The financial ecosystem of pharmaceutical R&D

An evidence base to inform further dialogue

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The financial ecosystem of pharmaceutical R&D: An evidence base to inform further dialogue.

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Executive summary

What constitutes socially acceptable pharmaceutical prices? To what extent are these prices driven by research and development (R&D) costs? Where is public investment in pharmaceutical R&D most needed to resolve the system's potential failure to address unmet societal needs? How do incentives affect investment decisions? How can socially responsible licensing be shaped? These and other questions are central to societal debates about innovative pharmaceutical drugs. To enable well-informed debates, a better understanding of the financial ecosystem of pharmaceutical R&D and how it operates is crucial. This need has prompted the Dutch Ministry of Health to commission a descriptive study to provide an objective fact-base.

This study's overarching conclusion is that a drug's expected financial return ultimately determines whether it is developed up to launch. Assessment of expected financial return incorporates multiple interconnected factors, including but not limited to commercial potential, investment cost, availability of capital, the potential for scientific and medical advancement, strategic fit and risk. The relative importance of these factors varies by investor and evolves as drugs move through the drug-development continuum. **A drug's expected financial return is driven by its expected revenue potential. Therefore, global governments and (private) insurance companies' expected willingness to pay for new drugs considerably influences the supply of novel drugs and the distribution across therapeutic areas.** Other important factors influencing the supply of novel drugs are the pace and nature of scientific advances, the ability of R&D systems to leverage data and digital technology advances to inform innovative clinical trial designs, and regulatory developments.

The two arguments of this conclusion are set out below, after an overview of the pharmaceutical R&D market.

Pharmaceutical R&D is a multistakeholder and increasingly complex $300bn global market

A growing recourse to collaboration between executors of pharmaceutical R&D has taken place over recent decades, increasing the number of potential routes for launching novel drugs. This study distinguished roughly seven different archetypes of pharmaceutical development routes to provide an overview.

Big biopharma is the largest funder of pharmaceutical R&D, representing almost two-thirds of total R&D investment of circa $300bn in 2020 globally. Public-sector and not-for-profit organisations account for more than a quarter, and the remaining 10% is attributable to venture capitalists (VCs). VC investment is proliferating rapidly, mainly driven by the Asia-Pacific region (APAC).

For the company executing the R&D, the average out-of-pocket R&D costs to develop one drug are $280–$380m. In contrast, a single approved drug costs the system $2.4–$3.2bn on average. The latter figure includes the costs for drugs that fail to reach the market and capital costs.

Ultimately, a drug's expected financial return determines whether it is developed up to launch

A drug's expected financial return ultimately determines whether it is developed up to launch. Early research is often funded by public-sector and not-for-profit organisations mainly motivated by creating societal impact. However, private investment is needed to bring a drug to launch. VC investment is particularly important for overcoming the 'translation gap', and big biopharma plays a crucial role in financing late-stage clinical development phases.

Private investors seek sufficiently high risk-adjusted financial returns for their investors and shareholders, and their assessment of expected financial returns varies. VCs look for assurance of a likely end-market for potential new products, picking science-based investments across their portfolio that will outperform the average risk profile of early-stage companies. As products progress through development stages and the risk profiles begin to diminish, big biopharma conducts assessments of commercial potential. These assessments are driven by more detailed assumptions of addressable patient populations, levels of unmet need, drug-value propositions, expected uptake and pricing potential. They must then weigh that return against the investment required to bring a product to market and broader strategic considerations across the entire product portfolio.

Expected global willingness to pay considerably influences the supply and distribution of novel drugs

The expected willingness to pay for new pharmaceutical drugs in key global markets considerably influences the supply of novel drugs and the distribution across therapeutic areas. Lower expected willingness to pay for drugs could result in fewer novel drugs being launched in the coming decades. Due to affordability issues in key global markets – largely driven by the higher prices associated with more personalised approaches and segmented markets – willingness to pay may come under pressure. Drugs with the highest expected willingness to pay are most likely to be developed within the life-sciences sector. Other areas, such as some non-life-threatening diseases and areas where suboptimal alternative treatments exist, may thus struggle to secure investment.

For conciseness, this report focuses on the study's key insights and **more in-depth insights into the landscape's complexity are presented in three separate annexes**. Annex A contains the quantitative analyses conducted for this study and covers topics not explicitly addressed in this report, such as analyses of ongoing development programs, revenue potential and drug-developer corporate finance. **An online database is available, from which all graphs in the annex may be reproduced**. **In addition, the eNPV model built for this study is publicly available**. Annex B discusses the changing R&D landscape through an evolutionary and future-focused lens. Annex C uses future financial-ecosystem scenarios for pharmaceutical R&D as a research tool to reflect on considerations to prepare the system for potential future developments.

Managementsamenvatting

Wat zijn maatschappelijk aanvaardbare prijzen voor geneesmiddelen? In welke mate worden deze prijzen bepaald door de kosten van onderzoek en ontwikkeling (R&D)? Waar zijn overheidsinvesteringen het sterkst nodig om mogelijk systeemfalen op te lossen, om zo onvervulde medische behoefte te adresseren? Hoe beïnvloeden prikkels investeringsbeslissingen? Hoe kan het maatschappelijk verantwoord licentiëren worden vormgegeven? Deze en andere vragen staan centraal in het maatschappelijk debat over innovatieve geneesmiddelen. Om dit debat goed geïnformeerd te voeren is het van cruciaal belang te begrijpen hoe het financiële ecosysteem van geneesmiddelen R&D functioneert. Het Ministerie van Volksgezondheid, Welzijn en Sport (VWS) heeft daartoe een beschrijvend onderzoek laten uitvoeren.

Uit het beschrijvend onderzoek blijkt dat het verwachte financiële rendement de belangrijkste factor is die bepaalt of een geneesmiddel tot lancering wordt ontwikkeld. De beoordeling van het verwachte financiële rendement bestaat uit meerdere onderling samenhangende factoren. Hieronder vallen onder meer: het commerciële potentieel, de investeringskosten, de beschikbaarheid van kapitaal, het potentieel van een wetenschappelijke en medische doorbraak, de strategische fit en het risico. Het relatieve belang van deze factoren verschilt per investeerder en per fase van geneesmiddelen R&D. **Het verwachte financiële rendement van een geneesmiddel wordt bepaald door de verwachte inkomsten. De bereidheid van overheden en (particuliere) verzekeraars om te betalen voor nieuwe geneesmiddelen is daarom van grote invloed op het aanbod van nieuwe geneesmiddelen en de spreiding ervan over de therapeutische gebieden.** Andere belangrijke factoren die van invloed zijn op het aanbod van nieuwe geneesmiddelen zijn het tempo en de aard van wetenschappelijke ontwikkelingen, het vermogen van R&D-systemen om innovatieve klinische studies op te zetten door ontwikkelingen op het gebied van data en digitale technologie, en ontwikkelingen op het gebied van regulering.

Hieronder zetten we de twee argumenten van de conclusie uiteen, na eerst een overzicht van de markt van geneesmiddelen R&D te geven.

Geneesmiddelen R&D is een steeds complexere wereldmarkt met meerdere stakeholders die goed is voor $300 miljard

De laatste decennia zijn uitvoerders van geneesmiddelen R&D steeds meer gaan samenwerken. Daardoor is het aantal potentiële routes voor de lancering van nieuwe geneesmiddelen toegenomen. Dit onderzoek geeft een overzicht hiervan door zeven verschillende archetypes van farmaceutische ontwikkelingsroutes te onderscheiden.

Grote biofarmabedrijven zijn de grootste financiers van geneesmiddelen R&D en zijn verantwoordelijk voor bijna tweederde van de wereldwijde totale R&D-investeringen. In 2020 was dit circa $300 miljard. Overheids- en non-profitorganisaties nemen meer dan een kwart voor hun

rekening en de resterende 10% is afkomstig van venture capital fondsen (VCs). De investeringen van VCs nemen snel toe, vooral in de regio Azië-Pacific (APAC).

Voor de uitvoerder van R&D zijn de gemiddelde directe R&D-kosten voor de ontwikkeling van één geneesmiddel $280-$380 miljoen. Daarentegen kost een enkel goedgekeurd geneesmiddel het systeem gemiddeld $2,4-$3,2 miljard. In dit laatste bedrag zijn ook de kosten meegenomen voor geneesmiddelen die niet op de markt komen en de kapitaalkosten.

Uiteindelijk bepaalt het verwachte financiële rendement of een geneesmiddel tot lancering wordt ontwikkeld

Het verwachte financiële rendement is uiteindelijk de belangrijkste factor die bepaalt of een geneesmiddel tot lancering wordt ontwikkeld. Vroegtijdig onderzoek wordt vaak gefinancierd door overheids- en non-profitorganisaties. Zij zijn voornamelijk gemotiveerd om maatschappelijke impact te realiseren. Private investeringen zijn echter nodig om een geneesmiddel op de markt te brengen. Investeringen van VCs zijn met name van belang om de zogenaamde "translation gap" te overbruggen, en grote biofarmabedrijven spelen een cruciale rol bij de financiering van de latere fases wanneer er grote klinische studies plaatsvinden.

Private investeerders streven naar een voldoende hoog, naar risico gewogen financieel rendement voor hun investeerders en aandeelhouders. Hun beoordeling van het verwachte financiële rendement varieert:

- VCs streven naar zekerheid van een afzetmarkt voor potentiële nieuwe producten. Hierbij kiezen zij op basis van wetenschappelijke inzichten in welke bedrijven zij investeren. VCs verwachten op basis van hun inzichten dat deze bedrijven beter presteren dan het gemiddelde risicoprofiel van bedrijven met producten in vroege ontwikkelingsfases.
- Naarmate producten zich verder in de ontwikkelingsfase bevinden en het risicoprofiel afneemt, beoordelen grote biofarmabedrijven het commerciële potentieel. Deze beoordelingen zijn gebaseerd op meer gedetailleerde aannames over de patiëntenpopulaties die kunnen worden bereikt, de mate waarin medische behoeftes nog niet zijn vervuld, de waardepropositie van het geneesmiddel, de verwachte uptake en de verwachte verkoopprijs. Vervolgens wegen ze dat rendement af tegen de investering die nodig is om een product op de markt te brengen. In deze beoordelingen nemen ze ook de bredere strategische overwegingen voor de hele productportefeuille mee.

De verwachte wereldwijde betalingsbereidheid beïnvloedt de levering en de spreiding van nieuwe geneesmiddelen sterk

De verwachte wereldwijde betalingsbereidheid van overheden en (particuliere) verzekeraars voor nieuwe geneesmiddelen beïnvloedt in belangrijke mate het aanbod van nieuwe geneesmiddelen en de spreiding ervan over de therapeutische gebieden:

- Een lagere verwachte betalingsbereidheid voor geneesmiddelen zou ertoe kunnen leiden dat er de komende decennia minder nieuwe geneesmiddelen op de markt komen. Als gevolg van betaalbaarheidsproblemen op belangrijke wereldmarkten - grotendeels gedreven door de

hogere prijzen die gepaard gaan met meer gepersonaliseerde geneesmiddelen en gesegmenteerde markten - kan de betalingsbereidheid onder druk komen te staan.

- De geneesmiddelen met de hoogste verwachte betalingsbereidheid zijn de geneesmiddelen die het meest waarschijnlijk ontwikkeld zullen worden in de lifesciences sector. Andere geneesmiddelen, zoals voor sommige aandoeningen die niet-levensbedreigend zijn of binnen gebieden waarvoor suboptimale alternatieve behandelingen bestaan, kunnen daarom moeite ervaren om investeringen aan te trekken.

Vanwege de wens tot beknoptheid concentreert dit rapport zich op de belangrijkste inzichten van de studie. **Meer diepgaande inzichten in de complexiteit van het ecosysteem presenteren we in drie afzonderlijke bijlagen.** Annex A bevat de kwantitatieve analyses die voor dit onderzoek zijn uitgevoerd en behandelt onderwerpen die niet expliciet in dit rapport aan bod komen, zoals analyses van lopende ontwikkelingsprogramma's, het inkomstenpotentieel van geneesmiddelen en de bedrijfsfinanciering van geneesmiddelenbedrijven. **Er is een online database beschikbaar waaruit alle grafieken in de bijlage kunnen worden gereproduceerd. Bovendien is het eNPV-model dat voor dit onderzoek is ontwikkeld openbaar beschikbaar.** In Annex B staat het veranderende R&D-landschap vanuit een historisch en toekomstgericht perspectief beschreven. Annex C beschrijft overwegingen om het financiële ecosysteem voor te bereiden op mogelijke toekomstige ontwikkelingen. Hierbij zijn toekomstige scenario's van het financiële ecosysteem voor geneesmiddelenontwikkeling en -onderzoek gebruikt als onderzoeksinstrument.

Contents

1 Study objective and conclusion

1.1 Understanding the financial ecosystem of pharmaceutical R&D enables well-informed societal debate

What constitutes socially acceptable pharmaceutical prices? To what extent are these prices driven by research and development (R&D) costs? Where is public investment in pharmaceutical R&D most needed to resolve the system's potential failure to address unmet societal needs? How do incentives affect investment decisions? How can socially responsible licensing be shaped? These important questions dominate social debates on balancing innovative drugs' value versus expenditure.

To conduct well-informed debates, it is crucial for governments and other stakeholders to better understand how the financial ecosystem of pharmaceutical R&D operates. Knowing how key investment decisions are taken and financed helps answer the questions above. In addition, insights on how it has developed over recent decades and how it may further evolve provide crucial input for societal debate.

1.2 To meet this need, the Dutch Ministry of Health commissioned a descriptive study to provide an objective fact-base

While there are numerous publications on the phases of R&D and the overall level of investment, *how* and *why* different R&D financial ecosystem participants invest is less well researched and understood. Therefore, the Department of Pharmaceutical Affairs and Medical Technology at the Dutch Ministry of Health, Welfare and Sports (VWS) commissioned a descriptive study into the financial ecosystem of pharmaceutical R&D, selecting a consortium consisting of Strategies in Regulated Markets (SiRM), L.E.K. Consulting LLP (L.E.K.) and RAND Europe to conduct the study.

This study's objective is to describe the international financial ecosystem of pharmaceutical R&D from drug-target selection to launch. To do so requires insights into investors and executors' interests, considerations and choices and the associated financial transactions that lead to a drug being developed and made available to the patient.

Our goal is to identify facts, trends and insights. In doing so, our study aims to contribute to an objective basis for a dialogue on the functioning of the financial ecosystem of pharmaceutical R&D. In addition, this study sheds light on the broader features of the healthcare innovation landscape influencing this financial ecosystem's evolution in a way that can help achieve policy goals. However, providing specific policy recommendations is outside the remit of the commissioned study.

We used a mixed-methods approach, combining desk research and quantitative data with in-depth interviews and workshop-based stakeholder engagement. Since the quantitative analyses

are based on historical data, they may not show future developments. Full methodological details are described in Appendix 1. Both quantitative and qualitative methods have strengths and weaknesses. While quantitative data provides useful and important indications of the state of the financial ecosystem, it cannot answer all question types, and quality may be limited. In contrast, qualitative approaches may lack representativeness due to the limited number of interviewees per stakeholder type. However, they can help elicit diverse actors' in-depth experiential knowledge of areas unsuited to quantitative investigation. Triangulating the results of quantitative analyses with qualitative findings increases the robustness of study results by combining both methods' strengths.

1.3 Study conclusion and readers' guide

This study's overarching conclusion is that a drug's expected financial return ultimately determines whether it is developed up to launch. Assessment of expected financial return incorporates multiple interconnected factors, including but not limited to commercial potential, investment cost, availability of capital, the potential for scientific and medical advancement, strategic fit and risk. The relative importance of these factors varies by investor and evolves as drugs move through the drug-development continuum (Chapter 3).

A drug's expected financial return is driven by its expected revenue potential. Therefore, global governments and (private) insurance companies' expected willingness to pay for new drugs considerably influences the supply of novel drugs and the distribution across therapeutic areas. Other important factors influencing the supply of novel drugs are the pace and nature of scientific advances, the ability of R&D systems to leverage data and digital technology advances to inform innovative clinical trial designs and regulatory developments (Chapter 4).

Before Chapters 3 and 4 explain these two conclusions in more detail, Chapter 2 provides an overview of the pharmaceutical R&D market. It describes its increasingly complex nature with multiple stakeholders collaborating across national and continental borders.

The study has provided multiple in-depth quantitative and qualitative insights relevant to understanding the financial ecosystem of pharmaceutical R&D. For conciseness, this report focuses on the study's key findings, presenting more in-depth insights into the landscape's complexity in separate annexes: A (Text box 1), B (Text box 2) and C (Text box 3).

Annex A contains the full results of the quantitative analyses conducted for this study. The slide deck includes circa 40 figures and more than 70 graphs. **An online database is available from which all graphs may be reproduced**. The annex starts with stakeholder characterisation and descriptions of R&D executors and investors, including analyses of ongoing development programs, revenue potential and drug-developer corporate finance not explicitly addressed in this report. Annex A presents an in-depth analysis of investment rationale, **including a publicly available eNPV model built for this study**. In addition, the annex includes a section on drug-developer corporate finance, discussing accounting principles, dividend payments and share buy-backs. Finally, the annex presents eight case studies to provide real-world illustrations of drug-development routes.

Text box 1. Annex A contains the full results of the quantitative analyses conducted for this study.

Annex B sets out the changing R&D landscape through an evolutionary and future-focused lens. It describes key changes over the past decade influencing pharmaceutical R&D's financial ecosystem and what it looks like today, setting out key influences on its future financial ecosystem by describing likely trajectories and uncertainties.

Text box 2. Annex B sets out the changing R&D landscape through an evolutionary and future-focused lens.

Annex C considers issues currently meriting stakeholder consideration as part of efforts to optimise the future financial ecosystem for pharmaceutical R&D. It uses scenarios as a research tool to enable stakeholder discussion. By including a mix of more likely and extreme possibilities for the future, these scenarios were used to help stakeholders reflect on ways to minimise risks, maximise future opportunities and manage challenges. Annex C considers relevant themes for supporting this financial ecosystem's evolution in a way that can help achieve policy goals for the appropriate supply of affordable and accessible innovation and economic competitiveness from innovation activities.

Text box 3. Annex C describes future scenarios for the financial ecosystem of pharmaceutical R&D and the key learning points drawn from them.

The contents of this report derive from the quantitative and qualitative analyses included in Annexes A, B and C. Results of quantitative analyses presented in the report include references to specific sources. Qualitative statements are either based on the annexes or referenced in the text.

A glossary of terms used in this report is provided in Appendix 2.

2 Pharmaceutical R&D is a multistakeholder and increasingly complex $300bn global market

There has been increasing collaboration between pharmaceutical R&D executors, increasing the potential routes to launching novel assets (§2.1). Big biopharma is the largest funder of pharmaceutical R&D, representing almost two-thirds of total R&D investment of circa $300bn in 2020. Public-sector and not-for-profit organisations account for more than a quarter, and the remaining 10% is attributable to VCs. The latter is rapidly proliferating, driven mainly by the Asia-Pacific region (APAC) (§2.2). For the company executing pharmaceutical R&D, average out-of-pocket costs to develop one drug are $280–$380m, whereas capitalised costs for a single approved drug cost the system $2.4–$3.2bn (§2.3).

This chapter describes some important elements of the pharmaceutical R&D's financial ecosystem. Additional descriptive information on the system and its actors is available in Annex A.

2.1 Growing collaboration between R&D executors has increased potential routes to launch

Various executors perform pharmaceutical R&D (Figure 1). Their activity depends primarily on the development phase:

- Academic institutions and public research groups (PRGs) / not-for-profit organisations[1] are principally concerned with target selection, i.e. identifying disease targets, although they may also play a role in later phases.
- Biotechnology companies (biotech) or small/medium-sized biopharmaceutical companies (SMEs) are most active in drug discovery, preclinical development and early-stage clinical development. Drug discovery involves finding and optimising a drug candidate that interacts with the disease target. In the preclinical development phase, the safety and efficacy profiles of the drug candidate are tested in animal models and subsequently in human trials in clinical-development phases.
- Medium/large-sized biopharmaceutical companies (big biopharma) are active throughout the whole value chain. They are the critical late-stage clinical development executors. The

[1] PRGs and not-for-profit organisations with intramural labs/capabilities are similar to academic institutions and often housed in universities. They conduct early-stage research and may oversee asset development until early clinical development.

responsibility is typically transferred to big biopharma from the end of phase 1 or during phase 2. However, biotech/SMEs seeking to commercialise their assets themselves are increasingly carrying out such work.

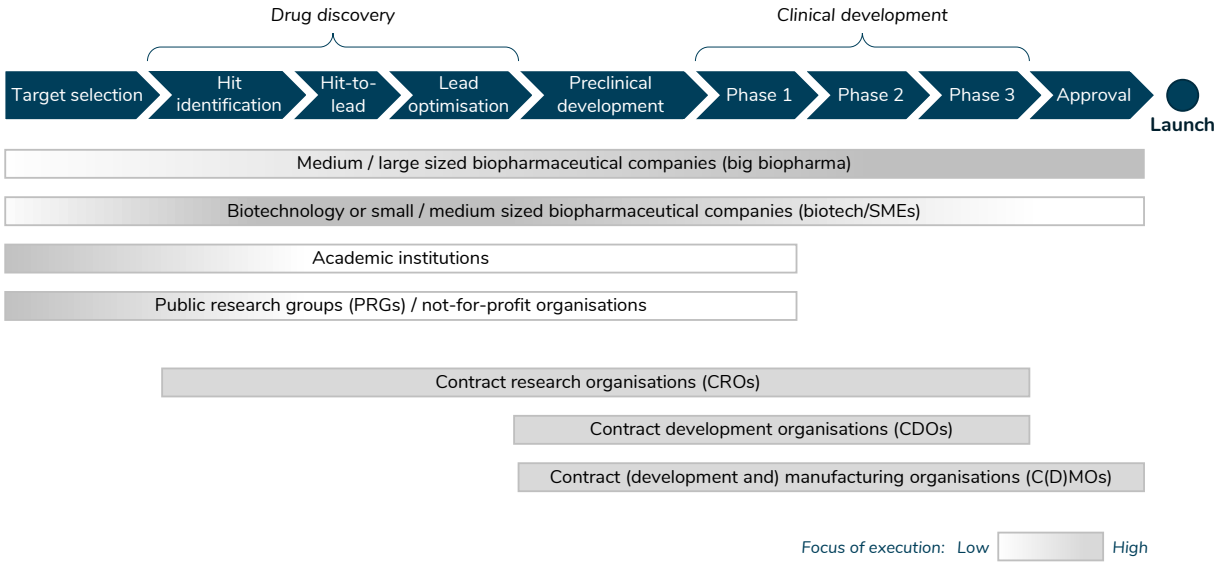

Figure 1. All executors are concerned with early-stage R&D. For late-stage development (i.e. the end of phase 1 or during phase 2) responsibility is typically transferred to big biopharma. However, independent biotech/SMEs seeking to commercialise their assets themselves are increasingly carrying out such work.

In addition, executors outsource elements of R&D to service providers such as contract research organisations (CROs), contract development organisations (CDOs) and contract-development and/or manufacturing organisations (CMOs, CDMOs). CROs are involved from drug discovery to clinical development and specialise in different stages of the R&D process. Hence different CROs likely play different roles along the R&D chain. CDOs come into play from preclinical to clinical development. CDMOs/CMOs play a role from preclinical development to launch and beyond.

Although big biopharma and, to a lesser extent, biotech/SMEs can develop a drug from target selection to launch, the R&D route often involves collaboration. Indeed, the growing collaboration between different executor types over the last decade (Text box 4) has increased potential routes to launching novel assets, which have become more complex, often involving multiple steps.

Zolgensma (Figure 2) provides a recent example of collaboration between different types of executors. Designed to treat spinal muscular atrophy (SMA) caused by genetic changes in the SMN1 gene, Zolgensma originated from a small/medium platform-technology biopharma (ReGenX) whose assets were in-licensed for development by Avexis. After data from phase 2 studies were announced, Avexis signed a deal with ReGenX to in-licence the exclusive global rights to use their assets. During phase 3 studies, Avexis was acquired by Novartis.

Text box 4. Example of collaboration between different types of executors.

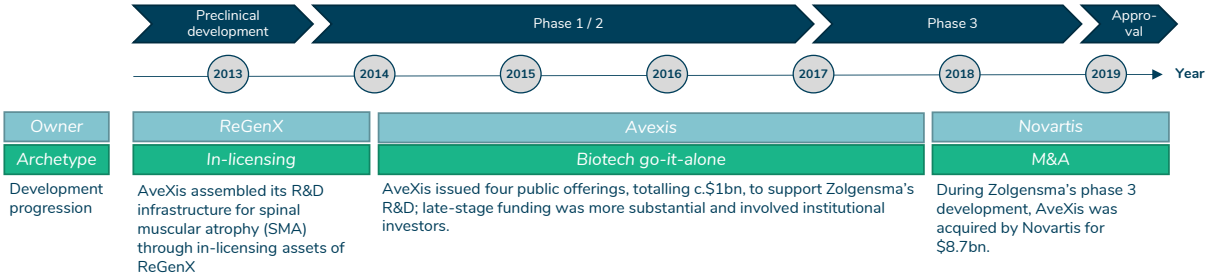

Figure 2. Different types of executors collaborated in the development of Zolgensma.

Although numerous potential R&D routes to drug launch exist, this study distinguished roughly seven archetypes to provide an overview (Figure 3).[2] These archetypes are based on the asset's origin at preclinical development and the drug marketeer's ultimate actions. Possible asset origins include big-biopharma internal discovery, big-biopharma carve-out,[3] a repurposed drug[4] by an external company,[5] biotech/SME drug discovery or academic/PRG drug discovery. In practice, routes are usually a hybrid of these archetypes, depending on individual companies' specific products, technologies, goals and circumstances, largely context-dependent.

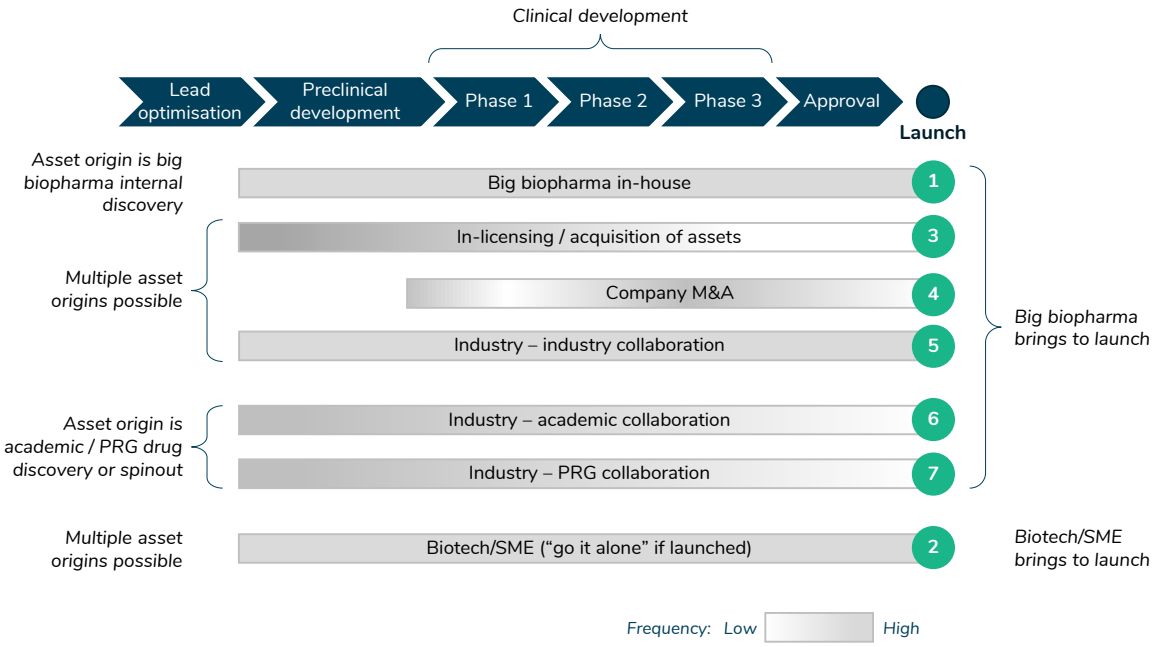

Figure 3. Although potential routes to launch novel drugs are complex and involve multiple steps, roughly seven different archetypes were distinguished.

The first two of the seven archetypes represent isolated R&D, i.e. involving minimal collaboration between different executors (Text box 5):

1 **Big biopharma in-house**: From internal R&D to launch, asset development remains within big biopharma. In-house R&D is used to discover lead compounds, including the repositioning of drugs.

[2] The most common route is not necessarily the preferred route but reflects options on the table at any given time.
[3] Big biopharma can divest assets that are not in active development, which may be carved out as a biotech/SME.
[4] Assets that have been previously trialled or launched in other indications repurposed as a lead for use in a novel indication.
[5] Not being the originator company or spin-out of the originator company.

2 **Biotech/SMEs 'go it alone'**: Asset development happens exclusively within biotech/SME through to launch. The company itself may discover the asset or it may be a big-biopharma carve-out, a repurposed drug or an academic/PRG discovery. Efforts of biotech/SMEs to 'go it alone' are becoming increasingly popular, especially in the United States (US) and, to a lesser extent, in Europe. Commercialising their assets themselves enables biotech/SMEs to capture more value. Their ability to pursue a growth strategy and move into later R&D stages depends on the therapeutic and technological focus and the size of patient populations. In addition, it depends on revenue position, the ability to attract capital, and the ability to outsource parts of the R&D process, such as clinical trials and manufacturing, to CROs, CDOs and CMOs. Section 2.1.6 of Annex B describes this development in more detail.

A recent example of **big-biopharma in-house** is Piqray (alpelisib), a small molecule targeting various oncology indications. It was discovered and developed by Novartis through to launch. Zynteglo (betibeglogene autotemcel), a gene therapy for transfusion-dependent β-thalassaemia, is a recent example of **biotech/SMEs 'go it alone'**. It was discovered and developed by bluebird bio through to launch.

Text box 5. Examples of isolated R&D archetypes.

The next two archetypes are translational (Text box 6):

3 **In-licensing or acquisition of assets**: This route describes the transfer of asset ownership during R&D via asset in-licensing or acquisition of assets, whereby only the asset rights are purchased, not the whole company. Various asset origins are possible in this route. Most in-licensing deals happen earlier in the process than company M&A, i.e. in drug discovery or the preclinical-development phase.[6, 7]

4 **Company mergers and acquisitions (M&A)**. In this route, asset ownership is transferred to big biopharma[8] during the R&D process via company M&A. The acquired company may, for example, be a big-biopharma carve-out or an academic/PRG spin-out. Most M&A occurs at the preclinical development phase and in phase 2.[9, 10]

The deal between Novartis and The Medicines Company (SME) during the approval phase is a recent example of company M&A. The deal mainly concerned Leqvio (inclisiran), which treats atherosclerotic cardiovascular disease of familial hypercholesterolemia by lowering cholesterol on top of standard of care. Vitrakvi (larotrectinib), a small molecule kinase inhibitor for cancer treatment, is a recent example of **asset in-licensing**. It was discovered by Loxo Oncology (biotech) and in-licensed by Bayer (a big biopharma company) during phase 2 clinical development.

Text box 6. Examples of translational archetypes.

[6] In 2018, 39% of the in-licensing deals were in the research stage, 21% in the preclinical-development phase, 12% in phase 1 or phase 1/2, 10% in phase 2, 10% in phase 3 and 8% filed. Source: L.E.K. analysis of Pharmaprojects.
[7] See Annex A (Section 3 - Financial Instruments Analysis) for more analyses, e.g. changes over time and the deal values of licensing deals per executor.
[8] Typically big biopharma, but asset ownership could be transferred to SMEs too.
[9] In 2018, 36% of the M&A deals by most advanced asset were in the preclinical-development phase, 11% in phase 1, 32% in phase 2 and 21% in phase 3. Source: L.E.K. analysis of Pharmaprojects.
[10] See Annex A (Section 3 - Financial Instruments Analysis) for more analyses, e.g. values of equity deals per executor.

Finally, the last three archetypes are collaborative (Text box 7):

5 **Industry-industry collaboration**: All asset origins are possible in this type of collaboration. In this archetype the originator may share product development responsibilities and costs with another industry player to access capabilities and reduce the development-cost burden on the originator.

6 **Industry-academic collaboration**: The asset originates from an academic drug discovery or spinout in this route. While early drug-development stages may be pursued internally by academic institutions, capital requirements often necessitate the involvement of an industry collaborator.

7 **Industry-PRG/not-for-profit collaboration**: The asset originates from a PRG discovery or PRG spin-out in this type of collaboration. Like academic institutions, the PRG typically needs an industry partner for later-stage development.

A recent example of **industry-industry collaboration** is Shionogi and Roche co-development of Xofluza (baloxavir marboxil), an oral endonuclease inhibitor for the influenza virus. An example of **industry-academic collaboration** is the collaboration between the University of Washington and Sage Therapeutics to develop Zulresso (brexanolone), a neuromodulator for postpartum depression. The collaboration between Roche, PTC therapeutics and Spinal Muscular Atrophy Foundation for Evrysdi (risdiplam), an oral splice modifier in SMA, is a recent example of **industry–PRG/not-for-profit collaboration**.

Text box 7. Examples of collaborative archetypes.

In addition to more detailed information on the Zolgensma development route (Text box 4), Annex A (Section 6 – Case studies) includes six case studies describing development routes combining multiple archetypes. Of these, four concern the innovative/orphan therapies Darzalex (daratumumab), Luxtuma (voretigene neparvovec-rzyl), Keytruda (pembrolizumab) and Yescarta (axicabtagene ciloleucel). Additionally, the Galapagos Pharma case study describes an example of R&D failure, while the Abilify (aripripazole) case study examines a therapy's life-cycle evolution.

2.2 Big biopharma was the largest contributor to circa $300bn total global investment in R&D in 2020, followed by public funders and strongly growing VC investment

Multiple investors play a role in financing pharmaceutical R&D. Like the executors, their activity depends primarily on the development phase (Figure 4).

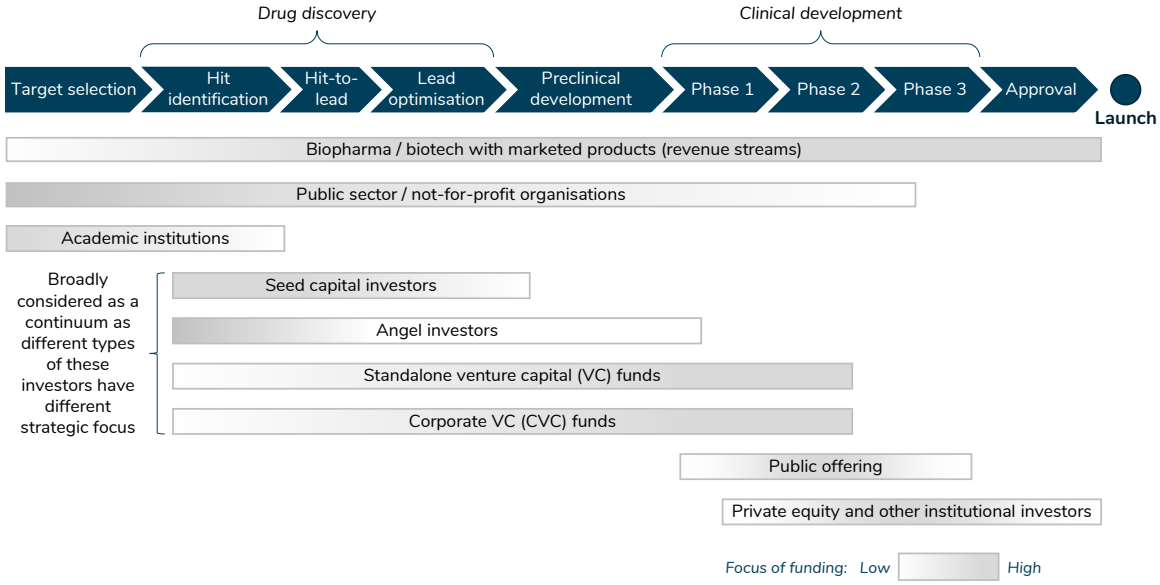

Figure 4. Public-sector and not-for-profit funders principally invest in early-stage development. Private investors come into the picture after the drug-discovery phase. Big biopharma is a key late-stage investor, funding the majority of phase 3 clinical trials.

- Public-sector and not-for-profit organisations typically fund initial research towards target selection and drug discovery in academic institutions or biotech/SMEs, although funding can continue into the early stages of clinical development. Several academic institutions have internal funding sources (e.g. revenue earned from technology transfer spin-outs), reinvesting some in research programs. Some private investors are also active in drug discovery, such as angel investors[11] and early-stage venture capital (VC) funds[12] providing seed capital.
- VCs make high-risk investments in early-stage technologies but may also invest in clinical development phases (phases 1 or 2) once preliminary data is available. Corporate VCs (CVC) are a specific type of VC where biopharma companies invest in an affiliated unit to make equity investments in promising start-up companies, usually related to the company's own industry. Standalone VC funds are individual companies that manage venture funds.
- Biopharma and biotech with marketed products are significant funders throughout all development phases, reinvesting a portion of earnings of the company into R&D.[13] Small-to-medium biopharma relies on a mixture of external funding and internal R&D investment,

[11] Angel investors are industry experts with an interest in funding R&D. They are more likely to invest in earlier stages given the high costs of clinical development. More sophisticated angel investors may support early clinical trials.
[12] VCs invest money pooled from wealthy individuals, insurance companies, (corporate) pension funds and foundations.
[13] In 2019, circa 20% of top-10 pharma's revenue was reinvested into R&D.

depending on their operating cash flow. Although other investors play a role, big biopharma is the key late-stage investor, funding the majority of phase 3 clinical trials.

- Capital can also be raised via public markets through initial public offerings (IPOs). IPOs enable companies to access a global pool of capital to support business scale-up, debt repayment and investments in future R&D projects. We have seen special-purpose acquisition companies (SPACs) emerge in this context. With no commercial operations, these companies are created exclusively to raise capital through an initial public offering (IPO) to acquire or merge with an existing company. Their longevity remains to be seen.
- Private equity and other institutional investors come into the picture in later clinical-development stages:
  - Private equity has typically focused on branded consumer and specialty pharma/generic products rather than R&D. However, these firms are increasingly investing in biotech/SMEs and/or partnering with big biopharma to develop portfolios of new drug candidates with low internal priority at big biopharma companies.
  - In recent years, investors who have not historically invested in life sciences (e.g. pension and sovereign funds) have entered the market, looking to realise this sector's potentially greater and more stable returns. For example, pension funds have tended to invest in areas exposed to lower degrees of clinical risk, such as royalty streams on already approved technologies and drugs.

Analysis conducted for this study shows that total global investments in R&D by biopharma, public sector/not-for-profit organisations and venture capital funds were circa $300bn in 2020 (Figure 5):

- Private investment by biopharma companies of circa $195bn accounts for almost two-thirds of total investment.[14] The top fifteen biopharma companies' R&D spend contributed more than half of this.
- Public-sector (circa $65bn) and not-for-profit (circa $10bn) funding represents more than a quarter.
- The remaining 10% ($30bn) is attributable to VCs. Although VC investment only represents 10% of total deal value, in terms of the number of deals it is estimated to represent a much higher percentage.[15]

[14] This amount is based on the EvaluatePharma database. R&D spend from this database should reflect actual R&D spend, including basic licenses, and is not affected by M&A, equity transactions and asset purchases. Only upfront costs of basic licenses and milestone payments can appear under R&D expenses on the P&L and therefore might affect the results slightly. Also, about 5% of the total spend had an unknown region allocated in the EvaluatePharma database. We allocated this proportionally based on the remaining 95%, also introducing a slight risk of misrepresentation.

[15] Due to incomparable data sources, we could not provide specific estimates for the number of deals for each funder and investor.

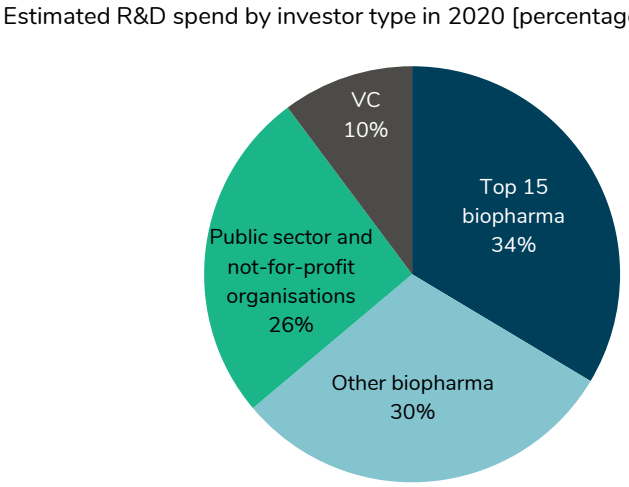

Figure 5. Total R&D investments were circa $300bn in 2020: almost two-thirds were attributable to private investment by biopharma. The amount excludes the cost of capital and anything not directly related to R&D, such as sales and marketing. Sources: Thomson Reuters (Eikon) Private Equity Screener (for VCs), EvaluatePharma (biopharma), public-sector organisations (Organisation for Economic Co-operation and Development [OECD] Government Budget Allocations for Research and Development for 'Health') and not-for-profit organisations (OECD, Association of Medical Research Charities, ResearchAmerica, Healthresearchfunders).

After a decade of relatively modest growth, global VC investment has seen strong and accelerating growth in recent years, starting from a low base. This growth is likely driven by advances in drug research, residual unmet need,[16] a wider group of investors and better exit opportunities (a growing number of large company acquisitions and IPOs) fuelling investor confidence. VC investment has shown the highest growth compared to other private and public investors, with a 14.2% compound annual growth rate (CAGR) between 2011 and 2019, followed by private biopharma investment with a 4.1% CAGR. Public-sector and not-for-profit investments have remained relatively stable (Figure 6). The growth of VC investment is primarily driven by deal value rather than deal count. Increasing deal values are driven by increased valuations, increased competition among VC's and increased VC fund sizes.

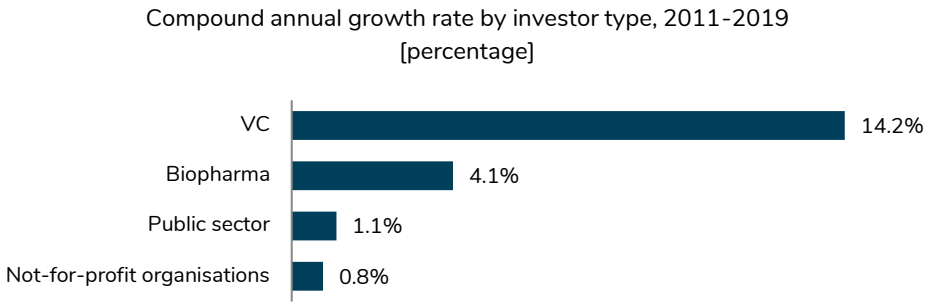

Figure 6. VC investment has shown the highest growth over the 2011–2019 period, followed by private biopharma investment. Public-sector and not-for-profit investments have remained relatively stable. Sources are the same as for Figure 5 (above).

[16] Where there is a significant unmet need, it is typically easier to demonstrate efficacy due to lower thresholds and standards of care. This means it is often easier to demonstrate value to patients/the healthcare system and command higher pricing.

For all four types of investors, most spending is from North America (Figure 7). Europe (including the UK) is the second-largest contributor, followed by the Asia-Pacific (APAC) region.

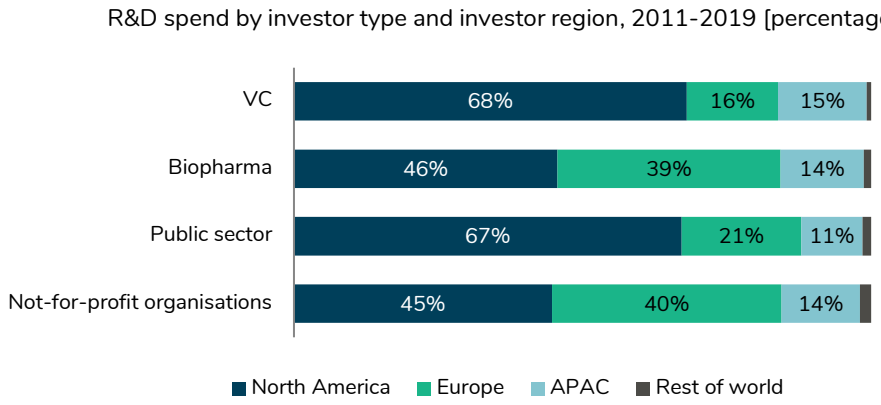

Figure 7. The majority of spending is from North America in all four types of investors. Europe is the second-largest contributor, followed by APAC. Sources are the same as in Figures 5 and 6 (above).

The global collaboration landscape is evolving, and the APAC region is investing heavily in building competitive pharmaceutical R&D sectors and attracting investors. The APAC region shows a positive CAGR from 2005 to 2020 for all types of investors, whereas, Europe has seen some – albeit limited – public-sector and not-for-profit funding contraction.

The APAC region's CAGR growth could influence global collaboration opportunities and competitive dynamics. There is concern that Europe risks lagging behind APAC countries in the future due to the different availability of capital and the strong growth of the pharmaceutical market expected in this region. Additionally, APAC countries are investing in the quality and regulation of R&D. Europe faces challenges in harmonising regulation across countries. Section 3.4 of Annex C details the issues related to global collaboration and competition.

Section 3 of Annex A (Quantification of R&D, Venture capital investment) includes more cross-sections of the above data by investor type, time-period and geography.

2.3 Developing one drug costs an executor an average of $280–$380m in out-of-pocket costs, whereas capitalised costs to the system for a single approved drug are $2.4–$3.2bn

The R&D costs of a drug largely depend on the perspective taken. Whether successfully launched or not, an executing company's out-of-pocket R&D costs for one compound are an estimated $280–$380m (§2.3.1). If including the R&D costs of drugs that fail, however, the estimated out-of-pocket costs to the system for developing one approved drug increase considerably to $1.2–$1.7bn (§2.3.2). Adding the cost of capital, the total R&D cost to the system adds up to an estimated $2.4–$3.2bn per single approved drug (§2.3.3).

These cost estimates are based on an analysis of the literature from 2010 to 2020. Annex A (Section Methodology and glossary) includes a complete list of consulted studies. The costs estimate broadly triangulates with other studies conducted, although some authors find slightly lower estimates (Paul et al., 2010); (DiMasi, Grabowski, & Hansen, 2016); (Gupta Strategists, 2019); (Wouters, McKee, & Luyten, 2020).

2.3.1 Regardless of whether successfully launched, a single compound's development costs the executor $280–$380m in average out-of-pocket costs

To develop one drug costs the company executing the R&D between $280 and $380m (Figure 8). These out-of-pocket costs represent all costs directly associated with the R&D of the drug in question.

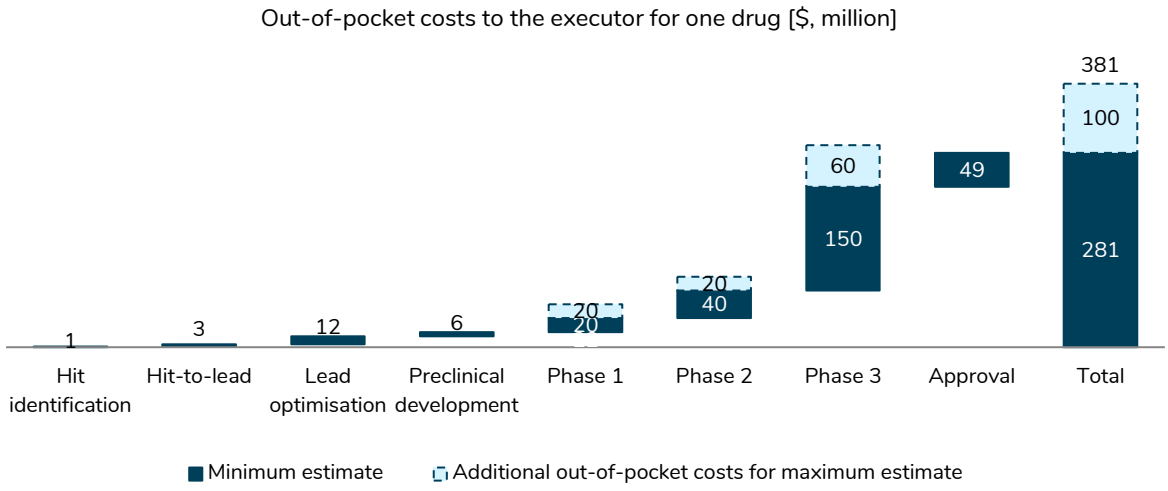

Figure 8. For the company executing its R&D, the out-of-pocket costs for one drug's development range from $281 to $381m (DiMasi & Grabowski, 2007); (DiMasi, Grabowski, & Hansen, 2016); (Paul et al., 2010).

Although there is limited existing literature directly comparing the cost of clinical development between different drug modalities, data suggests the following key differences:

- The out-of-pocket clinical-development costs of orphan drugs are circa two-thirds that of non-orphan drugs (Jayasundara et al, 2019).[17] Clinical trials for orphan drugs require fewer subjects. In addition, orphan drugs do not always require separate phase 2 and 3 clinical trials if unmet patient needs mean they are on accelerated-access pathways, substantially reducing total trial duration. Increased patient-recruitment challenges partially offset this due to lower disease prevalence and incidence, which increase the duration of clinical trials.[18]
- Large molecules such as antibodies, proteins and cell therapies are 20–25% more expensive to develop than small molecules (DiMasi, Grabowski, & Hansen, 2016). Such compounds are generally more time-consuming and complex to develop than smaller molecules.

[17] Other studies have found lower estimates for the R&D costs of orphan drugs compared to non-orphan drugs (Berdud, Drummond, & Towse, 2020). The magnitude of the difference varies across studies, depending on the methodology used.
[18] Leading to a lack of natural disease progression data, recruitment challenges due to the geographic dispersion of eligible participants and a lack of community medical expertise for conducting trials.

2.3.2 Developing one approved drug costs the system between $1.2 and $1.7bn in average out-of-pocket costs

Since many compounds do not reach the launch stage, their out-of-pocket costs must also be accounted for when calculating the out-of-pocket R&D costs to the system. Including the R&D costs of 'failures', the out-of-pocket costs to the system for the development of one approved drug are between $1.2 and $1.7bn (Figure 9).[19]

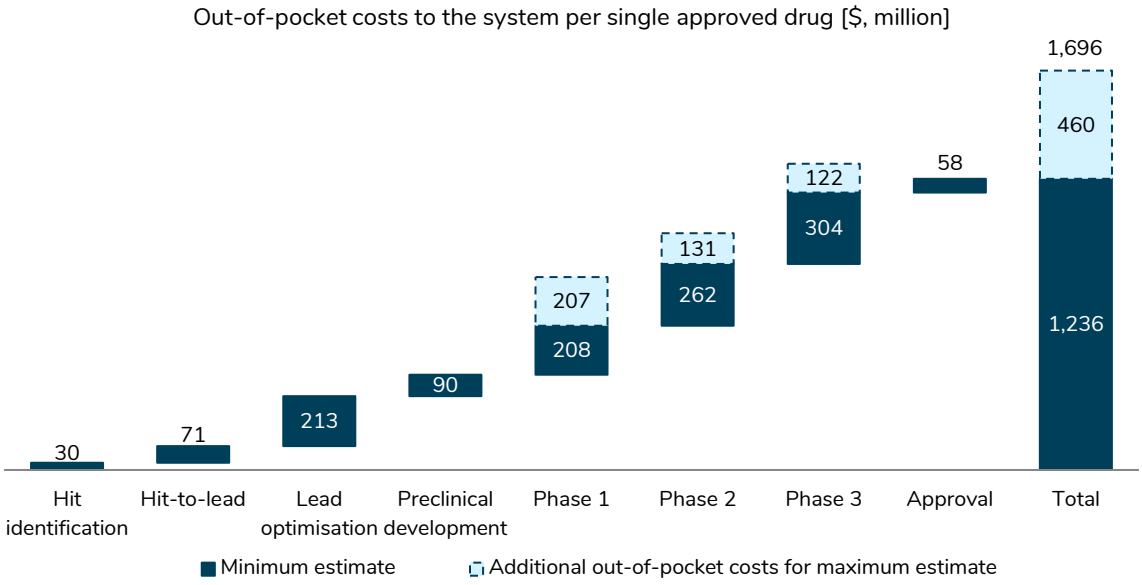

Figure 9. The out-of-pocket costs for the development of a single approved drug range from $1.2 to $1.7bn (DiMasi & Grabowski, 2007); (DiMasi, Grabowski, & Hansen, 2016); (Paul et al., 2010); (Thomas et al., 2016).

To calculate this range, we have multiplied the out-of-pocket costs for each compound at each phase by the number of attempts required, based on the cumulative probability of success (PoS) in reaching launch (Table 1).[20] From hit-identification to successful approval, the cumulative PoS is 3%, with the lowest PoS between phases 2 and 3.

[19] These are 'molecule only' costs and do not include the costs of exploratory discovery research (target identification and validation) or other 'non-molecule' costs/overheads, e.g. salaries for employees not directly engaged in research and development activities but supporting R&D organisation. These represent approximately 20–30% of the total costs.
[20] The costs of the target-selection phase are not included in these total out-of-pocket costs since they are not always linkable to a specific drug's development.

Table 1. The total out-of-pocket costs consist of the out-of-pocket costs for each compound at each phase multiplied by the number of attempts required, based on the cumulative probability of success (PoS) of reaching launch.

	Hit iden-tificat.	Hit-to-lead	Lead optimi-sation	Pre-clinical	Phase 1	Phase 2	Phase 3	Appro-val	Total
Phase success PoS	80%	75%	85%	69%	63%	31%	58%	85%	
Cum. PoS to launch	3%	4%	6%	7%	10%	15%	49%	85%	
Attempts per launch	29.5	23.6	17.7	15.1	10.4	6.5	2.0	1.2	
Cost per attempt (2020 $m)	1	3	12	6	20-40	40-60	150-210	49	281–381
Total phase cost per approved drug (2020 $m)	30	71	213	90	208-415	262-393	304-426	58	1,236–1,696

2.3.3 The total capitalised R&D costs to the system are an estimated $2.4–$3.2bn per single approved drug

Out-of-pocket costs subsequently need to be capitalised to account for the cost of capital. The cost of capital represents the return a company must achieve to justify the cost of a capital project such as developing a drug. The cost of capital encompasses both equity and debt costs, weighted according to the company's capital structure. This calculation is known as the weighted average cost of capital (WACC). A company's investment decisions about a new project should always generate a return exceeding the firm's capital costs for financing it. Otherwise, the project will not generate a sufficient return to warrant the investment risk.

Figure 10 shows the cumulative capitalised costs for a single approved drug for high-estimate out-of-pocket costs of $1.7bn with a 10% WACC. Because of different risk profiles, the cost of capital varies per phase and per company type. This analysis used a range of 8% to 12%, chosen according to biopharma's historic WACC range and consistent with what a big biopharma would typically assume.

A drug's average R&D duration is circa fourteen years: 5–6 years from hit identification to preclinical development, circa 1.5 years for a phase 1 study, 2–3 years for a phase 2 study and circa 3 years for a phase 3 study. The approval process takes about 1.5 years. Due to this relatively long R&D phase, capital costs represent a significant proportion of the total cumulative costs.

The cost of capital can range from $0.8bn using the WACC range's lower limit of 8% and $1.2bn out of pocket costs (minimum estimate from Figure 9) to $1.9bn using the WACC range's higher limit of 12% and $1.7bn out-of-pocket costs (maximum estimate from Figure 9).

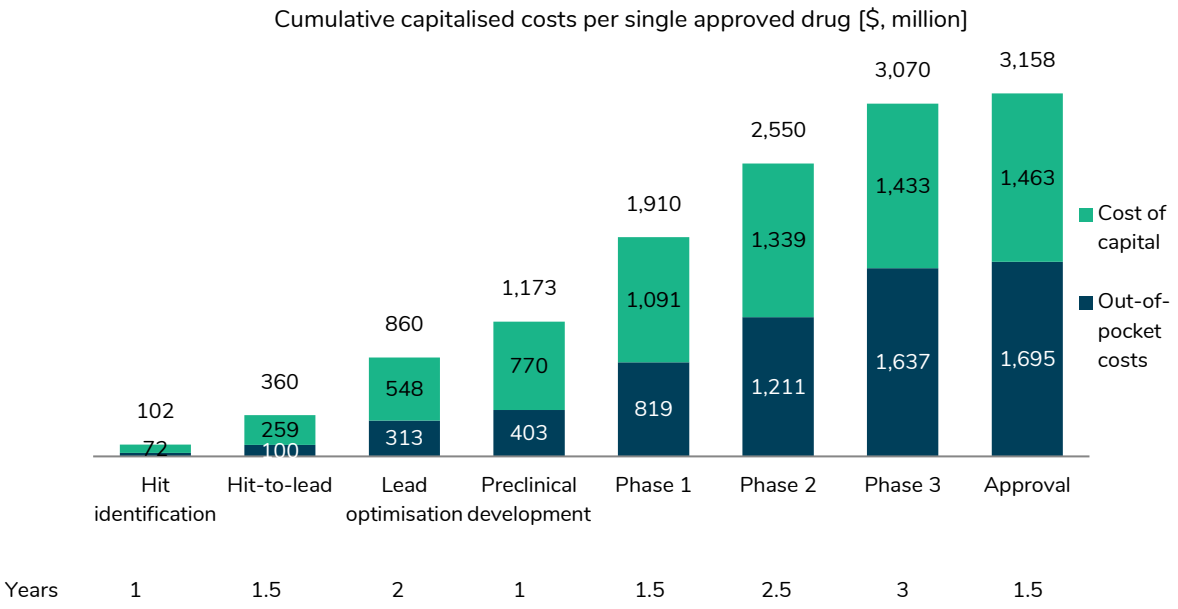

Figure 10. The cost of capital represents a significant proportion of total cumulative costs (WACC of 10% used).

Capitalised R&D costs have increased over the past decades: circa 172% from the late 1980s to the late 2000s (DiMasi et al., 2016) and 92% from 2010 to 2020 (Deloitte Centre for Health Solutions, 2021). Two key drivers of increasing R&D costs are:

- A decreasing clinical success rate, from circa 21% in the 1990s to circa 11% in the 2010s (DiMasi, Grabowski, & Hansen, 2016). The clinically meaningful thresholds required for approval have increased, given the standards of care for many indications. In addition, payers are unwilling to reimburse drugs that do not demonstrate meaningful value for patients (and the health system) beyond the existing standard of care.
- Increasing clinical-development timeframes (circa 7.1 years in 2020) (Deloitte Centre for Health Solutions, 2021) due to the growing complexity in trial designs, since a higher bar for reaching endpoints leads to a more challenging drug-development pathway. Recruitment challenges have also increased as the number of simultaneous trials data capture/analysis issues requiring increasingly costly techniques have risen.

While out-of-pocket R&D costs have been increasing, the cost of equity capital has declined since 2000 (DiMasi, Grabowski, & Hansen, 2016).

Although total capitalised R&D costs are rising, specific measures can help reduce costs. Smarter, more adaptive clinical trial designs could reduce trial sizes and clinical-development timeframes, thus reducing R&D costs. However, this depends on increased data diversity and digital advances such as machine learning, potentially creating time and cost-related efficiencies in identifying successful candidate compounds. Innovative clinical trial regulation also has a role in supporting trial-design innovation and adaptation at scale.

While decreasing R&D costs do not necessarily guarantee reduced pharmaceutical prices, more drugs might be developed if more compounds reach financial-investment thresholds.

3 Ultimately, expected financial return determines whether a drug is developed up to launch

A drug's expected financial return ultimately determines whether it is developed up to launch. Public-sector and not-for-profit organisations often fund early research, primarily to create societal impact (§3.1). However, private investment is needed to bring a drug to launch. VC investment is particularly important in overcoming the 'translation gap', and big biopharma play a crucial role in financing late-stage clinical-development phases. Private investors seek sufficiently high risk-adjusted financial returns for their investors and shareholders. The assessment of expected financial return varies per type of investor and as drugs move through the drug-development continuum (§3.2).

3.1 Early research is often funded by public-sector and not-for-profits primarily motivated to create societal impact

Public-sector and not-for-profit organisations typically fund the initial research that can lead to target selection and drug discovery in academic institutions or biotech/SMEs (although their funding can continue into the early clinical-development stages). Such organisations are willing to make early-stage investments with a high risk of failure because they are primarily motivated by creating societal impact and advancing scientific understanding and innovation.

Public-sector and not-for-profit organisations primarily use grant funding to invest in R&D. In addition, public-sector investment in the infrastructure supporting clinical trials is necessary for fostering the life-sciences ecosystem – robust infrastructures can de-risk investment for the private sector and stimulate further investment.

Though different models exist, public-sector and not-for-profit organisations do not typically accumulate financial returns from their acquired funding. Challenges to securing sufficient resources may require not-for-profit organisations to seek innovative ways of raising funds to reinvest in efforts towards societal impact (see the example of Kalydeco in Text box 8). For example, they might use grant funding for the early stages with an option to invest through an associated profit vehicle later. This is already happening, although the scale remains small.

Since only a few therapies were available to treat the symptoms of cystic fibrosis (CF) in the late 1990s, the Cystic Fibrosis Foundation (CFF) looked to support the development of disease-modifying therapies. CFF wanted to make strategic investments in pharma companies aimed explicitly at cystic-fibrosis-therapy development. In 2000, CFF partnered with Aurora Biosciences to identify disease-modifying molecules. Vertex Pharma acquired Aurora Biosciences in 2001 but did not invest heavily in this CF franchise due to a heavy strategic focus on virology. When Kalydeco entered phase 1 trials in 2006, CFF funded an additional $37m. The successful results of this phase encouraged Vertex to invest in building more R&D and commercialisation capabilities for the CF franchise. Moreover, CFF funded an additional $75m after phase 2 trials began. After approval in 2012, Kalydeco became commercially successful. CFF benefited by selling their royalty rights for Kalydeco in a $3.3bn deal they reinvested in CF research. This case study is described in more detail in Annex A, slides 232 to 237.

Text box 8. The Kalydeco case study shows how not-for-profit organisations seek innovative ways to invest in efforts focussed on societal impact.

Early-stage public-sector and not-for-profit investment is essential to encourage further private-sector investment and fuel pipelines (Toole, 2007). This type of funding can play an important role in shifting the calculus of financial return towards areas that may otherwise be underfunded.

3.2 Bringing a drug to launch requires private investors motivated by expected financial returns

Towards the end of drug discovery, private-sector investment in pharmaceutical R&D becomes indispensable. VC investment has proved crucial to overcoming the so-called translation gap and big-biopharma funding to finance clinical development phases (§3.2.1). Since private investors seek sufficiently high risk-adjusted returns for their investors and shareholders, financial metrics are a crucial determiner in assessing investment opportunities – although other factors play a role too (§3.2.2).

3.2.1 Private investment is significant in efforts to overcome the 'translation gap' and finance clinical-development phases

As a result of the high level of uncertainty and imbalance of risk and reward that can deter some investors, biotech/SMEs face challenges of raising capital during preclinical and early clinical trials. The funding gap that often occurs in this period has been referred to as the translation gap (Seyhan, 2019) (Figure 11).

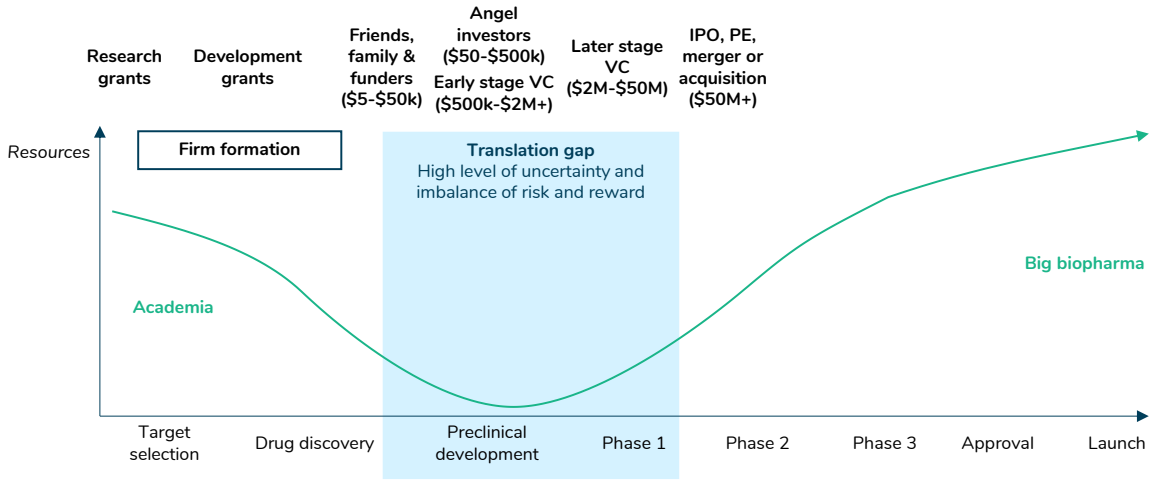

Figure 11. Biotech/SMEs face challenges raising capital during preclinical and early clinical trials due to the high level of uncertainty and imbalance of risk and reward that can deter some investors: the so-called translation gap.

Typically, angel funders and early-stage VCs with deep-industry expertise are willing to invest in early-stage, high-risk settings. After preclinical development, later-stage VCs increasingly invest, and big biopharma may look towards M&A, as preliminary trial data backs assets and the risk lowers.

Later in the R&D process – after closing the translation gap – costs usually increase dramatically towards phase 3 (Table 1). This phase tests the efficacy of a compound in a large and diverse population pool (n≥250). Biotech/SMEs often cannot absorb these costs themselves, which is why big biopharma comes into the picture in late-stage clinical trials. They are typically better placed than biotech/SMEs to conduct late-stage clinical trials due to in-house capabilities and the benefits of economies of scope and scale for most late-stage R&D.

At the same time, biotech/SMEs' efforts to 'go it alone' have become increasingly popular, especially in the US and, to a lesser extent, in Europe (§2.1). Their ability to move into later R&D stages depends, among other factors, on the therapeutic and technological focus and the size of patient populations.

3.2.2 Expected financial return is a key determining factor in private investors' investment decision-making

For private investors expected financial return is a critical driver determining investment decision-making and the selection of compounds developed. VCs seek sufficiently high returns for their investors. Big biopharma is driven by consistent value creation, i.e. share price accretion and stable dividends – for their shareholders. Annex A contains more detail on big-biopharma accounting principles, dividend payments and share buy-backs.

The assessment of expected financial return varies per type of investor and as drugs move through the drug-development continuum.

Transaction timelines and financial instruments

Most deals happen in discovery/preclinical phase and phase 2, with big biopharma more focused on later development stages (Figure 12). It is important to remember that transactions may not be

the investor/company's preferred type, as broader factors such as strategy and market conditions also influence financial instruments.

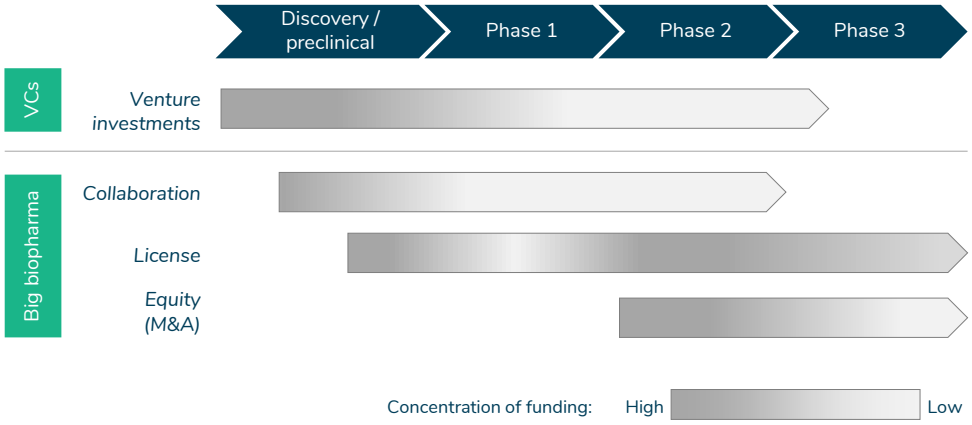

Figure 12. Most deals happen in discovery/preclinical phase and phase 2, with big biopharma more focused on later development stages.

Typical VC transaction timepoints along the R&D value chain are as follows:

- Typical VC investment entries are at preclinical stages, even more so in the US than in the European Union (EU). Our analysis of five EU and five US VCs shows that most EU biopharma investments occur at preclinical stages, but that investments are made in phases 1 and 2 and sometimes even in phase 3. The selected US VCs invested more heavily in the preclinical stages, with most funds conducting 60–100% of first investments at this stage. VCs have more investment opportunities in clinical stage companies in the EU, because they IPO later than in the US. Annex A provides a detailed analysis is available on slides 184 to 199.
- Although VC investment entry focusses on preclinical stages, a fund will typically feature a minority of clinical-stage investments. Such investments are part of a risk diversification strategy, as clinical stage assets typically carry a higher PoS and a shorter time to exit.
- Standalone VCs typically divest their equity investments following clinical proof of concept – i.e. at the end of phase 1 or during phase 2 – through sale to pharmaceutical companies or through IPO. CVCs may divest later in clinical development when the asset/company is de-risked and the associated parent company looks to acquire it.

Typical transaction timepoints and financial instruments through which big biopharma makes external investments are as follows:

- Big biopharma uses collaboration agreements in earlier development stages, typically before clinical development, allowing them to access small biotech's operating model and innovations.
- This also holds for in-licensing, which big biopharma uses when there is a patentable product. Licenses are used predominantly for preclinical assets as well, but also for phase 1 and 2 clinical development.
- As assets are becoming de-risked, equity investments become more attractive for big biopharma. When clinical proof of concept is shown – i.e. at the end of phase 1 or during phase 2 – deals typically occur via M&A. Big biopharma is increasingly willing to pay premiums to diversify their portfolio and support their R&D pipeline. Although premiums are

complex to quantify, some studies report a sharp increase in goodwill (i.e. intangible assets in balance-sheet) in large pharma companies since 2000. Goodwill was close to zero in 2000 and has reached c.$207bn in 2018 in total for the ten largest pharmaceutical companies, with a median 60% premium for the 16 publicly traded pharmaceutical companies acquired in the first half of 2018.

Traditionally, big biopharma was less likely to acquire early-stage assets due to higher risk rates of most early-stage assets prior to clinical development. Although diverse factors influence whether R&D is done internally or sourced externally, big biopharma has increasingly looked towards external sources of innovation. Slide 61 in Annex A shows that this is especially true for larger players. Big biopharma is interested in external sourcing because there is increased competition for de-risked breakthrough technologies in later stages. In addition, they are mindful of reduced financial return for in-house R&D and the costs associated with in-house investments.

Investment decision-making

Investment decision-making principally happens at investment entries and exits (mostly VCs). In addition, at the end of each development phase, a decision is made to (dis)continue funding the compound's R&D (big biopharma) or make milestone payments (VCs).[21]

At investment entry, VCs look for assurance of a likely end market for potential new products. They focus on picking investments to place capital across their portfolio that will outperform the average risk profile of early-stage companies. Before investing in new technology, VCs conduct due diligence focusing on the technical capabilities of the technology and the ability to potentially address an unmet need. Subsequently, VCs look at short-to-medium-term expected financial returns. In addition, investments are also heavily driven by strategic objectives, especially for CVCs.

Typically, CVCs that report to Business Development (BD) have more strategic alignment with the company portfolio looking to fill the pipeline, while CVCs reporting to the CFO generally have more financial motivation and may invest in potential competitors. CVCs reporting to BD may have more late-stage investments more aligned towards M&A and licensing, with a lower expected financial return. Some CVCs view their primary role at the forefront of innovation in core therapeutic areas. While generating favourable financial returns is important, it may be secondary to the parent company's strategic goal.

Big biopharma conducts commercial-potential assessments as products move through development stages and their risk profile diminishes. Such assessments cover more detailed assumptions of addressable patient populations, level of unmet need, drug value proposition, the expected uptake level and pricing potential. They assess whether an investment opportunity aligns with the company's current strengths and supports therapeutic-area leadership or strategic diversification. The opportunity also needs to fit within the broader mission to improve patient health and wellbeing. Maintaining or growing the top-line sales is critical for revenue-generating

[21] VCs fund in series, starting with early-stage seed funding and Series A and B during the drug-discovery phase and subsequently in later-stage funding Series C and D.

companies, resulting in high investments to keep revenues stable. A final essential consideration driving R&D decision making is the ability to fund the required phases of development.

Valuation methods

To value investments, VCs and big biopharma select the most suitable financial metrics at different stages of the R&D pathway, based on data availability and valuation purpose (Figure 13).

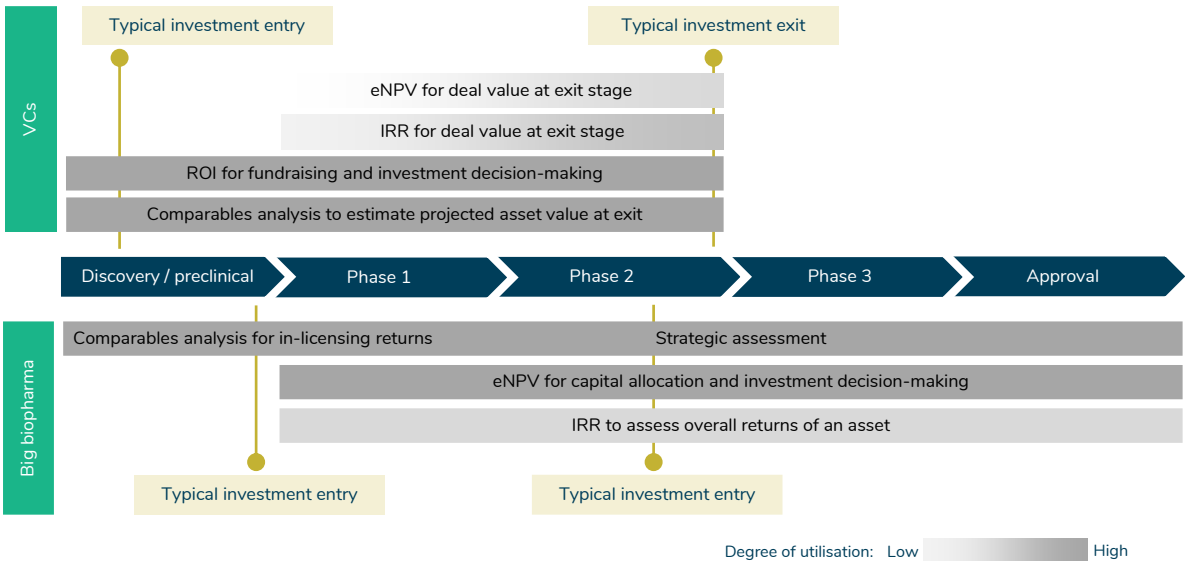

Figure 13. Private investors select the most suitable financial metrics at different stages of the R&D pathway based on data availability and valuation purpose.

VCs mostly use return on investment (ROI) as a financial metric for fundraising and investment decision-making. ROI is commonly used to communicate the profitability of an investment in a simplified context but does not necessarily factor in the period of investment, and estimation of future asset value may be difficult (Text box 9).

Return on Investment (ROI) measures the total growth of an investment over a given investment period, expressed as a multiple or percentage of the initial investment. ROI is commonly used to communicate the profitability of an investment in a simplified context and is the most straightforward method for measuring investment returns. However, the period of investment is not factored into the calculation. Future asset value may also be difficult to accurately estimate at the time of initial investment, based on fluctuations in the inflation rate, market growth and production costs. Thus, ROI is insufficient to capture investment-risk and capital-cost variations when comparing investment options with different time and risk profiles. Under these circumstances, a net present value (NPV) model is more commonly applied.

Text box 9. ROI is commonly used to communicate the profitability of an investment in a simplified context but does not factor in the period of investment, and estimation of future asset value may be difficult.

VCs have internal ROI benchmarks to inform the amount of capital they can invest in an asset. These benchmarks are based on the projected asset value at exit from comparables analysis. Comparables analysis allows investors to evaluate an investment in an early-stage company or asset with limited visibility on cash flow (Text box 10). Big biopharma also performs comparables analyses to estimate investment returns for preclinical in-licensing agreements, although these investments are mostly based on strategic fit.

Investors often conduct a **comparables analysis** when evaluating an investment in an early-stage company or an asset with limited visibility on future cash flow. This analysis aims to estimate the growth potential of an investment against the historical investment returns of a basket of comparables of similar backgrounds, size and risk. Investors aim to determine the company's pre-money valuation and then the potential profitability based on the multiple at exit of comparators. Scenario modelling can then be used to understand a potential weighted-average return on investment. Comparables analysis and **ROI** can be used together to determine the amount of capital to invest.

Text box 10. Comparables analysis allows investors to evaluate an investment in an early-stage company or asset with limited visibility on cash flow. Comparables analysis is often used in combination with ROI.

VC investors typically expect a 2.5–3x net ROI and/or a 20–25% internal rate of return (IRR). For VCs to achieve these expectations, they generally need a circa 4–5x ROI multiple averaged across investments in their portfolio with a 3–8 year holding period depending on the stage. VCs have a portfolio of investments to arrive at this multiple, allowing them to diversify and reduce overall risk. They will typically invest in a mixture of low-risk (circa 2–3x ROI) and high-risk investments (circa 10x ROI), accepting that a proportion of these may generate no returns. They seek diversification in the therapeutic area, development stage, target disease/mechanism and through reinvestments based on milestones.[22] CVCs look at ROI and portfolio-building in a similar way to standalone VCs, although they may lean towards strategic incentives based on their relationship with their parent company.

Data suggest that, after accounting for failure rate and timelines, life-science investments generate returns above or in line with other VC-focused sectors, such as Fintech or IT (Figure 14).[23] In investment Series A and Series D, the risk-adjusted annualised return for life-science companies is 10% and 17%, respectively, in line with Fintech and ahead of other industries. Only Fintech provides higher annualised risk-adjusted returns in Series B and C rounds. Throughout funding rounds, Life Sciences outperforms VC as a whole.

[22] VCs may make several investments in the same company as a de-risking strategy, typically achieved via multiple investments within the same fund. Some investors have a total investment budget for a company but stagger the amount invested in each series and only continue to invest when companies fulfil development milestones.
[23] PitchBook data from 2020 compares the non-risk-adjusted and risk-adjusted annualised returns by series and industry, comparing Life Sciences with IT, cybersecurity, Fintech and all VC. The risk-adjusted number accounts for an 'out-of-business' adjustment, a compounded failure risk used to account for capital investment into companies that never reached an exit.

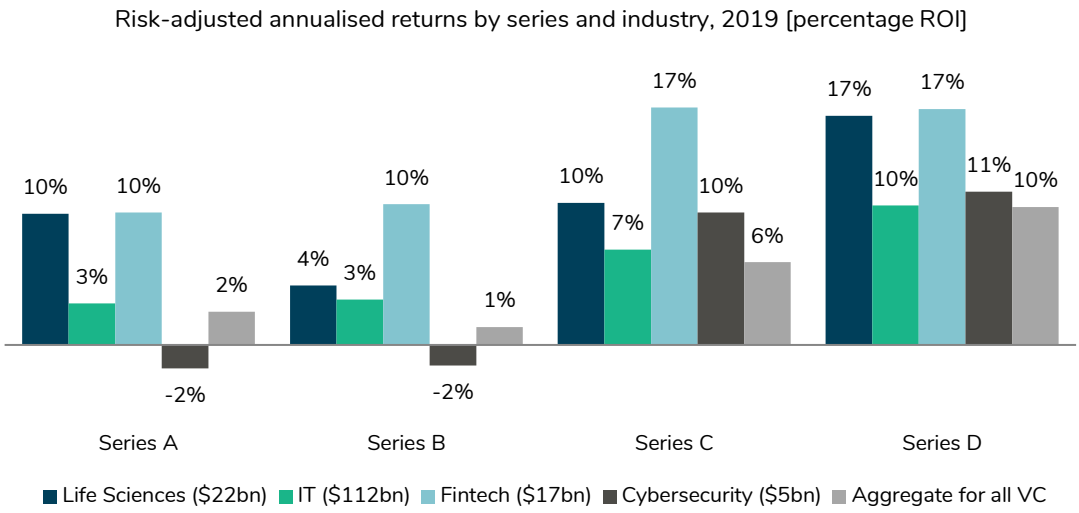

Figure 14. After accounting for failure rate and timelines, Life Science investments generate returns above or in line with other VC-focused sectors, such as Fintech or Cybersecurity. Source: PitchBook.

As investments mature and enter clinical-development phases, the safety and efficacy data generated enables risk-adjusted net present value (eNPV) and internal rate of return (IRR) to be estimated more accurately (Text box 11). PoS values that determine eNPVs are easier to estimate accurately at this stage; the cumulative PoS is higher and there is more visibility on expected revenue and costs.

A **net present value (NPV) model** expresses an investment's profitability by measuring the present value net cash inflow over a calendar period. All revenues and costs assumed in the NPV model are multiplied by the probability of realising or incurring them, and these adjusted values are used to calculate net cash inflow. NPV models are useful for comparing different investment options as they account for the time value of money. An alternative way to express investment profitability based on the NPV is the **internal rate of return (IRR)**. The IRR is the discount rate that makes the NPV of future cash flows equal to zero. For relatively risky investments, e.g. pharmaceutical assets in clinical development with risk of trial failure, a risk-adjusted NPV (**eNPV**) is used where NPVs are multiplied by PoS rates.

Text box 11. NPV models are useful for comparing different investment options, as they account for the time value of money. IRR is an alternative way to present NPV. For relatively risky investments, eNPV is used.

Big biopharma has internal IRR benchmarks for assessing the profitability of internal and external assets. Internal assets are assessed at the end of each developmental phase based on emerging data and whether they meet IRR benchmarks and are sufficiently profitable to carry into the next phase. Externally acquired assets must typically surpass IRR thresholds. Some big-biopharma companies have higher targets for IRR to compensate for the cost of in-licensing, given they will be paying a premium.

When an asset transitions from preclinical to clinical development, big biopharma uses more robust financial metrics such as eNPV, driven by the high costs of clinical trials and the need to understand cost-benefit trade-offs at a granular level. Big biopharma also uses eNPVs to determine an external asset's value in in-licensing deals as it provides a dollar value for the investment. Annex A provides the methodology and results of an eNPV model built for this study. The model is also publicly available in Excel.

VCs also use eNPVs and IRRs to determine the exit-stage deal value of investments since these are the metrics buyers (e.g. big biopharma) use to evaluate assets.

4 Willingness to pay considerably influences supply of novel drugs and the distribution across areas

The expected willingness to pay for new pharmaceutical drugs in key global markets considerably influences the supply of novel drugs and their distribution across therapeutic areas. Lower expected willingness to pay could result in fewer novel drugs being launched in the coming decades. Willingness to pay may come under pressure due to affordability issues in key global markets such as Europe and the US (§4.1). Drugs with the highest expected willingness to pay are most likely to be developed within the life sciences sector. Other areas, such as certain non-life-threatening diseases and areas where suboptimal alternative treatments exist, may therefore struggle to secure private investment (§4.2).

4.1 Lower expected willingness to pay for pharmaceutical drugs could result in fewer novel drugs being launched in the coming decades

As explained in Chapter 3, a drug's estimated revenue potential ultimately drives financial return. The estimated revenue potential is the expected number of patients treated with the drug multiplied by the drug's expected post-launch price. The latter is driven by governments and (private) insurance companies' willingness to pay for the drug. Therefore, the expected willingness to pay for drugs in key global markets strongly influences investor confidence and the life-science sector's investment attractiveness compared to other economic sectors, such as Fintech, Greentech, etc.

Other important factors influencing the supply of novel drugs include the pace and nature of scientific advances, the ability of R&D systems to leverage data and digital technology advances and regulatory developments (Text box 12). These and other factors are discussed in more detail in Annex C.

In addition to expected willingness to pay, various other factors influence the supply of novel drugs in different ways, e.g. influencing which areas are invested in, how long R&D takes, how much it costs and how it is implemented. For example:

- The pace and nature of scientific advances influence the supply of innovation in the pharmaceutical space and the private sector's willingness to invest in higher-risk therapeutic areas. Without breakthroughs in science and technology, pharmaceutical R&D would most likely focus on lower-risk clinical innovation areas, leading to drugs that only offer incremental improvements in care.
- R&D systems' ability to leverage data and digital-technology advances can impact R&D's nature, pace and costs. For example, the ability to use data and digital advances has implications for designing smarter and potentially less costly trials, with potential implications for using machine learning and other digital advances to more efficiently identify successful candidate compounds for pharmaceutical R&D.
- Regulatory developments can also impact R&D costs and investor appetites for investments in specific geographies. For example, regulatory developments can support innovation and adaptation in trial designs at scale to improve efficiency and reduce trial costs. Efforts to tackle fragmented regulation in some global regions (e.g. via reimbursement, regulation of new technologies, intellectual-property policies, approvals for drug repurposing, rules related to data use and re-use by industry) can also affect a region's attractiveness to investors.

Text box 12. Other important factors influencing the supply of novel drugs include the pace and nature of scientific advances, the ability of R&D systems to leverage data and digital technology advances and regulatory developments.

Over recent decades, there has been a move away from 'blockbuster' drugs towards more personalised approaches and segmented markets. This shift suggests growing investments in indications affecting smaller patient populations than the mass markets characterising the 'blockbuster' model. Moreover, curative products for which current payment models are not well suited are being developed. To ensure appetising returns for investors, the pricing of these drugs per patient is relatively high under current pricing models. Therefore, they have a considerable potential health-budget impact, creating affordability challenges for payers. In addition, the payment of high prices – demonstrating high willingness to pay – increases prelaunch valuations of novel compounds in the pipeline.

Willingness to pay for new drugs is traditionally higher in the US than in Europe, primarily because the US healthcare system is a predominantly private and fragmented market lacking the monopsony of many European single-payer healthcare systems. In addition, a number of European healthcare systems utilise health technology assessments to make recommendations on drug pricing and reimbursement, a mechanism that is lacking in the US at present, despite The Institute for Clinical and Economic Review (ICER) gaining traction. However, ensuring affordability has recently become a topic of debate in the US, just as in Europe. Affordability issues in key global markets such as the US or Europe could translate into a lower willingness to pay. A shift in pricing policies could significantly change the landscape as payers balance rewarding innovation with pharmaceutical affordability and accessibility. Such changes could result in fewer compounds

meeting the expected financial return threshold and therefore fewer novel drugs being launched, as illustrated by the positive elasticity of drug development on market size (Figure 15).

An increase in market size would – after the increase is fully absorbed by the R&D system which may take up to 20 years – result in an increase in the number of drugs being developed. Similarly, it is likely that a reduction in market size would result in fewer drugs being developed. This latter effect has been researched by the Congressional Budget Office (CBO), who found an elasticity of 0.5: a 10% decrease in market size would result in 5% fewer drugs being developed. What kind of drugs would be impacted or the effects on overall public health have not been researched.

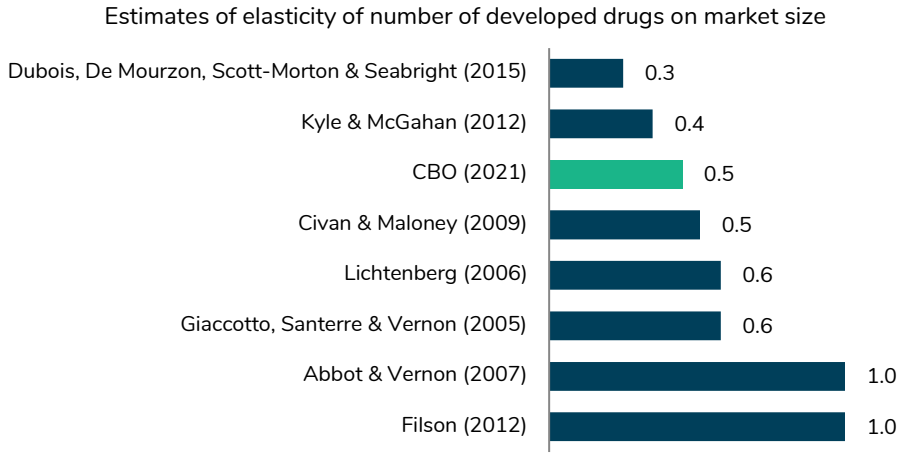

Figure 15. The elasticity of the number of developed drugs on the market size differs between 0.3 and 1.0. A few other studies even find estimates above 2, for example Acemoglu and Linn (2004), Finkelstein (2004) and Blume-Kohout & Sood (2013). However, some of these studies researched slightly different effects and/or used older data.

Ultimately, there is a trade-off between affordability and the need to reward innovation and encourage investment. To determine this balance requires an alignment in health policy, research policy and industrial policy since these policies' respective interests may vary, leading to potentially conflicting policy measures.

4.2 Drugs with the highest expected willingness to pay are the most likely to be developed, leaving several areas currently underserved

As discussed in the previous paragraph, expected willingness to pay influences investments in new drug development and, therefore, in the number of novel drugs launched. Within the life-sciences sector, a drug's expected price or the expected willingness to pay determine the attractiveness of specific therapeutic or clinical areas compared to others.

The anticipated price likely to be paid for a drug largely depends primarily on improvement in health outcomes it offers compared to existing standards of care. In numerous countries, pricing decisions are informed by exploring a drug's cost-effectiveness, e.g. by calculating the drug's incremental cost-effectiveness ratio (ICER) compared to existing standards of care. The ICER indicates the cost of one additional quality-adjusted life-year (QALY). As such, pricing is primarily high in disease areas where no effective alternative treatments exist, especially regarding life-

threatening diseases. Illustrating this, our analysis of 19 funds across five EU and five US VCs shows that therapeutic areas such as oncology are the most attractive for VCs, closely followed by neurology and immunology. Therapeutic areas such as obstetrics-gynaecology and psychiatry were the least invested in by VCs (Figure 16).

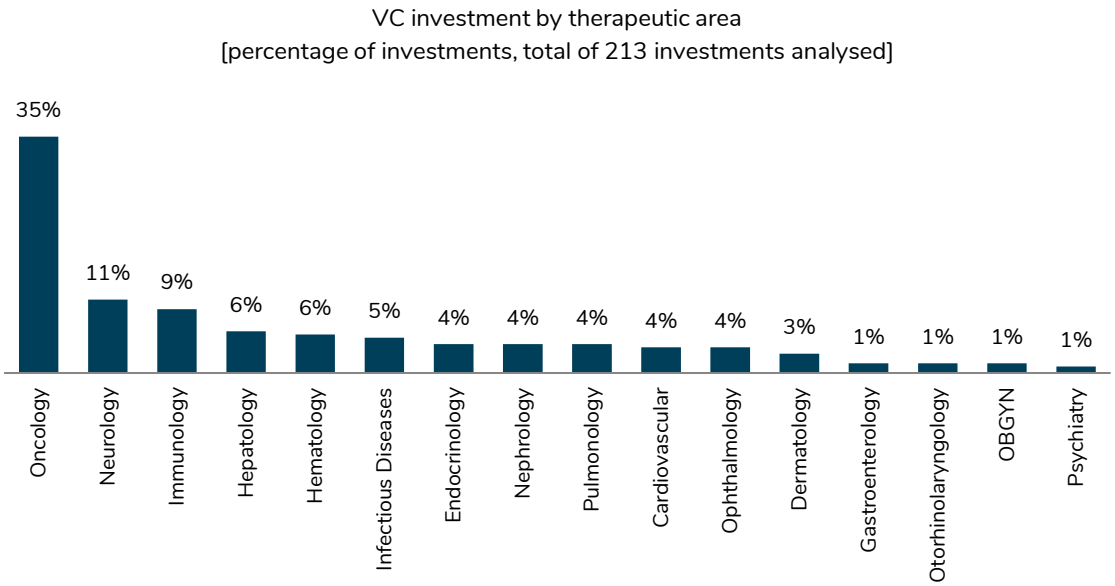

Figure 16. Oncology is the most attractive therapeutic area for VC investment, followed by neurology and immunology. Therapeutic areas such as obstetrics-gynaecology and psychiatry were the least invested in by VCs. Source: LEK analysis of 19 VC funds of five EU and five US VCs. Annex A, section 3 contains more results of this analysis.

In areas where alternative treatments do exist, payers often use reference-pricing models. Under these models, payment is often limited to the average or lowest price of drugs in a specific therapeutic category. Even though R&D investment in these areas could still create societal value, therapeutic and clinical areas where suboptimal alternative treatments exist may struggle to secure private investment for pharmaceutical R&D. Examples include antihypertensives and diabetes drugs, which still have substantial side effects nowadays. However, reference pricing leads to low expected revenue potential for these drugs, lowering investor appetite. Antibiotics are another example. However, in this case, the potential market size for new compounds is lowered by the widespread availability of competitive cheap generic alternatives and constrained by stewardship concerns, i.e. the 'fire extinguisher problem'. This concept refers to an important tool to have but not necessarily to use (Klug et al.,2021) since novel antibiotics are necessary to combat resistance problems. The challenges to creating a viable market can limit investor appetite, which has resulted in biotech/SMEs and big biopharma having multiple innovations on the shelf that did not progress because of lack of funding – so-called 'zombie innovations'.

Compounds with the most favourable business cases are most likely to be developed. This may lead to suboptimal allocation of available funds in tackling diverse areas of unmet need, with potentially significant losses for society. For the optimal allocation of available funds, societies could better prioritise which drugs are needed and create viable markets for them. This shift would boost investor confidence and give direction to executors of R&D in priority areas of unmet need, giving a clear signal of societal desires and likely willingness to pay. Any prioritisation efforts

would need to consider the balance of diverse therapeutic areas, highly innovative and incremental innovation and drug-repurposing opportunities. Section 3.3 of Annex C describes the challenges to creating a sustainable landscape in more detail.

European efforts on orphan drugs are an example of effective prioritisation and incentivisation. Incentives were introduced because the business case for orphan drugs was insufficient due to low patient numbers. In the late 1990s, Europe extended patent exclusivity, followed by adaptive pathways for market entry[24] and a higher willingness to pay per QALY in European countries.[25] These European policies stimulated executors and investors to develop orphan drugs, resulting in many orphan drugs entering the market circa 15–20 years later (Haffner, Torrent-Farnell, & Maher, 2008).[26] Both the relative and the absolute number of orphan medicinal products granted market authorisation by the EMA have increased over the last decade (Figure 17).

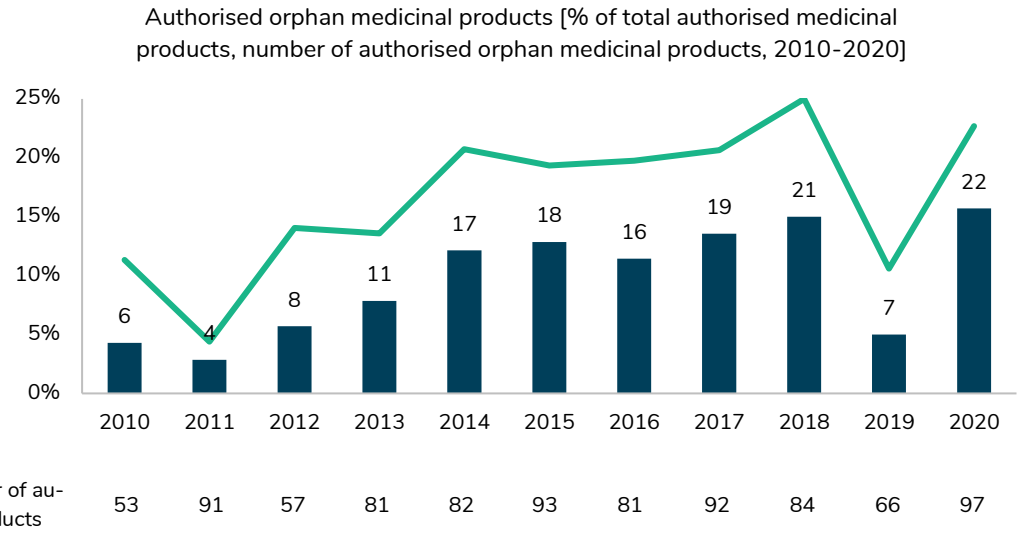

Figure 17. Both the relative and the absolute number of orphan medicinal products granted market authorisation by the EMA have increased over the last decade. Source: EMA annual reports, press releases and human drugs highlights.

The eNPV model developed for this study clearly demonstrates the current attractive business case for orphan drugs. This model shows that the eNPV for orphan drugs consistently outperforms the eNPV for non-orphan drugs through preclinical and clinical phases, expressing higher profitability (Figure 18). The positive eNPV amounts before proof of concept are of particular note, i.e. at the end of phase 1 or during phase 2.

[24] Adaptive pathways are based on three principles: iterative development, gathering evidence through real-life use to supplement clinical trial data and early involvement of patients and health-technology-assessment bodies in discussions on a medicine's development. Source: EMA website.
[25] These measures might not work in all contexts or with all orphan drugs.
[26] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L 18, 22.1.2000, p.1), last amended by Regulation (EC) No 596/2009.

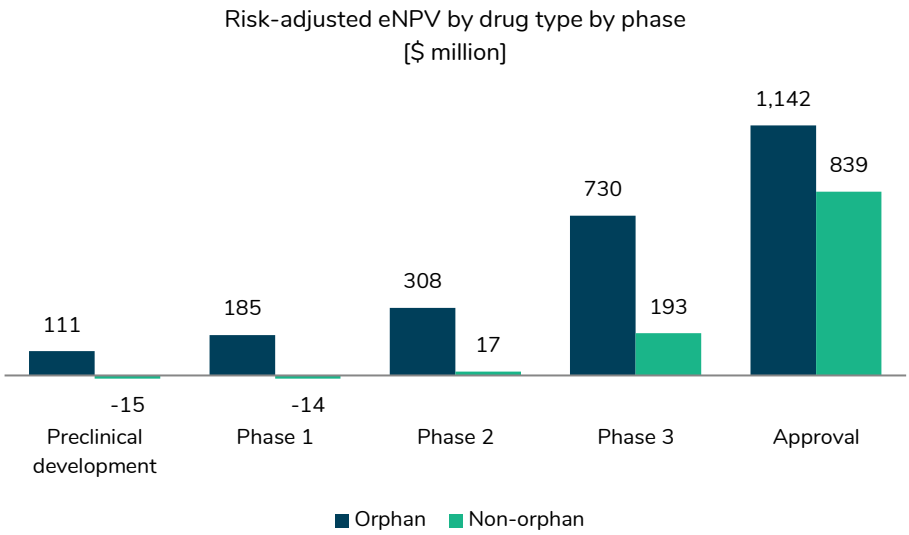

Figure 18. The eNPV model developed for this study shows that the eNPV for orphan drugs consistently outperforms the eNPV for non-orphan drugs through preclinical and clinical phases. This eNPV model is based upon an analysis from L.E.K. (see Annex A), assuming 50% of orphan drugs are required to perform a phase 3 trial and the remaining 50% have been granted accelerated approval.

Given the increase in the number of orphan drugs entering the market in the past decade, Europe may question whether investing in orphan drugs has become too attractive compared to other non-orphan drugs. There might be a risk that non-orphan compounds will be less able to attract investors along the R&D process because these investors are more drawn to orphan compounds, promising higher expected revenue potential and lower R&D costs.

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Appendix 1. Methodology and limitations

This descriptive study used a mixed-methods approach combining desk research and quantitative data with in-depth interviews and engagement with stakeholders. Both quantitative and qualitative methods have strengths and weaknesses. Although quantitative data can provide good evidence, data quality may be limited and cannot answer all question types. In contrast, qualitative approaches may lack representativeness due to the limited number of interviewees per stakeholder type but help elicit evidence based on diverse actors' experiential knowledge that may be unsuited to quantitative investigation. Triangulating the results of quantitative analyses with qualitative findings increases the robustness of the study results by combining both methods' strengths.

The study's execution was divided into seven work packages: four were executed by L.E.K., two by RAND Europe and one by SiRM. L.E.K. conducted the quantitative work, supplemented by interviews. RAND Europe executed most qualitative work by conducting in-depth interviews with diverse stakeholders and organising a workshop where participants could engage with possible future scenarios. SiRM synthesised the findings of all work packages and wrote the final report in collaboration with L.E.K. and RAND Europe.

More specifically, the mixed-methods approach entailed the following research activities:

- Examining, analysing and classifying existing knowledge and information on the financial ecosystem by reviewing academic and 'grey' literature, including industry publications.
- Supplementing existing knowledge with new research based on analysis of (proprietary) databases and financial statements adding concrete quantitative data. The following databases were consulted: Citeline Datamonitor Healthcare, Citeline Pharmaprojects, Cortellis, Eikon, EvaluatePharma, OECD Government Budget Allocations for Research and Development (GBARD) for 'Health', OECD/Association of Medical Research, Charities/ResearchAmerica/ Health Research Funders, Orbis, PitchBook, Thomson Reuters (Eikon) Private Equity Screener.
- Conducting 56 interviews to enrich the knowledge base. L.E.K. conducted 25 interviews with industry experts while RAND Europe conducted 31 semi-structured interviews with experts from multiple stakeholder groups:
  - The pharmaceutical industry and wider life-sciences industry
  - The associated financial investment community (e.g. stand-alone VC groups, corporate VC-groups and institutional investors)
  - Representatives from the academic research community specialising in life-sciences innovation finance (e.g. experts from business schools) and academics affiliated with the life-sciences innovation industry
  - A sample of experts from the wider public and not-for-profit sector (e.g. public research and innovation funding bodies, charities or patent associations)

  - Policymaking representatives (national or international/pan-governmental bodies).
- Developing scenarios on plausible future directions of the financial ecosystem of pharmaceutical R&D as a research tool to enable stakeholders to explore relevant aspects and considerations related to managing potential challenges and maximising opportunities for ensuring a financial ecosystem that is fit for the future.

Full details of this study's methodology and limitations are described below by modality: secondary research, analysis of proprietary drug development and investment databases, interviews and the scenarios workshop. In addition, a scientific advisory committee (SAC) guided the study, as described at the end of this appendix.

Secondary research by L.E.K.

Description

Secondary research began by sourcing multiple scientific papers relevant to the research questions. The study team subsequently complemented these with investment databases to compile an overview of development timelines, pharmaceutical R&D costs and success probabilities. Additionally, we used annual company reports, press releases and corporate websites for numerous other analyses. All sources used in secondary research are provided in Annex A for each specific analysis.

Limitations

One critical limitation concerning the average costs of developing a new molecular entity (§2.2) is that they are strongly influenced by specific parameters, introducing risk in the precision of obtained values. We have tried to mitigate the risk of imprecise values by triangulating between different sources for the same parameter. However, limited data were available on specific subjects, such as the differences in out-of-pocket costs between drugs developed for therapeutic areas and orphan/non-orphan drugs.

Additionally, the VC portfolio risk-management analysis might be slightly geographically biased due to the focus on the US and Europe (§4.1). Since no database was available, we had to base our analysis on secondary research. We constructed a database of 19 VC funds for this analysis, representing a relatively small sample.

Analysis of proprietary drug development and investment databases by L.E.K.

Description

We used the following proprietary drug development and investment databases for the study (see Annex A for more detail):

- Citeline Datamonitor Healthcare
- Citeline Pharmaprojects
- Cortellis Deals Intelligence
- Eikon

- EvaluatePharma
- OECD Government Budget Allocations for Research and Development (GBARD) for 'Health'
- OECD/Association of Medical Research Charities/ResearchAmerica/ Health Research Funders
- Orbis
- PitchBook
- Thomson Reuters (Eikon) Private Equity Screener.

Limitations

The Cortellis database provides the highest coverage of biopharma transactions of all proprietary datasets available to us. However, coverage is likely to be relatively limited for specific transaction types. Grants are a good example, given the inherent difficulty tracking the numerous grants awarded to R&D executors. Cortellis could not provide strict definitions for each player type, leading to potential ambiguity in data classification, e.g.what counts for a pharma company compared to a biotech company. This limitation aside, a review of included organisations in each player 'type' category confirms our understanding that pharma companies have a relatively stronger commercialisation focus. In contrast, biotech companies focus more strongly on biotechnology R&D. However, the line between the two groups remains indistinct, and results should be interpreted with this in mind. Cortellis also has a field labelled 'transaction type' for each record. To synthesise a higher-level analysis, we grouped each transaction type into financial 'instrument classes'. We grouped deals tagged with multiple transaction types, representing less than 1% of all deals, with the transaction type 'loans' in the 'others' category; this also introduces a small potential for mislabelling information.

We used multiple sources for investments from the not-for-profit sector for the OECD/Association of Medical Research Charities/ReserachAmerica/Health Research Funders data because no pharmaceutical R&D database was available for this group of investors. This approach required us to make multiple assumptions, introducing potential error. We used data for the US, UK and France as a proxy for not-for-profits' global investments in pharmaceutical R&D. The attribution to different geographies is based upon the ratio of OECD GBARD, while France is used as a benchmark for European investments by not-for-profit organisations. However, the key charitable grant-giving entities, such as the Wellcome Trust and the Bill and Melinda Gates Foundation, are included, limiting the risk of erroneous investment allocation.

Estimated investment-deal values (i.e. estimated equity invested by a fund in a company in a given investment round) were available for approximately 88% of deals in the Thomson Reuters (Eikon) Private Equity Screener database. However, we had to make assumptions for the remaining 12% of deals without investment-value estimates. We approximated their deal value based on (i) the investment round and (ii) the investment year and took a three-round moving average was taken for investment-round averages to dampen the impact of artificially low bridging rounds of investment. We took the round-eight average for the relevant year for the minority of deals falling in investment rounds beyond round eight.

Data in the EvaluatePharma database derives from the R&D expenses reported in each company's annual report and profit and loss (P&L) statement. We believe data from EvaluatePharma R&D spending reflects actual R&D spending, including basic licenses, and is not affected by M&A,

equity transactions and asset purchases. Only upfront costs of basic licenses and milestone payments can erroneously appear under R&D expenses on the P&L and, therefore, might affect the results slightly. Also, about 5% of the total spend had an unknown region allocated in the EvaluatePharma database. We allocated this proportionally based on the remaining 95%, introducing a slight risk of misrepresentation.

Unfortunately, the OECD GBARD for 'Health' database had no dataset available on different governments' pharmaceutical R&D. We assumed the vast ratio of GBARD for 'Health' is spent on research ultimately relevant to pharmaceutical development. Therefore, indirect government funding, such as tax measures and changes in government allocations within health research and development budgets, is not taken into account.

Data from the Citeline Datamonitor Healthcare is available for the US, EU5[27], Japan and the rest of the world (ROW). Given the lack of clarity on coverage and the lack of reliable scale-up factors for the APAC area, we combined this region with ROW for the specific analysis using the Citeline Datamonitor Healthcare. To determine the drug revenue's destination region, we assigned the company headquarters' country to each drug marketer. This may have overrepresented geographies with more company headquarters than revenues and underrepresented geographies with fewer company headquarters.

When we combined the Citeline Pharmaprojects database with the Eikon and Orbis databases, it was impossible to match all 5000 (approximately) active project executors/originators. Therefore, for our analysis, we assumed these companies to be pre-revenue – thus falling into the 'Revenue rank below 800' category – as companies without revenue are unlikely to be listed in the Eikon or Orbis databases. If any companies not successfully matched between databases do turn out to have revenue, they will have been misclassified.

Interviews by L.E.K. and RAND Europe

Description

A total of 56 semi-structured interviews were conducted: 25 by L.E.K. and 31 by RAND Europe.

The interviews included experts from multiple stakeholder groups, which included:

- Pharmaceutical and wider life-sciences industries
- The associated financial investment community, e.g. stand-alone VC groups, corporate VC groups and institutional investors
- Academic researchers specialising in life sciences innovation financing (e.g. experts from business schools) and academics affiliated with life-sciences innovation
- A sample of experts from the wider public and not-for-profit sectors, e.g. public research and innovation funding bodies, charities or patient associations
- Policymakers from national and international/pan-governmental bodies.

[27] France, Germany, Italy, Spain and the United Kingdom.

Limitations

Our study's primary limitation identified is its sample size. We recognize that there may be views to consider in future research efforts in addition to those from our 56 interviews. However, these in-depth interviews provided substantial detail and nuance, involving key senior-level experts and practitioners across diverse stakeholder groups. Interviewees often commented on macro-level issues, linking them to financial considerations where possible as the financial and non-financial aspects of the pharmaceutical R&D ecosystem are intimately related.

A second limitation is the geographical spread of our interviewees. This study has an international focus, but the US, the UK and the Netherlands were overrepresented in the interviewee group compared to other geographies. However, this limitation was partially mitigated by many interviewees' relevant expertise working across geographies in a wide variety of roles.

Scenarios workshop by RAND Europe

Description

The scenarios used in the workshop were developed by:

- Identifying a longlist of key factors that may influence the pharmaceutical R&D landscape in the next decade based on insights from prior work packages and consultation with this study's SAC
- Conducting an influence analysis to determine the most important and influential factors in the future pharmaceutical R&D system
- Shortlisting the key influencing factors
- Developing projections for how each factor included in the future scenarios may develop over the next ten years
- Performing a consistency analysis to judge how consistent it would be for combinations of projections for different influencing factors to appear in the same future scenario
- Performing a cluster analysis to identify plausible future scenarios based on consistency analysis by:
  - Using specialised software to complete this task
  - Triangulating software outputs with the research team's qualitative expertise and integrating lessons learned from the SAC
- Developing narratives for three future scenarios to produce scenarios that are distinct, clear and easy to engage with.

After introducing the workshop procedure and the scenarios involved, the workshop consisted mainly of a series of discussions between participants. Participants engaged with three scenarios of how the pharmaceutical R&D landscape might evolve in the coming decade. The discussions occurred in three subgroups and were centred around the following two questions:

- What are the key challenges and risks in each scenario, and what are their implications for financing pharmaceutical R&D?
- What are the key opportunities in terms of potential actions that could be taken today to make the most of opportunities and manage the potential risks presented by each scenario?

The subgroup discussions were followed by plenary sessions asking participants to reflect on themes common to all three scenarios and key takeaways regarding actions aiming to prepare the financial ecosystem more effectively for the future.

A total of 16 participants from different stakeholder groups attended the workshop. Each stakeholder group was represented in each discussion subgroup. Representatives from L.E.K., SiRM, the Netherlands Ministry of Health, Sports and Wellbeing, Vereniging Innovatieve Geneesmiddelen and HollandBio also observed the workshop.

Limitations

All workshops involve a trade-off between the number of participants and the depth of discussion. To manage this trade-off, RAND Europe invited representatives of diverse stakeholder groups, facilitating in-depth discussion in smaller mixed-stakeholder-group breakout sessions and collective feedback in the plenary session. Although the workshop attracted renowned experts from diverse stakeholder groups, some individuals did not attend but may have contributed valuable points of view.

As with all future-focused methods, choosing which scenarios to engage participants entails a degree of subjective judgement. The research team sought to include quantitative and qualitative scenario-development approaches, integrate expertise from across the project team, consult the SAC on factors to consider, and develop scenarios informed by the outputs of prior phases of this project. This combination of approaches supports the robustness of the selected scenarios. In addition, the team developed the scenarios as a tool for enabling reflection and discussion rather than a rigid set of predictions.

Scenarios were also selected in the context of project and workshop aims. Therefore, it is plausible that researchers might select different scenarios for other projects with different aims, even given the same input variables and projections.

Scientific Advisory Committee

VWS installed a Scientific Advisory Committee (SAC) during the study to provide methodological guidance to the researchers. The SAC provided feedback on the methodology used and the robustness and credibility of the study results. Additionally, they provided potential interview candidates and consultancy on developing workshop scenarios.

The SAC consisted of four people, listed below with their current (main) occupations:

- Sander van Deventer: Operating Partner at Forbion, professor Translational Gastroenterology University of Leiden
- Suerie Moon: Co-director Global Health Care Graduate Institute Geneva
- Gerard van Odijk: Chairman of the board of Bavarian Nordic A/S and independent advisor in the healthcare sector
- Valérie Paris: Member of the High Authority of Health in France.

The SAC met five times during the study: the first meeting was about the inception report, the three subsequent meetings were on the preliminary results, and the last meeting was about the draft final report.

Appendix 2. Glossary of terms

Terminology	Definition
Angel investors	Industry experts with interest in funding R&D.
Approval	The process in which the regulatory authorities decide whether a new drug can be supplied to the market.
CAGR	Compound annual growth rate.
Capitalised costs	The sum of out-of-pocket costs and the costs of capital.
Carve-out	Partial divesture of a business unit in which a parent company sells a minority interest of a subsidiary to outside investors.
Clinical trials	Trials testing the compound on human participants, comprising phase 1, 2 and 3 trials.
Comparables analysis	The process of comparing companies based on similar metrics to determine their enterprise value.
Discount rate	The weighted average cost of capital (WACC) is the discount rate that should be used for discounting future cash flows with a risk that is similar to that of the overall firm.
Drug discovery	The process by which drugs are discovered, comprising hit identification, hit-to-lead and lead optimisation.
Drug repurposing	A process of identifying new therapeutic use(s) for existing or available drugs.
Hit identification	The identification of (a group of) compounds that interact with the disease target.
Hit-to-lead	The evaluation and validation of desirable compounds to identify promising lead compounds.
IPO	Initial Public Offering: An offering of company shares sold to institutional and retail investors on the stock exchange.
IRR	Internal Rate of Return: A discount rate that makes the net present value (NPV) of all cash flows equal to zero in a discounted cash flow analysis.
Lead optimisation	The optimisation of the interaction between the disease target and the selected compounds.
Milestone payment	Payments from asset owners to license partners/research collaborators when assets reach certain development/sales milestones.
NPV	Net Present Value: Investment returns expressed as the amount of capital at the present time.
Out-of-pocket costs	Costs paid for directly rather than being put on account or charged to some other organisation.
Phase 1	Trials focused on safety testing.
Phase 2	Trials focused on dose selection and efficacy testing.
Phase 3	Trials focused on efficacy testing on a larger scale.
PoS	The Probability of Success of a compound being launched.
Preclinical (trials)	Trials with *in vitro* and *in vivo* models for which dosing (pharmacokinetics) and drug safety (toxicology) data are collected.
Risk-adjusted return	The calculation of the (potential) profit from an investment that accounts for the degree of risk that must be accepted to achieve it. The risk is measured against that of a virtually risk-free investment.
ROI	Return On Investment: The ratio between net income and investment.

Terminology	Definition
Seed capital	The money raised to begin developing an idea for a business or new product.
Series A	The first significant round of venture capital financing undertaken by companies with preliminary data and a business model.
Series B	The second round of venture capital financing for initial business development and up-scaling.
Series C	The third round of venture capital financing for initial business development and up-scaling.
Series D	The fourth round of venture capital financing to fuel further expansion and prepare for an exit (e.g. IPO).
Target selection	The process of using basic research to understand the link between a potentially 'druggable' target in the body and a disease state.
WACC	The Weighted Average Cost of Capital.