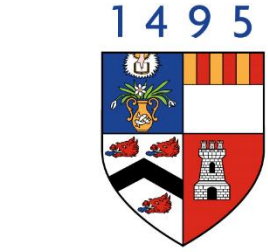

UNIVERSITY OF ABERDEEN

BUSINESS SCHOOL

Financing Biomedical Research with Healthcare Derivatives as a Potential Means to Reduce Therapy Prices

BY CHRISTIANE WIRRIG (ID 51879518)

A dissertation submitted in partial fulfilment of the requirements for the degree of Master of Science (Econ) in Finance and Investment Management at the University of Aberdeen

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Declaration

This dissertation is submitted in part requirement for the degree of MSc (Econ) Finance & Investment Management at the University of Aberdeen, Scotland. It has not been submitted in support of any other degree application. This dissertation is solely my work. The work of other authors is recognised and appropriately referenced.

Christiane Wirrig

Contents

ABSTRACT

As drug prices keep rising, worries about future affordability of novel cures within existing healthcare systems increase. Rare disease therapy poses a particular economic challenge because it incurs high costs for only few patients. Life sciences investors demand high returns due to the significant failure risk in drug development. This translates into considerable research financing costs. High drug prices are to ensure timely returns for manufacturers before the expiry of their exclusivity protection, which staves off competitors. Whenever healthcare payers decide against covering therapy costs, the burden is passed on to patients. For future healthcare systems to cater for all patients adequately, innovative solutions are needed. This project investigates healthcare derivatives as a novel research funding source. It proposes a preliminary framework and trials its theoretical application in a hypothetical rare disease case study involving the world's currently most expensive drug. The chosen scenarios indicate limited potential for healthcare derivatives in reducing firms' financing costs but suggest that drug sales may be possible at cheaper prices. Healthcare derivatives may be more suitable for diseases with large patient populations. More detailed investigation and modelling is required.

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

$ US dollar

ARRA American Recovery and Reinvestment Act

BLA Biologics License Application

CF cash flow(s)

CPU client potential user(s)

CVC corporate venture capital

DR discount rate

EMA European Medicines Agency

EPR external price referencing

EU European Union

FDA US Food and Drug Administration

FY financial year

GDP Gross Domestic Product

HCCO healthcare call option(s)

HCD healthcare derivative(s)

HCF healthcare futures contract(s)

HTA Health Technology Assessment

ICT information and communication technology

IIPU institutional investing potential user(s)

IND Investigational New Drug

IPO initial public offering(s)

IPU investing potential user(s)

IQR interquartile range

IVS intense ventilation support

MC market capture

NCHS US National Center For Health Statistics

NHS National Health Service

NICE National Institute for Health and Care Excellence

NIH National Institutes of Health

NME New Molecular Entity(-ies)

NPV net present value

OC opportunity cost

OD orphan drug(s)

OECD Organisation for Economic Cooperation and Development

OF organ futures

PbR payment by results

PIPE private investment in public equity

R&D research & development

RD rare disease(s)

RIPU retail investing potential user(s)

SIB social impact bond(s)

SMA spinal muscular atrophy

TA total assets

UK United Kingdom

US(A) United States (of America)

V vintage (year)

VC venture capital

WW worldwide

Y year

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I am grateful to Rebecca Stewart, CEO of Rare Revolution Magazine, for helping me understand the perspective of patients and carers better and for pointing out the importance of different players in healthcare systems.

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Thanks to his incredible patience and support Sid, as ever, was the most amazing wingman on yet another excursion on this life's journey.

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I am blessed with some great family members, friends and acquaintances who just go with the flow and never cease to encourage me along the way.

CHAPTER 1. INTRODUCTION

Specialist medical care comes at a high cost. With ever-advancing biomedical innovation, prices of new drugs keep increasing (Schneider, Vogler 2019). Brand-name pharmaceutical expenditure cuts deeply into the pockets of healthcare payers (Kesselheim, Avorn et al. 2016). Rare disease (RD) treatments extract large sums for only a small number of people (Meekings, Williams et al. 2012). The world's currently most expensive drug, Novartis' RD cure Zolgensma, incurs a one-off cost of over $2M per patient (Novartis 2019a). Even though a great scientific achievement, its price has been questioned (Luxner 2019, Malik 2019).

The targeted drug development process usually takes over a decade (Van Norman 2016). In addition to companies' own revenues, the main research and development (R&D) funding sources encompass private and public equity investments, debt financing and public grants (Morrison, Lähteenmäki 2019, Moses, Matheson et al. 2015). The number of drugs that made it successfully onto the market has declined over the last decades (Mestre-Ferrandiz, Sussex et al. 2012). At the same time, R&D costs have risen steadily (DiMasi, Grabowski et al. 2016). Owing to the considerable risk of failure, R&D financing costs are estimated to amount to nearly 50% of total expenses. Consequently, manufacturers set prices with the aim to profit quickly from newly released treatments before patents expire or competitors develop alternatives (Kesselheim, Avorn et al. 2016).

Patients may not gain access to cutting-edge therapies because they are unaffordable for most households and strain private and public health insurers (Szegedi, Zelei et al. 2018, Robinson, Brantley et al. 2014). If pharmaceuticals took a larger share of healthcare budgets (OECD, EU 2018), other provisions might suffer. Whilst healthcare costs must be tightly controlled, this should not be to the detriment of patients and frustration of medical professionals (Jackson, Paterson et al. 2014). Thus, the healthcare industry requires innovative solutions to manage spending in ways that cater for all patients. Instead of investigating solutions to pay for expensive treatments, this project poses the complementary question whether therapy prices can be lowered by changing R&D financing.

To this end, the project explores healthcare derivatives (HCD), a radically new suggestion for biomedical R&D funding first described in an online opinion piece (Ferrante-Schepis 2018). The aim of this work is to introduce the concept of HCD, not to develop optimised financing models. Fundamental rules for a preliminary HCD framework are created. A case study tests in retrospect the theoretical application of these rules to permit Zolgensma sales below its market price.

Chapter 2 establishes the context for this research in a review of relevant publications. Chapter 3 explains the research methodology. Chapter 4 presents the proposed HCD framework and results from the Zolgensma case study. Conclusions and future considerations are discussed in Chapter 5.

CHAPTER 2. LITERATURE REVIEW

This literature review [1] introduces current systems and challenges concerning healthcare spending, pharmaceutical R&D processes and RD therapy. R&D costs and drug pricing are examined. Established R&D funding sources as well as innovations in healthcare financing are outlined.

2.1 HEALTHCARE SPENDING

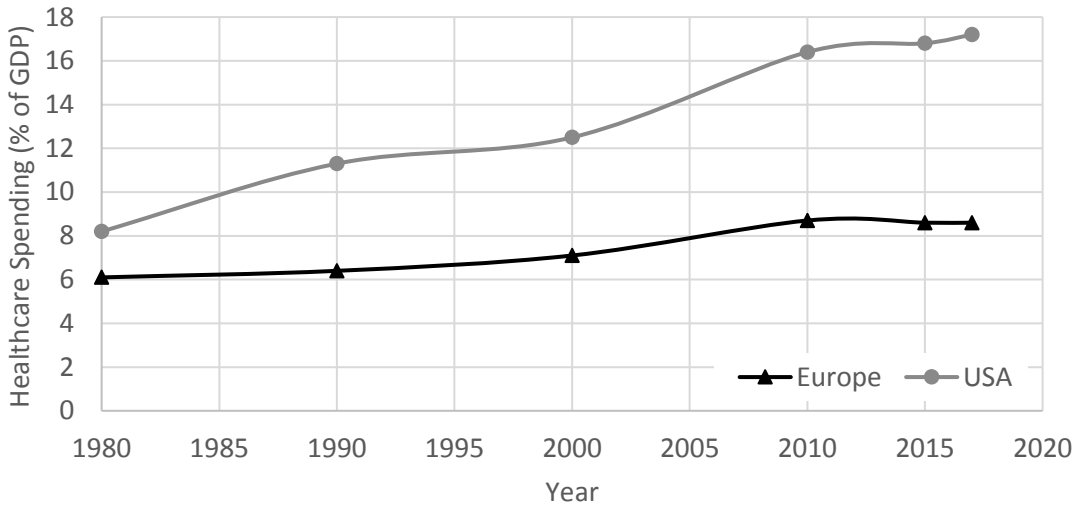
Healthcare funding mechanisms can differ greatly between countries, from public or social systems in Europe to heavy reliance on private provisions in the United States of America (USA) (Rogowski, Hartz et al. 2008). One common component is that marketing approval does not necessarily make a treatment available to patients if payers refuse to cover its costs. The only other choice then are out-of-pocket payments by patients. Decisive for this hurdle are advisory bodies like the National Institute for Health and Care Excellence (NICE), which makes recommendations to the United Kingdom's (UK) National Health Service (NHS) and is also referred to by private health insurers. Such agencies generally apply some form of Health Technology Assessment (HTA) that weighs up clinical benefits and economic cost-effectiveness (Moreno, Epstein 2019). A comparative study based on NICE-appraised drugs from 1999–2005 found no difference between the UK and USA in the level of favourable coverage recommendations, with just under 90% of dugs passing the assessments (Cohen, J., Cairns et al. 2006). Conditional coverage and emphasis on cost-effectiveness were more common in the UK, whilst cost-sharing, i.e. required contributions by policyholders, was higher in the USA. In terms of actual coverage, only 36% of total retail pharmaceutical expenditure was covered by US government and compulsory schemes in 2015; together with voluntary health insurance coverage amounted to 70% (OECD 2017a). In the UK and across the European Union (EU) 70% and 64%, respectively, of all pharmaceutical costs were covered by public and compulsory schemes in 2016 (OECD, EU 2018). Figure 1A suggests that healthcare spending in the USA and Europe approached a plateau in the 2010s. Indeed, all healthcare expenditure categories experienced a decline in member countries of the Organisation for Economic Cooperation and Development (OECD) after the 2008 financial crisis; spending on pharmaceuticals dropped by 0.5% annually (Figure 1B).

[1] The terminology in healthcare-relevant finance literature is inconsistent because of the interconnectedness of the underlying sciences. Consequently, sources refer to pharmaceutics, biotechnology, biomedicine and related life sciences whose definitions may overlap.

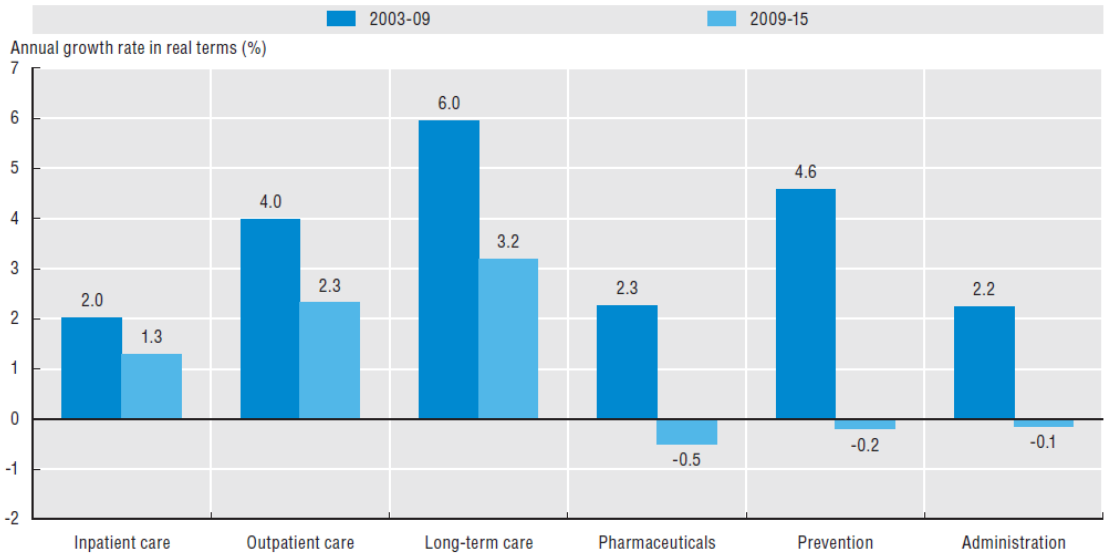
Figure 1. Healthcare spending trends

[A] This chart was generated from data on total public and private healthcare spending as a percentage of Gross Domestic Product (GDP) from 1980 to 2017 (EFPIA 2019). Note that European data are non-weighted averages from 27 countries. **[B]** This reproduced chart shows the average annual expenditure growth rates per capita for healthcare services in OECD member countries during 2003–15 (OECD 2017a).

[A] European and US healthcare expenditure



[B] OECD healthcare expenditure growth rates

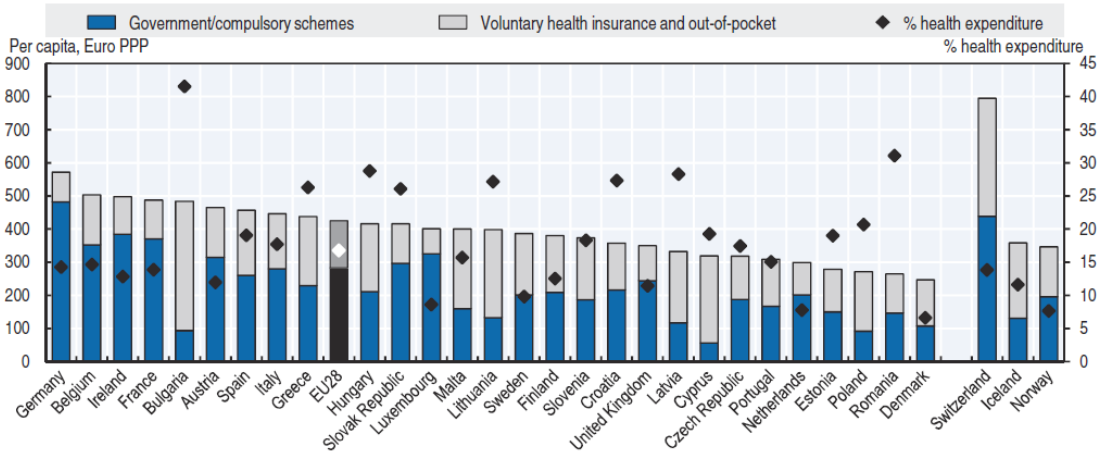


source: OECD 2017a

Approximately one-sixth of average European healthcare spending went towards non-hospital pharmaceuticals in 2016 (Figure 2). If drug prices rose faster than other healthcare costs due to increasing R&D costs (Gottlieb 2017), coverage could possibly either decrease or pharmaceutical spending might hurt other healthcare areas. Whilst overall cost control is important, rigid restrictions on prescriptions can cause physicians professional conflict (Jackson, Paterson et al. 2014).

Figure 2. European pharmaceutical expenditure

This reproduced chart shows the pharmaceutical retail expenditure per capita (primary axis) and as a proportion of healthcare spending (secondary axis) in European countries in 2016 (OECD, EU 2018). Inclusion of hospital pharmaceuticals would increase expenditure by 30%.



source: OECD, EU 2018

2.2 Drug Prices

Drug prices incorporate several components along the supply chain from manufacturer to sales outlet (Figure 3). There is also a distinction to be made between the retail price set by industry and the reimbursement price set by healthcare payers (Stargardt, Schreyögg 2006).

Figure 3. Components of European pharmaceutical retail prices

This reproduced graphic shows the share in drug retail prices of each main participant in the supply chain (EFPIA 2019). Data are non-weighted averages from 23 European countries in 2017.

source: EFPIA 2019

Pharmaceutical firms enjoy two levels of exclusivity protection through intellectual property and regulatory provisions, which are meant as incentives to stimulate innovation but also allow them to set high retail prices (Kesselheim, Avorn et al. 2016). In the USA, 10% of prescriptions drugs are such brand-name pharmaceuticals, yet they account for 72% of drug expenditure. Prices drop thanks to competition when generics, i.e. essentially copies of the original drugs, enter the market after the exclusivity period. Payers may use their negotiating power to lower reimbursement prices during the exclusivity period. However, their influence is especially limited in the USA. The burden is shifted to patients' out-of-pocket contributions, which has led to non-compliance with treatment regimens and avoidable consequential healthcare costs.

Three main strategies are used to set reimbursement prices: determination by manufacturers or the government and external price referencing (EPR), i.e. basing domestic prices on foreign ones. The latter two are common across Europe, but their implementation is heterogeneous and stark price differences exist between countries (Kos 2019). Because the USA adhere to the first strategy, US drug prices are generally higher than in other industrialised countries (Table 1). However, US adoption of EPR is currently debated (Sullivan 2019). EPR is not without drawbacks (Kos 2019, Stargardt, Schreyögg 2006). Countries might overprice drugs by basing their decisions on list prices, not confidentially discounted actual prices. Changes in reference countries affect domestic prices, and manufacturers might launch drugs strategically by starting with countries that can bear higher charges. This helps firms generate sufficient profitability for investors to tolerate the high R&D risk and finance future developments (Moreno, Epstein 2019). Nevertheless, a sustainable balance between manufacturers and payers is needed. Whilst some countries have successfully reduced price levels using appraisal or control measures, a tendency towards increasing launch prices has been described in OECD countries (Schneider, Vogler 2019). Of note, net US prices of branded drugs increased by only 0.3% in 2018 and major publicly listed industry players lost market value due to various investor concerns (Morrison, Lähteenmäki 2019).

Table 1. Different drug prices in industrialised countries

This reproduced table shows average prices for top-selling drugs in selected countries in 2015 (Kesselheim, Avorn et al. 2016). US prices are shown undiscounted and at estimated payer discounts.

	Monthly Price, US $				
	United States				
Drug	Nondis-counted Price	Estimated Discounted Price	Canada	France	Germany
Adalimumab (Humira), 40 mg biweekly	3430.82	2504.50	1164.32	981.79	1749.26
Fluticasone/salmeterol (Advair), 250 µg, 50 µg daily	309.60	154.80	74.12	34.52	37.71
Insulin glargine (Lantus), 50 insulin units daily	372.75	186.38	67.00	46.60	60.90
Rosuvastatin (Crestor), 10 mg daily	216.00	86.40	32.10	19.80	40.50
Sitagliptin (Januvia), 100 mg daily	330.60	168.61	68.10	35.40	39.00
Sofosbuvir (Sovaldi), 400 mg daily	30 000.00	17 700.00	14 943.30	16 088.40	17 093.70
Trastuzumab (Herceptin), 450 mg every 3 wk	5593.47	4754.45		2527.97	3185.87

source: Kesselheim, Avorn et al. 2016

2.3 Pharmaceutical R&D Process

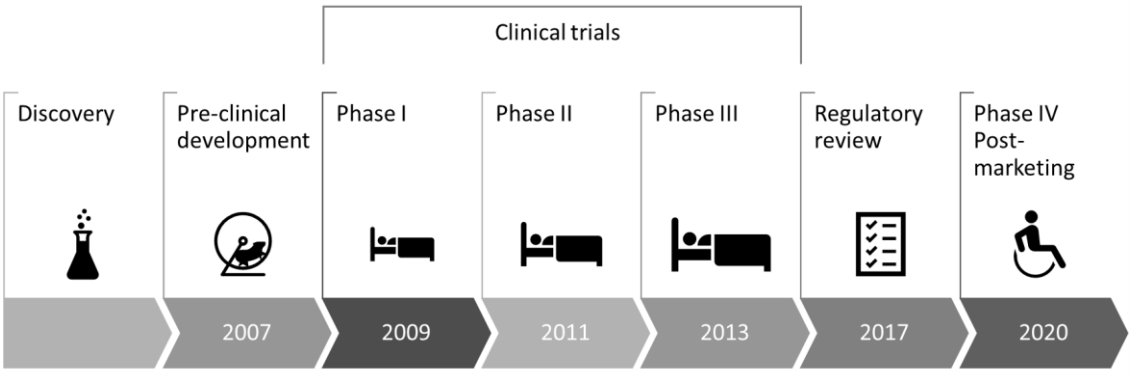
Drugs originate from basic research that eventually leads to detailed understanding of molecular mechanisms underlying a disease process. A lot of this research is performed in academic institutions, which may retain patents and trigger commercialisation by licensing or selling their intellectual property rights to firms (Van Norman, Eisenkot 2017). The drug discovery process begins when potential therapeutic targets have been identified (Leffel, LeClaire et al. 2016). Compounds capable of manipulating disease mechanisms to prevent, improve or cure a condition become drug candidates. A pre-clinical phase investigates their therapeutic potential and safety for human testing. Early product development advances in parallel. Regulatory approval, through the Investigational New Drug (IND) application to the US Food and Drug Administration (FDA) or a Clinical Trial Application to European authorities, must be obtained before clinical trials commence. Sometimes Phase 0 trials are completed on healthy volunteers to confirm pre-clinical predictions. Otherwise there are usually four clinical stages. In the first, the compound is tested on healthy individuals or target patients, in the second and third on the target population. Trial size increases with each stage. This clinical development consumes half of the total R&D budget (Figure 4B). Successfully tested compounds require marketing authorisation before commercial use, in the USA either through a New Drug Application or a Biologics License Application (BLA), in the EU (and Iceland, Norway, Liechtenstein) through a centralised Marketing Authorization from the European Medicines Agency (EMA) or other inter-

state processes. Full market availability can be delayed, e.g. by 14 months for NICE appraisals, until reimbursement conditions are clarified (Cohen, J., Cairns et al. 2006). Once on the market in Phase IV, the drug's therapeutic performance is monitored, for example, to identify long-term side effects. Figure 4A illustrates the described timeline. The US process takes 12 years on average; although some drugs can take 'short-cuts' through accelerated processes (Van Norman 2016).

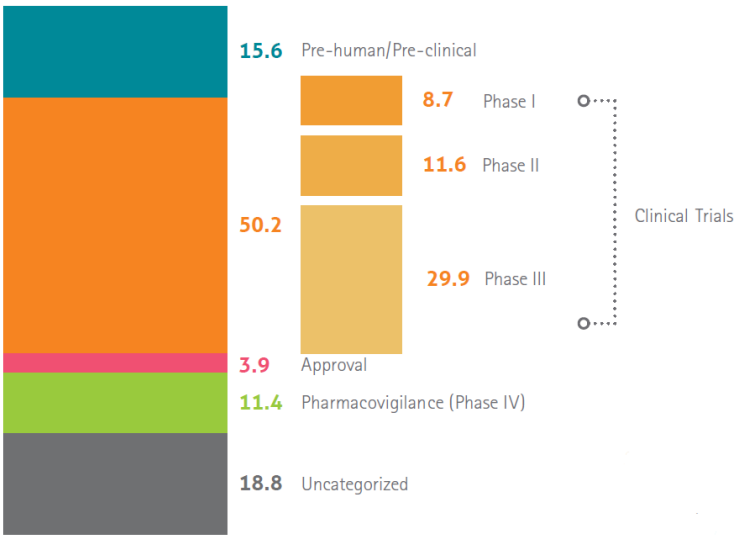
Figure 4. Drug development process

[A] This timeline illustrates the hypothetical journey of a drug that received FDA approval in 2019 showing the start of each stage based on 2 years pre-clinical development, 2.5 years for Phase I, 2 years for Phase 2, 3.5 years for Phase 3 clinical trials and 2 years for regulatory review (Van Norman 2016) with a 1-year allowance for HTA (Cohen, J., Cairns et al. 2006). Early exploratory stages are generally difficult to quantify. **[B]** This reproduced chart depicts the proportion of R&D funds that pharmaceutical companies allocated to each development stage in 2017 (EFPIA 2019). All values are percent (%) of the total investment.

[A] Drug development stages



[B] Allocation of R&D investments



source: EFPIA 2019

2.4 R&D Costs

Pharmaceutical R&D costs are notoriously difficult to quantify. Studies often focus on compounds without previous approval, so-called New Molecular Entities (NME) (FDA 2018). It has been argued that cost estimates should consider all types of approvals because ignoring the cheaper development of line extensions creates an upward bias (Frank 2003). In addition, researchers use different methods, assumptions and data sources, which can lead to considerable variations between estimates. Most results in Table 2 arise from one of two common approaches. These are to either use financial statement analysis and relate it to drug approvals or to source R&D expenses for specific drugs, e.g. via surveys, and apply R&D phase-relevant adjustments. Studies using financial statements can never be sure about R&D-related line items. For example, large companies may develop NME, non-NME and medical devices, but their statements do not distinguish between project expenditures. Such analyses usually apply generic timeframes. Consequently, post-approval costs are factored in alongside pre-approval costs for drugs released early in the observation period. Altogether, financial statement analysis is a crude way of assessing R&D costs but also convenient because data are publicly available. In contrast, expenditure surveys tend to be confidential. This has attracted considerable criticism because it does not allow for direct independent verification, and conflict of interest is suspected when such studies have financial links to pharmaceutical companies (Prasad, Mailankody 2017, Avorn 2015, Collier 2009). However, indirect verification with public data of a study using proprietary data revealed comparable results (Adams, Brantner 2006).

It is unclear whether company size influences R&D costs (Mestre-Ferrandiz, Sussex et al. 2012). Although some disagree (Ringel, Tollman et al. 2013, Dimasi, Grabowski et al. 1995), it has been suggested that R&D costs of large firms are higher than of small ones despite other size advantages (Herper 2013a, Adams, Brantner 2006). One complicating factor is that studies measure size differently, e.g. by drug count, R&D expenditure or revenue. Additionally, analyses only include successful small companies causing survivorship bias, whilst cost-driving failures are integrated in the financials of large firms.

Table 2. Published R&D costs

Cash and capitalised pre-tax, pre-approval R&D costs per NME from various publications are listed from the newest to oldest reviewed study. Values are in published US dollars ($) and inflation-adjusted to 2018 $ in square brackets [ ] (A-Table 13). Methodological approaches for these estimates are briefly summarised. Capitalisation (compounding) accounted for opportunity cost (OC) at the given discount rate (DR). Adjustments for failure risk acknowledge expenditure on drugs that did not reach approval.

Cost per Drug		**Approach**
Cash	**Capitalised**	
$3,350M	-	equity analyst consensus estimates of company R&D expenses 3 years before approval divided by number of approvals, thus cost of failure included; own calculation of mean for published 2009–18 data - (EvaluatePharma® 2019)
$648M [$664M]	$757M [$775M]	median total R&D costs from financial statements of 10 companies with 1 FDA-approved cancer drug and no other drugs marketed but in R&D, thus cost of failure included; 7.3 years R&D on average; 7% DR (2017 $) - (Prasad, Mailankody 2017)
$1,395M [$1,504M]	$2,558M [$2,757M]	confidential R&D cost survey with 10 multi-national companies covering 106 drugs (chemicals, biologics), 4 R&D stages in 10.7 years; failure risk adjustment; 10.5% DR (2013 $) - (DiMasi, Grabowski et al. 2016)
$351M–$5,300M	-	median 10-year R&D spending before most recent approval from financial statements of 100 companies of varying size divided by number of approvals, thus cost of failure included; range shown for companies with 1 drug approved–above 4 approvals; no inflation-adjustment - (Herper 2013b)
$1,011M [$1,129M]	$1,506M [$1,681M]	confidential resource surveys with 16 global companies covering 97 R&D projects of which ≤ 18 per clinical phase, 6 R&D stages in 11.5 years; failure risk adjustment; 11% DR (2011 $) - (Mestre-Ferrandiz, Sussex et al. 2012)
$873M [$1,018M]	$1,778M [$2,074M]	blinded pipeline and productivity data from 13 global companies sourced from industry membership organisation, 8 R&D stages in 13.5 years; failure risk adjustment; 11% DR (2008 $) - (Paul, Mytelka et al. 2010)

Cost per Drug		Approach
Cash	**Capitalised**	
$443M [$646M]	$868M [$1,266M]	adaptation of DiMasi et al. (2003) method to publicly available data on 3,181 compounds, 5 R&D stages in 12.2 years; failure risk adjustment; 11% DR (2000 $) - (Adams, Brantner 2006)
$403M [$588M]	$802M [$1,169M]	confidential R&D cost survey with 10 multi-national companies covering 68 drugs (chemicals, biologics), 5 R&D stages in 11.9 years; failure risk adjustment; 11% DR (2000 $) - (DiMasi, Hansen et al. 2003)
$227M [$331M]	-	US domestic annual average of 7-year R&D spending by major companies divided by number of approvals, thus cost of failure included; 2000 $ - (Young, Surrusco 2001)

Accounting for OC, i.e. the forgone return from alternative investments, causes variations between estimates due to different assumptions about the DR, duration and number of included R&D stages and lag periods. Exploratory stages are either excluded or implied in a pre-clinical phase because such costs are nearly impossible to assign to specific drugs and may be heavily supported by public grants (Galkina Cleary, Beierlein et al. 2018, Chakravarthy, Cotter et al. 2016). Cost allocation is either equal across the entire R&D period or acknowledges differences between stages. Changes in trends can cause variations in estimates covering different periods. For example, during 2004–11 pre-clinical research costs declined by 2.3%, whereas Phase III spending rose by 4.9% (Moses, Matheson et al. 2015).

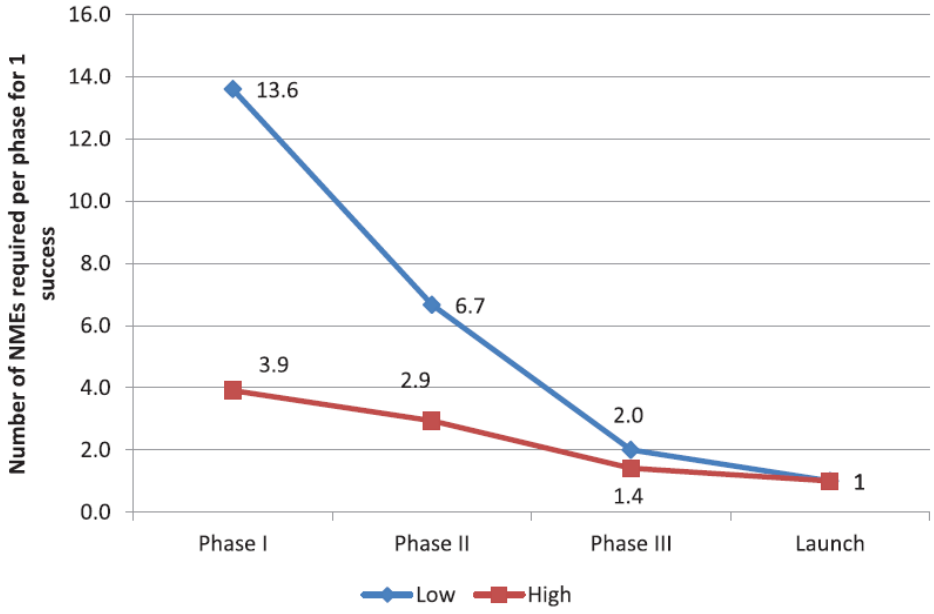
A related key factor is failure risk. Firms investigate several candidates, but not all enter the market. 4–14 Phase I compounds are needed to produce one successful drug (Figure 5). Factoring the costs of discontinued projects into the costs of successful drugs yields the total resource requirements per marketed drug, not only their direct costs (DiMasi, Grabowski et al. 2016).

Thus, beyond cash spending, development duration and success probability are critical in determining the overall R&D costs per drug (Mestre-Ferrandiz, Sussex et al. 2012, Adams, Brantner 2006). DiMasi's group assures that their DR were based on actual financing costs and failure rates on publicly available information (DiMasi, Grabowski et al. 2015). However, the US consumer advocacy group Public Citizen and others have criticised success and discount rates as tools for deliberate overestimation of actual costs (Avorn 2015, Young, Surrusco 2001). Arguing that there is no OC to pharmaceutical companies because they have no choice but to perform R&D misses the point that investors can always select alternatives (Chit, Chit et al.

2015). This pressure determines R&D financing costs, which translate into firms' own OC. In fact, the FDA recognises the significance of the cost of capital to pharmaceutical firms (Gottlieb 2017). This concept is crucial in relating future revenues to past costs to make sensible investment decisions. One-fifth of drugs are abandoned because of strategic portfolio decisions (Waring, Arrowsmith et al. 2015). Strictly, any cost estimates factoring in success rates represent the result, not cause, of corporate decision-making. Another point of contention is the magnitude of the cost reduction through special tax treatment of R&D expenses, which is generally ignored in resource estimates (DiMasi, Grabowski et al. 2016, Young, Surrusco 2001). The crux of the matter is that DiMasi's group and Public Citizen have different priorities. Consumer advocacy and patient lobby groups care less about theoretical economic costs to the company and more whether cash outlays justify drug prices. In conclusion, economic R&D resource estimates should be treated as tools that help decision-making and track the evolution of costs and production efficiency, not to justify drug prices (Frank 2003).

Figure 5. Required investigational compounds for one success

This reproduced chart shows the required number of NME per R&D phase to achieve one marketing approval based on a meta-analysis of success rates (Mestre-Ferrandiz, Sussex et al. 2012). The applied low and high success rates were 49–75% for Phase I, 30–48% for Phase II and 50–71% for Phase III.



source: Mestre-Ferrandiz, Sussex et al. 2012

2.4.1 Cost Trends

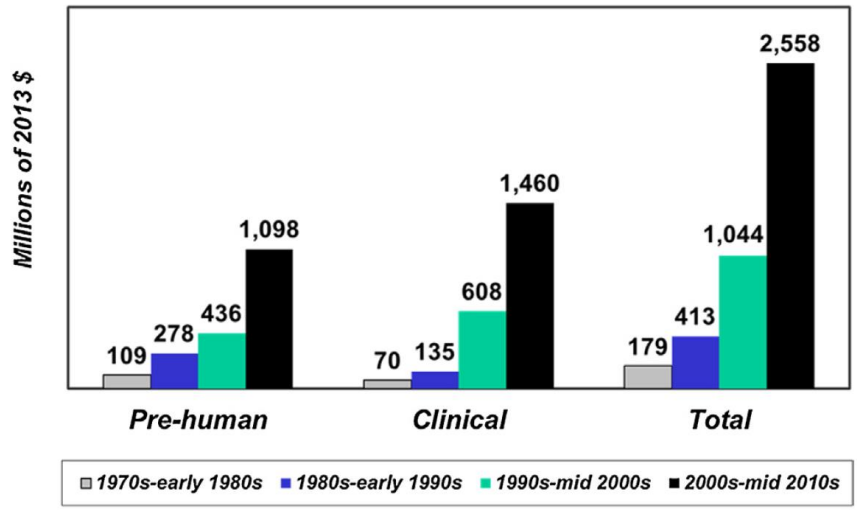
Table 2 indicates that R&D expenditure has increased over time. Figure 6 expands on this and illustrates that marketing approvals declined simultaneously. Consequently, the cost per

marketed drug increased. Scannell et al. (2012) coined this phenomenon Eroom's Law – the reverse of Moore's Law, which describes exponential technology improvement. Nevertheless, it appears that the global downward trend was halted in the mid-2010s (Figure 6B). FDA-only NME approvals suggest a similar trend reversal after 2010 partially thanks to novel approaches in personalised medicine and immunotherapy (Long 2017).

Figure 6. R&D expenditure trends

[A] This reproduced chart depicts the increase in capitalised R&D costs per NME (2013 $) from the 1970s to the mid-2010s (DiMasi, Grabowski et al. 2016). It shows the total and break-down into the two main stages of drug development, pre-human (pre-clinical) and clinical. **[B]** This table shows global total and average annual NME approvals during 1990–2018 in 5-year periods. The table layout was inspired by the source paper. Data were directly copied for 1990–2009 (Mestre-Ferrandiz, Sussex et al. 2012) and expanded with data for 2009–2018 from the updated version of the underlying report (EFPIA 2019). This caused an inevitable overlap in 2009. **[C]** This reproduced chart depicts the number of FDA-approved NME per billion US dollars of inflation-adjusted R&D expenditure from 1950 to 2010 (Scannell, Blanckley et al. 2012). The downward trend illustrates Eroom's Law.

[A] Capitalised R&D cost trend

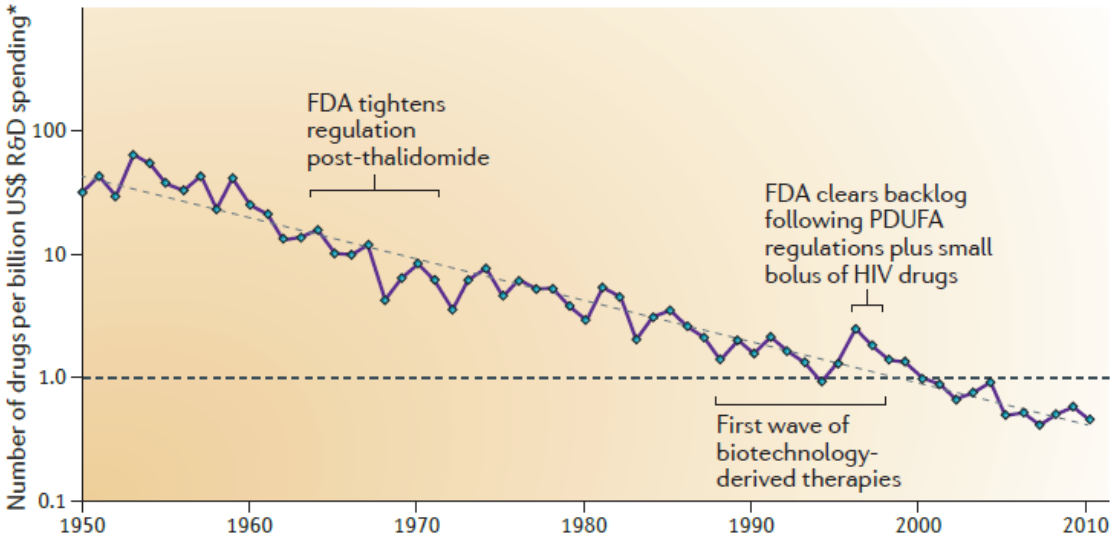


source: DiMasi, Grabowski et al. 2016

[B] NME approval trend

Years / Approvals	1990–1994	1995–1999	2000–2004	2005–2009	2009–2013	2014–2018
Total	215	207	162	146	179	267
Annual Average	43	41	32	29	36	53

[C] Eroom's Law



source: Scannell, Blanckley et al. 2012

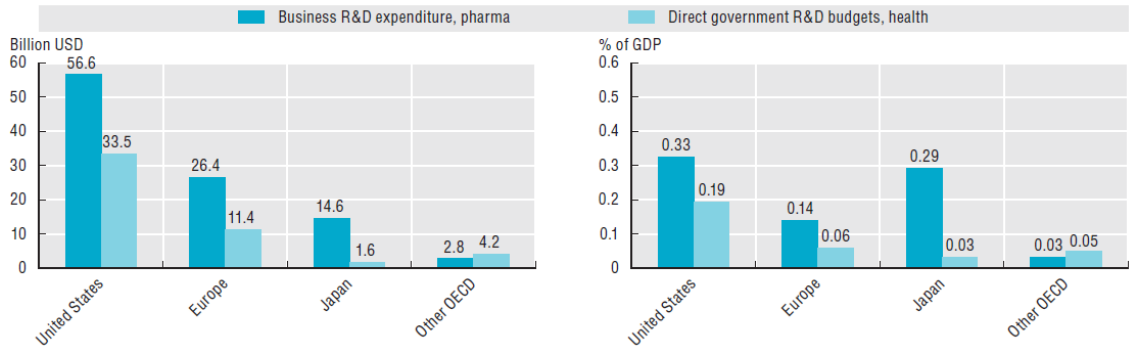
2.5 R&D Funding

The top 10 pharmaceutical companies spent on average 21.6% of their prescription drug sales on R&D in 2018 (EvaluatePharma® 2019). This is forecast to drop to 18% by 2024. Across the biotechnology sector 42% of 2018 revenues were channelled back into R&D, roughly a 10% increase from 2017 (Morrison, Lähteenmäki 2019). Besides retained earnings, R&D investments come from various sources. Biomedical R&D in OECD countries receives considerable funds from both business and government budgets but also some support from charities and other private organisations as US data demonstrate (Figure 7). Therapeutic priorities of the two largest US funders, the National Institutes of Health (NIH) and pharmaceutical firms, can differ (Moses, Matheson et al. 2015, Dorsey, Thompson et al. 2009). Public funding is subject to political pressure but also considers threats to the wider public, which is why, for example, infectious diseases are generally an NIH focus. US public resources have decisively contributed to drug discovery. More public than corporate funding went towards basic research that resulted in drug development in the USA from the late 1980s to early 2000s; industry funding dominated in subsequent R&D stages (Chakravarthy, Cotter et al. 2016). The NIH contributed 20% of its budget to research that led to every NME approved by the FDA during 2010–16 based on funding acknowledgements in academic papers (Galkina Cleary, Beierlein et al. 2018). However, cumulative public and private US biomedical R&D funding stagnated from the mid-2000s to early 2010s (Moses, Matheson et al. 2015, Dorsey, de Roulet et al. 2010). The 2016 US '21st Century Cures Act' is to re-invigorate biomedical innovation by bolstering NIH funding and, controversially, easing FDA requirements (Kesselheim, Avorn 2017).

Figure 7. Pharmaceutical business and government R&D funding

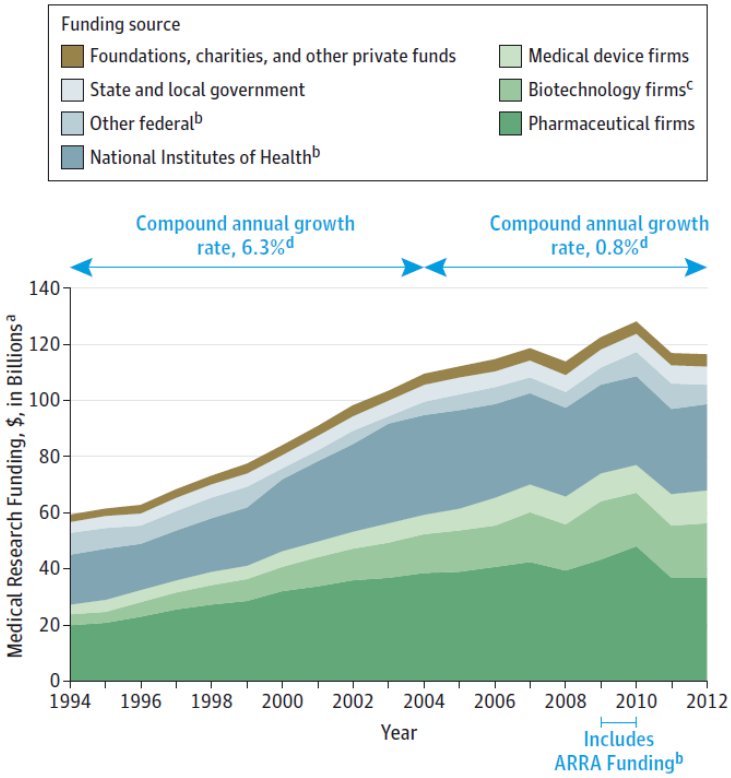
[A] The reproduced left-hand chart shows OECD pharmaceutical businesses R&D expenditure alongside health-related R&D government budgets in US dollars; the right-hand chart shows their value as percentage of GDP (OECD 2017a). Underlying country data are from the most recent available year during 2011–14. Europe includes 21 shared member countries of the EU and OECD, Iceland, Norway and Switzerland. **[B]** This reproduced chart shows the composition of medical research funding (2012 $) in the USA from 1994 to 2012 (Moses, Matheson et al. 2015). The annual compound growth rate was calculated for two periods, 1994–2004 and 2004–12.

[A] Funding sources of OECD members



source: OECD 2017a

[B] Funding sources in the USA



ARRA … American Recovery and Reinvestment Act

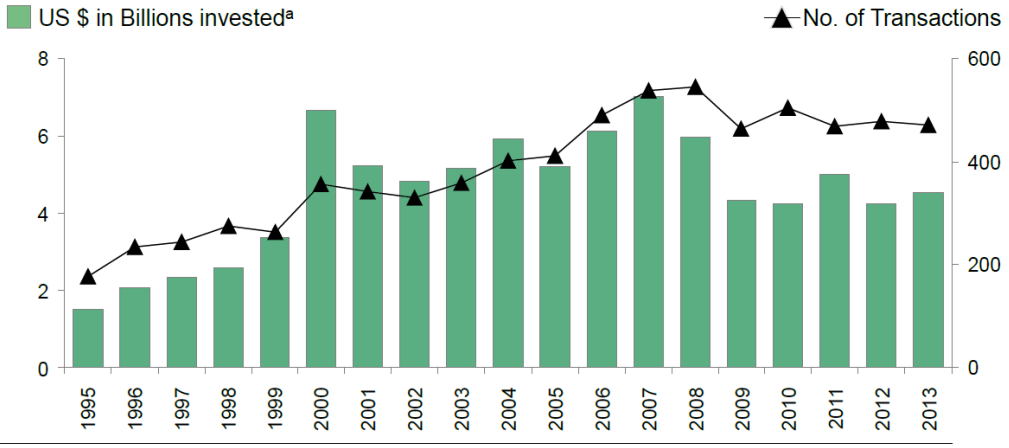
source: Moses, Matheson et al. 2015

Equity financing can be critical in propping up company R&D resources. Survey data suggest that 60% of healthcare-focused venture capital (VC) flows into pharmaceutical and biotechnological developments (Fernald, Janssen et al. 2018). VC investment was susceptible to the 2008 financial crisis (Bains, Wooder et al. 2014) and remained stagnant until 2013 but recovered in subsequent years (Figure 8A/D). Presumably by using a broader basket of companies others found that life science VC investments dropped from 36% in 2009 to 20% in 2014 of VC investments across all industries despite an overall increase in risk capital across sectors (Fleming 2015). Additionally, a shift from early- to late-stage R&D investments was observed (Fleming 2015, Bains, Wooder et al. 2014). At least in the biotechnology sector this seems to have been reversed in recent years (Morrison 2019). Amongst VC strategies 'hybrid funds' have emerged that mix internal corporate and external private VC resources (Wilson, Minshall 2018). The number of hybrids grew from 3% of standard corporate VC funds in 2006 to 32% in 2017. Data also suggest that corporate and hybrid VC rose in 2015–17 above prior levels (Figure 8B). Further private equity transactions with angel investors are difficult to ascertain due to their confidential and decentralised nature. OECD data from 2015/16 suggest that 20% of US and 14% of European angel deals were with healthcare/biotechnology firms (Figure 8C). Public biotechnology equity in form of initial (IPO) and follow-on public offerings saw tremendous interest in 2018 (Figure 8D). IPO tended to follow extensive VC investments (Morrison 2019).

Figure 8. Equity investments in life science companies

[A] This reproduced figure characterises VC investments (2012 $) in biotechnology companies during 1995–2013 (Moses, Matheson et al. 2015). **[B]** This reproduced chart shows total standard corporate and hybrid VC investments in pharmaceutical and biotechnology companies during 2006–17 (Wilson, Minshall 2018). **[C]** The charts show 2015/16 business angel investments in different sectors as a percentage of total angel deals in Europe and the USA (OECD 2017b). Charts were modified using the source data template. **[D]** This reproduced chart shows the global funding mix of biotechnology companies during 2013–18 (Morrison, Lähteenmäki 2019). Note that partnership valuations include unrealised milestone-driven payments.

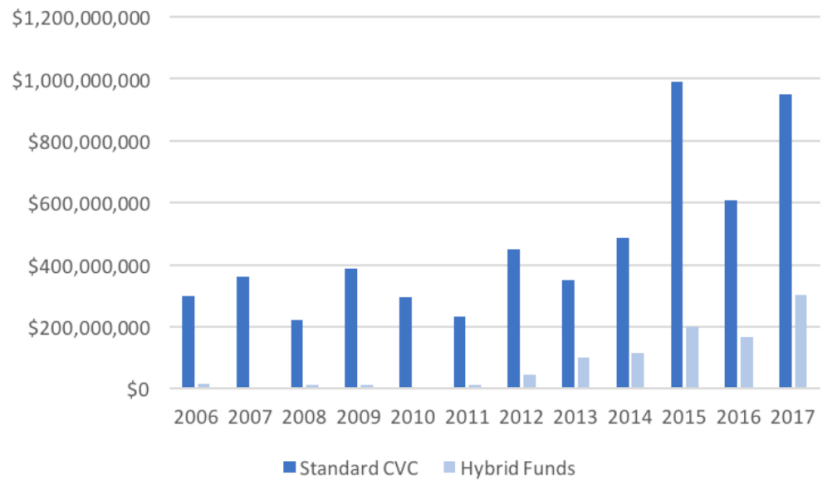
[A] Biotechnology VC investments



	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Biotechnology VC investment, US $ in Billions	1.5	2.1	2.3	2.6	3.4	6.6	5.2	4.8	5.2	5.9	5.2	6.1	7.0	6.0	4.3	4.3	5.0	4.3	4.5
Total VC investment, US $ in Billions	14.5	19.8	25.5	35.5	87.8	163.1	61.3	32.1	27.5	31.4	30.7	34.6	38.4	34.6	22.4	25.1	31.0	27.7	29.4
Biotechnology VC as a percentage of total VC	10%	11%	9%	7%	4%	4%	9%	15%	19%	19%	17%	18%	18%	17%	19%	17%	16%	15%	15%
No. of biotechnology transactions	176	235	244	275	264	357	341	330	358	402	412	489	538	544	463	504	469	478	470
Average investment per biotechnology transaction, US $ in Millions	9	9	10	9	13	19	15	15	14	15	13	13	13	11	9	8	11	9	10

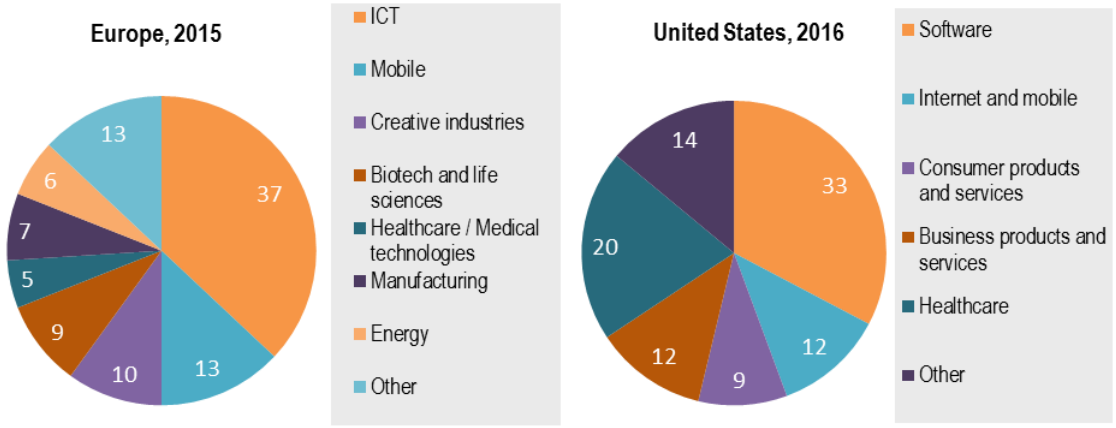
source: Moses, Matheson et al. 2015

[B] Pharmaceutical corporate and hybrid VC investments



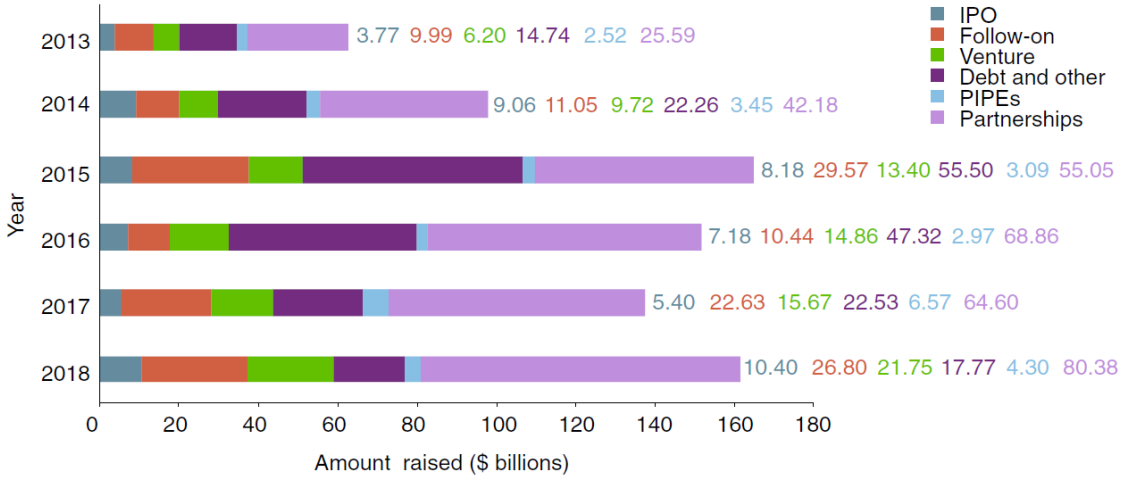
CVC … corporate venture capital
source: Wilson, Minshall 2018

[C] Angel investments across sectors



ICT … information and communication technology
modified from source: OECD 2017b

[D] Biotechnology funding mix

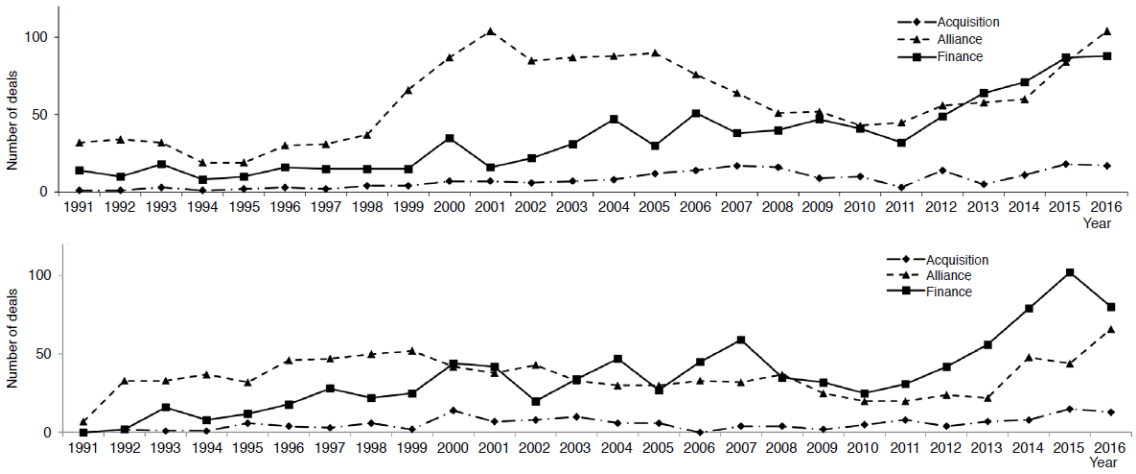


PIPE … private investment in public equity
source: Morrison, Lähteenmäki 2019

Besides private and public equity investments, alliances between small biotechnology and large pharmaceutical companies are an attractive option, with a focus on early-stage research during the 1990s (Lerner, Shane et al. 2003, Nicholson, Danzon et al. 2002). Figure 8D illustrates the continued prominence of partnerships in the biotechnology investment mix. The appeal of such deals changes over time and with technological focus (Figure 9). Interestingly, research alliances can act as indicators of technological quality to VC investors (Hoenig, Henkel 2015).

Figure 9. Evolution of funding sources for different technologies

These reproduced charts show the global number of deals during 1991–2016 realised by companies pursuing either antibody (top) or cell and gene therapies (bottom) (Makino, Lim et al. 2018). Acquisitions include full and partial acquisitions and buyouts. Alliances are, for example, licensing arrangements or joint ventures. Financing deals exclude public sources, e.g. grants.

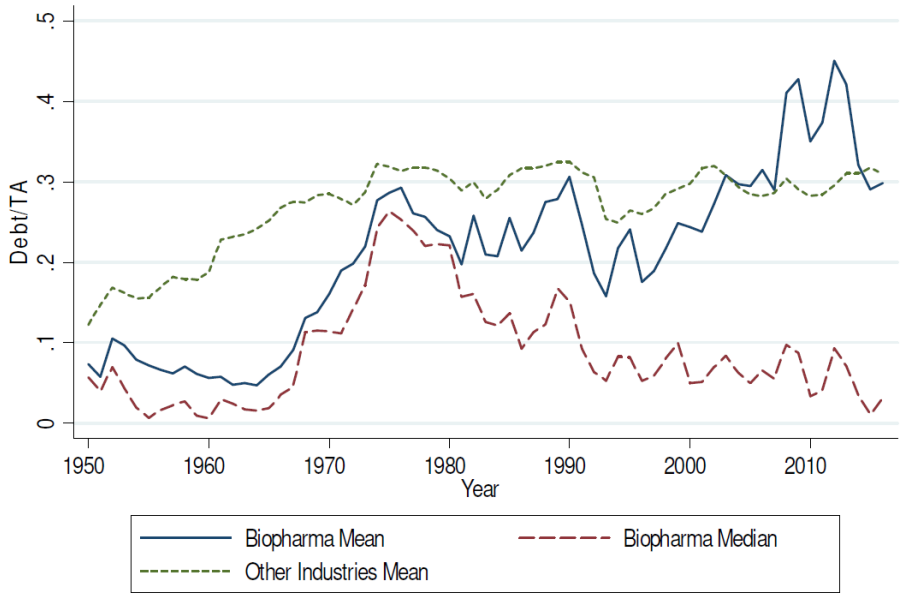


source: Makino, Lim et al. 2018

Figure 8D shows that overall debt levels of biotechnology companies vary over time. Those figures hide the heterogeneity of the use of debt financing between companies. As shown in Figure 10 median debt has decreased since the mid-1970s, whilst mean debt has risen. This indicates that some firms have taken on large debt and pulled the mean upwards, whereas most companies have reduced their debt.

Figure 10. Biopharmaceutical debt levels

This reproduced chart shows company debt as the sum of long- and short-term debt relative to total assets (TA) during 1950–2016 (Thakor, Lo 2018). The biopharma industry is comprised of biotechnology and pharmaceutical companies. The chart also shows debt in all other industries.



source: Thakor, Lo 2018

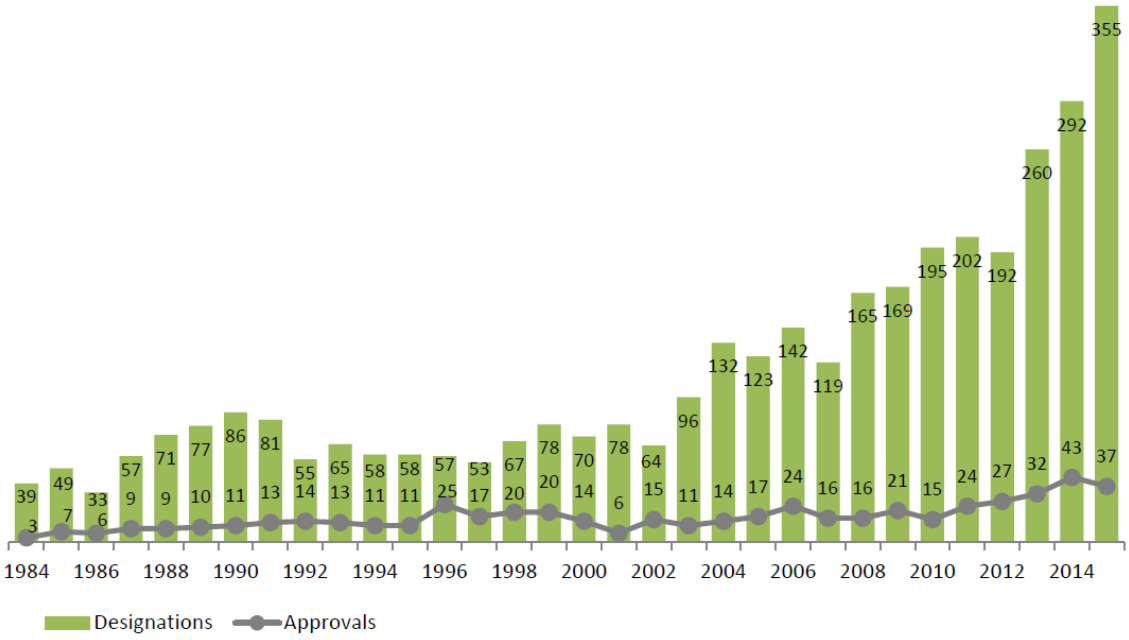
2.6 Orphan Drugs

Orphan drugs (OD) pose a particular economic challenge to pharmaceutical developers and healthcare payers alike. These drugs specifically target RD (EMA 2019, FDA 2017, FDA 2013). There are 5,000–8,000 RD affecting 6–8% of the European population. In the USA, RD are defined as usually debilitating or life-threatening conditions affecting less than 200,000 people, in the EU less than 5 in 10,000 people. Orphan designation may also be granted for drugs targeting diseases with larger patient populations when it is unlikely that sales will recover the R&D costs. Orphan designation requests to the FDA more than doubled from 2012 to 2017. Figure 11 depicts the increases in the US R&D trend since the 1983 Orphan Drug Act and in the worldwide sales forecast until 2024. As part of its 2017 modernisation plan, the FDA enhanced its focus on OD application processing to eliminate their backlog and commit to 90-day review periods (same as EU). All this signifies the rising importance of OD development nowadays.

Figure 11. Orphan drug development trends

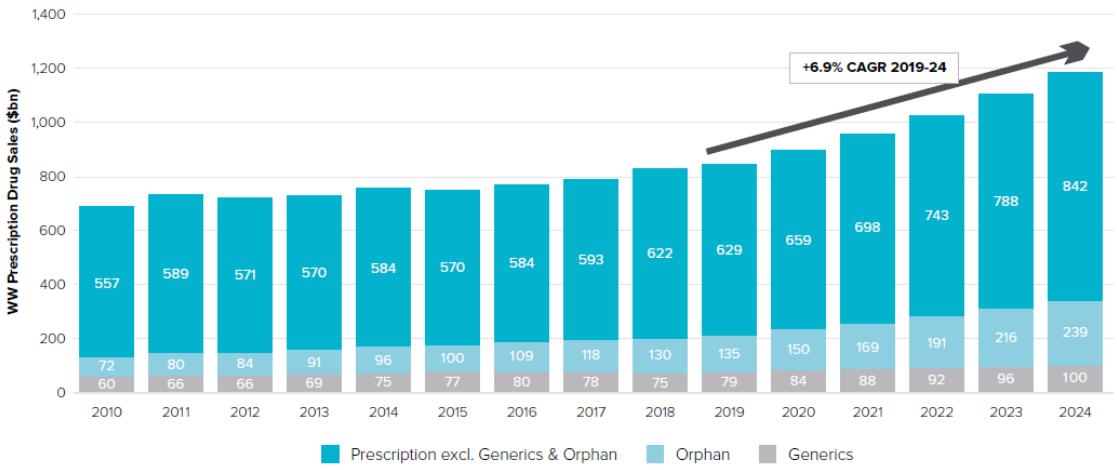
[A] This reproduced chart shows the number of granted OD designations and marketing approvals by the FDA during 1984–2015 (Long 2017). **[B]** This reproduced chart shows worldwide (WW) total prescription drug sales from 2010 until the 2024 forecast (EvaluatePharma® 2019). It distinguishes between OD, generics and all other prescription drugs.

[A] FDA orphan designations and approvals



source: Long 2017

[B] Worldwide prescription drug sales



CAGR … Compound Annual Growth Rate
source: EvaluatePharma® 2019

OD development is incentivised through a range of benefits, such as a 7- and 10-year exclusivity period following marketing approval in the USA and EU, respectively, fee reductions, potential tax credits, grants and accelerated patient access (EMA 2019, FDA 2017, FDA 2013). The

exclusivity period does not only see off competition but also buys time to establish networks in the fragmented global RD community (Phillips 2013). At 32.9% the approval probability of OD in Phase I is above the all-drug average of 10.4% (Hay, Thomas et al. 2014), and the development time from Phase II to launch can be 1.5 years shorter on average compared to non-OD (Meekings, Williams et al. 2012). Bearing in mind that clinical trials are usually also smaller, this suggests that OD R&D costs are lower than for other drugs. However, logistics and other trial aspects are often problematic and can add costs. OD might be less susceptible to competition from generics because of their biologic or genetic base (Kumar Kakkar, Dahiya 2014). Hence, marketing to the small patient populations tends to be cheaper. However, with more companies entering the OD market, this may change and reduce the current potential for profitability. Whilst OD seem an attractive niche to exploit, the commercial risk is high in healthcare systems that are not ready for huge price tags as the failure of the $1M-drug Glybera has shown (Mullin 2017).

Studies with a single-minded focus on profitability disregard the realities of current and future affordability. The budgetary impact of OD varies greatly across Europe (Table 3). 29–93% of OD were eligible for some form of European public reimbursement in 2015 (Szegedi, Zelei et al. 2018). There was a 16.7-fold difference in absolute OD spending per capita between 7 European countries in 2013/14 with a tendency towards higher spending in wealthier countries. OD coverage also varies greatly between US healthcare plans and generally requires out-of-pocket contributions from patients (Robinson, Brantley et al. 2014). Existing US reimbursement mechanisms are deemed unsustainable in a future with highly-priced treatments (Schmickel, Perry et al. 2019). A private insurance may never see the long-term savings from covering an expensive treatment when policyholders switch provider. Also, payments are mostly not performance-based, meaning that there is no compensation for treatment failures.

Table 3. Budgetary impact of orphan drugs in Europe

A systematic review of 13 academic publications from 2010–16 revealed the budgetary impact of OD on European healthcare systems (Schlander, Dintsios et al. 2018). The table was adapted from its source.

	Mean	**Range**
Annual budget impact (€)	678M	2.6M–4,620M
Pharmaceutical expenditure (%)	2.7	0.7–7.8
Annual per-capita spending (€)	8.41	1.32–20.23

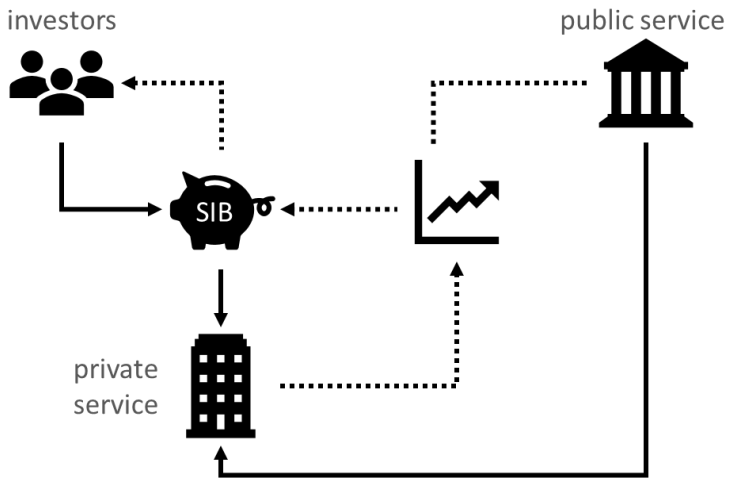
2.7 Financial Innovation in Healthcare

2.7.1 Social Impact Bonds

Social Impact Bonds (SIB) are financial instruments based on payment by results (PbR) contracts designed to delegate solving social challenges from the public to the private sector (Figure 12). Since the world's first UK pilot in 2010 attracted £5M investment, funds for further UK SIB development were released in 2012, and SIB were launched in other countries (Cabinet Office 2017, G8 Social Impact Investment Taskforce 2014). PbR schemes date back further. In 2015 the 52 PbR schemes that had been launched during 2009–15 across 6 UK government departments were worth over £15B (Morse 2015). To date it is difficult to evaluate whether SIB are any more effective than conventional PbR schemes in producing social benefits (Edmiston, Nicholls 2018). Evidence is either hard to collect or success is difficult to define due to the complexity of social issues as well as variations in SIB configurations and hurdles within existing frameworks (Arena, Bengo et al. 2016).

Figure 12. General principle of SIB

The public service responsible for tackling a certain social challenge outsources the solution to a private service. The latter attracts funds from private investors through a SIB. The value of returns received by the public service as a result of the private service's activities determines the rate of return for investors. Steps along the unbroken lines are prerequisites for realising the steps along the dotted lines.

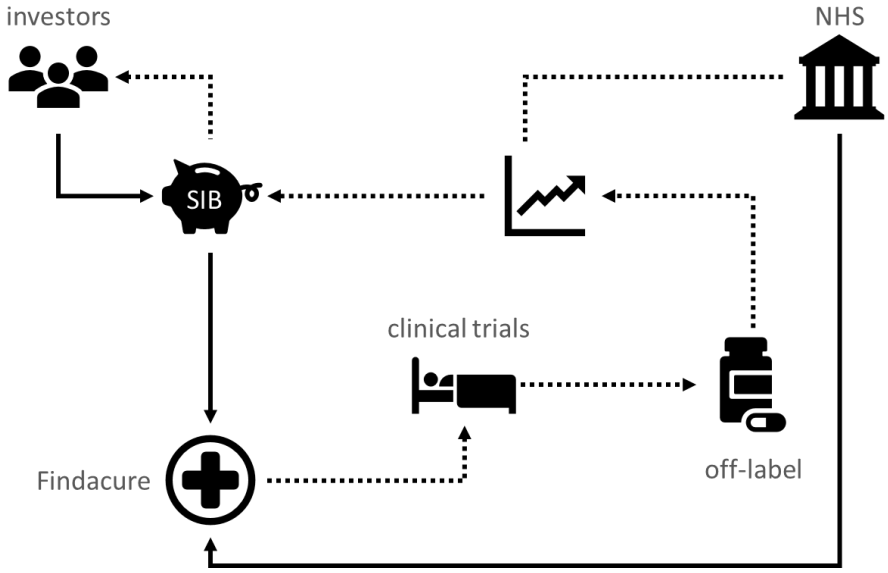


In 2015 the UK charity Findacure started developing the case for a SIB that finances research on drug repurposing for RD (Findacure 2017). Figure 13 outlines the basic framework. Drug repurposing finds alternative uses for marketed drugs or those that failed clinical R&D and holds great promise for RD (Pushpakom, Iorio et al. 2018). Repurposed drugs do not necessarily require new regulatory approval because they can be prescribed 'off-label' at the discretion of

physicians in the EU and USA (Weda, Hoebert et al. 2017, Eaton, Sima et al. 2016). This means that drugs can be administered for purposes outside their marketing authorisation. During 2012–17 nearly 170 drugs underwent repurposing R&D of which 10% were FDA-approved and 72% in clinical trials by 2018/19 (Polamreddy, Gattu 2019). 70% of Phase I/II funding came from academia, the remainder from industry. Non-profit and public organisations contributed substantially towards research grants worth $230M.

Figure 13. Findacure's Rare Disease Drug Repurposing SIB

Once the NHS commissions Findacure with the research into drug repurposing for RD, Findacure raises funds for clinical trials from SIB investors. Successful drugs are made available for RD treatment through off-label prescriptions. Improved patient conditions reduce NHS healthcare spending. A portion of the resulting NHS savings is channelled into the SIB to pay investors and fund further research.



RD cost-of-illness models suggest that non-responders to first-line intervention and symptomatic treatment of disease consequences are main drivers for annual NHS costs (Eljamel, Ghosh et al. 2019, Eljamel, Griffiths et al. 2018). Clearly, there is a need to improve first-line strategies and lower follow-on costs. Even though OD are on the rise, so are their prices (Yates 2019, Meekings, Williams et al. 2012). Thus, first-line failures will likely become costlier over time. Findacure's economic rationale is that cheap off-label prescriptions will reduce NHS expenditure by improving RD patients' conditions in the absence of other effective cures (Thompson 2017). A fraction of these savings will pay SIB investors. Additionally, the social system will be relieved if patients and their carers become able to pursue jobs, pay tax and claim less welfare support. Non-healthcare costs of the RD Friedreich's ataxia amount to £12M annually according to Findacure's economic model. Table 4 shows projected NHS savings from

Findacure's proof-of-concept study. The NHS rejected the SIB mid-2017 on strategic grounds (Findacure 2017). Nevertheless, two of the three repurposing projects in Findacure's proposal have been moved forward independently since.

Table 4. Findacure's NHS cost and savings estimates

Findacure selected three RD for a SIB proof-of-concept study (Findacure 2016). The cost-of-illness model estimated total annual NHS costs based on the displayed patient numbers, which do not necessarily capture the entire UK patient population. The budget impact model generated estimates of cumulative NHS savings over a 5-year period, which is the proposed SIB duration.

Rare Disease	Annual NHS Costs	Patient Count	5-year NHS Savings
Congenital hyperinsulinism	£4.6M	3,286	£0.5M
Wolfram syndrome	£1.0M	64	£0.7M
Friedreich's ataxia	£7.6M	2,261	£1.1M

2.7.2 Eye Bonds

The currently debated US bill 'Faster Treatments and Cures for Eye Diseases Act' is to start a 5-year $1B 'Eye Bond' pilot programme (Bishop 2019). It would provide loans to vetted scientists to translate basic research into cures for blindness. Loans would be bundled and 50% government-backed to diversify the risk and increase attractiveness to long-term investors, like insurance companies, that usually shun early-stage research (Petrou 2019). If passed, this bill will signal the beginning of 'Bio Bonds', a new way of socially responsible impact investing (Taft 2019).

2.7.3 Organ Futures

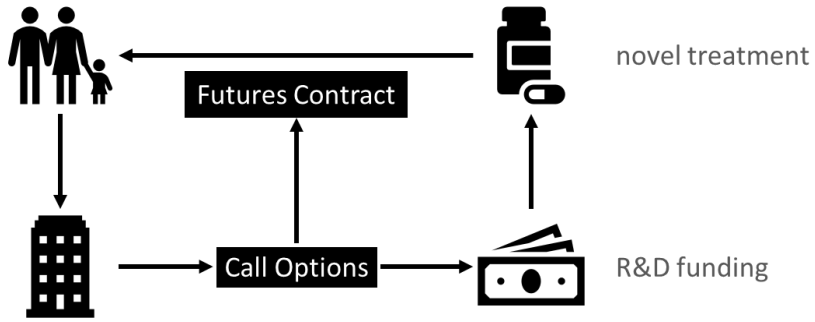
Between 1986 and 1994, four seminal academic proposals on 'organ futures' (OF) were published (Crespi 1994, Cohen, L. R. 1989, Hansmann 1989, Schwindt, Vining 1986). Although the details differ, all four advocate incentivising cadaveric organ donations with payments via futures contracts to increase the supply of much needed transplant organs. However, OF never came into existence mainly due to ethical and social concerns over the profitable sale of human body parts (Fukai 2019, Gillespie 2019). Nevertheless, they represent imaginative interdisciplinary attempts to leverage alternative financial vehicles to aid healthcare.

2.7.4 Healthcare Derivatives

A radically new and unexplored idea is to fund biomedical R&D with HCD[2], namely a combination of call options and futures contracts (Ferrante-Schepis 2018). This could be split into two instruments or combined into a single HCD. The former is outlined in Figure 14. The options are essentially a form of pre-sale or insurance that promises access to a drug that is still in development at the time of options issue. The investor's return for sharing the R&D risk with the company is the saving on therapy costs locked in by contractually agreed futures prices well below regular treatment costs. Should the HCD holder not require the therapy, they can sell their HCD. Each scheme is limited to a specific disease. Since HCD purchases are non-refundable if the treatment fails testing/approval, HCD are a cheap source of finance.

Figure 14. Healthcare derivatives – basic idea

Individuals obtain call options from a pharmaceutical company either directly or through their health insurance provider. These options bestow the right to purchase a futures contract for a specific therapy that is still in development. The revenue from the options sale is used by the pharmaceutical company to fund its R&D. If the treatment makes it onto the market, patients can obtain it through the futures contract at a previously agreed price.



2.8 SUMMARY

From this literature review it is apparent that the management of healthcare spending is becoming increasingly challenging as drug prices rise. This is particularly true for RD therapy because financial innovation has not kept pace with the progress in biomedical R&D. Even though various R&D funding sources are available to companies, these often come at a high economic cost. After lengthy and risky development processes manufacturers seek timely returns from successful drugs, whilst healthcare payers must balance commitments to all patients and across different services.

[2] The financial terms 'options' and 'futures' should be regarded more as loan words than definitions. To experts it will become apparent that HCD only relate to basic elements of the original derivatives. Hence, background knowledge on these is not required here.

CHAPTER 3. METHODOLOGY

3.1 LITERATURE REVIEW

A literature review was carried out to establish a knowledge base and prepare the context for research findings. The review targeted English-language publications with emphasis on the USA and Europe. It focused on academic publications but also included governmental, professional and media sources. Employed search engines for most sources were PubMed, Google Scholar and Primo. Reference lists from academic publications also provided suggestions for further reading. Non-academic publications were discovered in industry-relevant email newsletters or by direct online search. Findacure's (2016) unpublished report was provided by Richard Thompson with permission to display data. Otherwise, only freely accessible publications were used. Consequently, insights are limited to publicly available sources and University of Aberdeen subscriptions and exclude industry reports or articles behind paywalls.

3.2 DATA COLLECTION

General demographic and inflation statistics were sourced from databases provided by Eurostat, OECD and the US National Center for Health Statistics (NCHS). Further primary and secondary data were sourced from academic publications. Any other primary data were not collected, for example through surveys or data requests to relevant organisations, due to the short time available for research.

Governmental and peer-reviewed academic sources bear sufficient credibility and accuracy to be considered trustworthy. Any conflicts inherent in the used data are discussed where appropriate.

3.3 DATA PRECISION

All calculations were executed in Microsoft Excel using exact figures. Results are presented as rounded numbers, e.g. whole persons. Thus, at times small imprecisions may appear in the presented data due to rounding error.

3.4 FRAMEWORK DEVELOPMENT

To develop the HCD framework, a similar approach to authors of academic papers on OF was taken (Crespi 1994, Cohen, L. R. 1989, Hansmann 1989, Schwindt, Vining 1986). Essentially, key criteria and processes were discussed in a general speculative manner. Consideration of specific

national healthcare and regulatory systems was deliberately avoided to provide an overarching introduction of this novel idea.

Whenever the text refers to such general terms as ‘treatment’, ‘therapy’ or ‘cure’ these may represent pharmaceuticals, medical devices, surgery or any other medical/pharmaceutical intervention.

3.5 Case Study

Since HCD do not exist, a hypothetical quantitative case study was deemed to be an appropriate illustration of the newly developed framework (Feagin, Orum et al. 1991).

The case study uses Zolgensma, a gene therapy indicated for children under 2 years of age with the life-threatening rare genetic disease spinal muscular atrophy (SMA) Type 1. Zolgensma, also onasemnogene abeparvovec-xioi or AVXS-101, was approved by the FDA on 24 May 2019 (FDA 2019a, FDA 2019b). At $2.125M sales price it is currently the world’s most expensive drug (Novartis 2019a). Unsurprisingly, this has caused considerable public discussion and concern over affordability by health insurers (Luxner 2019, Malik 2019, Yates 2019).

Not only is Zolgensma topical, its high price and small target population are interesting key features for this case study. Zolgensma exemplifies the economic challenge that RD therapy poses to the healthcare industry. Exploring HCD as a potential solution gives this research real-life relevance.

The case study examined in retrospect how HCD could have been used for Zolgensma financing. Both a retail and an institutional investor strategy were pursued. The former was kept simple, as it served mainly to refine the HCD approach and provide an initial gauge of its financing potential. The latter incorporated more detailed considerations.

Several important simplifications were made to create workable scenarios:

- Since EMA approval (Luxner 2019) and launch of worldwide sales were assumed in 2019, study design and conclusions were equally based on data from the USA and EU. Both territories were treated as homogenous markets ignoring any inter-/national complexities.
- Since post-approval delays, e.g. HTA, were disregarded, marketing approval gave immediate full patient access. The effect of the uncertainty over whether/when the approved treatment becomes available in the investor’s jurisdiction was thus neglected.
- Where reference is made to calendar years, each year (including 2019) was treated as a full sales year.

- Zolgensma was considered the only first-line treatment for the target population. Consequently, payers were assumed to cater for 100% of eligible patients.
- Timeframes for investment choices predominantly depended on past events defined by US OD approval procedures. In reality, event dates would not have been known in advance. HCD-transacting entities would probably employ models or experience to forecast key time points. This increased uncertainty would have effects on investor numbers not considered here. Additionally, approval and further appraisal processes differ between jurisdictions and disease groups. Consequently, different investment strategies may be required.

Altogether, considerations and conclusions in this case study were based on idealised scenarios and cannot be translated directly into reality. HCD sales volumes were almost certainly overestimated. Simplifications were introduced because delving into the complexity of the pharmaceutical industry and international differences went beyond the scope of this project, but also because it is unpredictable how relevant processes would change with HCD in place. For example, most HTA might happen before approval when payers assess their investments.

3.6 R&D Cost Estimation

R&D cost estimation is complex and time-consuming (section 2.4). Since the case study merely required benchmark R&D costs, these were taken from the latest work of an often-cited research group (DiMasi, Grabowski et al. 2016). A single academic reference was chosen to avoid additional inaccuracy by including other sources. Even though the estimate of $2,558M (2013 $) capitalised pre-approval R&D costs has been criticised as too high, it is, in fact, not the highest available figure (Table 2), and a previous estimate from DiMasi's group had been verified independently (Adams, Brantner 2006). Consensus R&D costs for a genetic RD treatment, like Zolgensma, are unavailable. Non-clinical/technological costs may be higher than for biologics/chemicals, clinical costs lower than for non-OD (Meekings, Williams et al. 2012). To avoid any unnecessary speculation, it is deemed acceptable to use an approximation that potentially errs on the upside. Nevertheless, the case study inherits its limitations.

The estimate was inflation-adjusted to the nearest complete year using US annual consumer price index-based growth rates (OECD 2019) as follows:

$$\mathrm{Cost}_{2018} = \mathrm{Cost}_{2013} * \prod_{t=2014}^{2018} (1 + r_t)$$

where: t … year, r … inflation rate

The benchmark costs were also used to create a series of compounded R&D costs at increasing rates to match the discounted case study revenues. To this end, the continuous compounding applied by the original researchers (DiMasi, Hansen et al. 2003) was crudely retraced as follows:

$$\text{Compounded Cost} = \text{Cash} * e^{rt}$$

where: t … years, r … DR

3.7 Market Size Estimation

The Zolgensma target market is comprised of 0–2-year-old SMA Type 1 patients. Since SMA is an RD, population statistics are difficult to find and often involve considerable speculation. For this case study SMA Type 1 patient numbers were derived by applying academically published estimates of annual new cases (incidence) and total existing cases (prevalence) to national birth and population statistics. US statistics were sourced from OECD and NCHS (OECD 2018, Hamilton, Martin et al. 2018, Hamilton, Martin et al. 2017). EU (28 countries) statistics were sourced from Eurostat (Eurostat 2019a, Eurostat 2019b). The resulting market size estimates were refined further by extrapolating the sub-population of 0–2-year-old SMA Type 1 patients and by applying probabilities for survival and physical deterioration based on academically published data.

3.8 Derivatives Pricing and Investing

One set of hypothetical HCD prices was created arbitrarily for each investor strategy in the case study. The objective was neither to mimic geographic price disparities nor to optimise pricing or investment strategies, but to demonstrate how the HCD framework can be applied in theory.

Options pricing was driven by time and uncertainty. As time progressed and uncertainty declined with pre-approval milestone achievements, options prices increased. From one year after FDA approval options prices were held constant temporarily to reflect the guaranteed availability of Zolgensma and allow for more patient data to accumulate. Thereafter, one more price rise was to reflect the increased certainty from successful clinical application. Futures prices were set relative to actual and recommended Zolgensma prices with the aim to sell below the current market price.

Strategic purchasing decisions were influenced by medical eligibility, R&D uncertainty and HCD prices. The retail and the more refined institutional HCD purchasing strategies allowed for different investment horizons.

The retail scenario was terminated after 4 years of drug sales because it mainly served as a preparatory stage for the more relevant institutional scenario. The artificial end for the institutional strategy was set after 10 years of drug sales, as any longer-term speculations would not be informative because, for example, the emergence of competitors, regulatory or price changes cannot be predicted without deeper market research and expertise. Additionally, by the 10-year mark both US and EU exclusivity periods will have expired (EMA 2019, FDA 2013). Presumably Novartis expects break-even by then.

The HCD schemes did not explore the impact of set-backs. Zolgensma's path to regulatory approval was straightforward. It was assumed that therapeutic application will be successful overall. This was to keep the theoretical demonstration simple and to avoid speculation that would require industry-specific expertise.

3.9 Break-even Analysis

Break-even was achieved when HCD revenues matched R&D costs assuming that the company received 100% of sales revenues. Operating and other expenses incurred by delivering the treatment and running the HCD scheme were ignored to focus solely on recouping R&D costs. This simplification served to illustrate the original intent of the HCD scheme, not to inform realistic investment decisions.

Revenues were assessed as undiscounted and discounted cash flows (CF). Discounting is used in the net present value (NPV) approach (Brealey, Myers et al. 2011). It converts all CF to the same time value by discounting future revenues and compounding pre-sales using a DR.

At break-even NPV = 0 using this formula:

$$NPV = -\ R\&D\ Costs + \sum_{t=i}^{T} \frac{CF_t}{(1+r)^t}$$

where: t … financial year, i … year defined by investment schedule, r …annual DR

CHAPTER 4. RESULTS

4.1 FRAMEWORK FOR HEALTHCARE DERIVATIVES

The HCD proposed in this study are based on the idea presented in section 2.7.4. They comprise healthcare call options (HCCO) that bestow the right to buy healthcare futures (HCF) for a specific medical treatment at an agreed price. The purpose of HCD is to reduce treatment prices by lowering the financing costs during the R&D period and to guarantee therapy prices below the market rate. This section suggests key rules and considerations for such a scheme.

4.1.1 Transacting Parties

HCD issuers are companies developing a therapy. These companies may issue HCD directly or through a specialised intermediary like an investment bank or insurance provider. As long as development or provision of the treatment are not discontinued, the issuer must honour all sold HCCO rights and maintain the scheme as originally intended for existing investors but may close the scheme to new investors. This responsibility is transferred to the new owner if the issuing company is acquired and remains in force in subsequent take-overs.

HCD investors are entities that are likely to use the therapy. They are henceforth referred to as investing potential users (IPU). These may be retail (RIPU) or institutional IPU (IIPU). RIPU are private individuals, most likely patients or their parents. Guardians may acquire HCD on behalf of minors. Upon maturity the latter can choose whether to continue the scheme simply by managing their payments. IIPU are healthcare payers such as insurance providers, community finance organisations, patient groups or charities. Their clients are henceforth referred to as client potential users (CPU).

4.1.2 Regulatory Oversight

HCD schemes require regulatory approval. The assessor could be the same agency that gives marketing approval for treatments, e.g. FDA, or appraises cost-effectiveness, e.g. NICE. Considerable proficiency is required to evaluate research quality and claims made by the issuer as well as the impact of regulations and payer attitudes. Independent watchdog organisations are also desirable.

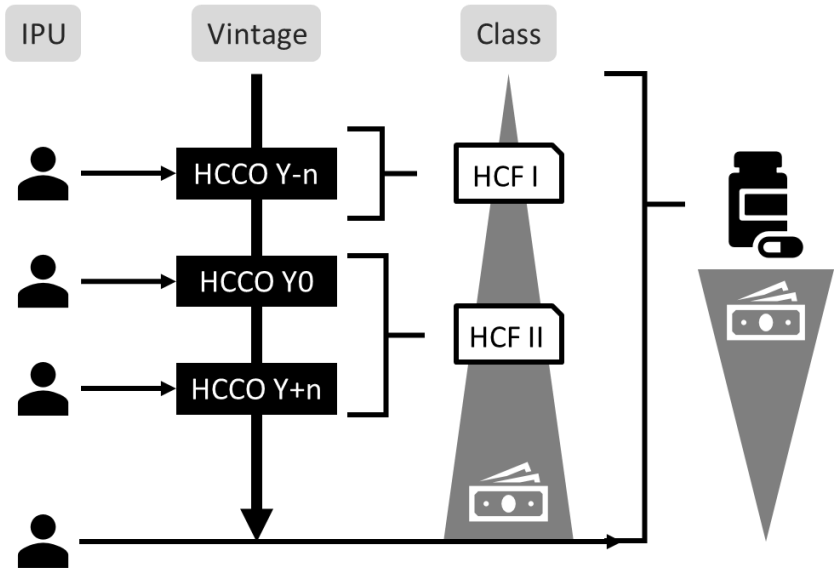
The eligibility of IPU must be verified. RIPU must prove their understanding of both medical and financial consequences of joining the scheme. IIPU, like sophisticated investors, are expected to make well-informed decisions and require less protection. However, their trustworthiness should be evaluated. For example, if insurances offer policies that promise access to HCD-funded cures, policyholders must be able to rely on such benefits if therapies become available.

Commercial HCD marketing should underlie similar controls as exist now for pharmaceuticals and risky financial investments.

4.1.3 Investing

It is envisaged that HCCO are issued annually; each issue represents a new HCCO vintage with fixed start and end dates. IPU in each financial year (FY) constitute the same investing cohort but may originate from different vintages, i.e. joined the scheme in different years. HCCO bought before the year in which the treatment is marketed (Y0) give the HCCO holder the right to buy HCF class I. HCCO acquired from Y0 onwards provide the right to buy HCF class II. Further HCF classes may be considered but are not discussed here. Figure 15 illustrates the described cascade.

Figure 15. Healthcare derivatives cascade



IPU purchase annual HCCO vintages. Vintages before year (Y)0 bestow the right to buy HCF class I; vintages from Y0 onwards bestow the right to buy HCF class II. HCF enable IPU to obtain the treatment at an agreed price. HCCO and HCF prices increase over time whilst the treatment's market value decreases. Once the combined annual HCD cost equals the treatment's market price, the HCD scheme will not accept new investors, and the treatment is procured through traditional mechanisms.

HCCO prices must always be significantly below HCF prices. One main purpose of HCCO for IPU is to avoid committing a high sum of money to the HCF upfront. HCCO function essentially as insurance. HCCO vintages have the same price all year, i.e. there is no pro rata or any other adjustment. This is to prevent IPU from waiting until year-end with HCCO purchases. HCD prices from Y0 onwards should be sufficiently high to incentivise investment before Y0 to support the issuer's objective of reducing R&D financing costs. HCD prices increase with time and certainty

about regulatory and therapeutic success. In case of adverse events, e.g. disappointing clinical trials, HCCO prices fall for existing and future IPU provided R&D continues.

Quite likely the financial valuation of the marketed treatment declines over time due to competition, process optimisations, regulatory/political pressures or other factors. Once the treatment's market value equals the combined annual HCCO/HCF price, the scheme closes naturally to new investors, as the treatment can be obtained by regular procurement. Note that the treatment's market price is not paid by anyone participating in the HCD scheme.

HCF only go on sale once the treatment is on the market. Possession of an active HCCO is compulsory to access HCF. Hence, IPU must renew their vintage annually like an insurance premium. The renewal may be at the original vintage price or a price adjusted for inflation or other factors. Such adjustments must by disclosed upfront by the issuer. If the IPU wishes to terminate their contract, they simply let the HCCO expire at year-end.

Once the treatment is available, HCCO can be executed anytime. IIPU must execute their HCCO stock in the order of vintages. Otherwise IIPU would maintain cheap early contracts and execute later expensive ones first. The flexible HCF due date depends on the IPU's need for the treatment. This is comparable to proposed OF where payment is triggered by organ extraction (Cohen, L. R. 1989, Crespi 1994).

In principle, HCCO fees are non-refundable unless issuers choose to offer rebates upon execution to allow for higher HCCO prices. Essentially, IPU would pay the HCF price minus all HCCO payments if the treatment became reality. This way IPU would have covered the company's OC, spared it the need for other funding sources and shared the R&D risk. Another enticement for IPU would be to make HCF payments dependent on treatment success similar to proposals by Takeda Pharmaceutical and Bluebird Bio for their own therapies (Takada 2019, APhA 2019).

4.1.4 Trading Restrictions

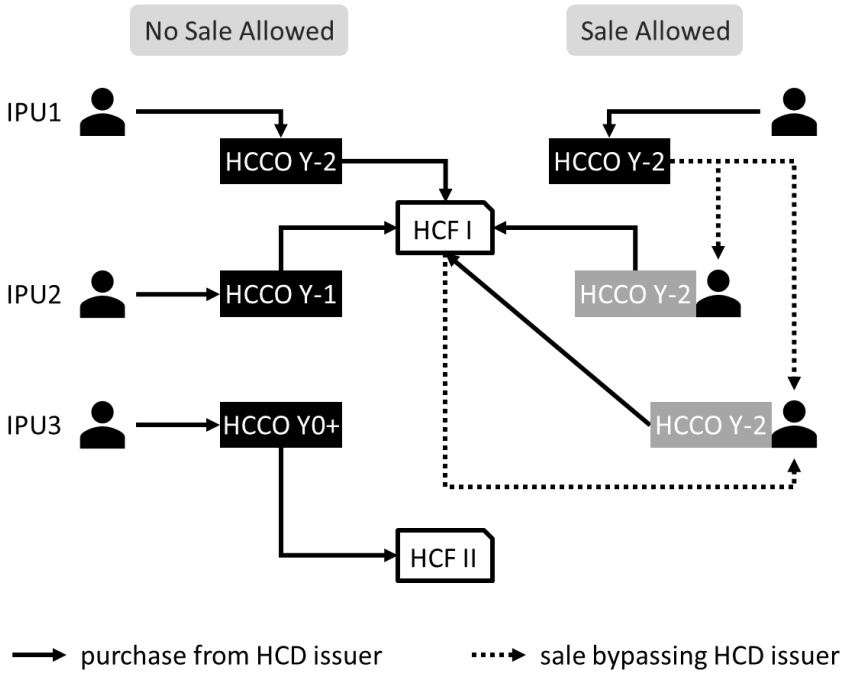
In contrast to the original article (Ferrante-Schepis 2018), this proposal does not permit IPU to sell their HCD for two main reasons. Firstly, it can result in substantial losses to the HCD-issuing company (Figure 16). For example, if early buyers sell their low-priced HCD, other IPU avoid the higher costs of joining the scheme later. This defeats the HCD scheme's purpose. Secondly, it can be considered unethical profiteering by early buyers to sell cheaply acquired HCD at a profit to desperate patients. For example, early-stage HCCO may be offered at excessive one-off prices because the patient saves on subsequent recurring maintenance fees to the issuer or gains access to HCF I.

To limit fraudulent trading by RIPU, only one treatment-specific HCCO per RIPU should be permitted unless a guardian purchases for several minors. Eligibility verification would be aided by registering the patient details in these contracts. This assumes that one HCF delivers the entire treatment package, e.g. repeat interventions.

Figure 16. Impact of HCD sales permission

This graphic illustrates a simple trading scenario involving three IPU and starting two years before release of the treatment (Y-2) to illustrate the loss of income to the HCD-issuing company. The left-hand side depicts the HCD buying cascade without any trading permitted between IPU. On the right-hand side the same actors operate in a market that allows unrestricted sale of HCCO and HCF.

For simplification not all possible IPU trades are considered. IPU1 solely obtains HCCO Y-2 to sell for a profit. IPU2 exercises the call option to obtain HCF I either to use the treatment or to sell HCF I to IPU3. Similarly, IPU3 may purchase from IPU1 to obtain the otherwise inaccessible HCF I. Altogether, the issuer only generates income from the maintenance fees for HCCO Y-2 and the sale of HCF I. Even if only IPU3 was genuinely interested in the cure and, thus, the only actor in a market without sales permission, the issuer would still gain higher revenues from IPU3's purchases of the more expensive HCCO Y0+ and HCF II.



Transfers of HCD from one IPU to another are allowable provided the original buyer transfers all rights to the new HCD owner at no financial gain to either side. It is at the discretion of the issuer to charge administrative fees for this service. Fees would make it a net-negative transaction for the original buyer and, thus, provide little incentive for most people to engage in transfers. Of

course, it means that a wealthy RIPU can obtain an early vintage and transfer it to a less wealthy person, e.g. a family member, later when the fees would otherwise be higher. Nevertheless, such altruism is ethically desirable, and the company benefits from early revenues. The transfer possibility is crucial for IIPU to commit to bulk purchases and offer the treatment to CPU.

4.1.5 Timing

An important question is at which stage of the R&D process companies should be allowed to issue HCCO. Whilst investment in pre-clinical stages is needed, the uncertainty for IPU is extremely high and issuers may only be able to charge very low HCCO prices. HCF pricing is also very difficult because total R&D costs are unknown at that point. Thus, the issuer risks mispricing the HCF. In clinical stages the potential treatment details and cost projections are much better defined. Existing life science investment decision models can help develop new strategies that consider R&D stages (Soenksen, Yazdi 2017).

For pre-clinical stages an alternative HCD framework may be more useful that considers a funding pool, even involving several companies (Ferrante-Schepis 2018). HCCO may give access to a percentage discount rather than fixed-price HCF. This idea is not further explored here.

4.2 Zolgensma Case Study

The gene therapy Zolgensma is delivered as a one-time administration to cure a SMA Type 1 patient for life at a price of $2.125M (Novartis 2019a). It promises to be therapeutically superior (Al-Zaidy, Pickard et al. 2019, Dabbous, Maru et al. 2019) and more cost-effective than current alternatives (Malone, Dean et al. 2019). However, meeting conventional cost-effectiveness thresholds would require a sales price of $1.1M–$1.9M (ICER 2019)[3]. In the case of RD traditional criteria may be waived by healthcare payers if additional benefits exist.

In this case study the theoretical Zolgensma market size is estimated to evaluate the potential of HCD sales to finance its R&D using benchmark cost estimates. A retail and an institutional investor strategy are examined.

4.2.1 R&D Costs

A benchmark for R&D costs was established as the basis for the HCD financing break-even analysis. It was based on the published estimates of $1,395M and $2,558M pre-approval R&D costs without and with (10.5% DR) capitalisation, respectively (DiMasi, Grabowski et al. 2016).

[3] Note that all current evaluations are based on relatively short and small clinical trials. Thus, therapeutic and financial long-term outcomes of Zolgensma therapy are highly speculative.

Since these values are in 2013 dollars, they were adjusted to $1,504M and $2,757M in 2018 dollars using a cumulative inflation rate of 7.79% (Table 5).

Table 5. US inflation 2014–18

Annual US inflation rates were compounded to calculate the cumulative rate for the period from 2014 to 2018.

Year	2014	2015	2016	2017	2018	Cumulative
Inflation Rate (%)	1.62	0.12	1.26	2.13	2.44	**7.79**

4.2.2 Market Size

HCD revenue estimation requires the number of potential investors. To determine the Zolgensma target market of 0–2-year-old SMA Type 1 patients either disease prevalence or incidence can be used.

SMA Type 1 prevalence has been reported at 0.04–0.28 per 100,000 persons (Verhaart, Robertson, Wilson et al. 2017). Since Zolgensma has only been approved for patients under 2 years, this sub-population must be quantified. In the absence of clinical data, the proportion of 0–2-year-olds amongst existing SMA Type 1 cases was estimated using published data originating from the Global SMA Patient Registry (Verhaart, Robertson, Leary et al. 2017). The resulting crude estimate of 65% (Table 6) might overstate the actual percentage because it assumes that all 0–2-year-olds in the registry had SMA Type 1. Most SMA Type 1 patients are expected to be in this age group. Conversely, there may be a bias in the database towards older patients, as likelihood of being captured increases with age. SMA Type 1 registrations constituting 18% when SMA Type 1 accounts for 60% of all SMA incident cases (Verhaart, Robertson, Wilson et al. 2017) suggests that 0–2-year-olds, especially 0–1-year-olds, were under-represented in the registry. Altogether, the two flaws may offset each other to some degree.

Table 6. Estimation of SMA Type 1 age distribution

The approximate age distribution of existing SMA Type 1 cases was estimated using published data (Verhaart, Robertson, Leary et al. 2017). Assuming that all 0–2-year-olds in the source database suffered from SMA Type 1 allows their proportion to be calculated by dividing the number of all 0–2-year-olds by the number of all SMA Type 1 cases.

SMA Type	Age	Patient Count	Proportion of Registry Population	Registry Population
Publication				
All	0–2 years	544	12%	SMA Patients
1	All	833	18%	SMA Patients
Estimation				
1	0–2 years	544	65.3%	SMA Type 1 Patients

A comprehensive meta-analysis estimated SMA Type 1 incidence at 6 per 100,000 live births noting that most underlying studies originated from Europe and ethnicity as well as parental consanguinity influence SMA incidence (Verhaart, Robertson, Wilson et al. 2017). Another study gauged incidence at 8.5–10.3/100,000 based on a smaller literature review (Lally, Jones et al. 2017). Nevertheless, this case study used a conservative 6/100,000 incidence for the estimation of SMA Type 1 market size in geographies with a high proportion of Caucasians and little consanguinity. To construct the total annual target population, the survival rate of SMA Type 1 children must be considered for the first two years of life. Published estimates propose 40%–50% survival probability in year 1 and 25%–40% in year 2 (Farrar, Vucic et al. 2013, Chung, Wong et al. 2004, Zerres, Rudnik-Schöneborn 1995). An observational study suggests that the combined probability for survival or not needing intense ventilation support (IVS) at 1 and 2 years is approximately 50% and 20%, respectively (Finkel, McDermott et al. 2014). This case study conservatively used 40% and 25% chance of survival in the first and second year, respectively.

Since access to the US market is secured and EMA approval anticipated in the second half of 2019 (Luxner 2019), the average annual SMA Type 1 target populations were calculated in both geographies to gauge the Zolgensma market size. Interestingly, the upper bound of the US SMA Type 1 prevalence estimate for 2016, 906 persons (Table 7), is not far below the 1,180 average prevalent US cases in 2016 estimated in another study when it applied international survival statistics to US demographics (Lally, Jones et al. 2017). Here, Zolgensma market size was estimated at 329 and 527 annual cases in the USA and EU, respectively, based on average

prevalence (Table 7). Based on incidence, it was estimated at 393 and 514 annual cases in the USA and EU, respectively.

Estimating average Zolgensma market size by incidence and prevalence gave comparable values. However, quantification of incidence here and in publications involved less speculation than prevalence. Also, patients would most likely come from the 0–1-year-old population who have a higher chance of treatment eligibility and success than children in advanced disease stages. Since treated patients are theoretically cured for life, future prevalence will decline and predominantly include patients not eligible for Zolgensma treatment. Altogether, incidence-based values appear to be the more reliable measure for Zolgensma market size estimation and were used for further calculations.

Table 7. Estimation of the SMA Type 1 target population

[A] Median SMA Type 1 prevalent and incident cases were calculated at 0.04 or 0.28/100,000 prevalence and 6/100,000 incidence using 10 years of birth and population data from the USA and EU from 2008 to 2017. The total annual prevalence range was calculated by dividing the annual population count by 100,000 and multiplying by 0.04 or 0.28. Total annual incidence was calculated by dividing the annual number of live births by 100,000 and multiplying by 6. **[B]** The 0–2-year-old sub-population was derived by taking 65% (Table 6) of the total median prevalence. **[C]** Alternatively, the 0–2-year-old sub-population was derived by adding together annual median incidence and the survivors of the first (40%) and second (25%) year. All figures are presented as number of persons.

[A] SMA Type 1 prevalence and incidence

Year	Population		Prevalence		Number of Births		Incidence	
	USA	EU	USA	EU	USA	EU	USA	EU
2008	304,094,000	500,297,033	122–851	200–1,401	4,247,700	5,469,434	255	328
2009	306,771,500	502,090,235	123–859	201–1,406	4,130,700	5,412,572	248	325
2010	309,338,400	503,170,618	124–866	201–1,409	3,999,400	5,411,129	240	325
2011	311,644,300	502,964,837	125–873	201–1,408	3,953,600	5,266,162	237	316
2012	313,993,300	504,047,749	126–879	202–1,411	3,952,800	5,230,626	237	314
2013	316,234,500	505,163,053	126–885	202–1,414	3,932,200	5,081,671	236	305
2014	318,622,500	507,235,091	127–892	203–1,420	3,988,100	5,137,147	239	308
2015	321,039,800	508,520,205	128–899	203–1,424	3,978,500	5,107,668	239	306
2016	323,405,900	510,181,874*	129–906	204–1,429	3,941,109*	5,148,166	236	309
2017	325,719,200*	511,373,278*	130–912	205–1,432	3,853,472*	5,074,875	231	304
Median			**126–882**	**202–1,413**			**238**	**311**

** released estimated/provisional data*

[B] SMA Type 1 target population based on prevalence

Age	USA	EU
All, Range (Mean)	126–882 (504)	202–1,413 (807)
0–2 Years, Range (Mean)	**82–576 (329)**	**132–923 (527)**

[C] SMA Type 1 target population based on incidence

Region	Live Births	Y1	Y2	Total 0–2-years
USA	238	95	59	**393**
EU	311	125	78	**514**

4.2.3 Retail IPU Strategy

RIPU may be parents of SMA Type 1 children who purchase HCD in areas where no other cover is available. Since parents do not plan for a child with SMA, their investment horizon is defined by the time of diagnosis and eligible treatment age.

SMA genetic testing can already be carried out during pregnancy (NHS 2017). Theoretically, affected parents may choose to acquire HCCO from Y-3. However, the proportion of tested parents who deliver a child with SMA Type 1 is unknown. Hence, this RIPU strategy only considered live births and began sale of HCCO from Y-2, as children above 2 years are not eligible for treatment. Thus, rational parents would not invest any sooner unless they speculated that Zolgensma's indication will subsequently be broadened. Such speculation was ignored here, and it could be argued that such a case warrants a separate set of HCD.

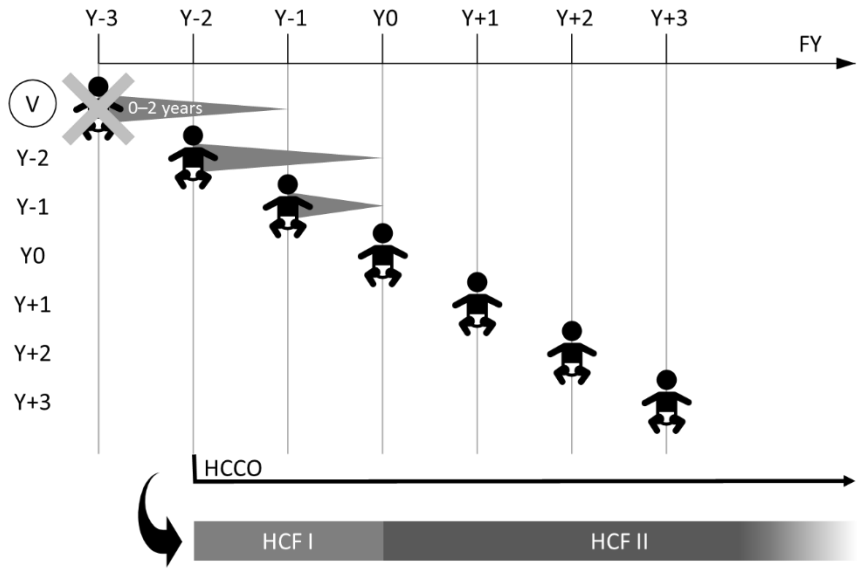
It was further assumed that the diagnosis is always made within the first year of life. RIPU obtain the HCCO immediately thereafter, i.e. within the same year, and opt for HCF purchase once available (Y0) or in the year of diagnosis (Y+n). Thus, from Y0 only one HCCO is needed to acquire the HCF. No other treatment exclusion factors but age and death were considered in the estimation of RIPU numbers.

Figure 17 illustrates the RIPU investment schedule constructed based on the above criteria and shows the resulting RIPU cohorts and HCF counts in each FY.

Figure 17. RIPU strategy overview

[A] The RIPU strategy schedule until Y+3 was based on the following assumptions. There are no rational RIPU before HCCO vintage (V) Y-2. Vintages before Y0 give the right to buy HCF I, later vintages give access to HCF II. Each RIPU cohort per FY is comprised of different HCCO vintages depending on survival and uptake of treatment. HCF come on sale from Y0 and are invoked each FY by all RIPU. **[B]** The absolute RIPU cohort counts and **[C]** resulting proportions in each FY were incidence-based estimates. Displayed cohort counts assumed 100% market capture. 'Same year' means that the relative vintage year equals the FY. **[D]** The number of anticipated HCF purchases was derived from cohort counts from Y0 onwards.

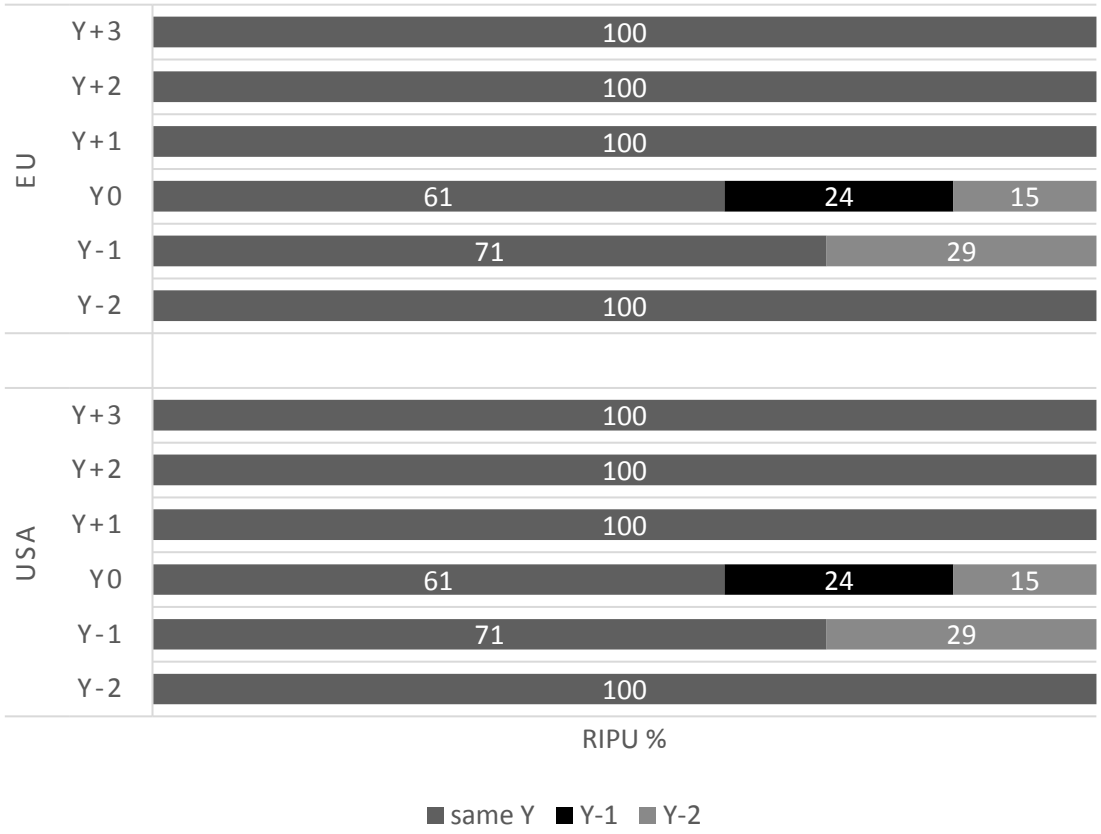
[A] RIPU strategy schedule



[B] Counts of annual RIPU cohorts

FY / V	Y-2	Y-1	Y0	Y+1	Y+2	Y+3	Y-2	Y-1	Y0	Y+1	Y+2	Y+3
	USA						EU					
same Y	238	238	238	238	238	238	311	311	311	311	311	311
Y-1			95						125			
Y-2		95	59					125	78			
Total	238	333	393	238	238	238	311	436	514	311	311	311

[C] Proportions of annual RIPU cohorts



[D] HCF counts

FY / HCF Class	Y0	Y+1	Y+2	Y+3	Y0	Y+1	Y+2	Y+3
	USA				EU			
I	155				202			
II	238	238	238	238	311	311	311	311
Total	393	238	238	238	514	311	311	311

To estimate potential revenues from the RIPU strategy, hypothetical HCD prices were set at approximate fractions of the current Zolgensma sales price (Figure 18A). The HCF II price was chosen close to the recommended cost-effective sales price of $1.1M (ICER 2019). Projected total HCD sales from the USA and EU generated $2.4B undiscounted revenues by 4 years post-approval at 100% market capture (Figure 18B). Only 2% ($48.8M) of these originated from HCCO sales. Break-even with benchmark out-of-pocket R&D costs of $1.5B was reached at 62% market capture (A-Figure 23).

RIPU's short investment horizon did neither generate early nor high enough HCCO sales to pay for R&D expenditure. However, HCF sales generated substantial undiscounted revenues within

few years at prices below the current Zolgensma market price. Nevertheless, the required market capture is unrealistic, as simulated HCF prices are still beyond affordability for many. The RIPU strategy serves mainly as a thought-experiment to illustrate the HCD framework at an individual investor level.

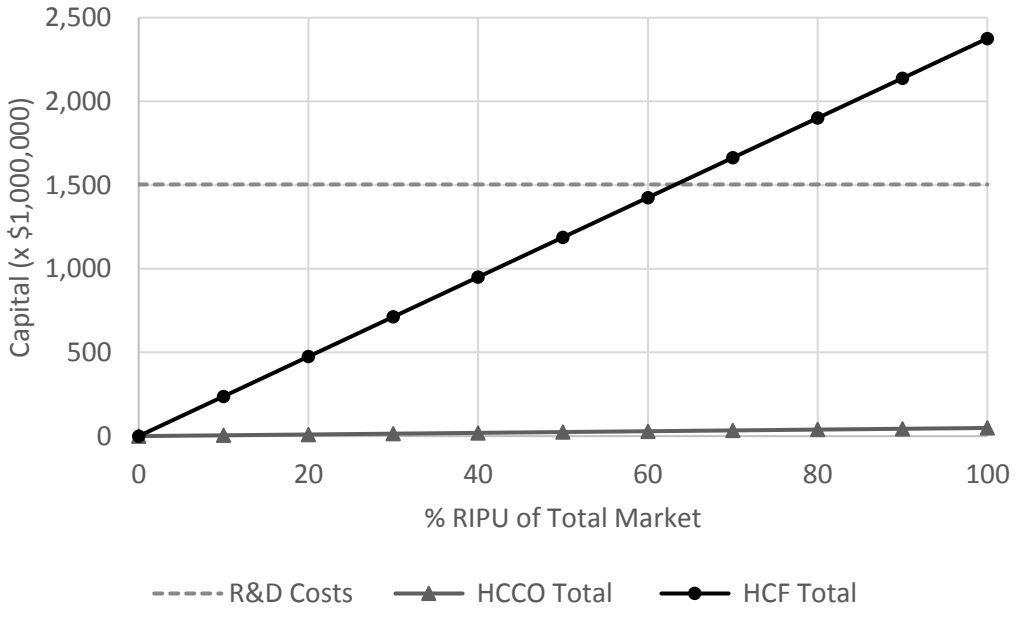
Figure 18. HCD revenues by end of Y+3

[A] HCD prices were set at fractions of $2M, the approximate current Zolgensma sales price (actual: $2.125M). **[B]** These prices and the RIPU strategy were used to simulate undiscounted combined revenues from the USA and EU depending on market capture. The sales period spanned from Y-2 to Y+3. The chart displays revenues from HCCO and HCF sales separately. Out-of-pocket R&D costs were plotted alongside. Find the underlying data in A-Table 14.

[A] HCD pricing scheme

HCD		Simulated Price	Approx. % of Current Price
HCCO Vintage Year	Y-2	$5,000	0.25
	Y-1	$7,500	0.375
	Y0	$10,000	0.5
	Y+1	$20,000	1
	Y+2	$20,000	1
	Y+3	$20,000	1
HCF Class	I	$500,000	25
	II	$1,000,000	50

[B] Simulated revenues by market capture



4.2.4 Institutional IPU Strategy

IIPU have longer investment horizons than RIPU because their goal is to lock in low treatment prices for prospective patients. Since RIPU represent patients needing Zolgensma, the same counts also quantify CPU. The composition of CPU cohorts was assumed to be equal to RIPU from Y0 (Figure 17, Table 9A) across all US and European IIPU but may differ for individual organisations depending on their client base. It was assumed that all CPU receive Zolgensma through IIPU in the year of drug release (Y0) or diagnosis (Y+n).

Not all CPU may be eligible for treatment because of poor physical condition, second birthday before possible treatment or any other contraindication. IVS need was quantified as a proxy for disease progression (Table 8). At least 15% of up to 1-year-old and 59% of up to 2-year-old SMA Type 1 patients were at risk of requiring IVS.

Table 8. CPU risk of requiring intense ventilation support

Data from a published observational study (Finkel, McDermott et al. 2014) were used to gauge the proportion of patients at risk of needing IVS, which is an indicator of severe physical deterioration. Note that the original study distinguished SMA Type 1B and C recent and chronic cases, which was irrelevant for this case study.

Using the given age ranges and fractions of study participants needing IVS, absolute patient numbers were calculated for two age groups. The CPU risk, i.e. the risk of patients requiring IVS, was then calculated by dividing the age group count by the Type 1 total. For 0–12-months-old children only a minimum count (*) could be derived, as the exact age breakdown of the study was unknown. Thus, the actual CPU risk may be higher for this age group.

	Type 1B		**Type 1C**		**Type 1**	
	Recent	**Chronic**	**Recent**	**Chronic**	**Total**	
Publication						
Patient Count	8	10	6	10	34	
IVS Onset Median (IQR) Age [Months]	3.5 (2–5)	13.5 (8–21.5)	10 (8–18)	13 (8–21)	-	
IVS Patients of Total	25%	80%	50%	70%	-	
Analysis						
IVS Onset by Age	**Patient Count**					**CPU Risk**
0–24 Months	2	8	3	7	20	**59%**
0–12 Months	2	1*	1*	1*	5	**15%**

IQR … interquartile range

Even though not a contraindication (AveXis 2019b), IVS requirement suggests that CPU may be too ill for Zolgensma treatment. Hence, CPU risk was interpreted as exclusion risk. Altogether, 39% of US and EU CPU in Y0 were at high risk of being excluded from Zolgensma therapy (Table 9). The total (and risk-adjusted) CPU estimates in Y0 were 393 (267) in the USA and 514 (349) in the EU; in each consecutive year estimates were 238 (203) CPU in the USA and 311 (266) in the EU.

Table 9. Annual CPU profile

[A] CPU cohorts were defined according to HCCO vintage years and correspond to RIPU cohorts (Figure 17). The Y0 cohort consisted of three CPU vintages; consecutive years only of the same-year vintage. The exclusion risk was assigned by age group with patient age being a result of the calculation of CPU using survival probabilities. **[B]** CPU counts were adjusted according to the exclusion risk of each vintage. The total number of CPU for the 10 years following FDA approval is also shown.

[A] Annual CPU composition

Vintage	**Y+n**	**Y0**	**Y-1**	**Y-2**
Patient Age (Years)	0–1	0–1	1–2	1–2
Exclusion Risk	low (15%)		high (59%)	
USA				
CPU Count	238	238	95	59
% CPU of Y0 Total	-	61	24	15
% CPU of Y+n Total	100	-	-	-
EU				
CPU Count	311	311	125	78
% CPU of Y0 Total	-	61	24	15
% CPU of Y+n Total	100	-	-	-

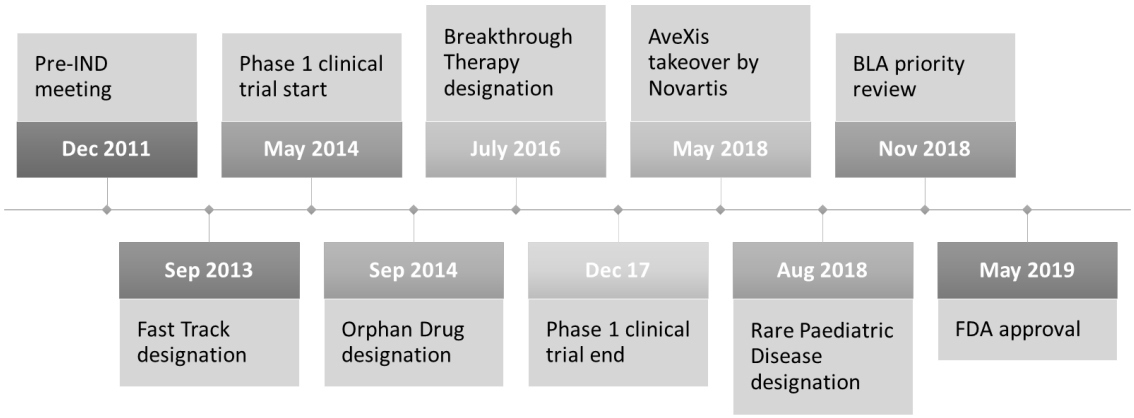
[B] CPU counts for IIPU strategy

Relative Year	**Case Year**	**All CPU**	**Adjusted CPU**	**All CPU**	**Adjusted CPU**
		USA		**EU**	
Y0	2019	393	267	514	349
Y+n	2020–28	238	203	311	266
Total		**2,534**	**2,093**	**3,316**	**2,739**

To delineate the HCD investment period developmental milestones for Zolgensma were identified as points of interest for IIPU (Figure 19). Of particular note before approval in 2019 (FDA 2019a) were the clinical trial in 2014 with successful completion in 2017 (AveXis 2019a), the acquisition by Novartis (Novartis 2019b) and the BLA in 2018 (Byrnes 2019). The earliest point of interest was the pre-IND meeting in 2011.

Figure 19. Zolgensma milestones

This timeline lists US regulatory milestones (Byrnes 2019, FDA 2019a), a key clinical trial (AveXis 2019a) and the acquisition of Zolgensma's original developer AveXis by pharmaceutical giant Novartis (Novartis 2019b).



A hypothetical pricing scheme was developed with HCCO prices increasing annually until Y+1 to incentivise early investment and once more in Y+5 (Table 10). If prices were purely milestone-driven, the HCCO issuer would risk that IIPU wait until just before the next price/milestone announcement and skip years between milestones (e.g. 2015). Key events from 2017 justified steeper price increases. HCF classes were offered at the same constant prices as in the RIPU scheme.

Table 10. IIPU pricing scheme

HCCO pricing was designed so that prices increase by 50% each year from Y-8 to Y-3, then double until Y+1, remain constant until Y+4, then double once more in Y+5 and remain constant until phase-out in Y+9. The rationale for HCF prices was the same as in the RIPU strategy (Figure 18).

Relative Year	Case Year	HCCO Price $	HCF Price $
Y-8	2011	300	500,000
Y-7	2012	450	
Y-6	2013	675	
Y-5	2014	1,013	
Y-4	2015	1,519	
Y-3	2016	2,278	
Y-2	2017	4,556	
Y-1	2018	9,113	
Y0	2019	18,225	1,000,000
Y+1	2020	36,450	
Y+2	2021	36,450	
Y+3	2022	36,450	
Y+4	2023	36,450	
Y+5	2024	72,900	
Y+6	2025	72,900	
Y+7	2026	72,900	
Y+8	2027	72,900	
Y+9	2028	72,900	

A hypothetical investment schedule was created with HCCO purchase beginning in Y-7 when the result of the pre-IND meeting was ascertained (Table 11). IIPU then kept adding HCCO annually according to anticipated CPU counts until Y0. The last lot of purchases was in Y+4 before the next price increase and covered the required number of HCCO to last until Y+9. HCF I were obtainable until end of Y+6 thanks to pre-Y0 HCCO vintages.

Table 11. HCD investment schedule

The hypothetical HCD purchasing schedule encompassed a timeframe from Y-8 to Y+9. At the end all HCD were used up. **[A]** The example schedule displays unadjusted CPU counts from the USA. It was assumed that HCCO payments were due at the start of each FY to maintain access to the respective HCF. No new HCCO purchases were made in Y-8, Y+1 to Y+3 and after Y+4. HCCO that had been exercised disappeared from the schedule. HCF counts represent purchases throughout each FY based on CPU counts. **[B]** This resulted in the displayed year-end HCF counts. All active Y-n HCCO vintages in each FY from Y0 onwards bestowed access to HCF I; all active Y0+ vintages gave access to HCF II. HCF were not on sale until Y0. The HCF I count shown in Y-1 represents the HCF available at the start of Y0, a portion (393) of which was used up during that year.

[A] Purchasing schedule

FY / V	Y-8	Y-7	Y-6	Y-5	Y-4	Y-3	Y-2	Y-1	Y0	Y+1	Y+2	Y+3	Y+4	Y+5	Y+6	Y+7	Y+8	Y+9
HCCO Count																		
Y-8																		
Y-7		238	238	238	238	238	238	238	238									
Y-6			238	238	238	238	238	238	238	83								
Y-5				238	238	238	238	238	238	238	83							
Y-4					238	238	238	238	238	238	238	83						
Y-3						238	238	238	238	238	238	238	83					
Y-2							393	393	393	393	393	393	393	238				
Y-1								238	238	238	238	238	238	238	238			
Y0									238	238	238	238	238	238	238	238		
[…]																		
Y+4													476	476	476	476	476	238
HCF Count																		
Y0									393									
Y+1										238								
Y+2											238							
Y+3												238						
Y+4													238					

V \ FY	Y-8	Y-7	Y-6	Y-5	Y-4	Y-3	Y-2	Y-1	Y0	Y+1	Y+2	Y+3	Y+4	Y+5	Y+6	Y+7	Y+8	Y+9
Y+5														238				
Y+6															238			
Y+7																238		
Y+8																	238	
Y+9																		238

[B] HCF classes available at year-end

FY	Y-1	Y0	Y+1	Y+2	Y+3	Y+4	Y+5	Y+6	Y+7	Y+8	Y+9
HCFI	1,820	1,428	1,190	952	714	476	238	-	-	-	-
HCFII	-	238	238	238	238	714	714	714	476	238	-

HCCO contributed approximately 10% to the combined US and EU HCD revenues resulting from the described investment and pricing schemes (Table 12). HCCO revenues before Y0 constituted approximately one-quarter of total HCCO revenues before and one-third after compounding. This reveals the higher value of early cash flows to the HCD issuer. Total undiscounted revenues were $4,145M and $3,453M from all and risk-adjusted CPU, respectively, and sat well above the benchmark out-of-pocket R&D costs of $1,504M. Discounting by 10.5% reduced these revenues to $2,641M and $2,170M, respectively, and below the benchmark capitalised R&D costs of $2,757M. Considering the impact of OC, it is noteworthy that Novartis offers an interest-free 5-year instalment plan to US buyers (Novartis 2019a), which reduces the NPV of each sale to $1.8M (A-Table 15). This case study assumed instant and complete payment for simplicity.

Table 12. HCD revenues per vintage year

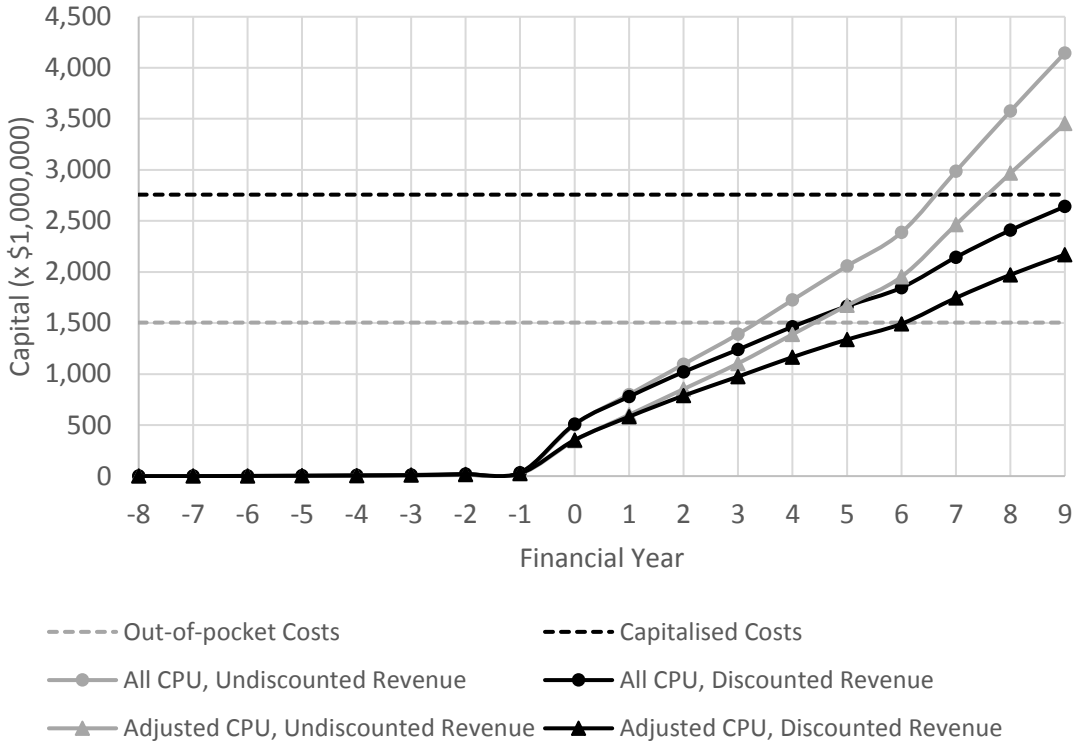
This table shows the undiscounted and discounted (10.5% DR) combined revenues from the USA and EU generated by each HCCO vintage from all and risk-adjusted CPU by Y+9. Note that HCCO vintage years are essentially FY with regards to HCF, since there are only two HCF classes. HCF II were sold from Y+7. All revenues are multiples of $1,000,000. Also listed are the proportions of HCCO and HCF of total HCD revenues (%HCD) and the proportion of HCCO revenues before Y0 of total HCCO revenues (%Y-n). Find the underlying data in A-Table 16 and A-Table 17.

Vintage	All CPU		Adjusted CPU		All CPU		Adjusted CPU	
	undiscounted				discounted			
	HCCO	HCF	HCCO	HCF	HCCO	HCF	HCCO	HCF
Y-8	-		-		-		-	
Y-7	2.0		1.7		2.9		2.5	
Y-6	2.7		2.4		3.7		3.2	
Y-5	4.1		3.6		5.0		4.4	
Y-4	6.1		5.5		6.8		6.0	
Y-3	9.2		8.2		9.2		8.1	
Y-2	31.4		21.8		28.2		19.4	
Y-1	40.0		34.2		32.0		27.3	
Y0	80.1	453.2	68.3	307.8	58.0	453.2	49.4	307.8
Y+1	-	274.7	-	234.3	-	248.6	-	212.0
Y+2	-	274.7	-	234.3	-	224.9	-	191.9
Y+3	-	274.7	-	234.3	-	203.6	-	173.6
Y+4	220.3	274.7	187.9	234.3	119.2	184.2	101.7	157.1
Y+5	-	274.7	-	234.3	-	166.7	-	142.2
Y+6	-	274.7	-	234.3	-	150.9	-	128.7
Y+7	-	549.3	-	468.5	-	273.1	-	232.9
Y+8	-	549.3	-	468.5	-	247.1	-	210.8
Y+9	-	549.3	-	468.5	-	223.7	-	190.8
Subtotal	395.9	3,749.2	333.5	3,119.0	265.0	2,376.0	222.1	1,947.8
Total	4,145.1		3,452.6		2,641.0		2,169.9	
%HCD	9.6	90.4	9.7	90.3	10.0	90.0	10.2	89.8
%Y-n	24.1		23.2		33.1		31.9	

Projected undiscounted revenues from all and risk-adjusted CPU broke even with out-of-pocket costs in Y+4 and Y+5, respectively (Figure 20). Whilst break-even with capitalised costs was not reached by discounted revenues in the first 10 years of Zolgensma marketing in the USA and EU, Japan was excluded from this analysis (Novartis 2019a). With revenues being close to costs in Y+9, additional HCD sales would probably lead to break-even within the given timeframe. For comparison, total discounted Zolgensma revenues from all and risk-adjusted CPU at market price would break even in Y+1 and Y+2, respectively (A-Table 20).

Figure 20. HCD revenues per financial year

The running totals of undiscounted and discounted (10.5% DR) combined HCD revenues from the USA and EU from all and risk-adjusted CPU from Y-8 to Y+9 were plotted alongside the break-even R&D cost targets, i.e. out-of-pocket costs of $1,504M and capitalised costs of $2,757M. Find the underlying data in A-Table 18 and A-Table 19.



To investigate break-even requirements at discounted revenues in the combined USA/EU market, the pricing and investment schemes could be optimised. The number of available HCF I could also be capped both to encourage early investment and generate higher revenues sooner. Modelling any such modifications was beyond the scope of this study. Alternatively, the effect of different DR on break-even in the presented IIPU strategy was explored, as DR was a point of contention in the R&D cost debate (DiMasi, Grabowski et al. 2015, Avorn 2015).

The used source publication states out-of-pocket and compounded R&D costs at 10.5% (DiMasi, Grabowski et al. 2016). To calculate costs at other DR, the continuous compounding in the source was retraced by calculating the representative number of compounding years, which was a simplification of the original method. Result verification is in A-Figure 24. This approach revealed Y+9 break-even points at 10.1% and 8.0% DR for all and adjusted CPU, respectively (Figure 21; A-Figure 25). This demonstrates clearly the importance of the DR in capital investment and pricing decisions.

Figure 21. Effect of increasing discount rates

[A] To calculate capitalised R&D costs at increasing DR, the number of representative compounding years in the original publication (DiMasi, Grabowski et al. 2016) was identified using the continuous compounding formula. **[B]** This enabled a series of compounded R&D costs to be plotted alongside combined accumulated discounted HCD revenues from the USA and EU at Y+9 from all and risk-adjusted CPU. Find the underlying data in A-Table 21.

[A] Number of representative compounding years t

Identifying n using original data in 2013 dollars:

$$\text{Compounded Cost} = \text{Cash} * e^{rt}$$

$$\$2{,}558\text{M} = \$1{,}395\text{M} * e^{0.105*t}$$

$$t = \frac{\ln\left(\frac{\$2{,}558\text{M}}{\$1{,}395\text{M}}\right)}{0.105}$$

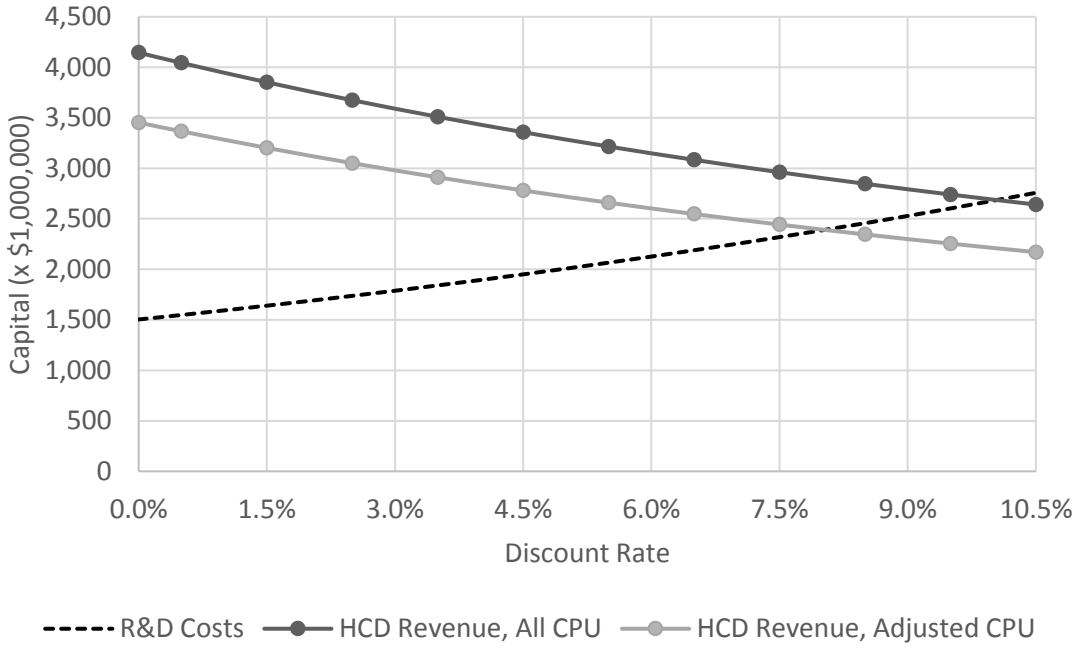
$$\underline{\mathbf{t = 5.77}}$$

Verifying n using inflated data in 2018 dollars:
(expected result: $2,757M; see 4.2.1)

$$\text{Cost} = \$1{,}504\text{M} * e^{0.105*5.77}$$

$$\underline{\text{Cost} = \$2{,}757\text{M}}$$

[B] Effect of discount rates on costs and revenues



4.3 SUMMARY

Applicable aspects of the proposed HCD framework were used to model an illustrative case study that examined in retrospect Zolgensma R&D financing and sales using HCD. Together with market size estimates, the simple RIPU strategy helped to quantify the patient perspective in preparation of the IIPU strategy. The IIPU strategy suggests that HCD-facilitated drug sales below market price may produce substantial cash revenues. However, economic break-even was highly dependent on the DR.

CHAPTER 5. CONCLUSIONS & DISCUSSION

The ambition of this project was to launch an intriguing idea from an online media article into the academic realm. Taking an interdisciplinary approach by marrying biomedicine and finance, the developed HCD framework adds to existing proposals that widen the use of financial vehicles in healthcare.

The idea's originator speculated that HCD could be used to raise funds for pharmaceutical R&D from the public assuming that millions of people invest (Ferrante-Schepis 2018). In contrast, the RD case study here indicates that pre-approval HCCO revenues may be very low in relation to R&D costs due to low patient numbers. Even the longer investment horizon of IIPU may not eliminate the need for other funding sources sufficiently to directly reduce OC, which can account for almost half of R&D economic costs (DiMasi, Grabowski et al. 2016). Despite very optimistic CPU counts and resulting considerable potential cash revenues from HCF-guaranteed drug prices below market value, break-even at discounted revenues was not achievable at high DR within the presumed OD exclusivity period. Negative NPV projections advise against using HCD to finance R&D. Nonetheless, RD HCD schemes might lower OC indirectly by helping to negotiate favourable conditions for other financing avenues in a similar way as grants and VC signal confidence (Islam, Fremeth et al. 2018, Davila, Foster et al. 2003). HCCO sales allow the issuer to quantify prospective customers credibly, which increases certainty of projected revenues.

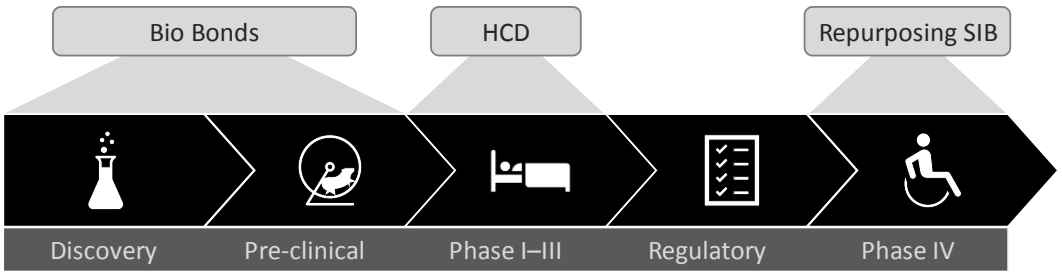
From a firm's perspective, an important question is whether HCD schemes are better suited for 'mass diseases' like common cancers or microbial infections. The high patient numbers promise many early HCD investors. On the other hand, HCD can facilitate the alignment of drug pricing with payers' requirements, in particular for expensive RD therapies, to achieve optimal coverage conditions and maximal market access. Otherwise an approved cure might become a commercial failure (Mullin 2017). From an OD payer's perspective, HCD are attractive if they result in significant cost reductions and, ideally, invite earlier involvement in the R&D process. Of note, the stipulated Zolgensma price cuts to 25% and 50% of its market price would still leave payers with huge lump sums. Thus, payment would remain a challenge in current healthcare systems (Schmickel, Perry et al. 2019, Szegedi, Zelei et al. 2018). However, being able to help 2–4 patients for the same expense as one can make a difference in the context of RD considering the high social and healthcare costs per patient (Eljamel, Ghosh et al. 2019, Eljamel, Griffiths et al. 2018, Thompson 2017).

HCD should be seen as one innovation that complements others (Figure 22). For example, Bio Bond-funded early research (Taft 2019) might lower a firm's OC and drug repurposing financed

by Findacure's SIB (Findacure 2016) would add future revenues by extending drugs' uses. Altogether, project planning would need to way up traditional and novel financing choices. Since both healthcare spending and R&D investments were susceptible to the effects of the 2008 financial crisis (OECD 2017a, Bains, Wooder et al. 2014), more resilience should be built into these systems, for example, by diversifying R&D financing vehicles.

Figure 22. Target R&D stages of novel financing vehicles

Three radically novel proposals for alternative R&D financing can be employed complementarily because they target different stages of the pharmaceutical R&D process. Bio Bonds fund primarily early-stage research leading into clinical trials (Taft 2019). HCD focus on funding clinical trials in Phases I–III and drug repurposing SIB are deployable in Phase IV (Findacure 2016).



5.1 Limitations and Suggestions

The described HCD framework is a theoretical draft that requires adaptation to various jurisdictions. Assessing the ramifications of such implementation demands extensive research and professional expertise.

The case study illustrates HCD principles through simplified scenarios, which omitted multiple real-life complexities. It depended heavily on secondary data and speculations about costs, market size and investor choices. Working with industry insiders would provide crucial insights in the way pharmaceutical companies, insurances and other relevant organisations make investment and financing decisions. This would help develop more realistic scenarios and break-even analyses. Financial modelling could optimise investment and pricing strategies. Improvements in future technologies and practices, like routine newborn screening (Ross, Clarke 2017), will enable more accurate RD quantification to improve market size estimations and inform pricing.

Whilst it is implied that potential R&D cost and drug price reductions with HCD financing may reduce healthcare spending, this project does not provide evidence for such an effect. It may well be that increased demand for previously unaffordable treatments has the opposite or no effect on current trends in total healthcare expenditure despite lower costs per patient. Historic

data on the evolution of past treatments would inform forecasts on the budgetary impact of potential HCD-driven cost reductions.

5.2 OUTLOOK

Healthcare payers must become more vigilant and monitor pharmaceutical product pipelines to anticipate releases and prepare their payment capacity (Rao, Kapp et al. 2018). Concurrently, companies must increase their efforts in early stakeholder involvement, especially regarding payers and patients (Hughes-Wilson 2014, O'Hagan, Farkas 2009). HCD drive both by design – investor discipline and integrated R&D processes. Due to their pre-approval investments, payers must continuously ensure HCD prices are justified and examine alternative developments. With HCD available, some insurers may become specialists in OD coverage because patients will prefer the most experienced and most likely supplier to cover their needs (Stewart 2019).

At their full potential, HCD could become a borderless new type of health insurance. Just as other financial derivatives can be traded internationally, so could patients or payers invest in promising biomedical research and benefit from the latest cures. Trading regulations must be tighter than for existing derivatives because human lives are directly affected. At the same time, the rigidity of current systems must be loosened to remove barriers to financial innovation as Novartis' chief executive officer has highlighted (Narasimhan 2019).

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CHAPTER 7. APPENDIX

7.1 INFLATION ADJUSTMENT OF PUBLISHED R&D COSTS

A-Table 13. Inflation factors for 2018-adjustment

Annual US inflation data were used to calculate the cumulative factor to multiply with the published R&D costs in section 2.4, Table 2 to obtain the respective 2018 $ values. The relevant years are highlighted in grey.

Year	Inflation Rate (%)	1+Rate	Cumulative Factor
2001	2.83	1.028	1.46
2002	1.59	1.016	1.42
2003	2.27	1.023	1.40
2004	2.68	1.027	1.37
2005	3.39	1.034	1.33
2006	3.23	1.032	1.29
2007	2.85	1.029	1.25
2008	3.84	1.038	1.21
2009	-0.36	0.996	1.17
2010	1.64	1.016	1.17
2011	3.16	1.032	1.15
2012	2.07	1.021	1.12
2013	1.46	1.015	1.09
2014	1.62	1.016	1.08
2015	0.12	1.001	1.06
2016	1.26	1.013	1.06
2017	2.13	1.021	1.05
2018	2.44	1.024	1.02

7.2 RIPU Revenue Estimation by Market Capture

A-Table 14. HCD revenues by Y+3

Underlying data for the chart in section 4.2.3, Figure 18B

Each RIPU cohort count in the strategy schedule was multiplied with the respective hypothetical HCD prices in section 4.2.3, Figure 18A. Annual revenues were added together to arrive at the accumulated revenues from HCD sales at Y+3. Similarly, RIPU counts were summed up to obtain the number of HCD sold. Calculations were repeated at gradually increasing market capture (MC) from 10% to 100%.

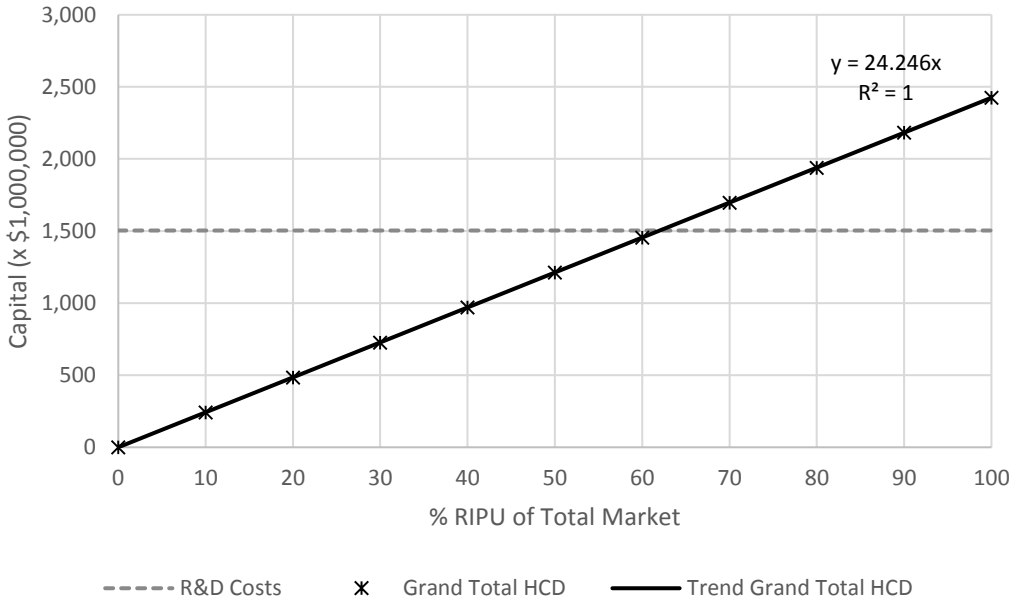
%MC	10	20	30	40	50	60	70	80	90	100
HCCO Count										
USA	168	336	503	671	839	1007	1174	1342	1510	1678
EU	220	439	659	878	1098	1317	1537	1756	1976	2195
Total	**387**	**775**	**1162**	**1549**	**1936**	**2324**	**2711**	**3098**	**3485**	**3873**
HCF Count										
USA	111	221	332	443	553	664	775	885	996	1107
EU	145	290	434	579	724	869	1013	1158	1303	1448
Total	**255**	**511**	**766**	**1022**	**1277**	**1533**	**1788**	**2043**	**2299**	**2554**
HCCO Revenue (x $1,000,000)										
USA	2.1	4.2	6.3	8.4	10.6	12.7	14.8	16.9	19.0	21.1
EU	2.8	5.5	8.3	11.1	13.8	16.6	19.3	22.1	24.9	27.6
Total	**4.9**	**9.8**	**14.6**	**19.5**	**24.4**	**29.3**	**34.1**	**39.0**	**43.9**	**48.8**
HCF Revenue (x $1,000,000)										
USA	102.9	205.8	308.8	411.7	514.6	617.5	720.4	823.4	926.3	1,029.2
EU	134.7	269.3	404.0	538.7	673.3	808.0	942.7	1,077.3	1,212.0	1,346.6
Total	**237.6**	**475.2**	**712.8**	**950.3**	**1,187.9**	**1,425.5**	**1,663.1**	**1,900.7**	**2,138.3**	**2,375.8**

A-Figure 23. HCD revenues trendline

Underlying data for the comment on break-even in section 4.2.3, *page 42*

HCD revenues were simulated as described in section 4.2.3, Figure 18. A linear trendline for total HCD revenues was generated in Microsoft Excel.

The trendline had the following formula: y = 24.246x (perfect fit with $R^2 = 1$). Setting y = 1,503.7 revealed the break-even point at 62% market capture.



7.3 NOVARTIS INSTALMENT PLAN

A-Table 15. Discounted revenues from Novartis' financing plan

Underlying data for the comment on the NPV of Zolgensma sales via Novartis' instalment plan in section 4.2.4, page 49

The 5 equal annual instalments of $425,000 in the financing plan were discounted at 10.5%. FY0 is the year of the first instalment. Calculating the sum of all discounted cash payments reveals the NPV at FY0. The loss due to discounting is the difference between cash and discounted values.

FY	**0**	**1**	**2**	**3**	**4**	**Total**
Cash $	425,000	425,000	425,000	425,000	425,000	**2,125,000**
Discounted Value $	425,000	384,615	348,068	314,994	285,062	**1,757,740**
Difference $	-	-40,385	-76,932	-110,006	-139,938	**-367,260**

7.4 IIPU Revenue Estimation by Vintage Year

A-Table 16. Undiscounted revenues in the USA and EU

Underlying regional data for the revenue estimations in section 4.2.4, Table 12

This table shows the undiscounted revenues from the USA and EU generated by each HCCO vintage from all and risk-adjusted CPU by Y+9. Note that HCCO vintage years are essentially FY with regards to HCF, since there are only two HCF classes. HCF II were sold from Y+7. All revenues are multiples of $1,000,000.

V	All CPU				Adjusted CPU			
	USA		EU		USA		EU	
	HCCO	HCF	HCCO	HCF	HCCO	HCF	HCCO	HCF
Y-8								
Y-7	0.9		1.1		0.7		1.0	
Y-6	1.2		1.5		1.1		1.4	
Y-5	1.8		2.3		1.6		2.1	
Y-4	2.7		3.5		2.4		3.1	
Y-3	4.0		5.2		3.6		4.7	
Y-2	13.6		17.8		9.4		12.3	
Y-1	17.3		22.7		14.8		19.4	
Y0	34.7	196.3	45.4	256.9	29.6	133.3	38.7	174.5
Y+1		119.0		155.7		101.5		132.8
Y+2		119.0		155.7		101.5		132.8
Y+3		119.0		155.7		101.5		132.8
Y+4	95.4	119.0	124.8	155.7	81.4	101.5	106.5	132.8
Y+5		119.0		155.7		101.5		132.8
Y+6		119.0		155.7		101.5		132.8
Y+7		238.0		311.4		203.0		265.6
Y+8		238.0		311.4		203.0		265.6
Y+9		238.0		311.4		203.0		265.6
Total	**171.5**	**1624.1**	**224.4**	**2125.1**	**144.5**	**1351.1**	**189.1**	**1767.9**

A-Table 17. Discounted revenues in the USA and EU

Underlying regional data for the revenue estimations in section 4.2.4, Table 12

This table shows the discounted (10.5% DR) revenues from the USA and EU generated by each HCCO vintage from all and risk-adjusted CPU by Y+9. Note that HCCO vintage years are essentially FY with regards to HCF, since there are only two HCF classes. HCF II were sold from Y+7. All revenues are multiples of $1,000,000.

V	All CPU				Adjusted CPU			
	USA		EU		USA		EU	
	HCCO	HCF	HCCO	HCF	HCCO	HCF	HCCO	HCF
Y-8								
Y-7	1.2		1.6		1.1		1.4	
Y-6	1.6		2.1		1.4		1.8	
Y-5	2.2		2.8		1.9		2.5	
Y-4	2.9		3.9		2.6		3.4	
Y-3	4.0		5.2		3.5		4.6	
Y-2	12.2		16.0		8.4		11.0	
Y-1	13.9		18.2		11.8		15.5	
Y0	25.1	196.3	32.9	256.9	21.4	133.3	28.0	174.5
Y+1		107.7		140.9		91.8		120.2
Y+2		97.4		127.5		83.1		108.8
Y+3		88.2		115.4		75.2		98.4
Y+4	51.7	79.8	67.6	104.4	44.1	68.1	57.6	89.1
Y+5		72.2		94.5		61.6		80.6
Y+6		65.4		85.5		55.7		72.9
Y+7		118.3		154.8		100.9		132.0
Y+8		107.1		140.1		91.3		119.5
Y+9		96.9		126.8		82.6		108.1
Total	**114.8**	**1029.2**	**150.2**	**1346.7**	**96.2**	**843.8**	**125.9**	**1104.0**

7.5 IIPU Revenue Estimation by Financial Year

A-Table 18. HCD revenues from all CPU in the USA and EU

Underlying data for the chart in section 4.2.4, Figure 20

The running totals of undiscounted and discounted (10.5% DR) combined HCD revenues from the USA and EU from all CPU were calculated from Y-8 to Y+9. All revenues are multiples of $1,000,000.

FY	Undiscounted Revenue				Discounted Revenue			
	USA	EU	Total	Running Total	USA	EU	Total	Running Total
Y-8	-	-	-	-	-	-	-	-
Y-7	0.1	0.1	0.2	0.2	0.2	0.3	0.5	0.5
Y-6	0.3	0.4	0.6	0.9	0.5	0.6	1.1	1.6
Y-5	0.5	0.7	1.2	2.0	0.8	1.1	1.9	3.6
Y-4	0.9	1.1	2.0	4.0	1.3	1.7	3.0	6.6
Y-3	1.4	1.8	3.3	7.3	1.9	2.5	4.4	10.9
Y-2	3.2	4.2	7.4	14.7	3.9	5.1	9.0	20.0
Y-1	5.4	7.0	12.4	27.1	5.9	7.8	13.7	33.7
Y0	206.0	269.6	475.6	502.7	206.0	269.6	475.6	509.3
Y+1	128.5	168.1	296.6	799.3	116.3	152.1	268.4	777.7
Y+2	128.3	167.8	296.1	1095.4	105.0	137.4	242.5	1020.2
Y+3	127.9	167.4	295.4	1390.7	94.8	124.1	218.9	1239.1
Y+4	144.8	189.5	334.3	1725.0	97.1	127.1	224.2	1463.3
Y+5	143.9	188.3	332.2	2057.2	87.4	114.3	201.7	1665.0
Y+6	142.8	186.9	329.7	2387.0	78.5	102.7	181.1	1846.1
Y+7	259.6	339.7	599.4	2986.4	129.1	168.9	298.0	2144.0
Y+8	255.3	334.1	589.4	3575.7	114.9	150.3	265.2	2409.2
Y+9	246.6	322.7	569.3	4145.1	100.4	131.4	231.8	2641.0

A-Table 19. HCD revenues from risk-adjusted CPU in the USA and EU

Underlying data for the chart in section 4.2.4, Figure 20

The running totals of undiscounted and discounted (10.5% DR) combined HCD revenues from the USA and EU from risk-adjusted CPU were calculated from Y-8 to Y+9. All revenues are multiples of $1,000,000.

FY	Undiscounted Revenue				Discounted Revenue			
	USA	EU	Total	Running Total	USA	EU	Total	Running Total
Y-8	-	-	-	-	-	-	-	-
Y-7	0.1	0.1	0.2	0.2	0.2	0.2	0.4	0.4
Y-6	0.2	0.3	0.5	0.7	0.4	0.5	1.0	1.4
Y-5	0.4	0.6	1.0	1.7	0.7	0.9	1.6	3.0
Y-4	0.7	1.0	1.7	3.5	1.1	1.4	2.6	5.6
Y-3	1.2	1.6	2.8	6.2	1.6	2.1	3.8	9.3
Y-2	2.4	3.2	5.6	11.8	3.0	3.9	6.8	16.2
Y-1	4.3	5.6	9.9	21.7	4.7	6.2	10.9	27.0
Y0	141.3	184.9	326.2	347.9	141.3	184.9	326.2	353.2
Y+1	109.3	143.0	252.4	600.2	98.9	129.4	228.4	581.6
Y+2	109.2	142.8	252.0	852.2	89.4	117.0	206.4	788.0
Y+3	108.9	142.5	251.4	1103.6	80.7	105.6	186.4	974.3
Y+4	123.4	161.4	284.8	1388.4	82.7	108.3	191.0	1165.3
Y+5	122.8	160.6	283.4	1671.8	74.5	97.5	172.0	1337.4
Y+6	121.8	159.4	281.2	1953.0	66.9	87.6	154.5	1491.8
Y+7	221.5	289.8	511.2	2464.3	110.1	144.1	254.1	1746.0
Y+8	217.8	284.9	502.7	2967.0	98.0	128.2	226.2	1972.1
Y+9	210.4	275.3	485.6	3452.6	85.6	112.1	197.7	2169.9

7.6 Revenues at Market Price

A-Table 20. Zolgensma revenues at market price

Underlying data for the comment on break-even points at Zolgensma market price in section 4.2.4, page 51.

Revenue calculation at Zolgensma market price was subject to the same assumptions as the IIPU base data. The sales price was discounted at 10.5% to generate annual revenues. 'Global' denotes combined revenues from the USA and EU. Revenues were separated for all and risk-adjusted CPU. The benchmark capitalised R&D costs of $2,757M were used for NPV calculation. The first positive NPV points are highlighted in grey. Except for CPU all figures are multiples of $1,000,000. CPU are number of persons.

		USA		EU		USA		EU		Global					
		CPU				Revenue				Total Revenue		Running Total		NPV	
FY	Price	All	Adjusted	All	Adjusted	All	Adjusted	All	Adjusted	All	Adjusted	All	Adjusted	All	Adjusted
0	2.1	393	267	514	349	835.1	567.4	1,092.3	741.6	1,927.4	1,309.0	1,927.4	1,309.0	-829.9	-1,448.3
1	1.9	238	203	311	266	457.7	390.4	598.1	511.5	1,055.8	901.9	2,983.1	2,210.9	225.8	-546.4
2	1.7	238	203	311	266	414.2	353.3	541.2	462.9	955.4	816.2	3,938.6	3,027.1	1,181.3	269.8
3	1.6	238	203	311	266	374.8	319.7	489.8	418.9	864.7	738.7	4,803.2	3,765.8	2,046.0	1,008.5
4	1.4	238	203	311	266	339.2	289.3	443.3	379.1	782.5	668.5	5,585.7	4,434.3	2,828.5	1,677.0
5	1.3	238	203	311	266	307.0	261.8	401.2	343.1	708.1	605.0	6,293.9	5,039.2	3,536.6	2,281.9
6	1.2	238	203	311	266	277.8	237.0	363.0	310.5	640.9	547.5	6,934.7	5,586.7	4,177.4	2,829.4
7	1.1	238	203	311	266	251.4	214.4	328.5	281.0	580.0	495.4	7,514.7	6,082.1	4,757.4	3,324.8
8	1.0	238	203	311	266	227.5	194.1	297.3	254.3	524.8	448.4	8,039.5	6,530.5	5,282.2	3,773.2
9	0.9	238	203	311	266	205.9	175.6	269.1	230.1	475.0	405.8	8,514.5	6,936.3	5,757.2	4,179.0

7.7 IIPU Revenue Estimation by Discount Rate

A-Table 21. HCD revenues at increasing discount rates

Underlying data for the chart in section 4.2.4, Figure 21B

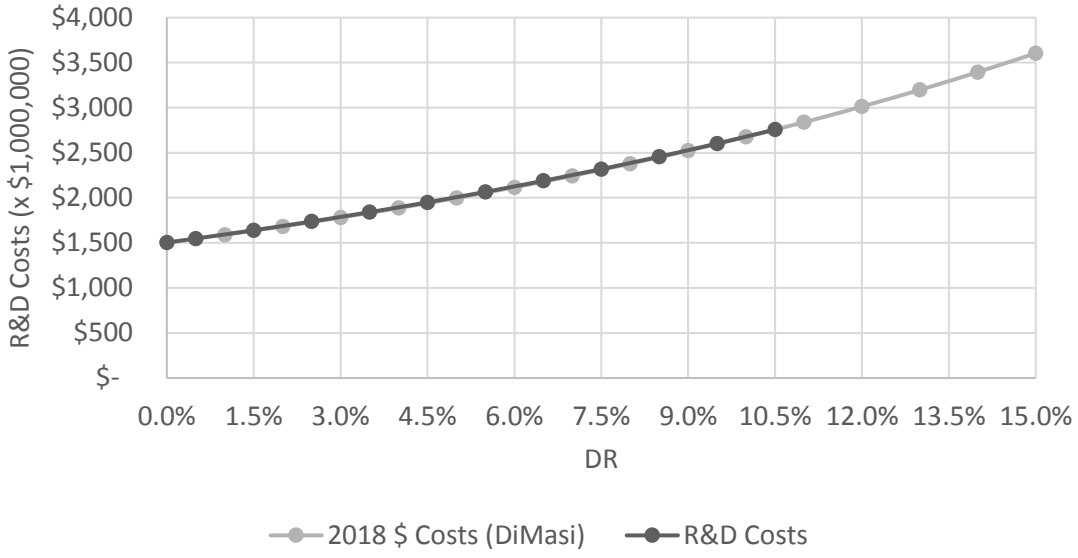
Y+9 accumulated HCD revenues from all and risk-adjusted CPU in the USA and EU were discounted at increasing DR. R&D costs were calculated by continuous compounding as described in section 4.2.4, Figure 21. All figures are multiples of $1,000,000.

DR	All CPU			Adjusted CPU			R&D Costs
	USA	EU	Total	USA	EU	Total	
0.0%	1,795.6	2,349.5	4,145.1	1,495.6	1,957.0	3,452.6	1,503.7
0.5%	1,751.6	2,291.9	4,043.4	1,458.1	1,907.8	3,365.9	1,547.7
1.5%	1,668.5	2,183.2	3,851.7	1,387.2	1,815.2	3,202.4	1,639.7
2.5%	1,591.7	2,082.6	3,674.3	1,321.7	1,729.4	3,051.1	1,737.2
3.5%	1,520.4	1,989.4	3,509.8	1,260.9	1,649.9	2,910.8	1,840.5
4.5%	1,454.3	1,902.9	3,357.2	1,204.6	1,576.1	2,780.7	1,949.9
5.5%	1,392.9	1,822.6	3,215.5	1,152.2	1,507.6	2,659.8	2,065.8
6.5%	1,335.9	1,747.9	3,083.8	1,103.6	1,443.9	2,547.5	2,188.6
7.5%	1,282.8	1,678.4	2,961.2	1,058.3	1,384.7	2,442.9	2,318.7
8.5%	1,233.3	1,613.7	2,847.0	1,016.1	1,329.5	2,345.5	2,456.6
9.5%	1,187.1	1,553.3	2,740.4	976.7	1,278.0	2,254.7	2,602.6
10.5%	1,144.1	1,496.9	2,641.0	940.0	1,229.9	2,169.9	2,757.3

A-Figure 24. Comparison of R&D cost calculations

Underlying chart for the comment on verification of R&D costs in section 4.2.4, page 52

The R&D costs in the source publication were adjusted from 2013 to 2018 US dollars (DiMasi, Grabowski et al. 2016) and plotted alongside R&D costs calculated as described in section 4.2.4, Figure 21. The overlap shows that both approaches yield very similar curves.



A-Figure 25. Trendlines for HCD revenues and R&D costs

HCD revenues in Y+9 were simulated as described in section 4.2.4, Figure 21. Polynomial trendlines with y-intercepts fixed at the undiscounted values were generated in Microsoft Excel. $R^2 \sim 1$ shows perfect fit of each.

Setting each of the HCD revenue trendline equations equal to the R&D costs equation and solving for x revealed the break-even points at 10.1% and 8.0% DR for all and adjusted CPU, respectively.