide so that hospital pharmacists can make the drug in-house\textsuperscript{329}.

As well as buying ByoSynthema, the French company AAA also bought the Dutch IDB Group in January 2016 for €29.9m. At the time, the IDB Group was the only supplier of Lutetium 177 following ‘good manufacturing practices guidelines’ (GMP).\textsuperscript{330} Lutetium 177\textsuperscript{331} is the raw material used by pharmacists to prepare Lutetium Oxodotreotide. By buying AAA, therefore, Novartis acquired the raw material maker of Lutetium 177.

The Dutch Ministry of Economic Affairs & Climate recently approved pharmaceutical compounding of expensive medications if the raw materials are produced according to GMP-guidelines. Last year, the Dutch Ministers of Health, and Economic Affairs & Climate\textsuperscript{332} revoked a clause in 1995 patent law, granting pharmacists the right to prepare medicines for individual patients.\textsuperscript{333}

Responding to Hordijk’s 2019 article, and the ensuing political and press interest, Novartis issued a statement in Dutch on its website that it would continue to deliver Lutetium 177 to enable hospitals

\begin{itemize}
\item \textsuperscript{326} Novartis’ R. Levin states in an email on 8 April 2019, that the Netter-1 study was conducted at at least 40 centres in multiple countries and was conducted and financed by AAA (on file with SOMO).
\item \textsuperscript{329} R. Levine, Novartis spokesperson, said in an 8 April 2019 email that health insurers have conveyed contradictory information to Novartis (on file with SOMO).
\item \textsuperscript{331} R. Levine, Novartis spokesperson, said in an 8 April 2019 email that the German company ITG also provides Lutetium-177 to Dutch hospitals (on file with SOMO).
\end{itemize}
to continue making the drug in-house. Novartis believes that the drug has approval status for reimbursement in the Netherlands. The company is currently having ‘open discussions’ and ‘price negotiations’ with the Minister of Health. “We recognize the special role of the Erasmus Medical Centre in Rotterdam in the early development of Lutathera and we are of course prepared for further dialogue on price and access.”

Although Novartis states that there has been no price increase since it became the medicine’s owner, there is still much uncertainty among hospital pharmacists about the future cost of the drug.

Prior to Novartis, Lutetium 177 costed €2,500 per dose but following Novartis’ recent purchase of a biotech company, Endocyte (for €1.8bn) which owns Luteium-PSMA (a drug similar to Lutathera but which treats prostate cancer,) it is possible that when the new drug goes to market, demand for it will be high, and the price of radioactive Lutetium will increase.

8.5 Concluding remarks

This case study on Lutathera clearly shows how a medicine developed and used by public institutes is taken by pharmaceutical companies for further development. In this case, the last in line – Novartis – goes on to sell the medicine for a high price.

It also shows the resentment that exists, from not only the public institutes that developed the medicine but also the public health insurers and the Dutch Government, about the way the current system allows pharmaceutical companies to sell such public developed medicines for a high price.

Though, as mentioned above, Novartis states on its website that ‘Lutathera’s price is carefully determined, and based on, among other things, the investments made to get the medicine registered; to make it available worldwide; and the benefit the treatment offers to patients’, the company fails to declare the investment it made in order to take over the company that held the relevant patents; Novartis offered AAA shareholders €3.3bn (US$3.9bn) for the company.

The case study clearly shows the urgency of attaching conditionalities to the licenses of patents that originate from UMCs regarding accessibility and affordability.

9 Conclusions and Recommendations

9.1 Conclusions

There is a lack of overview and transparency of public funding of biomedical R&D in the Netherlands

Data provided by the Dutch government (October 2018), indicates that, in 2017, through traditional channels – including the Ministries of Health, Wellbeing and Sports, and Education, Culture and Science – it provided funding of approximately € 780m for biomedical R&D, mainly to universities and public research institutions for fundamental research.

A large amount of public money is also invested in diverse schemes for start-ups, public venture capital funds and tax incentives. This includes money, for example, provided by the Ministry of Economic Affairs and then invested by regional development agencies, like the BOM and the NOM, in promising start-ups in an effort to foster economic development. Through different schemes and public capital venture funds there is an unreported, substantial amount of public money invested in biotech firms that work on applied research.

This lack of overview, as well as the lack of information provided by public capital venture funds, creates a lack of transparency about the total amount of public funding of medicine development in the Netherlands.

Universities are increasingly working on applied research

The role that universities and public research institutes play in applied research is growing. There are a number of reasons:

- Outsourcing: large pharmaceutical companies are stepping away from the early stages of drug development, preferring to leave this phase to universities and publicly funded research institutes.

- Large pharmaceutical companies are gradually changing ‘Research & Development’ into ‘Search & Development’ and universities play an instrumental role in the success of this strategy. Pharmaceutical companies are accessing external R&D cooperation with the academic world, resulting in the growing role of universities in applied research for drug discovery, and the expansion of public-funded drug development programmes.

The funding of biomedical R&D through seed and/or venture capital schemes does not necessarily yield public health benefits

European, national, and regional governmental funding bodies in the Netherlands act as capital investors and use so-called revolving funds.
The use of revolving funds and venture capital to finance drug development means there is less public accountability than when subsidies are granted, as financing decisions are made by the fund managers of the capital venture funds. This funding is also primarily based on economic indicators such as expected financial return, economic growth, foreign investments, and job creation. There are no conditionalities in place to safeguard affordable medicines for patients and healthcare systems.

There is a lack of policy coherence
There is clear tension between the public funding of drug development through capital venture investments, with the expectation of high returns on such investments, and the government need to avoid high prices in medicines.

The large pharmaceutical companies are profiting from the public spendings
What becomes clear from the case studies is that public funding in the Netherlands has been used to help develop medicines that are, or will be, sold at a very high price, making huge profits for the pharmaceutical companies that own the drug when it is brought to market. AstraZeneca, MSD, Novartis, and their shareholders are the beneficiaries of these profits whereas society, or tax payers specifically, receive little to no financial return on those public investments made throughout the R&D process, yet the public still must pay increasingly unaffordable prices for medicines (through their health insurance).

Attaching conditionalities to public funding of biomedical R&D

- Attaching conditionalities to public funding of biomedical R&D is still in its infancy in the Netherlands but the first steps are being taken to develop the principles of such conditionalities. It is important that the Dutch Government expressed its commitment to attach conditionalities to public funding of biomedical R&D.

- Large pharmaceutical companies increasingly seek to work in cooperation with academia. This, along with the trend of outsourcing applied research to universities and other public research institutes makes it more important than ever that clear conditions are attached to scientific knowledge generated through public funding, if the health impact of such developments are to be maximised.

- Venture capital funds established with public money should be more publicly accountable, transparent and have conditionalities attached to them. They currently state they are not in a position to impose conditionalities and that such conditionalities would conflict with their mission to achieve high returns on investments.

9.2 Recommendations

Policy coherence
Priorities need to be rebalanced. Currently, economic policies prevail at the expense of public health. When investment funds, for example, are evaluated on their success, it should not be on economic indicators alone. It seems incomplete to judge investment in drug development solely
on the amount of jobs created or the return on investment. Health indicators are equally important, and a more comprehensive assessment of success is one that balances public health with economic interests. Frameworks already exist, such as the Sustainable Development Goals (SDGs), that could be used to predict the social impact of public funding.

The Dutch Ministry of Health, Wellbeing and Sports would benefit from policy coherence as it has prioritised the issue of high drug prices and tried to get the restraining of drug prices on the European agenda. The Ministry of Economic Affairs and Climate would also benefit from policy coherence as it plays an instrumental role in the investments in biotech companies that take place through seed and/or venture capital schemes, where the expectation of high return on investments conflicts with the interest of the government to avoid high medicine prices. The funding of drug development through public venture capital funds can also mean that the public pays twice for the costs of drug development; Dutch health policy seeks to avoid this.

It is therefore recommend that the Dutch Government prioritises policy coherence of publicly funded projects concerning drug development, with the aim of looking not only at economic indicators but also the health impact of the investment.

**Transparency**
Ministries that channel funding of biomedical R&D should provide more transparency about the nature and amounts of funding, including public money invested by venture capital funds.

The Dutch Government should be transparent about all the publicly funded support given to drug development. Without complete transparency there can be no accountability. This report found that the amount of public funding of drug development is greater than that initially estimated by the Ministry of Health, Wellbeing and Sports. If a comprehensive oversight were available, stating all public investments in drug development, it would increase the negotiating position of governments and publicly funded research institutions.

We therefore recommend that the Dutch Government reassess the additional public funding streams uncovered in this report, and provide a publicly accessible document detailing the annual amounts of money invested in drug discovery.

**Conditionalities**
Attaching conditionalities to licenses developed with the help of public funding will result in better public return. It is recommended that the Dutch Government urgently pursues its commitment to attaching conditionalities to public funding of biomedical R&D. With the help of non-exclusive and social responsible licenses, universities can help maximise the public return on public investments.

Core elements and themes consistent and relevant for socially responsible licensing:

- To ensure a meaningful health impact for society;
- To ensure innovation and further development of the invention;
- To ensure the right of continuation of using the knowledge licensed, for own research goals and educational purposes;
To ensure knowledge sharing, such as sharing research findings through open access;
To ensure populations in need have access to end products;
To ensure affordability related to the pricing of the medication;
To ensure availability and production of the product;
Socially responsible licensing should transfer non-exclusive licenses, keeping the way open to revoking a license on the grounds of attached conditionalities such as those listed above, and thereby allowing more than one company to exploit the innovation, creating generic competition.

It is recommended that research be undertaken on the possibility of introducing a law at European level that requires applicants for marketing approval to state whether public funding was involved in the R&D of the medicine. Related to this, it is recommended that the possibility of implementing a similar act as the US Bayh-Dole Act (USA, 1980) at Dutch or EU level, be investigated. This legislation allows the federal government (or specifically the federal agency that funded the research which contributed to the invention) to revoke patents in order to alleviate any health or safety needs that are not being reasonably satisfied by the patent holder.

We therefore recommend that the Dutch government sets up a guiding framework for universities and other publicly funded research institutions to follow. The decision to fund a project with public money could be partially based on how well the organisation had applied the guiding framework on conditionalities in the past.

Credit: CC2.0 free image bay
Annexes

Annex I Total of private investments in 2015

An important indicator for success for the Dutch biotech sector are the private investments in the biotech companies which are often start-ups. The following overview gives the total of private investments in 2015, the year that Acerta Pharma was acquired by AstraZeneca. This list is compiled by HollandBio.

Table 5 Total of private investments

<table>
<thead>
<tr>
<th>Company</th>
<th>Partner</th>
<th>Date</th>
<th>Type</th>
<th>Amount in USD</th>
<th>Amount in EURO</th>
</tr>
</thead>
<tbody>
<tr>
<td>FABPulous</td>
<td>Venture Capital</td>
<td>februari</td>
<td>2,88</td>
<td>2,5</td>
<td></td>
</tr>
<tr>
<td>T-cell factory</td>
<td>Kite Pharma</td>
<td>maart</td>
<td>M&amp;A</td>
<td>21</td>
<td>19,1</td>
</tr>
<tr>
<td>uniQure</td>
<td>BMS</td>
<td>april</td>
<td>Licensing</td>
<td>50</td>
<td>46,3</td>
</tr>
<tr>
<td>uniQure</td>
<td>april</td>
<td>FOPO</td>
<td>89</td>
<td>88,5</td>
<td></td>
</tr>
<tr>
<td>Galapagos</td>
<td>iPO (Nasdaq)</td>
<td>mei</td>
<td>316,7</td>
<td>279</td>
<td></td>
</tr>
<tr>
<td>i-Optics</td>
<td>Venture Capital</td>
<td>mei</td>
<td>15,1</td>
<td>13,7</td>
<td></td>
</tr>
<tr>
<td>AM-Pharma</td>
<td>Pfizer</td>
<td>mei</td>
<td>M&amp;A</td>
<td>87,5</td>
<td>78</td>
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<tr>
<td>Lanthio</td>
<td>Morphosys</td>
<td>mei</td>
<td>M&amp;A</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Acerta Pharma</td>
<td>Venture Capital</td>
<td>mei</td>
<td>375</td>
<td>335</td>
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<td>FABPulous</td>
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<td>Pharming</td>
<td>Debt financing</td>
<td>juli</td>
<td>17</td>
<td>15,2</td>
<td></td>
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<tr>
<td>Kiadis Pharma</td>
<td>IPO (Euronext)</td>
<td>juli</td>
<td>36,6</td>
<td>32,7</td>
<td></td>
</tr>
<tr>
<td>Merus</td>
<td>Venture Capital</td>
<td>augustus</td>
<td>80,5</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>uniQure</td>
<td>BMS</td>
<td>augustus</td>
<td>Milestones</td>
<td>90</td>
<td>80,3</td>
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<tr>
<td>Night Balance</td>
<td>Venture Capital</td>
<td>september</td>
<td>4,6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Audion Therapeutics</td>
<td></td>
<td>september</td>
<td>2,85</td>
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<tr>
<td>BioNovion</td>
<td>Aduro</td>
<td>september</td>
<td>M&amp;A</td>
<td>32,5</td>
<td>29</td>
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<tr>
<td>Dezima</td>
<td>Amgen</td>
<td>september</td>
<td>M&amp;A</td>
<td>300</td>
<td>268</td>
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<tr>
<td>NovioGendix</td>
<td>MdxHealth</td>
<td>september</td>
<td>M&amp;A</td>
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<td>7,8</td>
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<td>Enzyppep</td>
<td>Venture Capital</td>
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<td>5,5</td>
<td>5</td>
<td></td>
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<tr>
<td>InteRNA Technologies</td>
<td></td>
<td>oktober</td>
<td>10,5</td>
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<td></td>
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<tr>
<td>Galapagos</td>
<td>Gilead</td>
<td>december</td>
<td>Licensing</td>
<td>725</td>
<td>668</td>
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<tr>
<td>Xeltis</td>
<td>December</td>
<td>December</td>
<td>Venture Capital</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Agendia</td>
<td>December</td>
<td>December</td>
<td>Venture Capital</td>
<td>6,9</td>
<td>6,8</td>
</tr>
<tr>
<td>Mimetas</td>
<td>December</td>
<td>December</td>
<td>Venture Capital</td>
<td>1,6</td>
<td>1,4</td>
</tr>
<tr>
<td>Acerta Pharma</td>
<td>AstraZeneca</td>
<td>December</td>
<td>M&amp;A</td>
<td>2500</td>
<td>2300</td>
</tr>
<tr>
<td>Total</td>
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<td>4807,94</td>
<td>4390,3</td>
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</table>
## Annex II 55 venture capital investment funds

The venture capital investment funds to which the Dutch government (EZ) contributed more than 200 million euro in 10 years (2005-2015).

<table>
<thead>
<tr>
<th>#</th>
<th>Fund Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5Square MKB Seed Fund 1</td>
</tr>
<tr>
<td>2</td>
<td>5Square MKB Seed Fund 2</td>
</tr>
<tr>
<td>3</td>
<td>Aescap Venture I Seed B.V.</td>
</tr>
<tr>
<td>4</td>
<td>Aglaia Oncology Seed Fund B.V.</td>
</tr>
<tr>
<td>5</td>
<td>Astor Participaties Technostarters B.V.</td>
</tr>
<tr>
<td>6</td>
<td>Axivate Capital B.V.</td>
</tr>
<tr>
<td>7</td>
<td>Biogeneration Ventures II B.V.</td>
</tr>
<tr>
<td>8</td>
<td>Brabant Life Sciences Seed Fonds B.V.</td>
</tr>
<tr>
<td>9</td>
<td>Business Angels Technostarters B.V.</td>
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<tr>
<td>10</td>
<td>Business Angels Technostarters II B.V.</td>
</tr>
<tr>
<td>11</td>
<td>Dutch Technology Fund I</td>
</tr>
<tr>
<td>12</td>
<td>E2 Cleantech1 B.V.</td>
</tr>
<tr>
<td>13</td>
<td>Enabling Technology Fund B.V.</td>
</tr>
<tr>
<td>14</td>
<td>Health Innovation Fund I B.V.</td>
</tr>
<tr>
<td>15</td>
<td>Health Innovation Fund II B.V.</td>
</tr>
<tr>
<td>16</td>
<td>Henq III Seed fund B.V.</td>
</tr>
<tr>
<td>17</td>
<td>HENQ Innovatiefonds II B.V.</td>
</tr>
<tr>
<td>18</td>
<td>HENQ Innovatiefonds1 B.V.</td>
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<tr>
<td>19</td>
<td>Holland Venture Technologie fund B.V.</td>
</tr>
<tr>
<td>20</td>
<td>Holland Venture Zorg Innovaties</td>
</tr>
<tr>
<td>21</td>
<td>Icos Cleantech Early Stage Fund II B.V.</td>
</tr>
<tr>
<td>22</td>
<td>ICT Venture B.V.</td>
</tr>
<tr>
<td>23</td>
<td>Mainport Innovation Fund II Seed Fund B.V.</td>
</tr>
<tr>
<td>24</td>
<td>Medsciences Seed Fund B.V.</td>
</tr>
<tr>
<td>25</td>
<td>MIF III</td>
</tr>
<tr>
<td>26</td>
<td>Newion Investment Capital Early-stage Fund B.V.</td>
</tr>
<tr>
<td>27</td>
<td>Nextgen Ventures</td>
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<td>28</td>
<td>OGC Dutch ICT Fund B.V.</td>
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<tr>
<td>29</td>
<td>Peak Capital II</td>
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<tr>
<td>30</td>
<td>PEAK Capital III B.V.</td>
</tr>
<tr>
<td>31</td>
<td>Percival Participations B.V.</td>
</tr>
<tr>
<td>32</td>
<td>Percival Participations II B.V.</td>
</tr>
<tr>
<td>33</td>
<td>Point-One Starter Fund U.A.</td>
</tr>
<tr>
<td>34</td>
<td>Prime Technology Ventures Technostarter v.o.f.</td>
</tr>
<tr>
<td>35</td>
<td>Seed Fund III C.V.</td>
</tr>
<tr>
<td>36</td>
<td>Solid Ventures B.V.</td>
</tr>
<tr>
<td>37</td>
<td>Start Green Consumer Products Fund B.V.</td>
</tr>
<tr>
<td>38</td>
<td>Start Green Fund B.V.</td>
</tr>
<tr>
<td>39</td>
<td>Support Seed Fond B.V.</td>
</tr>
<tr>
<td>40</td>
<td>Techfund B.V.</td>
</tr>
<tr>
<td>41</td>
<td>TechNano Fund B.V.</td>
</tr>
<tr>
<td>42</td>
<td>Technostartersfonds Zuid-Nederland B.V.</td>
</tr>
<tr>
<td>43</td>
<td>The Hatch Firm Innovation Fund B.V.</td>
</tr>
<tr>
<td>44</td>
<td>Thuja Capital Healthcare Seed Fund I B.V.</td>
</tr>
<tr>
<td>45</td>
<td>Thuja Capital Healthcare Seed Fund II B.V.</td>
</tr>
<tr>
<td>46</td>
<td>TIIN Techfund 2 B.V.</td>
</tr>
<tr>
<td>47</td>
<td>TIIN Techfund 3 B.V.</td>
</tr>
<tr>
<td>48</td>
<td>Vip Fund B.V.</td>
</tr>
<tr>
<td>49</td>
<td>VOC Capital Partners B.V.</td>
</tr>
<tr>
<td>50</td>
<td>VOC Capital Partners II B.V.</td>
</tr>
<tr>
<td>51</td>
<td>Vortex High Growth B.V.</td>
</tr>
<tr>
<td>52</td>
<td>Zeeuws Investeringsfonds B.V.</td>
</tr>
</tbody>
</table>

Annex III DVI-I and DVI-II investments

- Aglaia Oncology Fund II
- Endeit Fund II Coöperatief U.A.
- European Angels Fund S.C.A., SICAR – EAF Netherlands
- Forbion Capital Fund III
- Gilde Healthcare III
- Gilde Healthcare Services II
- Henq III
- HPE Fund II
- Karmijn Kapitaal
- Keen Venture Partners
- Life Sciences Partners V
- Newion Investments II
- Prime Ventures IV
- SET Fund II

DVI-II investments at 31.12.2017
- Gilde Healthcare IV
- Karmijn Kapitaal II
- BioGeneration Capital Fund III
- Finch Capital Fund II
- LSP Health Economics Fund 2
- Vortex Capital Partners II
- Newion Investments III

InnovFin Equity Final Recipient
Axign, Rigtersbleek-Zandvoort 10, 7521 BE Enschede, Netherlands, Equity financing
BC Therapeutics EU BV, Keplerstraat 34, 1171CD Badhoevedorp, Netherlands, Equity financing
Escalier Biosciences BV, Transistorweg 5J, 6534 AT Nijmegen, Netherlands

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Annex IV Funds in EIF’s portfolio

Funds in EIF’s portfolio they work with for the Dutch Growth Co-Investment Programme, and the Dutch Venture Initiative I and II include the following:

- LSP Health Economics Fund 2 C.V
- Vortex Capital Partners II Coöperatief U.A. (DVI 2)
- Newion Investments III (DVI 2)
- Finch Capital Fund II Coöperatief U.A. (DVI 2)
- HPE Institutional Fund II (DVI 2)
- Endeit Fund II Coöperatief U.A
- Gilde Healthcare Services II (DVI) / Gilde Healthcare III / Gilde Healthcare IV (DVI 2)
- Forbion Capital Fund II (DVI)/ Forbion Capital Fund II
- LSP V – Life Sciences Partners V (DVI)
- Aglaia Oncology Fund II (DVI)
- SET Fund II (DVI)
- Prime Ventures IV (DVI)
- Life Sciences Partners II B.V./ Life Sciences Partners III B.V.
- BioGeneration Capital Fund III
- Carduso Capital (DI)
- Henq III (DVI)
- Karmijn Capital (DVI)


### Annex V overview of drugs with academic discovery origins

<table>
<thead>
<tr>
<th>Compound Name</th>
<th>Target, Indication</th>
<th>Academic Institute</th>
<th>Industry Partner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel, Taxol, Abraxane</td>
<td>Microtubule stabilizer, Oncology</td>
<td>Research Triangle Institute</td>
<td>Bristol-Myers Squib</td>
</tr>
<tr>
<td>Vorinostat, SAHA</td>
<td>Histone deacetylase Inhibitor, Oncology</td>
<td>Sloan Kettering Cancer Center</td>
<td>Merck</td>
</tr>
<tr>
<td>Prezista, Darunavir</td>
<td>HIV protease inhibitor, HIV</td>
<td>Purdue University</td>
<td>Tibotech/J&amp;J</td>
</tr>
<tr>
<td>Tomudex, Raltitrexed</td>
<td>Thymidylate synthase inhibitor, Oncology</td>
<td>Institute of Cancer Research, UK</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Viread, Tenovir disoproxil fumarate</td>
<td>Reverse transcriptase inhibitor, HIV infection</td>
<td>Institute of Organic Chemistry and Biochemistry, Czech Republic, Rega Institute, Belgium</td>
<td>Gilead</td>
</tr>
<tr>
<td>Lamivudine, (−)-3TC, Epivir</td>
<td>Reverse transcriptase inhibitor, HIV infection</td>
<td>Emory University</td>
<td>GSK</td>
</tr>
<tr>
<td>Valstar, Valrubin</td>
<td>DNA topoisomerase II inhibitor, Oncology</td>
<td>Dana-Farber Cancer Institute, US.</td>
<td>Endo Pharmaceuticals</td>
</tr>
<tr>
<td>Paraplatin, Carboplatin</td>
<td>DNA alkylating agent, Oncology</td>
<td>Institute of Cancer Research, UK</td>
<td>Bristol-Myers Squib</td>
</tr>
<tr>
<td>Temodar or Temodal, Temozolomide</td>
<td>DNA methylation, Oncology</td>
<td>Malcolm Stevens Aston University, UK</td>
<td>ScheringPlough Corp.</td>
</tr>
<tr>
<td>Alimta, Pemetrexed</td>
<td>Dihydrofolate reductase/thymidylate synthase inhibitor, Oncology</td>
<td>Princeton University</td>
<td>Eli Lilly</td>
</tr>
<tr>
<td>Zidovudine, AZT, Azidothymidine</td>
<td>Reverse transcriptase inhibitor, HIV</td>
<td>Michigan Cancer Foundation</td>
<td>GSK</td>
</tr>
</tbody>
</table>

Source: Julie Frearson and Paul Wyatt, Drug Discovery in Academia- the third way?[^343^]
