

Annex B



> The financial ecosystem of pharmaceutical R&D

The changing R&D landscape through an
evolutionary and future-focused lens

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I Introduction and methods

1.1. Readers' guide

Annex B summarises a work package for this study investigating the drivers of pharmaceutical R&D financing, how they have evolved in the past and how they may evolve in the future. This work built on the study's existing mapping of the current landscape, providing a more in-depth exploration of relevant stakeholders' views about the implications of current pharmaceutical R&D financing and possible steps to help optimise the financial ecosystem for the future. We conducted semi-structured interviews with key stakeholders to complement more quantitative parts of the study and provide additional insights based on the experiential knowledge of stakeholders in pharmaceutical R&D's financial ecosystem.

In the contents that follow:

- We briefly overview the methodology used for the stakeholder interviews (Section 1.2).
- We reflect on key learning gained about changes in diverse areas of the pharmaceutical R&D ecosystem over the past decade and what it looks like today (Section 2.1).
- We consider factors that will play a role in how this ecosystem evolves and their implications for R&D financing in the future (section 2.2). According to some of the stakeholders we spoke to, some future influences are more certain than others. Understanding perceived certainties and uncertainties is important for decision-makers considering possible future actions to support a sustainable and effective financial ecosystem for pharmaceutical R&D.
- We also share stakeholder views on potential policy priorities to consider in making the financial ecosystem for pharmaceutical R&D fitter for the future (Section 2.3).

RAND Europe led this document and associated work package.

1.2. Methodology for stakeholder interviews

This part of the study comprised 31 semi-structured interviews with key stakeholders conducted by RAND Europe. Interviewees were selected via desk research and relevant professional networks in consultation with the scientific advisory committee for this project and the Department of Pharmaceutical Affairs and Medical Technology at the Dutch Ministry of Health, Welfare and Sports (VWS). Interviewees included (i) private-sector stakeholders (e.g. biotechnology companies, pharmaceutical companies, network initiative representatives), (ii) academic experts and consultants on the topic of pharmaceutical R&D, innovation and its financing, (iii) diverse types of investors (e.g. standalone venture capital, corporate venture capital, government and intergovernmental organisations, not-for-profits), and (iii) policymaking and regulatory body representatives. Interviewees were selected to represent diverse stakeholder groups and geographies.

The interviews were semi-structured to allow the interviewer to adapt the conversation based on each interviewee's expertise and provide opportunities for additional follow-up questions based

on initial responses. We created a topic guide for each stakeholder group that broadly covered the questions outlined in Text box 1 below. However, we adapted the exact questions asked in each interview to the stakeholder's sector. After each question, the interviewer asked additional probing questions where appropriate to understand the implications for pharmaceutical R&D financing, how trends have changed over time, how they may change in the future, who captures value and how.

Warm-up question on key influences likely to unfold in the future:

- 1 What are the biggest changes or influencing factors that will impact how pharmaceutical R&D is financed in the next ten years?

Historical evolution and how the pharmaceutical R&D ecosystem and financing landscape looks like today:

- 2 From a historical view, what have been the most significant changes over the past decade in how pharmaceutical R&D happens?

Exploring innovator behaviours:

- 3 Are SMEs/Biotechs increasingly trying to grow and move into later stage R&D? If so, why?
- 4 What factors drive large pharmaceutical-company decisions about whether to fund earlier-stage R&D internally or to look externally to source innovation?

Costs of R&D:

- 5 How have the costs of pharmaceutical R&D changed over time?
- 6 Why do cost estimates vary between studies that look at the cost of pharmaceutical R&D?

Investor dynamics in the landscape:

- 7 What is the investor landscape like, and how might it change in the future?
- 8 What has driven the growth of the venture capital (VC) sector in pharmaceutical R&D?
- 9 What factors motivate each type of investor in pharmaceutical R&D?
- 10 When and how is value captured from investments (e.g. timelines, types of transactions)?

Looking to the future:

- 11 Building on question one about key influences on the future, what is likely to happen, and what are the biggest unknowns or uncertainties about the financial ecosystem for pharmaceutical R&D in the future?

Areas for potential action:

- 12 What needs to change for the financial ecosystem for pharmaceutical R&D to be fitter for the future?

Text box 1. Sample topic guide for interviews.

1.2.1. Interview administration and conduct

Interviewees were invited to participate via email. The invitation included information about the study, a link to access a letter of support from VWS, and a link to access a project information sheet, privacy notice, and consent form. A total of 31 interviewees agreed to participate and

arranged an interview. After an initial invitation, we contacted interviewees again to follow up with them about their willingness to participate in an interview. We obtained informed consent via an online platform, with all interviewees consenting to participate in a recorded interview and have their information used in this study.

Most interviews were conducted via Microsoft Teams using video and voice-call functions, except two interviews completed via a written response. Interviews lasted between 30 minutes and 1 hour depending on interviewee availability, with the majority scheduled for 1 hour. The interviewer provided an overview of the study and interview before starting and reiterated (from the information sheet) that the interviewee may not be able to answer every question and could skip any question they felt unable or uncomfortable answering. The interviewer also verbally confirmed the interviewees' consent to be recorded before starting to record. A note-taker on the research team took detailed notes during each interview and afterwards from recordings. Although interviews were not transcribed, the note-taker used the recording to capture short verbatim quotes, where relevant, regarding particularly illustrative ideas or examples.

1.2.2. Interview analysis and reporting

RAND Europe thematically analysed interviews using a narrative synthesis approach, identifying the themes of each interview question, areas of concordance, and any areas of divergence of views between interviewees. For each interview question, one researcher read all detailed notes from each interview and identified themes within overarching coding categories. These categories concerned key changes over time influencing the pharmaceutical R&D ecosystem and how it looks today, influences on the future financial ecosystem of pharmaceutical R&D, and key areas where action may be needed to make the ecosystem fitter for the future. The research team used an anonymous code to report interviewees' views under each theme. We reference interviewees using an anonymised code throughout this report to protect the sensitive nature of their responses while indicating the weight of evidence under each theme.

We would like to emphasise that the purpose of this work package is not to quantify views but to share insights on the diversity of perspectives. The reader should interpret the reported views as representing the richness and variety of key experts' thinking and as a resource complementing quantitative insights gathered and analysed in this project's other work packages.

1.2.3. Limitations and caveats

The interviews provide a rich context supplementing insights from quantitative work packages on the financial ecosystem of pharmaceutical R&D. Both qualitative and quantitative approaches to studying the financial ecosystem of pharmaceutical R&D have their own merits and limitations, and the qualitative and in-depth interviews aimed to provide additional depth, nuance and context by bringing in diverse stakeholders' highly valued experiential knowledge.

However, there are some limitations to consider when interpreting the data. Since our sample was limited to 31 interviews, additional views may need to be considered in future research efforts. However, the interviews were in-depth, providing substantial detail and nuance and involving key senior-level experts and practitioners across diverse stakeholder groups. They largely revealed

complementary rather than opposing views. Where views were mixed, we highlight this in the document's narrative. It is also worth noting that non-financial and financial (e.g. investment dynamics, cost-related factors, pricing) aspects of the pharmaceutical R&D ecosystem are intimately related such that stakeholders commented on bigger-picture issues and, where possible, linked them to financial considerations.

Though internationally focused, our study sample has a higher representation from the Netherlands, US and UK than other geographies. However, many interviewees had expertise in working across geographies (including academics, consultants, industry representatives, investors, policymakers and regulators) and offered valuable international perspectives.

2. Findings

2.1. Key changes over the past decade have influenced how the financial ecosystem of pharmaceutical looks today

To identify important potential influences on the future landscape for financing pharmaceutical R&D, it is crucial first to reflect on and understand key changes in the pharmaceutical R&D landscape over the past decade and their relationship to how R&D is financed.

Based on findings from interviews, key changes in pharmaceutical R&D's financial ecosystem are summarised in Text box 2. Each theme is expanded on in the contents that follow.

- Scientific and technological breakthroughs have facilitated pharmaceutical R&D in new areas and enabled the involvement of more diverse types of innovators. However, such breakthroughs have also increased R&D costs and complexity.
- There has been a gradual shift from 'blockbuster' drugs towards more personalised approaches and segmented markets, suggesting investments in indications with smaller patient populations than the mass markets characterising the 'blockbuster' innovation model. However, depending on drug pricing, the market for smaller patient populations can still generate sizeable revenue and profit.
- Collaboration between diverse R&D actors has also grown over the last decade, with pharmaceutical companies increasingly looking externally to source early-stage innovation assets. New collaborations between different types of innovators (e.g. biotechnology companies, pharmaceutical companies and technology companies) are also emerging, as are new types of cross-sectoral relationships between funders and innovators (e.g. not-for-profits engaging more with industry than previously). Investor diversity and their appetite for investment have also increased. Moreover, we are seeing new investment models emerging, such as Special Purpose Acquisition Companies (SPACS) and mega-funds, to support capital needs and maximise the opportunities created by science; however, their longevity and traction remain to be seen.
- There is significant variation in how and when value is captured in pharmaceutical R&D, depending on factors including a company's strategic intent in pursuing a transaction and the state of the market. Risk levels will influence the scale of expected returns from value-capture related transactions. Mergers and acquisitions remain the dominant value-capture model for most biotechnology companies/SMEs.
- There have been improvements in the supply of research talent and labour mobility between academia and industry, although the latter may vary between countries.
- Availability and access to venture capital funding have increased, although this varies across geographies. Access to capital has remained highest in the US, with Europe and Asia-Pacific (APAC) regions also demonstrating growth. There are some concerns about whether Europe may risk lagging behind other growth markets in the future.
- There is more focus on scaling up biotechnology companies to engage in later R&D phases (rather than being acquired) than in the past. Biotechnology companies' ability to pursue a growth strategy and move into later R&D stages depends on many factors, not least the company's therapeutic and technological focus (e.g. more likely for areas like rare diseases and companies with platform technologies), ability to attract capital, revenue position and ability to outsource parts of the R&D process such as clinical trials and sales.

- Patient and public engagement with pharmaceutical R&D have become more prominent and influential, influencing how R&D is undertaken and the types of investments needed to support effective engagement.

Text box 2. Key changes in the past decade that have influenced pharmaceutical R&D and the financial ecosystem supporting it.

2.1.1. Scientific breakthroughs have led to new investment opportunities, R&D areas and types of innovators but also contributed to higher R&D costs

Over the past decade, significant scientific and technological advances have opened new research opportunities. However, they have also increased pharmaceutical R&D's costs and complexity in some areas (Int1 SVC, Int2 Acad&Consult, Int4 Acad&Consult, Int7 Pol&Reg, Int8 Biotech/SVC, Int9 NFP, Int10 Acad&Consult, Int11 Biotech, Int12 Biotech/SVC, Int13 SVC, Int16 Pharm, Int19 Pol&Reg, Int27 Pharm, Int31 Pharm). Examples of scientific and technological breakthroughs include advances in biologics R&D, new gene therapy prospects, novel immunotherapies, stem cell research, machine learning and artificial intelligence (Int1 SVC, Int2 Acad&Consult, Int7 Pol&Reg, Int12 Biotech/SVC). The nature of today's research is very different from a decade ago; for example, there has been a move towards 'biology-driven' over 'chemistry' driven innovation (Int2 Acad&Consult) and more focus on personalised medicine (Int11 Biotech).

R&D costs have increased as science and technology has become more complex (Int16 Pharm, Int24 Pol&Reg, Int31 Pharm), and there is a gap between what science makes possible and what healthcare systems and economies can afford to pay for (Int19 Pol&Reg). According to one expert source:

'The most costly part of development remain clinical studies. Moreover, as science progresses, so do regulatory requirements. It is more difficult and costly to run trials and register products today than it was even a decade ago. Even when regulators design special pathways to accept tailored data to support registration (as in the EMA PRIME scheme), HTA bodies and payers require the same amount or more to approve a product for reimbursement' (Anonymous)

Although R&D costs are generally recognised as high, different studies provide varied estimates of R&D costs. One interviewee highlighted that all point to the trend of rising costs over time (Int2 Acad&Consult). Variation in cost-estimate studies' results is mainly due to methodological and data-source differences (Int2 Acad&Consult, Int4 Acad&Consult, Int10 Acad&Consult, Int18 Acad&Consult, Int28 Acad&Consult). For example, some studies assume different drug-development success and failure rates or capital costs, sample different products and therapeutic areas, or cover different timeframes (e.g. whether pre-clinical costs are accounted for and how long post-licensing data are included) (Int2 Acad&Consult, Int4 Acad&Consult, Int10 Acad&Consult, Int18 Acad&Consult, Int28 Acad&Consult). The source of data matters when calculating costs (Int2 Acad&Consult, Int10 Acad&Consult, Int18 Acad&Consult, Int28 Acad&Consult). Some sources may be more conducive to breaking down costs in terms of marketing versus R&D (Int2 Acad&Consult, Int18 Acad&Consult, Int28 Acad&Consult), but other data sources are more transparent and reproducible (Int18 Acad&Consult, Int28 Acad&Consult). Differing cost estimates may also be explained, in part, by the different therapeutic areas covered.

For example, one interviewee noted that it is more expensive to run trials for diabetes and cardiovascular treatments than gene therapies (Int4 Acad&Consult) due to the population sizes needed for robust trials.

Despite significant scientific and technological breakthroughs in the past decade, some interviewees noted that success rates have declined (Int31 Pharm, Int28 Acad&Consult).

According to one expert source, the increasing challenges and complexities of pharmaceutical R&D are reflected in the greater development risk and decreasing probability of success for any given compound (Int31 Pharm).

One interviewee noted that science and technology developments also require increased collaboration between innovators and other healthcare system actors such as healthcare practitioners and patients and greater exchange of knowledge and insight than previously (Int27 Pharm). In part, this is related to a need to understand more segmented patient markets to target R&D for personalised therapies effectively.

2.1.2. The decline of blockbuster drugs has seen a gradual shift to more personalised and segmented patient markets, increasing R&D costs, decreasing patient populations per indication and affecting the sustainability of current financing models and pricing approaches

As introduced earlier, smaller patient populations per indication (i.e. more segmented markets) and a growing interest in more personalised medicine have gained momentum over the last decade (Int2 Acad&Consult, Int6 Pol&Reg, Int9 NFP, Int12 Biotech/SVC, Int14 Pharm, Int17 Acad&Consult, Int19 Pol&Reg, Int20 Biotech). Companies are using new science and technology developments to inform R&D for specific patient profiles rather than mass markets, largely because the pipeline for blockbuster products is sparse.

High R&D costs (due to the increasing R&D complexity associated with scientific and technological advances) and smaller patient populations for individual products have led to questions about the sustainability of pharmaceutical prices and current financial models supporting more personalised R&D approaches (Int6 Pol&Reg, Int9 NFP). The financial ecosystem is changing from the blockbuster era of pharmaceutical R&D regarding who funds it and how. Since many personalised drugs are complex, collaboration between specialist biotechnology companies and pharmaceutical companies is critical in this landscape. For example, in areas such as gene and stem cell therapy, innovation stems from the biotechnology sector and thus relies on both early VC capital and substantial investment from pharmaceutical companies for further development (Int5 R&D). Finding ways to decrease R&D costs and support greater affordability is an important policy issue. Smarter trial designs and innovative regulation could potentially support lower costs in the future (Sections 2.2.3 and 2.3.3).

2.1.3. Pharmaceutical R&D's collaboration dynamics have been changing, with pharmaceutical companies increasingly sourcing innovation assets externally, more collaborative R&D

landscapes emerging, and an increasing diversity of investors with a growing appetite for investment

Increased collaboration and external sourcing of innovation by pharmaceutical companies

Sourcing of early R&D assets by pharma companies

Pharmaceutical companies' growing recourse to collaboration and external sourcing of early-stage R&D assets has been happening for some time, with biotechnology companies cementing a role as critical sources of innovation (Int1 SVC, Int2 Acad&Consult, Int3 CVC, Int4 Acad&Consult, Int5 R&D, Int9 NFP, Int8 Biotech/SVC, Int11 Biotech, Int12 Biotech/SVC, Int13 SVC, Int14 Pharm, Int16 Pharm, Int17 Acad&Consult, Int19 Pol&Reg, Int 24 Pol&Reg, Int28 Acad&Consult). The increase in externally-sourced assets has been driven by pharmaceutical companies' efforts to manage R&D portfolios, de-risk investments and support increased specialisation through various transaction types such as Mergers and Acquisitions (M&A), in-licensing, or partnering (Int7 Pol&Reg, Int8 Biotech/SVC, Int1 SVC, Int14 Pharm). According to one interviewee:

'It's a much more heterogeneous landscape in terms of partnerships, types of deals and creativity in reaching the goal to build a sustainable pipeline' (Anonymous).

As illustrated by one expert source:

'Another trend is the ongoing shift from research largely conducted in-house (within the boundaries of a single company or institution) to collaborative research across scientific and organisational boundaries. This allows sharing of expertise, but also of costs and development risks.' (Anonymous)

Both pharmaceutical companies and VCs are now also looking towards academia and seeking to build companies from academic research (Int9 NFP). Biotechnology companies play a crucial role in translating academic science into practically relevant applications and have been responsible for much innovation in pharmaceutical R&D. For example, biotechnology companies have played a key role in pioneering new pharmaceutical targets and drug-development avenues associated with gene editing, radiopharmaceuticals and RNA technologies (Int24 Pol&Reg, Int27 Pharm).

Sourcing innovation externally is seen as lower risk and more efficient for pharmaceutical companies than investing heavily in early, high-risk, high-failure-rate discovery research internally (Int1 SVC, Int5 R&D, Int9 NFP, Int12 Biotech/SVC, Int15 CVC, Int16 Pharm, Int24 Pol&Reg, Int27 Pharm). Along with the desire to access specific assets from biotechnology companies/SMEs, pharmaceutical companies also seek to learn about new approaches to drug discovery and blue skies research from the biotechnology/SME firms they engage with (Int14 Pharm, Int20 Biotech).

Diverse factors influence whether R&D is internally undertaken or externally sourced. Examples include financial and strategic considerations, other projects in a company's development pipeline, estimates of the probability of success, potential scientific insights from development, internal capabilities in a pharmaceutical company, and other macro and microeconomic factors. Efforts to

carve out leadership in a particular area can also influence decisions to acquire assets externally or develop them internally, as companies seek to differentiate themselves.

For example, as pharmaceutical companies would find it costly to maintain internal knowledge and expertise in all therapeutic areas, several interviewees reported a tendency to reduce the number of therapeutic areas where they conduct research internally in favour of sourcing early R&D from biotechnology companies/SMEs (Int4 Acad&Consult, Int7 Pol&Reg, Int15 CVC, Int16 Pharm, Int21 Pharm). Pharmaceutical companies are currently willing to pay high premiums to access external innovation (Int4 Acad&Consult, Int5 R&D, Int10 Acad&Consult, Int13 SVC, Int14 Pharm). This is particularly true as assets progress further down the R&D process and become less risky (Int5 R&D, Int14 Pharm) and in cases where inactivity in particular therapeutic areas would constitute a reputational risk (Int10 Acad&Consult). According to one interviewee, once a molecule's clinical value has been demonstrated by Phase 1 or 2 clinical trials, it is more likely to be successfully developed and brought to market. Thus, acquisition after this point can help pharmaceutical companies reduce risk (Int1 SVC). However, pharmaceutical companies may strategically choose to conduct R&D internally in areas they want to be seen as leaders (Int1 SVC) or establish long-term partnerships and co-locate close to research and innovation hubs with active R&D cultures (Int14 Pharm).

For pharmaceutical companies to source external assets effectively, the skills to assess good investment and collaboration opportunities are critical. Alongside the ability to credibly 'pick' good opportunities, pharmaceutical companies have maintained and nurtured such skills by continuing to undertake internal R&D, despite an increased overall reliance on externally sourcing innovation (Int3 CVC, Int4 Acad&Consult, Int10 Acad&Consult, Int14 Pharm). As noted by one interviewee, there is a trade-off between internal and externally-sourced early R&D: buying assets externally comes at the expense of not doing something else internally, as investments are all funded from an existing resource pot (Int3 CVC). In addition, this interviewee reported that a pharmaceutical company will always know more about their own assets than about external ones (Int3 CVC). However, since pharmaceutical companies have seen their ability to secure new and innovative assets as a core factor in success and differentiation, many major companies have created their own investment vehicles via corporate venture funds (Int10 Acad&Consult, Int14 Pharm).

The timepoint in the R&D process that an asset is sourced is context-dependent.

Pharmaceutical companies externally sourcing innovation must balance the need for cheap assets and early decision-making influence on potential assets (from acquiring innovation earlier in the R&D process) with the need to reduce risk by acquiring innovation later in the process (Int1 SVC, Int14 Pharm, Int16 Pharm, Int25 Biotech). Pharmaceutical companies must also ensure that they do not destroy the value of externally acquired assets (Int14 Pharm, Int20 Biotech, Int27 Pharm). For example, if assets are acquired before biotechnology companies/SMEs have properly established the pipelines and platforms that initially made them attractive to pharmaceutical companies, there is a risk that early acquisition will limit their value (Int20 Biotech). Maintaining biotechnology companies/SMEs' staff and knowledge can help reduce this risk as both assets drive value (Int14 Pharm). Taking as much of an arm's-length approach as is appropriate can help

biotechnology companies/SMEs continue the work that originally made them valuable (Int20 Biotech). According to one interviewee:

‘The key thing is to retain the knowledge around the programme as long as possible. So the historical model from many years ago is that you’d acquire something, you’d basically get rid of all those people, you’d take it in house and then generally you’d make a mess of it, because you didn’t retain the knowledge. What you thought you gained a product, but what you really gained was an entity, with a lot of knowledge around it. Taking the knowledge further down the process becomes more and more important.’ (Anonymous).

Another expert added:

“I think if pharma can actually be a bit more sort of arm’s length for some of the biotech acquisitions, that can actually be beneficial because you sort of encourage the biotech to carry on doing what the biotech has been good at, but then bring in the pharma expertise for the later stage clinical trials and the regulatory side of it. If you could get that balance right, then both ends of that spectrum are able to deliver value. Ultimately the value flies back to the pharma, because they’ve made that acquisition.” (Anonymous)

Other aspects of collaboration dynamics

Society is also witnessing more technology convergence than in the past, leading to new players in the pharmaceutical R&D sector (Int7 Pol&Reg, Int13 SVC, Int16 Pharm, Int19 Pol&Reg, Int27 Pharm, Int30 NFP). For example, because biologicals are increasingly sophisticated molecules, the R&D process requires more sophisticated delivery systems for drugs and more device-enabled administration. Those conducting pharmaceutical R&D, therefore, are interacting more closely with the medical devices, diagnostics, imaging, AI, digital, data, and software applications sectors, leading to an increasingly open collaboration landscape with more and new types of actors (Int7 Pol&Reg, Int13 SVC, Int16 Pharm, Int27 Pharm).

New types of partnerships and collaborations are also emerging between different types of innovators (e.g. in the digital and data space, as discussed above) and between funders and innovators. For example, not-for-profits are broadening the scope of what they fund and the strategic partners they engage. One expert suggested that if a not-for-profit has a clear end goal in mind, they are now more likely to consider different types of partners than before (e.g. private-sector partners versus those in a purely academic setting) to help advance R&D at pace (Int30 NFP). This interviewee also noted more strategic partnerships and closer alliances between companies in pre-competitive spaces than in the past, with more partnerships between industry funding bodies and academia (Int30 NFP). The COVID-19 pandemic has also highlighted the importance of public-private collaboration for tackling public health and emergency-preparedness-related R&D (Int23 Pol&Reg, Int26 Pol&Reg, Int27 Pharm). For example, initiatives such as the European Health Emergency Preparedness and Response Authority (HERA) in the European Union and the Biomedical Advanced Research and Development Authority (BARDA) in the US are working to sustain and support further collaboration in this area (Int27 Pharm).

A diverse investor landscape

An increasingly collaborative R&D landscape has contributed to more diversity and fluidity in the investor landscape (Int1 SVC, Int10 Acad&Consult, Int17 Acad&Consult, Int20 Biotech). The complexity of the R&D process and the multiplicity of actors involved has led to a vibrant landscape of different types of investors. For example, those conducting pharmaceutical R&D across academia, research institutes, biotechnology companies/SMEs, not-for-profits and contract research organisations (CROs) have established funders in the public, not-for-profit, and private sectors (e.g. angel, seed capital and equity investors, standalone venture capital, corporate venture capital). These diverse investors have different capabilities in evaluating science and risk and a different appetite for investment risks (Int8 Biotech/SVC, Int15 CVC). See Text box 3 for a brief overview of key investor types and the R&D aspects they invest in.

Historically, **public-sector (government) spending** has gone towards early-stage research (Int3 CVC, Int5 R&D, Int6 Pol&Reg, Int10 Acad&consult, Int11 Biotech, Int15 CVC) and infrastructure (Int2 Acad&Consult, Int6 Pol&Reg) to help build R&D ecosystems, and more recently towards translational research. These investments have stimulated new science and technology areas and helped feed R&D pipelines. The public sector can invest in areas that others are less willing or able to. Examples include areas where the market fails due to the high investment risk and difficulty securing returns (Int18 Acad&Consult, Int7 Pol&Reg) and where special incentives are needed (e.g. antimicrobial resistance and rare diseases), including tax credits and other government incentives (Int8 Biotech/SVC). Public-sector funding is critical for drug development, as pharmaceutical companies build on basic science to create new drugs (Int3 CVC, Int11 Biotech). Public funding de-risks later investment by investing in early-stage and translational research, creating potential opportunities for private investors (Int5 R&D, Int13 SVC). Translational research connects academics with industry (Int5 R&D, Int7 Pol&Reg), an important step in ensuring the success of pharmaceutical R&D. Public-sector R&D investment also begets other societal benefits related to growing knowledge-based economies, trade accounts and attracting highly skilled people and taxpayers to a region (Int24 Pol&Reg). Public funding can support the development of biotechnology companies/SMEs (Int3 CVC, Int5 R&D, Int7 Pol&Reg). However, this investment is generally insufficient (Int3 CVC, Int5 R&D), and venture capital and private equity investments are needed to fuel the biotechnology/SME sector. The recent COVID-19 pandemic has temporarily increased public-sector funding, but some of the experts consulted suggest this is unlikely to continue post-pandemic (Int4 Acad&Consult, Int14 Pharm).

The not-for-profit sector has also played a key role in supporting early-stage research, but this generally occurs where an application to a specific disease has been established (Int5 R&D, Int11 Biotech, Int15 CVC). Not-for-profits have also played an essential role in mobilising patient populations, making them important actors in setting investment-priority agendas (Int5 R&D, Int19 Pol&Reg). Over time, not-for-profits have focused more on impact considerations when deciding what to fund than previously (Int30 NFP). Some not-for-profits are also considering ways to recoup their investments to support their sustainability and ability to reinvest funds into areas of need, including via royalties and considering equity and other types of financial transactions (Int30 NFP, Int29 NFP). Some not-for-profits have written conditions into their grants to realise returns

for successful investments (Int30 NFP). Some not-for-profits have also identified new sources of funding only available through social media and digital communities, using mechanisms such as crowdfunding (Int10 Acad&Consult).

In post translation phases (when basic science is advanced to more applied science), **private funding sources** become particularly important. As noted by one interviewee: *‘Turning science into medicines is a challenging task and there’s a need for private sector involvement’* (Anonymous).

Venture capital firms serve as the ‘incubator’ of promising innovations (generally stemming from academia or public research) by investing in SMEs/biotechnology companies that can develop scientific advances further (Int11 Biotech, Int2 Acad&Consult). Their role in the system is vital because, as illustrated by one expert, *‘VCs are the ones that decide what science to take forward because they are the ones that decide what is worth investing in and where the returns can be, and that reflects on the whole landscape.’* (Anonymous).

Corporate venture capital arms of large pharma also play an essential role in the landscape (Int10 Acad&Consult, Int14 Pharm). They can give pharmaceutical companies access to innovations that can help them differentiate from competitors. Pharmaceutical companies can more readily (and sometimes more cheaply) source assets from biotechnology companies they invested in for further development by investing through corporate VC arms.

Private equity has also become more interested in pharmaceutical R&D investments over the past decade, partly due to attractive returns. VCs and private equity are **attracting institutional investors** (e.g. pension funds, banks and endowments) and high-net-worth individuals (Int1 SVC, Int10 Acad&Consult) to invest in the pharmaceutical R&D space.

Incubators have also emerged as a source of seed money to nurture early-stage research (Int22 Biotech/SVC).

We are also seeing the emergence of some **new investment models**, such as **Special Purpose Acquisition Companies (SPACS)** and **megafunds**, to support capital needs. However, their potential and longevity are still unknown (Int 10 Acad&Consult, Int17 Acad&Consult, Int20 Biotech).

Text box 3. A brief overview of the key types of investors in pharmaceutical R&D according to interviewees.

Diverse factors influence the timing of investment decisions. In the private sector, these are primarily related to increasing the probability of success (Int1 SVC, Int2 Acad&Consult, Int3 CVC, Int4 Acad&Consult, Int12 Biotech/SVC, Int15 CVC). Although some VC investors are willing to make early investments before proof of concept (Int12 Biotech/SVC), many investors wait for either an identified biological target (Int2 Acad&Consult), proof-of-concept in animals (Int1 SVC), completion of Phase 1 clinical trials (Int13 SVC) or the company’s revenues or product portfolio to be established (Int3 CVC, Int4 Acad&Consult, Int15 CVC). However, quantitative data is needed to understand investment stages better. The amount of funding VCs provide is also at times motivated by increasing the probability of success. While some investors provide smaller investment pots to lower investment risk (Int1 SVC), they are also incentivised to ensure sufficient funding for an investment to reach the next value flexion point (either alone or together with other VCs). This strategy mitigates against companies having to seek additional mid-phase funding

before they have had the opportunity to add value to the asset they are developing (Int13 SVC, Int25 Biotech). Under-budgeting for clinical trials can be a significant challenge, and there are significant incentives to ensure trials are sufficiently funded (Int13 SVC).

Heterogenous and context-dependent ways of capturing value

How and when value is captured informs pharmaceutical R&D's investment and collaboration dynamics. Views around this vary substantially. Generally, the nature of value capture seems to be diverse and context-specific.

The timelines for investors and private sector companies to realise returns vary (Int4 Acad&Consult, Int12 Biotech/SVC, Int24 Pol&Reg). Only a few investors we spoke to provided returns estimates. These ranged from 2–3 years in one case (Int3 CVC) to 5–6 years in others (Int12 Biotech/SVC, Int20 Biotech).

There were mixed views about the benefits and limitations of seeking quick returns versus a longer-term orientation to investment. Some interviewees noted that biotechnology companies/SMEs and investors' timelines for realising returns have shortened over time, with more interest in quick returns than more significant returns on long-term investments (Int3 CVC, Int5 R&D, Int8 Biotech/SVC, Int13 SVC, Int15 CVC, Int20 Biotech, Int25 Biotech, Int28 Acad&Consult). According to one expert, this may make pharmaceutical R&D more similar to other start-up spaces from an investment standpoint (Int13 SVC), positioning investors as relay racers for the next round of funding rather than as company builders for the long term (Int3 CVC, Int28 Acad&Consult). From a biotechnology company/SME point of view, producing quicker returns (rather than more significant longer-term returns) makes them 'seem like superheroes' to investors, increasing the amount of capital available to them (Anonymous).

However, others noted that in comparison to the past, investors are more willing to make longer-term investments (Int10 Acad&Consult, Int11 Biotech, Int12 Biotech/SVC, Int14 Pharm, Int20 Biotech, Int22 Biotech/SVC), particularly in the US (Int11 Biotech, Int14 Pharm, Int20 Biotech, Int22 Biotech/SVC). Quantitative data would be needed to clarify the duration of investment. Some experts argued that these longer funding cycles allow biotechnology companies/SMEs to go further in the R&D process without being acquired by pharmaceutical companies (Int11 Biotech, Int14 Pharm, Int20 Biotech, Int22 Biotech/SVC) and to take more risks without worrying about the availability of capital (Int20 Biotech).

How different actors capture value in the pharmaceutical R&D system is variable and context-dependent. Some interviewees reported more flexibility in this regard than previously, noting that how value is captured depends on individual companies' specific products, technologies, goals and circumstances (Int1 SVC, Int14 Pharm, Int21 Pharm, Int25 Biotech, Int31 Pharm). As illustrated by one expert source:

'The type of transactions we do depends on the type of development assets, as well as various internal and external factors. It is difficult to speak of a general trend.'

(Anonymous)

Although one interviewee suggests that the types of transaction options used in the pharmaceutical R&D process have largely stayed the same (Int28 Acad&Consult), some experts noted that there is now more of every type of deal (e.g. those outlined in Text box 4) (Int2 Acad&Consult, Int10 Acad&Consult, Int13 SVC, Int14 Pharm, Int16 Pharm, Int25 Biotech). This is partly related to a more vibrant ecosystem: *‘What has changed is that it’s a much more heterogeneous landscape in terms of partnerships, types of deals and creativity in reaching the goal to build a sustainable pipeline’* (Anonymous).

The circumstances around a deal help dictate which way of capturing value is preferred, as overviewed in Text box 4. Moreover, one expert noted that society is becoming more creative in pursuing different types of transactions (Int15 CVC). Examples include models whereby royalties can be exchanged for a certain amount of pay or ownership or the ‘build-buy’ approach where companies can externalise an asset and repurchase it if milestones are met (Int15 CVC).

Transaction types and value creation

- **M&A:** Many interviewees indicated that most biotechnology companies/SMEs’ goal is to be acquired by pharmaceutical companies (Int1 SVC, Int15 CVC, Int22 Biotech/SVC, Int25 Biotech, Int26 Pol&Reg). This is especially true for companies developing single products rather than working on a broader portfolio/platform that would allow them to license some assets (Int25 Biotech). According to one interviewee, a pharmaceutical company may be more inclined to acquire a biotechnology firm when it fills a long-term strategic goal than when it represents a one-off asset that might be more affordable through partnering or licensing (Int11 Biotech). Since IPOs and acquisitions are the basic exit options available to biotechnology companies/SMEs and VC investors (Int3 CVC, Int20 Biotech), acquisitions tend to be the only options when there is a lack of a strong IPO market (Int3 CVC). Some interviewees noted that the number of acquisitions have increased over time (Int1 SVC, Int16 Pharm, Int19 Pol&Reg, Int 22 Biotech/SVC).
- **Initial Public Offerings (IPOs):** Although IPOs are also an option for biotechnology companies/SMEs and investors to capture value, this depends on the state of the market at any given time and the company’s visibility in public markets (Int1 SVC, Int3 CVC, Int8 Biotech/SVC, Int15 CVC, Int19 Pol&Reg, Int22 Biotech/SVC). Some biotechnology companies/SMEs use IPOs to secure enough funding to go it alone in the R&D process (Int1 SVC, Int11 Biotech, Int12 Biotech/SVC, Int20 Biotech). However, they are also used for securing additional funds on the way to seeking acquisition by pharmaceutical companies (Int1 SVC, Int8 Biotech/SVC, Int19 Pol&Reg, Int20 Biotech) or to raising value by increasing public visibility (Int8 Biotech/SVC, Int20 Biotech, Int22 Biotech/SVC). According to some of the experts, the IPO market is currently more attractive than before, leading to an increase in IPOs (Int8 Biotech/SVC, Int11 Biotech, Int16 Pharm, Int 9 Pol&Reg, Int22 Biotech/SVC), particularly in Asia (Int8 Biotech/SVC, Int19 Pol&Reg) and the US (Int 19 Pol&Reg, Int22 Biotech/SVC).
- **Licensing:** Licensing is primarily an option for companies with more than one asset to capture some value from their portfolio (Int25 Biotech) rather than single assets. For pharmaceutical companies, it can be a way to source innovation externally (Int4 Acad&Consult) or to bring products to market in other countries where they do not have the expertise to market products (Int8 Biotech/SVC). However, licensing is often not a first-choice transaction approach for biotechnology companies/SMEs. According to two interviewees, it leads to less value than a complete acquisition (Int11 Biotech, Int22 Biotech/SVC), at least when licensing occurs without the biotechnology company/SME

retaining majority ownership over the asset (Int11 Biotech). Licensing can be complicated from an investor standpoint because it relies on keeping the entity licensing the asset open (Int15 CVC). However, licensing is sometimes used strategically to build excitement around a company or asset before seeking an IPO or acquisition (Int1 SVC, Int 22 Biotech/SVC). Cross-licensing may also occur where companies agree to license to one another, although it is unclear how much this happens in the pharmaceutical industry (Int13 SVC).

- **Partnering:** Some interviewees mentioned that partnering between companies has increased in recent years (Int11 Biotech, Int14 Pharm, Int20 Biotech, Int 28 Acad&Consult). They report that pharmaceutical companies have become more collaborative, rewarding collaboration more generously than before (Int20 Biotech). Partnering can be a route to easier and lower-cost ways for pharmaceutical companies to access external innovation (Int2 Acad&Consult, Int14 Pharm), especially in areas where it cannot be accessed through acquisition or licensing (Int 10 Acad&Consult). However, partnering is not always transactional: there is not always a short-term financial return for either partner or a business case for partnering. Pharmaceutical companies sometimes partner with biotechnology companies/SMEs to develop internal innovation capabilities in areas where biotechnology companies/SMEs have an innovative edge (Int14 Pharm, Int20 Biotech). Like IPOs, partnering may also feature on the route to acquisition to build confidence around a company. An example is a co-marketing launch where an asset will stay under the control of the biotechnology company/SME until there is enough proof it will be successful. At this point, the pharmaceutical company acquires the asset (Int11 Biotech). Partnerships representing collaborations between multiple not-for-profits or between not-for-profits and private investors collaborating around a wider disease area have also become more popular, raising new questions around how value capture occurs, and how benefits will be distributed across investors (Int29 NFP, Int30 NFP).
- Interviewees discussed several **other ways to capture value**. While **SPACs and mega-funds** are becoming more popular as a financial vehicle for de-risking investments (Int17 Acad&Consult, Int20 Biotech), one interviewee identified SPACs as a reputational risk to biotechnology companies/SMEs, suggesting they are seen as a financial mechanism rather than a way to build companies and good science. According to this interviewee, SPACs were for companies that were not strong enough to do an IPO on their own (Int20 Biotech). Lastly, one interviewee mentioned **royalties**, although they did not consider them particularly attractive. They suggested they can potentially discourage later acquisitions and partnering due to the need for later investors to pay royalties to earlier investors (Int9 NFP) and take a long time to capture value.

Text box 4. Transaction types and value capture in pharmaceutical R&D.

Risk levels will influence the scale of expected returns. Given the risk involved in investing in pharmaceutical R&D, investors often expect high returns, particularly for early, riskier investments (Int8 Biotech/SVC, Int10 Acad&Consult, Int13 SVC, Int21 Pharm). One interviewee suggested that as risk becomes lower over the R&D lifecycle, some investors accept lower returns (Int8 Biotech/SVC). However, firm conclusions cannot be made without further research. The magnitude of returns is not clear from interview evidence. One interviewee mentioned that investors expect a two-to-three-fold return on an investment in a biotechnology company (Int20 Biotech); another reported expecting four-to-six times their initial investment (Int12 Biotech/SVC, Int22 Biotech/SVC). In general, an asset's value increases through the R&D process (Int12 Biotech/SVC, Int15 CVC, Int22 Biotech/SVC, Int 24 Pol&Reg), particularly once it is shown to be

effective in the clinical stage of development and risk decreases (Int12 Biotech/SVC, Int22 Biotech/SVC).

The valuation of biotechs/SMEs in the market depends on various factors. Examples include pharmaceutical companies' willingness to pay and ability to invest in other areas, e.g. if there are internal investments they can make to realise returns (Int4 Acad&Consult, Int8 Biotech/SVC, Int14 Pharm, Int22 Biotech/SVC). A company's performance on public markets can also affect valuation, e.g. Nasdaq (Int 22 Biotech/SVC). In addition, one interviewee mentioned that the speed of deals affects valuation, with companies more willing to spend higher sums on acquisitions and partnerships that happen quickly (Int13 SVC). Currently, biotechnology companies/SMEs are valued more highly than in the past (Int4 Acad&Consult, Int8 Biotech/SVC, Int14 Pharm, Int22 Biotech/SVC), particularly in the US where their valuation depends more on their potential future value rather than their current value (Int14 Pharm).

Views on the appropriateness of public and not for profit sector expectations for returns on investment (in cases where these funders expect financial returns) varied. Two interviewees commented that private-sector investors occasionally find public and not-for-profit sector expectations of the scale of returns unrealistic (Int5 R&D, Int13 SVC). However, it would be useful to also gather perspectives from public-sector stakeholders. Another interviewee noted that the public sector's investment benefits it in diverse ways beyond returns and patient benefit only. For example, the public sector benefits economically from creating employment, tax revenues and attracting talent to a region (Anonymous).

2.1.4. A growing talent pool and increasingly mobile labour markets have also stimulated new ideas and investment opportunities

The labour market and talent supply supporting pharmaceutical R&D have become more fluid and diverse over the past decade. Experts can move more freely between industry and academia than before (although this can vary across geographies and cultural contexts), enabling diverse learning, skills development and a more dynamic and vibrant R&D ecosystem overall (Int3 CVC, Int10 Acad&Consult, Int24 Pol&Reg).

Related growth in entrepreneurial cultures has also unfolded over the past decade, especially in the US but also in Europe, China and other APAC countries (Int3 CVC, Int24 Pol&Reg, Int1 SVC, Int13 SVC, Int27 Pharm). Government and not-for-profit research funding have played a key role in feeding the entrepreneur supply chain and supporting entrepreneurial mentalities, together with VC funding and the general availability of funding and capital (Int3 CVC, Int24 Pol&Reg). Universities play an important role in nurturing entrepreneurship, which is essential for pharmaceutical R&D's innovation supply chains. For example, university technology transfer environments in Europe have matured, and European universities are becoming more interested in entrepreneurial activity (Int1 SVC), which also spurs investment.

2.1.5. The availability of and access to funding for pharmaceutical R&D has improved over the last decade

More money is entering the marketplace now than ten years ago (Int3 CVC), especially from the private sector (e.g. standalone VCs, corporate VCs) (Int3 CVC, Int15 CVC). This increase has helped drive the investment landscape for pharmaceutical R&D. VC growth over the past decade has been vital in pharmaceutical R&D's innovation supply, as VCs fund biotechnology companies and SMEs that generally supply innovation to pharmaceutical companies for further development (Int3 CVC, Int2 Acad&Consult, Int12 Biotech/SVC, Int1 SVC, Int9 NFP, Int10 Acad&Consult, Int31 Pharm). Large pharmaceutical companies' dependence on external innovation has supported good returns on VC investment (Int3 CVC, Int2 Acad&Consult, Int4 Acad&Consult), and value creation in biotechnology companies has been more compelling for investors than previously (Int8 Biotech/SVC). VCs, corporate venture funds and private equity investors also have an increased appetite for investing in pharmaceutical R&D than in the past (Int3 CVC). According to one interviewee, society has also seen a growth in specialised life sciences investors in the corporate venture-capital world linked to pharmaceutical companies becoming more specialised in terms of their area of work (Int15 CVC). Particularly in the US, investors may be more willing to invest in multiple deals in parallel rather than wait for a payout from one investment before investing in another (Int3 CVC). The size of investments has also been increasing (Int3 CVC, Int10 Acad&Consult). However, parallel deal investment is not new to the sector; it may be that the scale of this activity has changed over time, but we lack quantitative data on this issue. The number and size of deals seem to be increasing. However, it is unclear whether there will be more consolidation or diversification in the VC sector – it is uncertain whether large funds will grow and smaller ones 'disappear', or alternatively whether there will be more competition towards a more extensive and diverse VC base (Int1 SVC).

Despite a trend of growth across regions, there continues to be less funding available in Europe than in the US (Int1 SVC, Int2 Acad&Consult, Int7 Pol&Reg, Int20 Biotech, Int27 Pharm). Some experts emphasised the high pharmaceutical R&D potential in Europe (Int1 SVC, Int4 Acad&Consult, Int8 Biotech/SVC, Int13 SVC, Int20 Biotech). However, several interviewees noted that Europe was lagging behind the US and that Europe and the US may face increased competition from China as a favourable investment location for pharmaceutical R&D (Int1 SVC, Int4 Acad&Consult, Int8 Biotech/SVC, Int13 SVC, Int20 Biotech, Int22 Biotech/SVC, Int24 Pol&Reg, Int27 Pharm). In part, differences relate to the availability of capital in the market, but they are also associated with the broader ecosystem and the availability of researchers, CROs and infrastructure (Int2 Acad&Consult). Regulatory hurdles may also make the European landscape less attractive to investors than the US (Int13 SVC, Int8 Biotech/SVC, Int20 Biotech). One interviewee suggested that despite significant funds in Europe, there is about five times less funding than the US for VC-stage companies for the same number of high-quality opportunities (Int1 SVC). This interviewee perceived a higher risk aversion to early investment in Europe than previously (Int1 SVC), but this merits further research – greater competition between investors for later-stage deals may also push more investors to earlier-stage deals. According to some experts, the European economic environment is better for seed stages and companies on the public markets than companies in the venture capital phase (Int1 SVC, Int13 SVC, Int20 Biotech).

There is a desire in the biotechnology community to build more European-based growth funds, with some ongoing initiatives already developing them (Int20 Biotech, Int22 Biotech/SVC, Int24 Pol&Reg). Achieving this depends on various factors, such as changes in the pension system (Int22 Biotech/SVC) and how public markets work – especially in better connecting EU IPO markets and facilitating IPOs (Int1 SVC, Int4 Acad&Consult, Int7 Pol&Reg, Int15 CVC). Other areas where interviewees noted possible improvements to help attract investments for growth funds included tax incentives (Int22 Biotech/SVC) and regulatory changes (Int7 Pol&Reg, Int24 Pol&Reg).

We could not obtain conclusive views on whether syndicated investments (where more than one investor comes together) have been increasing. According to one interviewee, the syndicated investor's role has been shrinking (Int3 CVC), but there is reason to believe this may change. However, quantitative data is needed to clarify this situation. Another interviewee perceived an increase in syndicated investments, reflecting the level of capital required to advance complex pharmaceutical R&D (Int10 Acad&Consult).

2.1.6. Efforts to grow and scale biotechnology companies are on the rise in some countries, but the ability to grow depends on a company's therapeutic and technological focus, the availability of growth capital and the ability to outsource some activities

Some countries' governments have increased their focus on scaling companies as a way of driving innovation economies (Int 5 R&D, Int 19 Pol&Reg). Most scale-ups are still based in the US – possibly related to more accessible funding. However, countries like the UK are also increasingly interested in strategies to scale biotechnology companies (Int7 Pol&Reg, Int11 Pol&Reg, Int19 Pol&Reg).

There is also evidence to suggest that an increasing number of biotechnology companies have been trying to grow and undertake later-stage R&D over the past decade rather than looking for early exits such as acquisitions by pharmaceutical companies (Int2 Acad&Consult, Int6 Pol&Reg, Int20 Biotech). Several interviewees commented on biotechnology companies' efforts to move into later stages of R&D, a trend that is likely to continue (Int2 Acad&Consult, Int4 Acad&Consult, Int5 R&D, Int6 Pol&Reg, Int9 NFP, Int10 Acad&Consult, Int11 Biotech, Int12 Biotech/ SVC, Int13 SVC, Int15 CVC, Int16 Pharm, Int20 Biotech, Int24 Pol&Reg, Int28 Acad&Consult). Some experts also noted increasing numbers of drug approvals from non-pharmaceutical companies (Int2 Acad&Consult, Int28 Acad&Consult). A biotechnology company/SME's decision to 'go at it alone' is primarily related to the desire to maximise value, which increases along the lifetime of the pharmaceutical R&D process (Int5 R&D, Int8 Biotech/SVC, Int10 Acad&Consult, Int11 Biotech, Int12 Biotech/SVC, Int22 Biotech/SVC, Int26 Pol&Reg). This is especially true after proof of concept in a clinical setting (Int22 Biotech/SVC). According to one expert source:

'...A company can achieve a far higher valuation if it has already successfully tested its product candidates in the clinic, and even higher valuations if the product is approved.'
(Anonymous)

However, this interviewee also noted that:

‘The company that invests most in the development process assumes most of the risk and may consequently expect to capture most of the financial value. In case of full development, the value is “captured” at a much later stage, i.e. when the product is registered and starts generating sales. Most venture capitalists do not have such long investment horizons and may opt for a quicker payback by encouraging a company to sell/out-license its invention or go public through offering of common stock.’ (Anonymous)

A biotechnology company’s ability to pursue a growth strategy and move into later R&D stages depends on many factors, not least the company’s therapeutic and technological focus (Int5 R&D, Int10 Acad&Consult, Int11 Biotech, Int15 CVC), **ability to attract capital** (Int2 Acad&Consult, Int20 Biotech, Int8 Biotech/SVC, Int11 Biotech, Int12 Biotech/SVC), **revenue position** (Int3 CVC) and **ability to outsource parts of the R&D process, such as clinical trials and sales** (Int5 R&D, Int6 Pol&Reg, Int8 Biotech/SVC, Int10 Acad&Consult, Int22 Biotech/SVC, Int25 Biotech). According to one interviewee, growth should be based on revenues – decisions to move into later R&D stages should be based on sufficient revenues to justify growth ambitions (Int3 CVC).

The greater availability of capital and growth funding enables some biotechnology companies to continue conducting later phases of R&D. However, the dominant global model for most biotechnology companies remains to be bought/acquired eventually, i.e. an M&A exit (Int2 Acad&Consult, Int3 CVC, Int5 R&D, Int8 Biotech/SVC, Int9 NFP, Int 10 Acad&Consult, Int 11 Biotech, Int 12 Biotech/SVC, Int 14 Pharm Int 15 CVC, Int20 Biotech, Int22 Biotech/SVC, Int25 Biotech) (See Section 2.1.3 for more information on dominant deal types). Only biotechnology companies/SMEs that can afford to can ‘go at it’ alone (Int8 Biotech/SVC, Int10 Acad&Consult, Int22 Biotech/SVC). Generally, investors are more likely to provide this funding to companies that already have a proven track record in R&D (Int3 CVC, Int11 Biotech, Int15 CVC) or where they are developing a platform technology or portfolio of products rather than a single product (Int20 Biotech, Int24 Pol&Reg). However, platform companies can license out the tech or an initial asset to create a revenue stream that then funds internal R&D to help them grow, becoming less dependent on external capital. The availability of funding can also depend on good IPO options (Int1 SVC, Int11 Biotech, Int12 Biotech/SVC, Int20 Biotech), which provide confidence to investors that there will be exit options for them (Int19 Pol&Reg). Some interviewees noted that the availability of more patient capital in the US (from investors willing to wait longer for returns) have contributed to more biotechnology companies/SMEs continuing later in the R&D process than in other countries (Int11 Biotech, Int14 Pharm, Int20 Biotech, Int22 Biotech/SVC). The ability of biotechnology companies/SMEs to successfully bring products to market also depends on success stories from other companies that have done the same, which encourages them to think ‘this can be done’ (Int12 Biotech/SVC, Int25 Biotech).

Biotechnology companies are more able to ‘go it alone’ in some areas than others. For example, companies active in orphan or rare diseases may find it easier to pursue R&D into later clinical research and development stages, not least because orphan diseases have smaller patient populations (Int5 R&D, Int11 Biotech). Smaller patient populations may require less capacity for distribution, manufacturing and sales (Int1 SVC, Int2 Acad&Consult, Int4 Acad&Consult, Int 5 R&D, Int11 Biotech, Int 12 Biotech/SVC, Int25 Biotech). Moreover, key opinion leaders in orphan

diseases may be more readily identifiable than in other disease areas, making it easier to conduct trials, marketing and sales in these areas (Int5 R&D, Int11 Biotech). According to one expert we spoke to:

‘Smaller companies are saying, well, if we’re only ever going to hit 20,000 patients in a market, we’ll do it ourselves. That has meant that it’s shifted to being a sellers’ market rather than a buyers’ market... it’s a sellers’ market in that large cap. Pharma need the assets, they’ve probably got overcapacity in their delivery of market-making to physicians and decision makers, and we are actually seeing in both directions US to Europe and Europe to US companies saying “You know what, I’m going to give it a go”.’ (Anonymous).

Biotechnology companies/SMEs’ ability to outsource parts of the R&D process, such as clinical trials and sales, also contribute to their capacity to continue later into the R&D process rather than be acquired (Int5 R&D, Int6 Pol&Reg, Int8 Biotech/SVC, Int10 Acad&Consult, Int22 Biotech/SVC, Int25 Biotech). For example, smaller trials can be outsourced to CROs rather than to larger pharmaceutical companies as they were in the past, and sales can also be outsourced (Int 5 R&D). One interviewee mentioned that biotechnology companies might find partnering with pharmaceutical companies expensive, also contributing to their desire to build internal capacity or outsource parts of the R&D process to other actors (Int10 Acad&Consult). It is also becoming easier to work virtually, so some biotechnology companies may have small offices and outsource activities to other established large labs (Int8 Biotech/SVC).

Many interviewees were keen to flag that pharmaceutical companies can add considerable value to the sector; biotechnology companies going into late R&D or marketing alone may not always be desirable. Pharmaceutical companies have particular strengths concerning clinical trials and regulatory approval, commercialisation, sales and marketing (Int1 SVC, Int4 Acad&Consult, Int6 Pol&Reg, Int7 Pol&Reg, Int9 NFP, Int11 Biotech, Int12 Biotech/SVC, Int16 Pharm, Int20 Biotech, Int21 Pharm, Int24 Pol&Reg, Int25 Biotech, Int26 Pol&Reg). Many interviewees noted that the vast majority of biotechnology companies/SMEs will eventually be acquired by pharmaceutical companies, even if this happens slightly later in the R&D process (Int1 SVC, Int6 Pol&Reg, Int7 Pol&Reg, Int9 NFP, Int11 Biotech, Int16 Pharm, Int20 Biotech, Int25 Biotech).

2.1.7. The rise of patient voice: Increased patient engagement in R&D

A growing focus on patient engagement in pharmaceutical R&D in recent years has provided momentum to solicit and amplify patient needs and preferences in every aspect of R&D. This influences how R&D is conducted and the investment types needed to support effective patient and public engagement with R&D processes (Int10 Acad&Consult, Int28 Acad&Consult). For example, there has been a growing interest in understanding which types of technologies can be used to lessen the burden of participating in research trials (Int10 Acad&Consult). Endpoints such as patient-reported outcomes are also becoming increasingly utilised (Int12 SVC Biotech).

We have also seen a more ‘science-savvy’ population gradually developing who better understand disease and health. For example, in light of COVID-19, individuals are developing a better understanding of what research concepts mean (e.g. placebos, statistics and disease understanding) (R&D Int 14). However, vocal anti-vaccine and anti-industry movements have also

emerged concurrently. How the future will unfold in terms of the types of science society engages with and how they process information and distinguish between facts and misinformation remains to be seen.

2.2. Key influences on pharmaceutical R&D’s future financial ecosystem: likely trajectories and uncertainties

Understating historical evolution is necessary but not sufficient to inform the future. In this light, we also interviewed experts on factors that may influence pharmaceutical R&D’s future financial ecosystem asking them to reflect on how factors are likely to unfold and the uncertainties regarding key influences. Table 1 summarises some of the key messages based on our analysis. We expand on each influence in the section that follows.

Table 1. Key influences likely to affect pharmaceutical R&D’s future financial ecosystem.

Theme	What we know: likely direction of travel	What we do not know: areas of uncertainty
Macro-level factors	Diverse macro-level factors will influence investor appetite for pharmaceutical R&D in the future. These can relate to the general state of the economy; unforeseeable events such as natural catastrophes, pandemics, or war/conflict; the relative competitiveness of sectors other than the life sciences; and general public attitudes to investing in health in the future.	How macro-level factors will unfold in the long term cannot be predicted. For example, there will likely be another pandemic, but its nature and when it will occur is more difficult to predict. Similarly, the general state of the global economy over the next decade is difficult to predict, even though the shorter-term impact of COVID-19 on many countries is clear. Some experts perceive that COVID-19’s detrimental impact on capital availability will be long-term, but this remains to be seen. The relative attractiveness of pharmaceutical R&D compared to other sectors remains to be seen, influencing pharmaceutical R&D investment. While health’s growing importance on policy agendas is inevitable, health investment levels and how they spill into pharmaceutical R&D are less certain.
Factors related to collaboration	Pharmaceutical companies will continue to source many innovation assets externally, and more open collaboration landscapes will unfold in conducting and funding pharmaceutical R&D.	However, pharmaceutical companies’ roles in more collaborative landscapes remain uncertain. It is unclear what the largest future investment areas will be and how different actors will collaborate. There is a general recognition that public health, infectious diseases and emergency-preparedness-related R&D will be a bigger priority than in the past, but whether areas like prevention or neurodegenerative diseases will also grow remains to be seen. The extent to which public and not-for-profit sector investors will adopt more commercial approaches to investment (e.g. expecting financial returns) is also unknown but will influence

	<p>collaboration dynamics and value capture. We see these practices gaining momentum in some countries, but the scale and pace at which they will challenge traditional investment behaviours is unclear.</p> <p>Some experts feel that more collaborative and blended investment (both financial and in-kind) be shared by more parties across the public and private sector, although this is uncertain.</p>
<p>Science and technology-related opportunities and complexities</p>	<p>Scientific and technological developments will continue creating new opportunities to advance pharmaceutical R&D, develop more personalised therapies for patients and create more segmented markets. However, pharmaceutical R&D will become ever more complex. Digital and data-driven innovation will transform pharmaceutical R&D alongside other advances in areas such as biologics and gene therapies, but this will not happen overnight.</p> <p>Despite a certainty that science and technology will continue to open new research avenues, how advancements will shape the R&D landscape and financing is less clear.</p> <p>More specifically, how and whether success rates and returns on investment from new areas of science and tech-driven pharmaceutical R&D will change and how these will influence investor appetite remains to be seen. New financial models may emerge to support increasingly costly and complex pharmaceutical R&D.</p> <p>How and whether society can keep up with the pace of scientific developments is unknown. In particular, societal ability to absorb the cost of innovative drugs and harness the opportunities presented by data and digital science-driven innovation is unclear.</p> <p>The impact of science and technology developments on R&D costs are also unclear. For example, once the infrastructure, regulations and practices for using real-world data in clinical trials and AI in drug discovery stabilise, R&D processes may become quicker and more efficient. This should make them cheaper, at least in theory. However, it is also plausible that AI will open up many new research questions related to pharmaceutical R&D, increasing the amount needed and its overall costs. This is difficult to foresee at present.</p> <p>Any potential innovative-drug failure on safety grounds could significantly impact investments in some areas of pharmaceutical R&D (e.g. gene therapies) but cannot be foreseen in advance.</p> <p>Public perceptions of new areas of science and whether new therapies like gene therapy will be well received remains to be seen, along with how public behaviours will influence investment.</p>
<p>Regulation-related factors</p>	<p>The ability to innovate in regulation will play a key role in investor confidence. Innovation in regulatory practices is essential, especially in regulation that can</p> <p>How quickly regulation will catch up with new opportunities presented by science and technology remains to be seen.</p>

	support innovative clinical trial designs but may take a long time.	Global policy positions about intellectual property protection for innovation in key areas of societal need can also be unpredictable, influencing investor appetite.
Factors related to the pricing of medicines	Decisions made in key global markets about how to approach drug pricing will have a global effect on investor appetite for pharmaceutical R&D, especially for complex drugs.	How drug pricing debates will evolve in key jurisdictions like the US is uncertain. What an innovative and sustainable financial model for reimbursing highly innovative acute therapies like gene therapies will look like is unclear.
Geography-related competitiveness	The geographical location of investors and markets will continue to evolve. Some countries (such as China and other APAC region countries) are investing heavily in bolstering life-sciences sectors, and new geographics may become increasingly attractive investment markets for the longer term.	Europe's future competitiveness in the global market is somewhat uncertain, given the rise of new players. Geopolitical decisions are likely to influence cooperation and competition dynamics with some emerging economies but how this will unfold remains to be seen.
Learning from innovation in response to the COVID-19 pandemic	The COVID-19 pandemic has evidenced the potential to conduct faster and more efficient R&D via innovative collaborations, novel approaches to risk-management and regulatory advancements.	Societal ability to sustain some of the practices witnessed in response to the COVID-19 pandemic remains to be seen. This uncertainty applies to practices such as remote and coordinated multi-centre trials at different locations in parallel, risk-taking in manufacturing-capacity investments prior to known R&D-process outcomes, and regulatory efficiency and support.

2.2.1. Macro-level factors will influence investor appetite for pharmaceutical R&D in the future

- **What we know:** Diverse macro-level factors will influence investor appetite for pharmaceutical R&D in the future. Such factors include the general state of the economy, unforeseeable events such as natural catastrophes, pandemics, or war/conflict, the relative competitiveness of sectors other than the life sciences, and general-public attitudes to investing in health.
- **What we do not know- the uncertainties:** The direction of these macro-level trends is unknown. How the economic climate will unfold and whether other sectors will become more attractive to investors is unclear. War and natural catastrophes are difficult to predict. Public attitudes to health and the percentage of GDP spent on health may rise, but what percentage of any gains would be channeled into R&D is less clear.

Text box 5. Key messages on macro-level influences on the future.

What we know about macro-level influences

Macro-level factors will determine the outlook for the financial ecosystem of pharmaceutical R&D. These macro-level influences concern the general state of the global economy, force majeure like

war/conflict and natural disasters, future pandemics, other sectors' attractiveness compared to the pharmaceutical R&D sector, and public attitudes to investing in health vis a vis other areas such as defence or education (Int3 CVC, Int4 Acad&Consult, Int8 Biotech/SVC, Int9 NFP, Int 26 Pol&Reg). However, how these macro-level factors will unfold is uncertain and difficult to predict.

What we do not know – the uncertainties related to macro-level influences

The general state of the economy will play an important role in the future pharmaceutical R&D ecosystem and the availability of capital. Whereas many economies will face short-term shocks recovering from the COVID-19 pandemic, the long-term direction is not known (Int1 SVC, Int3 CVC, Int4 Acad&Consult, Int8 Biotech/SVC, Int9 NFP, Int26 Pol&Reg, Int31 Pharm). The current investment landscape is generally considered healthier than in the past due to the improved availability of capital and the growing number of attractive investment opportunities (Int3 CVC). However, access to VC funding for European companies is still constrained (Int1 SVC, Int4 Acad&Consult) compared to the US (Int1 SVC). That said, the EU market's growth in entrepreneurialism may attract more investors in the next decade, increasing the potential to negotiate good deals (CVC Int 1). Historically, global investor appetite for pharmaceutical R&D investments has fluctuated, and longer-term investor appetite are unclear – especially regarding standalone venture capital (Int 3 CVC, Int8 Biotech/SVC).

The development of other competitive sectors also gives rise to uncertainties. VC investments depend on capital availability (Int4 Acad&Consult, Int9 NFP, Int10 Acad&Consult), and VCs will take their investment to other sectors (e.g. real estate, Fintech, cryptocurrency potentially) if these are considered more profitable (Int3 CVC, Int4 Acad&Consult, Int15 CVC).

Although challenging to foresee, events such as war/conflict, pandemics and natural catastrophes could also impact the general state of the economy and the availability of capital for pharmaceutical R&D (Int3 CVC, Int8 Biotech/SVC, Int26 Pol&Reg). Society may face a few problematic years post COVID-19 in terms of global economic recovery (Int4 Acad&Consult, Int26 Pol&Reg). As one interviewee noted, we have seen increased public funding for pharmaceutical R&D in response to the COVID-19 pandemic. However, the overall cost of the pandemic may lead to a decrease in public expenditure, potentially reducing biomedical research funding (Int4 Acad&Consult). According to one expert, the pandemic will have long-lasting effects on not-for-profits' fundraising and investments. This could have significant detrimental effects if the academic system loses a generation of researchers contributing to pharmaceutical R&D because they cannot access research funding. It will, therefore, also have a knock-on effect on the timelines for creating innovations (Int 29 NFP). As illustrated by one interviewee:

'I think one of the major challenges is post-pandemic, the impact on fundraising...that is going to have a massive knock-on effect for the next 20 years on the outputs of research, not only because of the publications but then the downstream 17 years bench to bedside point. And that, in that point, you have also lost a huge amount of skill from the system.'
(Anonymous)

The investments society makes into health more generally will also play a role in the financial ecosystem for pharmaceutical R&D, but how this will unfold is uncertain. One interviewee

suggested that health may represent a more significant share in the consumer market given how important it is for people to live better and longer (Int 24 Pol&Reg). If the percentage of GDP dedicated to health rises, the amount going into pharmaceutical R&D will depend on broader factors such as the general state of the economy, socio-political stability and how much R&D benefits from changes in wider healthcare-related expenditures. COVID-19 incentivised governments and international organisations to invest further in science and research. However, it is unclear whether – and at what pace – this may or may not translate into other areas of health-related R&D, including pharmaceutical R&D.

L.E.K. analysis for this study suggests that private-sector and larger biopharmaceutical/biotechnology companies contribute most R&D funds. L.E.K. analysis suggests that VC spending on pharmaceutical R&D is likely to continue growing in the future. However, government and NGO/not-for-profit spending on pharmaceutical-related R&D has been relatively flat and is likely to lose share compared to the other future funding sources. As biopharmaceutical R&D spending is growing moderately, its proportional contribution to the future landscape will likely remain relatively stable. Interviewees felt this broadly resonated with their views and experiences. However, they also felt that the availability of capital is likely to depend on other factors, including the broader macroeconomic variables described above.

2.2.2. Collaboration dynamics: R&D will become more collaborative in terms of actors and investors, but key areas of future investment are less clear

- **What we know:** Pharmaceutical companies will continue to externally source many innovation assets. More open collaboration landscapes will also unfold, with greater public-private collaboration in conducting R&D and increased convergence between life sciences and other sectors (e.g. IT). Policymakers, innovators and investors are likely to pay more attention to public health and emergency preparedness-related pharmaceutical R&D, although how this will be sustainably funded is less clear.
- **What we do not know – the uncertainties:** In an increasingly collaborative landscape, the future role of pharmaceutical companies is unclear. The largest investment areas and how different actors will collaborate within them also remain to be seen. The extent to which public and not for profit sector investors will adopt more commercial approaches to investment (e.g. expecting financial returns) is also unknown. Although such practices are gaining momentum in some countries, the scale and pace at which they will challenge traditional investment behaviours are unclear. Some experts feel that more collaborative and blended investment will be shared by more parties across the public and private sector, with some investments being financial and some being in-kind.

Text box 6. Key messages – the future collaboration landscape.

What we know about collaboration dynamics as an influencing factor

The R&D landscape has become increasingly collaborative over time; and we are likely to see even more collaborative innovation and investment for pharmaceutical R&D in the future, including public-private collaboration (Int2 Acad&Consult, Int5 R&D, Int7 Pol&Reg, Int10 Acad&Consult, Int14 Pharm, Int23 Pol&Reg, Int27 R&D, Int28 Acad&Consult), which may be better addressed through partnerships.

As already discussed, the growing recourse for pharmaceutical companies to source assets externally will continue (Int3 CVC, Int4 Acad&Consult, Int5R&D, Int24 Pol&Reg, Int2 Acad&Consult, Int9 NFP, Int1 SVC, Int8 Biotech/SVC, Int11 Biotech, Int12 Biotech/SVC, Int13 SVC, Int14 Pharm, Int16 Pharm, Int19 Pol&Reg). As such, the health of the investor landscape for SMEs and early-stage R&D will continue to be critically important in feeding the innovation supply chain. In this context, both standalone venture capital/seed capital and public investment in SMEs (e.g. government grants) will continue to matter greatly, as will corporate venture capital. The government's key role in filling funding gaps for early-stage research and supporting some translational research is likely to continue. However, government funding for research infrastructure (e.g. clinical trials infrastructure) may evolve to include more significant investment in advancing core data architecture to enable efficient data flows and enhanced use of real-world evidence in pharmaceutical R&D (Int6 Pol&Reg).

It is unclear whether large pharmaceutical companies will continue to have significant involvement in the entire R&D process (as they do today) or focus more exclusively on commercialisation, manufacturing and clinical trials. Some experts argue that pharmaceutical companies will always need to conduct some early R&D internally, not least to pick appropriate external innovation assets and identify promising opportunities in the SME sector (Int3 CVC, Int14 Pharm). Others note there may be a move towards more specialisation in commercial, manufacturing and regulatory functions (Int2 Acad&Consult, Int12 Biotech/SVC). It is also unclear to what extent pharmaceutical companies or new players in pharmaceutical R&D will adopt data- and digital-convenor roles (Int2 Acad&Consult).

According to some interviewees, R&D execution will become more collaborative. There will also be more collaborative investments across the public and private sector and more blended investments (Int10 Acad&Consult, Int29 NFP). Some investment is likely to be financial and some in-kind (e.g. through enabling access and use of R&D platforms, teams, infrastructure), particularly within the public sector (Int10 Acad&Consult). The private and public sectors have together funded pipelines of molecules moving through basic research into clinical testing for a long time. Such collaborative funding is not new but is likely to continue at an even greater scale in the future. For example, there is growing interest in the public sector to ensure sufficient funding for R&D infrastructure by turning to the private sector for support (Int10 Acad&Consult) and an increase in pre-competitive alliances between private-sector companies (Int14 Pharm), especially in currently intractable areas. However, in terms of amounts, private capital will likely remain dominant in funding pharmaceutical R&D (Int11 Biotch, Int4 Acad&Consult). According to one interviewee, there may also be more collaboration between not-for-profits, VC and philanthropic funding in specific clinical areas (Int29 NFP).

Although only highlighted by one expert, greater interaction between research funders, policymakers and regulatory bodies is also anticipated to enhance support for R&D and reduce uncertainties on regulatory approval and pricing pathways (Int26 Pol&Reg). According to one interviewee, this would lead to a more sophisticated investment landscape where investors look more at the overall system and its readiness to support innovation when making investment decisions (Int26 Pol&Reg). For example, according to this expert, pharmaceutical companies will want more upfront assurance about what will happen post-R&D in relation to uptake and

regulation, which will confer more investor confidence. Governments will also want to know more upfront about supply chain resilience, domestic manufacturing and pricing negotiations (Int26 Pol&Reg).

More convergence between sectors (e.g. IT and life sciences) is also expected in the increasingly collaborative landscape. The same is true for collaboration between R&D and the healthcare system (healthcare professionals and patients) to support more data and insight sharing to inform R&D (Int 7 Pol&Reg, Int13 SVC, Int16 Pharm, Int19 Pol&Reg, Int 27 Pharm).

Finally, some experts predict greater public and private-sector attention to public health, infectious diseases and emergency preparedness – especially in light of COVID-19 (Int14 Pharm, Int18 Acad&Consult, Int20 Biotech). However, how it will be funded remains unknown, including within the context of public-private collaboration (Int21 Pharm).

What we do not know – the uncertainties related to collaboration dynamics as an influencing force

There are many uncertainties in this collaborative future, including how different R&D innovators and investors will mobilise and determine investment priorities and what these will be (e.g. disease and clinical areas). It is unclear what the major investment and collaboration areas are likely to be in ten years.

What constitutes an attractive investment area can change over time, influencing where investments (and returns) might be made and how R&D collaborators focus their time, effort and resources. Although trends are helpful, it is unclear which specific areas will attract future investment. For example, despite major advances in areas like gene therapy, stem cell therapy and oncology, it is unclear whether a new and reinvigorated focus on neurodegenerative diseases and ageing will emerge given the need for more basic scientific advancement in this space (Int2 Acad&Consult, Int14 Pharm). It is also not known whether there will be more focus on specialty products for hospital-based treatments as opposed to community interventions (Int4 Acad&Consult). Moreover, it is uncertain whether cancer will continue to be a key investment area or whether we might find increasingly effective treatments over the next decade, continuing the trend of managing rather than curing cancer (Int2 Acad&Consult). According to one interviewee, we are currently seeing the normalisation and commodification of previously exciting, cutting-edge treatments (e.g. with breast cancer), opening the R&D landscape to the next big challenge and investment area (Int19 Pol&Reg). Another interviewee flagged that we may see more attention focused on R&D into repurposing existing drugs for new indications (Int29 NFP), which may entail companies conducting and collaborating on repurposing-related R&D on compounds that originated in other companies.

It is also unclear how much prevention-related R&D will be prioritised and who will collaborate in this space (Int 7 Pol&Reg, Int12 Biotech/SVC). According to one interviewee, better incentives for investing in prevention are needed (Int 7 Pol&Reg), especially as it can take large patient populations and many years to establish whether a preventative intervention works and demonstrate desired outcomes (Int12 Biotech/SVC). Another challenge related to early-prevention R&D is that the research is ethically challenging because the treatment options are uncertain.

Research participation may raise individuals' awareness that they are at a high risk of a condition for which treatment may be many years away and/or not materialise, causing them to worry about disease risk for which there is no cure/treatment (Int26 Pol&Reg).

Fundamentally new approaches to pharmaceutical R&D may emerge and attract diverse types of actors and collaborations. However, their nature is unknown (Int7 Pol&Reg), as is how swiftly financiers will embrace new scientific developments (Int13 SVC). For example, future drugs could aim to reduce the effects of ageing (Int7 Pol&Reg) alongside other breakthrough treatments, which would raise difficult questions about whether this type of R&D is ethical and affordability, willingness to pay and access (Int 7 Pol&Reg).

There have been some changes in investment cultures in public and not-for-profit sectors towards adopting more commercial approaches (not just focusing on societal returns). However, it remains unclear how much financial returns will factor into future investment in these sectors. The scale and pace these practices will embed into the financial ecosystem and challenge traditional investment behaviours remain to be seen.

In some geographies (most notably the US and some parts of Europe), academic culture is changing and becoming savvier in focusing on the practical impact on society and the expected returns for reinvestment into activities focusing on societal impact. However, whether academic research culture will change at pace and scale more widely across geographies remains to be seen (Int5 R&D). Some academic institutions are finding ways to free up financing or fundraise themselves to support basic research in targeted areas. However, it is unknown how much this will scale in the future (Int10 Acad&Consult). As discussed in earlier sections (see Section 2.1.3), not-for-profits are also considering ways to recoup their investments to support the sustainability and reinvestment of funds into areas of need, including via royalties, equity and other types of financial transactions (Int9 NFP, Int30 NFP, Int29 NFP). For example, some not-for-profits have written conditions into their grants to realise returns for successful investments (Int30 NFP), but it is unclear whether this will scale.

However, although some degree of change in expectations and motivations of different investors may be unfolding, the fundamental motivations of different types of investors are likely to remain stable over time. When asked about motivations for investments, several interviewees highlighted that while different investors are motivated by different goals, decisions are ultimately made by individuals influenced by their own personalities, interests and skills (Int3 CVC, Int13 SVC, Int20 Biotech). We overview key motivations in Text box 7.

- For **pharmaceutical investors**, returns and profitability tend to drive investment decisions (Int5 R&D, Int 7 Pol&Reg, Int9 NFP, Int10 Acad&Consult, Int11 Biotech, Int24 Pol&Reg, Int26 Pol&Reg, Int27 Pharm). Private-sector investors seek to provide value to shareholders (Int11 Biotech, Int27 Pharm) and invest where there is a higher probability of success (Int14 Pharm, Int27 Pharm: 'Industry will always try to maximise their profits' (Anonymous). Although returns and profitability ultimately determine most investment decisions, strategic considerations also play a role in private sector investment (Int10 Acad&Consult, Int14 Pharm, Int21 Pharm, Int25 Biotech, Int 26 Pol&Reg, Int27 Pharm, Int 31 Pharm). For example, companies may be willing to accept lower short-term financial returns in favour of investing in longer-term strategic areas or where they want to present

themselves to shareholders as a leader (Int10 Acad&Consult, Int21 Pharm, Int25 Biotech). Some companies have taken a strategic approach to investments, only investing in areas of strength (e.g. only pursuing an investment area if they will be among its top three companies), and ‘swapping’ assets outside these areas to build on their strengths (Int21 Pharm).

- **For corporate VC investors**, early investments in biotechnology companies/SMEs are often motivated to decrease the downstream cost for pharmaceutical companies that will later seek to acquire these companies (Int24 Pol&Reg). Societal needs, beliefs and values also play a role in private-sector investment. Some interviewees mentioned that pharmaceutical companies look to invest in areas with a real-world impact and within areas of unmet need, such as AMR (Int21 Pharm, Int27 Pharm). This shift towards value-based investing can be partly explained by the emergence of philanthropic founders donating large portions of their wealth to social issues. Employees also have a greater voice and want to work for socially conscientious companies (Int30 NFP). According to one interviewee, *‘I think we’ve started to see that companies [are] kind of developing more of a philanthropic ethos, and hopefully that will grow because that would be fantastic’* (Anonymous).
- **For standalone VC investors**, financial returns motivate investment decisions (Int1 SVC, Int4 Acad&Consult, Int5 R&D, Int10 Acad&Consult, Int12 Biotech/SVC, Int13 SVC, Int15 CVC, Int20 Biotech, Int22 Biotech/SVC, Int25 Biotech, Int 28 Acad&Consult). The probability of success is a big factor (Int3 CVC, Int7 Pol&Reg, Int13 SVC, Int15 CVC, Int25 Biotech): *‘At the end of the day, return on investment is really what the VCs are looking for, and it’s fairly brutal I would say on that. That does put... you could call it pressure on Biotechs, but that’s what you’ve signed up for. That’s the deal’* (Anonymous). VC investors have an interest in increasing their investments’ probability of success (Int1 SVC, Int2 Acad&Consult, Int3 CVC, Int4 Acad&Consult, Int12 Biotech/SVC, Int13 SVC, Int15 CVC, Int25 Biotech) and do so in several ways. VC investors often sit on boards for companies they have invested in (Int1 SVC, Int3 SVC) and try to steer the company towards financial success. As noted by one interviewee, *‘Venture capital is not just about counting money all day, it is about building companies and helping them grow’* (Anonymous). Although VC funding generally focuses on returns and the probability of success, societal impact also plays a role. VC investors are motivated to bring new drugs to people (Int1 SVC, Int3 CVC, Int22 Biotech/SVC, Int30 NFP, Int29), especially in areas where patients have a considerable voice in investment decisions, e.g. rare diseases (Int3 CVC). For the public and charitable sector, financial returns tend to be less important than societal impact and unmet societal need (Int2 Acad&Consult, Int4 Acad&Consult, Int7 Pol&Reg, Int9 NFP, Int11 Biotech, Int24 Pol&Reg, Int28 Acad&Consult, Int 29 NFP, Int 30 NFP).
- **Public-sector and not-for-profit investors are predominantly motivated by societal benefits. However, they are gradually considering the commercial savviness of their investments, aiming to reinvest gains into further research for societal benefit.** Some experts perceive that the public and not-for-profit sectors are seeking financial returns in new ways (Int9 NFP, Int10 Acad&Consult, Int13 SVC, Int28 Acad&Consult, Int29 NFP, Int30 NFP), and increasingly looking to measure their investments’ impact (Int29 NFP, Int30 NFP).

Text box 7. Key motivations of different types of investors.

2.2.3. Though they will continue creating new opportunities, science and technology will increase R&D complexity and financing uncertainties, raising questions about how society will keep up with the pace of scientific development

- **What we know:** Science will continue creating new opportunities to advance pharmaceutical R&D and develop therapies for patients, including through more personalised approaches and segmented markets. However, new scientific approaches will increase R&D complexity, and digital- and data-driven innovation will not transform pharmaceutical R&D overnight.
- **What we do not know – the uncertainties:**
 - How investment success rates and returns from new areas of science and tech-driven pharmaceutical R&D will unfold over the next decade and influence investor appetite is uncertain. It is also unclear whether new financial models will emerge to support increasingly costly and complex pharmaceutical R&D.
 - How and whether society will be able to keep up with the pace of scientific developments is also uncertain. This is particularly evident on two fronts: societal ability to absorb the cost of innovative drugs and harness the opportunities presented by data- and digital-science-driven innovation.
 - Any potential innovative-drug failure on safety grounds could also significantly impact a sector's investments but cannot be foreseen.
 - Public perceptions of new areas of science and technology, e.g. gene therapy and Artificial Intelligence [AI]) that will influence uptake are yet to become apparent. How public behaviours (including health-seeking behaviours) will influence investment is also unknown.

Text box 8. Key messages - science and technology: opportunity and complexity in the future.

What we know about influences related to scientific and technological developments

Science and technology will open new drug development opportunities but increase pharmaceutical R&D's complexity. This applies not just to cell and gene therapies but also to targeted formulations like nanoparticles that might overcome drug toxicities, opening target areas previously deemed 'undruggable' (Int 5 R&D). These complex drugs will change what comes to market and the actors introducing them – further diversifying the supplier chain (Int5 R&D). Pharmaceutical R&D is likely to depend increasingly on diagnostics (Int5 R&D, Int13 SVC, Int19 Pol&Reg). Thus, we are likely to see more investment in diagnostics (Int5 R&D, Int20 Biotech) and funding earlier biomarkers for patient stratification (Int20 Biotech). Whether success rates will improve remains to be seen (Int28 Acad&Consult).

The growing interest in biological over chemical sources of innovation is likely to continue (Acad&Consult Int 2). As noted by one interviewee:

'At the moment, it looks like we're going to run out of money before we run out of biology.'
(Anonymous)

The data and digital-innovation space will also transform the future of pharmaceutical R&D regarding how data and digital tech inform the R&D process. Digital and data-driven pharmaceutical R&D will help de-risk investment but take time to manifest at scale (Int3 CVC, Int6 Pol&Reg, Int13 SVC, Int14 Pharm, Int16 Pharm, Int19 Pol&Reg, Int26 Pol&Reg). Currently,

there is a gap in the pharmaceutical industry's ability to use these technologies, requiring investment to develop such capacities. Although it will be easier to collect data, it will be challenging to utilize and analyse the vast amounts of data collected through new technological developments (Int14 Pharm). As noted by one expert:

'There are areas within the industry that can benefit from cheaper, better, faster and smarter, but this is not going to happen overnight.' (Anonymous)

Regulations around clinical-evidence generation to support innovative trial designs will also need to adapt to new scientific and technological advancements (Int6 Pol&Reg). For example, data and AI will transform R&D and allow more to be done *in silico* (Int19 Pol&Reg), potentially changing how clinical trials are conducted. Data and digital innovation are also likely to challenge traditional CRO trial models due to a need for different ways of finding patients (e.g. online and through digital cohorts) and more active digital patient cohorts (Int19 Pol&Reg).

New scientific developments will reinforce R&D for more segmented markets, which will continue to influence R&D investment decisions depending on whether market viability is likely (Int2 Acad&Consult, Int6 Pol&Reg, Int9 NFP, Int20 Biotech, Int12 Biotech/SVC, Int14 Pharm, Int17 Acad&Consult, Int19 Pol&Reg). However, drug personalisation and segmented markets have the potential to increase and perpetuate inequalities if investment into expensive drugs only occurs in markets that can withstand higher costs. According to one interviewee, significant reform in the models used to incentivise R&D and pay for care would be more beneficial to more people than investing in R&D for expensive drugs aimed at small populations (Int19 Pol&Reg), but this area is uncertain.

Whereas scientific advances will drive investment opportunities, R&D investment also depends on politics, policy and public opinion. As emphasised by one expert:

'The future will be shaped by science because that's the key drive of pharmaceutical innovation, but eventually the go/no-go decisions and whether some treatment prospects will be fostered is going to be highly dependent on whether there is a market.'
(Anonymous).

New science and technology will need support from diverse financial instruments. The future balance of direct (e.g. grants, loans) and indirect (e.g. tax incentives, accelerated depreciation of capital) public-sector support instruments is also an area of uncertainty influencing pharmaceutical R&D's financial landscape (Int 23 Pol&Reg, Int19 Pol&Reg). Interest around tax incentives varies and has increased across some countries (Int19 Pol&Reg), but there has been debate around their effectiveness in enticing specific types of R&D (Int23 Pol&Reg). The optimal mix of public-sector investment support remains to be seen but must recognize that different instruments address different types of market failures.

What we do not know – uncertainties about the influences of scientific and technological developments

Uncertainty about financial models' fitness for the future

It is uncertain how advances in science and technology will drive success rates and returns on R&D investment, not least as it remains unclear how pricing policy environments will unfold (see Section 2.2.5). According to some experts, there is a pressing need for new financial models to support more complex R&D, but whether and how this will manifest is not clear (Int12 Biotech/SVC, Int20 Biotech, Int6 Pol&Reg, Int9 NFP, Int17 Acad&Consult). New models such as subscription-based approaches are being considered for areas where viable markets have been a challenge, and megafunds are also receiving increased attention as a possible way to tackle high-cost, high-risk R&D (Int17 Acad&Consult). Megafunds pool funding for several high-risk projects under a single fund. By combining many risky projects into a single financial entity, the risk may be reduced, helping raise capital to fund projects through debt securities, i.e. bonds. Access to debt financing is vital in this model because a larger pool of capital might be more willing and able to invest in debt than equity due to the relative sizes of the public debt and equity markets (Int17 Acad&Consult, Int28 Acad&Consult). These megafunds could involve multiple investors to tackle significant challenges (e.g. rare or infectious diseases). However, the concept is relatively nascent in terms of gaining traction.

Uncertainty about whether society will keep up with the pace of scientific and technological advances and how this will influence R&D costs and market viability

Society's ability to keep up with the pace of scientific development is also a big unknown in terms of absorbing the costs of highly innovative drugs (Int15 CVC, Int19 Pol&Reg). We face a growing gap between what science makes possible and what healthcare systems and economies can afford, e.g. immunotherapies, gene therapies and Parkinson's drugs (Int19 Pol&Reg). As illustrated by one interviewee:

'With expansionary monetary policies and an environment of low interest rates throughout the developed world, we see more venture capital pouring into medicines R&D, funding and driving up valuations of many biotechs. We have observed this trend in the last years and expect it to continue. The high valuations are indicative of the high expectations of return on investment, and it remains to be seen if society will be willing to reimburse the products at levels commensurate with those expectations.' (Anonymous)

Uncertainty about society's ability to keep up with scientific and technological developments also applies to the ability to keep up with and harness the benefits of data and digital advances, minimising risks and transforming R&D practices (Int10 Acad&Consult, Int6 Pol&Reg, Int4 Acad&Consult, Int14 Pharm, Int19 Pol&Reg). It remains to be seen whether more data-driven and digitally-enabled R&D will affect clinical trial costs. Scientific and technological advancements may reduce costs for parts of the pharmaceutical R&D process in the future (Int1 SVC, Int2 Acad&Consult, Int6 Pol&Reg, Int8 Biotech/SVC, Int10 Acad&Consult, Int11 Biotech, Int14 Pharm, Int20 Biotech, Int24 Pol&Reg, Int28 Acad&Consult, Int30 NFP). However, they may also increase costs in some areas (Int1 SVC, Int2 Acad&Consult, Int6 Pol&Reg, Int10 Acad&Consult, Int16

Pharm, Int19 Pol&Reg, Int24 Pol&Reg, Int27 Pharm, Int30 NFP), rendering the overall impact unclear (Int10 Acad&Consult, Int6 Pol&Reg, Int4 Acad&Consult, Int14 Pharm, Int19 Pol&Reg).

Advancements in identifying and validating targets and in data generation have decreased the per-unit cost of R&D, contributing to increased efficiency overall and decreased failure costs in many areas (Int2 Acad&Consult, Int6 Pol&Reg, Int8 Biotech/SVC, Int10 Acad&Consult, Int11 Biotech, Int14 Pharm, Int24 Pol&Reg, Int28 Acad&Consult, Int30 NFP). However, these technologies have the potential to increase short-term R&D costs by adding to the complexity of coordinating and integrating technologies into R&D (Int10 Acad&Consult, Int16 Pharm, Int19 Pol&Reg, Int27 Pharm, Int30 NFP) and making it more expensive to hire people to use these technologies (Int 24 Pol&Reg). In addition, while these technologies may reduce the per-unit cost of R&D, they may also lead to more research questions and R&D, raising the total cost of pharmaceutical R&D (Int1 SVC, Int2 Acad&Consult). AI may expose greater complexity, e.g. drug toxicology profiles and when/where drugs are safe in multimorbid patients (Int19 Pol&Reg). According to one interviewee:

‘The big disadvantage of digital is that it creates a huge amount of data. So actually collecting data is no longer the problems – it’s the algorithms you use and the way that you look at that data. So if you do that really really well, theoretically you’ll choose better disease targets and then you can follow that through the rest of the process’ (Anonymous)

There are likely long timelines for accruing benefits from increased R&D efficiency and cost-optimisation. In the short term, digitising R&D increases costs because new technologies need additional investment to integrate them into organisations and train individuals in using them (e.g. for specific pharmaceutical R&D and trials). The hope is that these technologies will ultimately justify upfront investments in the longer term. However, it is too early to tell whether this will translate into reduced R&D costs (Int10 Acad&Consult). In principle, once the infrastructure, regulations and practices of using real-world data in clinical trials and AI in drug discovery stabilise, R&D processes may become quicker and more efficient. This should make them cheaper, at least in theory (Int14 Pharm).

We also do not know the time lag for integrating data and digital innovation into pharmaceutical R&D, including innovative clinical-trial designs (Int10 Acad&Consult, Int6 Pol&Reg).

There is additional uncertainty about how best to regulate AI and other digital technologies in pharmaceutical R&D (Int24 Pol&Reg)- as we elaborate on in Section 2.2.4. Mitigating against misuse will require difficult regulatory decisions, and the cost of regulation is likely to increase given the expertise required to make effective and safe decisions (Int 24 Pol&Reg). Since clinical trials are a particularly costly part of the R&D system, how these are regulated – especially designs incorporating AI and other digital technologies – will considerably impact R&D costs.

The impact of data and digital technology on the emergence and positioning of new industry leaders (i.e. not traditional big pharma) also remains to be seen. We may see new investors (Int27 Pharm) and new types of companies conducting pharmaceutical R&D and diagnostics traditionally confined to pharmaceutical and biotechnology companies. For example, digital

giants like Google and Apple may get involved in the pharmaceutical R&D space (Int5 R&D, Int16 Pharm, Int27 Pharm).

Uncertainty with respect to public perceptions and public behaviours and their influences on investor appetite for specific pharmaceutical R&D areas

Whether the public will embrace innovations such as gene therapies and stem cell therapies remains to be seen, influencing investment in these R&D areas. Public perceptions of R&D areas and the industry more widely relate to how it is regulated, which informs investor appetite (Int21 Pharm). This also applies to new approaches to drugs that raise ethical debates, e.g. those aiming to reverse ageing (Int 7 Pol&Reg). Ethical and moral positions on these innovation areas are unclear (Int9 NFP, Int7 Pol&Reg), and views may vary across geographies and cultures. It remains to be seen whether a more science-savvy and engaged population influences the financial ecosystem in the future and what role it plays in setting the R&D agenda (Int14 Pharm, Int20 Biotech, Int21 Pharm).

Individual behaviours may also influence the future investment landscape, but exactly how and to what extent is yet to be seen (Int16 Pharm). For example, attitudes towards personal responsibility for healthy lifestyles, health-seeking behaviours and access to care can influence investment. The public will also have a growing role in advocating for government investment. According to one interviewee, there is a need for the public to raise issues around science and R&D with their political authorities to secure sufficient focus and investment – particularly in R&D areas/stages that are not commercially viable (Int29 NFP).

Policies around insurance also play a role, influencing which drugs will be paid for and by whom (e.g. public payers or private-sector insurance companies), and ultimately influencing market viability, sales estimates, investment returns and investor appetite.

2.2.4. Regulation will play a key role in determining investor confidence and will need to catch up with new opportunities presented by science and technology, but the timeliness of regulatory-practice innovation is unknown

- **What we know:** The ability to innovate in regulation will play a key role in investor confidence in supporting pharmaceutical R&D. Innovation in regulatory practices is essential – especially in innovative clinical trial designs.
- **What we do not know- uncertainties:** How quickly regulation can catch up with new scientific and technological developments/opportunities remains to be seen. This is especially true for better-targeted and more efficient and adaptive clinical trial designs. Global policy positions on intellectual property protection for innovation can also be unpredictable, influencing investor appetite.

Text box 9. Key messages - regulation and the future.

What we know about regulatory influences

There is a need for innovation in clinical-trial regulation, which will impact future pharmaceutical R&D (Int5 R&D, Int6 Pol&Reg, Int16 Pharm, Int20 Biotech). Unless we develop innovative clinical-trial models (Int6 Pol&Reg, Int13 SVC), clinical trials' required patient numbers

and costs will become challenging to support in the future. Clinical trial and regulatory costs are among the main drivers of high costs and potential low returns for pharmaceutical R&D (Int2 Acad&Consult, Int4 Acad&Consult, Int5 R&D, Int6 Pol&Reg, Int11 Biotech, Int13 SVC, Int16 Pharm, Int17 Acad&Consult, Int20 Biotech, Int21 Pharm, Int25 Biotech, Int27 Pharm, Int29 NFP, Int30 NFP). Patient identification, recruitment and retention are particularly costly (Int2 Acad&Consult, Int6 Pol&Reg, Int11 Biotech, Int16 Pharm, Int27 Pharm, Int29 NFP), particularly for rare diseases (Int16 Pharm, Int27 Pharm) and drugs with more than one indication (Int4 Acad&Consult, Int29 NFP). Data storage and privacy have also become more expensive (Int6 Pol&Reg), even as data-generation costs have decreased. As noted by one interviewee, trial costs have increased as drugs have become more effective (e.g. in cancer) because they require more patients and time to observe deaths and other adverse outcomes (Int11 Biotech).

There are many ways that innovation in clinical trials may support more efficient and smarter R&D practices. For example, there is a potential for better targeted and more efficient identification of study participants, improved eligibility criteria (e.g. dropping unnecessary criteria and accessing the right population for a drug), smarter trial designs (regarding data collection and adaptive designs), and better use of secondary/passively collected data with primary data (Int6 Pol&Reg). According to one expert, the regulatory process requirements for amending trial protocols are also seen as overwhelming, time-consuming and bureaucratic for many innovators, acting as an obstacle to adaptive trial designs (Int6 Pol&Reg):

‘We need [to] build toward the idea that amendments [to trials] can be amended in 24 hours or less and can be fully deployed. This can be solved by creating systems for quicker adaptations: the whole system must be electronically connected enough so that investigators and patients can be educated, study coordinators know what to do, investigational product looks different, the right consent forms are being used, changes in data collection can done seamlessly, datasets can be cross-checked etc. All this has to change.’ (Anonymous).

In addition, one interviewee commented that increasingly restricted indications (i.e. a specific drug’s applicability to fewer people) will likely increase the regulatory applications needed to get to market, increasing the need for a regulatory apparatus allowing a higher throughput of regulatory applications (Int6 Pol&Reg).

Government support and incentives for innovative trial designs will be needed to enable cost-containment while ensuring safe practice and removing disincentives for organisations with business models based on running large trials (Int6 Pol&Reg). Regulatory agencies will need to develop a clearer approach for dealing with innovative trial designs, especially for smaller and more targeted human trials in key therapeutic areas (Int5 R&D, Int6 Pol&Reg, Int20 Biotech, Int16 Pharm). According to one expert, CROs who make money from trials of large population sizes do not have incentives to innovate and decrease the number of trial participants (Int6 Pol&Reg).

What we do not know – uncertainties related to regulatory influences

As illustrated above, pharmaceutical R&D regulation needs to keep up with the times, but it is unclear how quickly this can happen (Int6 Pol&Reg, Int13 SVC, Int14 Pharm, Int26 Pol&Reg).

According to one expert, high demand on regulatory agencies will persist given current innovation levels. They also suggested that regulatory apparatus will need to accommodate more drugs coming through and long periods of real-world evaluation for individual products (Int6 Pol&Reg). The current system is unlikely to remain sustainable in the coming decade unless regulation adapts. As conveyed by one expert:

‘There was an increased desire from regulators to see real-world evidence, but the way that real-world evidence is collected is still a challenge for regulatory authorities. So they ask for new novel ways of demonstrating efficacy, but they haven’t quite caught up to speed on how real-world evidence is gathered, and they expect it to be analysed in a way that is specific for what has been done before. Regulators are behind the curve on how new data is being analysed.’ (Anonymous)

Outside clinical-trials regulation, global policy positions relating to IP protection are also sometimes uncertain (e.g. especially for matters of key global health significance), influencing the investor landscape (Int4 Acad&Consult, Int13 SVC, Int21 Pharm). Policy positions on IP-related matters can fluctuate, as seen during the COVID-19 pandemic. From an industry perspective, IP is a key asset, and IP protection is central to industry business models (Int 21 Pharm). At the same time, certainty about how IP will be treated globally (i.e. lack of turbulence and uncertainty) is also critical for effective negotiations and business planning. From a public policy perspective, positions on IP must be considered against the importance of ensuring fair and equitable access to global populations. Balancing these considerations will be vital for incentivising innovation in key public health areas, including future pandemics and public health challenges.

2.2.5. Pricing policy will remain a key driver of investment decisions, and uncertainty about how drug-pricing policies may change in key global markets will influence investor behaviours

- **What we know:** Decisions made in key global markets about drug-pricing approaches will have a global effect on investor appetite for pharmaceutical R&D, especially for complex drugs.
- **What we do not know- the uncertainties:** How drug pricing debates will evolve in key jurisdictions like the US is uncertain. It is unclear what an innovative and sustainable financial model for reimbursing highly innovative acute therapies (e.g. gene therapies) will look like in the future.

Text box 10. Key messages - pricing policy and the future.

What we know about pricing-related factors

Market viability and attractiveness – determined primarily by drug prices and market sizes – will remain a key driver of investment decisions for private-sector investors (Int1 SVC, Int3 CVC, Int5 R&D, Int11 Biotech, Int1 SVC, Int23 Pol&Reg, Int31 Pharm). According to one expert view:

‘It is worth noting that the single biggest incentive for developing new medicines is that those medicines are prescribed, used, and reimbursed at prices commensurate with the value they provide to patients and the healthcare system.’ (Anonymous)

The reimbursement environment will continue playing an important role in determining the availability of R&D investment capital. In particular, drug-pricing decisions made in key global markets such as the US will have a worldwide effect, as innovators see the US as a key market (Int5 R&D). Interest in the Chinese market's investment community and decisions related to pricing and regulation in this market will also continue growing (Int8 Biotech/SVC, Int24 Pol&Reg).

What we do not know – the uncertainties related to pricing as an influencing force

There is no doubt that the pricing debate will influence the investment landscape in pharmaceutical R&D going forward, but how key markets will approach drug-pricing decisions in the near and longer-term is less certain (Int1 SVC, Int3 CVC, Int5 R&D, Int11 Biotech, Int1 SVC, Int23 Pol&Reg, Int4 Acad&Consult, Int21 Pharm, Int26 Pol&Reg). For example, the US view on reimbursement significantly affects global investment in pharmaceutical R&D (Int5 R&D), and approaches to drug pricing can vary between political administrations. Europe also has a role in public policy that allows health systems to absorb the cost of innovations in a sustainable way for both public and private sectors. However, the European market is more fragmented than the US one, challenging reimbursement landscapes and increasing uncertainty for innovators regarding market size (Int21 Pharm). In addition, societies paying for healthcare worldwide have to make fundamental trade-offs, influencing what different markets can pay for and how, and the R&D investments made. As illustrated by one expert, governments in countries with over half a million people waiting for a wheelchair may elect to pay for wheelchairs rather than fund an enzyme-replacement therapy for a very rare disease (Int8 SVC). Policy actions related to managing pricing and competition will impact investor appetites in specific markets – some policy actions limiting competition can reduce prices but be prone to anti-competitive behaviours (Int8 SVC).

As introduced earlier, it is uncertain whether society can absorb the costs of new drugs driven by major scientific and technological breakthroughs (Int5 R&D, Int3 CVC, Int1 SVC, Int11 Biotech, Int1 SVC, Int21 Pharm). For example, gene editing could have the same investment attraction as monoclonal antibodies did when they came to market in the 2000s. However, whether the market can keep up is unknown (Int24 Pol&Reg). Some experts believe that the current pricing model for drugs for segmented markets with small patient populations is untenable in terms of high drug prices that society cannot afford (Int6 Pol&Reg, Int19 Pol&Reg). The high costs of more personalised approaches will influence whether and what to invest in, depending on who can or cannot pay globally and certainties/uncertainties about market viability (Int19 Pol&Reg). According to one interviewee commenting on ageing populations:

'The idea that the state will always be able to support with the very expensive end-stage treatment, regardless of how one lives their life, is a big unknown.' (Anonymous)

How high healthcare can reach as a percentage of GDP is also unknown (Int7 Pol&Reg).

Society lacks clarity on what a sustainable financial model for reimbursing highly innovative acute therapies like gene therapy looks like, and there is a lack of innovative financial solutions. Questions around fair pricing and the free market are particularly challenging for ground-breaking treatments (Int9 NFP, Int12 Biotech/SVC, Int16 Pharm), including one-time cures for rare or ultra-rare diseases (Int9 NFP, Int16 Pharm). It is unclear how pricing can ensure accessibility while also

incentivising R&D in these areas (Int9 NFP, Int16 Pharm). As one interviewee noted, the pricing system was designed for older drugs rather than ‘million-dollar plus gene therapies’ (Int16 Pharm). Several experts flagged the need for innovative financial models (Int12 Biotech/SVC, Int20 Biotech, Int6 Pol&Reg, Int9 NFP, Int17 Acad&Consult, Int21 Pharm). Gene therapy developers are still struggling with creating a sustainable business model that would allow payers and reimbursement systems to absorb the cost of these therapies. As one interviewee noted:

‘If you ask an R&D person today what keeps them up at night, in previous years that would be proof-of-concept, today it is the fact that they would develop something that would be a success from medical and scientific standpoint but would not reach patients because of access issues.’ (Anonymous)

How quickly outcome-based payment becomes widespread is unknown. However, we are likely to see more of it in the future, according to one interviewee:

‘In the past, there hasn’t been enough proper rewards for outcomes for medicines financing, and I think that’s something that’s possibly changing a little bit and could be a future trend... I think there will be more of a move to pay Pharma/Biotech based on outcomes rather than based on providing the medicine... I think historically the trend of paying at the point of purchasing the medicine has historically been the model, and I see that model changing into a much more outcomes-based approach, which is going to be quite complex.’ (Anonymous)

Views on how society might support affordability within innovative financial models vary. Many interviewees highlighted that pricing is based on a free market and decreasing pharmaceutical R&D costs would not necessarily lead to more affordable drug pricing (Int1 SVC, Int5 R&D, Int7 Pol&Reg, Int9 NFP, Int20 Biotech, Int21 Pharm, Int24 Pol&Reg, Int26 Pol&Reg). Some interviewees suggested that public-sector investments in pharmaceutical R&D could be used in pricing negotiations (Int2 Acad&Consult, Int4 Acad&Consult, Int5 R&D, Int16 Pharm, Int18 Acad&Consult), although this would need to be proportional to investment (Int4 Acad&Consult). However, others felt that this is unlikely to have traction and that there are public-sector benefits beyond contributing to bringing a drug to market (e.g. tax, employment and attracting business) (Int1 SVC, Int5 R&D, Int7 Pol&Reg, Int14 Pharm, Int26 Pol&Reg). According to one expert:

‘The sort of deals that you can ask for have to be proportional to the investments that you make. You can’t allow them [pharmaceutical companies] to run a clinical trial in your hospital and then say on this basis you’re going to globally price at cost’ (Anonymous).

Although it might be fair for public investment to influence pricing discussions, many interviewees reported that this is not how pricing works in practice (Int1 SVC, Int5 R&D, Int7 Pol&Reg, Int14 Pharm, Int26 Pol&Reg). Some highlighted that pricing negotiations are complex and involve multiple players (Int26 Pol&Reg); since pharmaceutical drugs are a global market, companies can move geographically to command higher prices for their drugs if a particular government tries to lower prices (Int1 SVC, Int5 R&D). The public sector also benefits pharmaceutical R&D from investment in other ways beyond drug prices, e.g. through jobs and tax revenue (Int1 SVC, Int14 Pharm), and through occasional financial returns such as through royalties, payments for success

and licensing agreements (Int4 Acad&Consult, Int13 SVC, Int28 Acad&Consult). Pricing agreements could also be detrimental to companies looking to sell assets later since the buying entity may need to respect pricing that they had not agreed to. One interviewee mentioned the need for 'parachute' clauses for biotechnology companies/SMEs to escape pricing agreements, making them attractive for acquisition by pharmaceutical companies (Int5 R&D).

Some interviewees suggested that lowering R&D costs could support affordability, allowing companies to realise returns even at lower prices (Int5 R&D). Since clinical trials are such a costly part of the R&D process, reducing clinical trial costs may be especially helpful in supporting affordability (Int2 Acad&Consult, Int3 CVC, Int4 Acad&Consult, Int5 R&D, Int6 Pol&Reg, Int8 Biotech/SVC, Int11 Biotech, Int13 SVC, Int14 Pharm, Int20 Biotech, Int25 Biotech, Int26 Pol&Reg, Int27 Pharm, Int28 Acad&Consult, Int29 NFP). The public sector could invest in clinical-trial infrastructure to help reduce costs (Int2 Acad&Consult, Int3 CVC, Int4 Acad&Consult, Int5 R&D, Int6 Pol&Reg, Int11 Biotech, Int14 Pharm, Int20 Biotech, Int26 Pol&Reg). Examples include investing in infrastructure for patient identification and recruitment (Int2 Acad&Consult, Int6 Pol&Reg, Int11 Biotech) and providing access to biological samples, real-world data and data-storage infrastructure for trials (Int3 CVC, Int5 R&D, Int6 Pol&Reg, Int11 Biotech, Int14 Pharm).

2.2.6. The geography of capital will evolve, with new markets becoming more competitive

- **What we know:** Where innovation in pharmaceutical R&D happens (in geographical terms) is evolving and will continue to evolve. For example, countries such as China will likely continue to grow investments in pharmaceutical R&D and strengthen its R&D quality and regulatory maturity. This may influence how and where investments flow into pharmaceutical R&D in terms of global distribution.
- **What we do not know- uncertainties:** Given the rise of new players, Europe's competitiveness in the global market will likely be influenced by policy decisions and the collaboration and competition dynamics between Europe and emerging global players in pharmaceutical R&D.

Text box 11. Key messages - geography and competitiveness in the future.

What we know about geography-related factors

The source of pharmaceutical R&D capital will continue to change, with new investment markets playing a more significant role in the future. For example, the role and influence of innovators in Asia is increasing globally, likely leading to more competitiveness in investment markets (Int3 CVC, Int7 Pol&Reg, Int8 Biotech/SVC). According to some interviewees, VC investment also continues to grow in countries like China, Singapore, Korea and Hong Kong (Int7 Pol&Reg, Int8 Biotech/SVC).

Europe's relative position and competitiveness in the future R&D investment market remain to be seen (Int4 Acad&Consult, Int7 Pol&Reg, Aca/SVC, Int24 Pol&Reg), partly depending on decisions made about the life sciences sector at the European level and on how international collaboration unfolds. Countries like China aspire to become world leaders in biotechnology, with significant investment and strong national political support (Int24 Pol&Reg). According to one interviewee, it is likely that China, India and Brazil will all become increasingly active in this space

(Int4 Acad&Consult). The quality of R&D and regulatory environment in China is also expected to improve, potentially influencing collaboration dynamics (Int27 Pharm).

What we do not know – uncertainties related to the role of geography:

Despite the APAC region's growing interest in partnering with European companies and the growth in capital available for European companies wanting to relocate (Int20 Biotech), it is unclear how future geopolitical developments will influence this dynamic (Int13 SVC). The degree to which US investors will become more interested in the EU market is also unknown (Int1 SVC).

2.2.7. Societal ability to learn from the past and sustain the lessons acquired will play a vital role in pharmaceutical R&D efficiency, but whether learning will be sustained is unknown

- **What we know:** The COVID-19 pandemic has evidenced the potential to conduct faster and more efficient R&D facilitated through innovative collaborations, novel approaches to risk management and regulatory advancements.
- **What we do not know – uncertainties:** Society's ability to sustain some of the practices witnessed in response to the COVID-19 pandemic remains to be seen. This applies to practices such as remote and coordinated multi-centre trials conducted in parallel at different locations, risk-taking in manufacturing capacity investments before R&D-process outcomes, and regulatory efficiency and rapid support.

Text box 12. Key messages - society's ability to sustain learning from the response to COVID19 in the future.

What we know about society's ability to learn from the past

The COVID-19 pandemic has evidenced the possibility of conducting faster and more efficient R&D to generate life-saving innovations (Int4 Acad&Consult, Int13 SVC, Int20 Biotech, Int21 Pharm, Int26 Pol&Reg, Int31 Pharm). As one expert illustrated:

'It showed how important a strong biopharmaceutical innovation ecosystem is to respond quickly to health crises. Industry showed it is capable of bringing innovation to patients very quickly when there is urgency and the right economic and regulatory frameworks are in place... Those medicines would not have been available so quickly without the support and flexibility of regulators, a strong IP framework, a strong scientific foundation to build on due to continuous high level of investments in R&D, and the presence of a large market for the products from which to recoup the investment. The pandemic was a rare event, but the lessons learned should apply also to other development efforts' (Anonymous).

Of course, public funding too was key in response to the COVID-19 crisis.

What we do not know – uncertainties related to learning from the COVID-19 pandemic:

Our ability to act on and sustain lessons from the COVID-response to enable smarter and more efficient R&D in the future is uncertain (Int4 Acad&Consult, Int13 SVC, Int20 Biotech, Int21 Pharm, Int26 Pol&Reg). It will be imperative to sustain lessons about R&D collaboration at speed and scale, running activities in parallel rather than sequentially (such as multiple trials and establishing manufacturing capacity in parallel to R&D, though undertaken at risk), and regulatory

efficiency and rapid support (Int3 CVC). However, there is uncertainty about society's ability to sustain and apply such learning and practices to other areas (Int4 Acad&Consult, Int20 Biotech, Int26 Pol&Reg). Some experts consider the COVID-19 approach as an 'exception' (Int4 Acad&Consult) that will be difficult to sustain and scale (Int26 Pol&Reg).

2.3. Making the financial ecosystem fitter for the future: stakeholder views on key areas requiring action

Experts were asked to briefly reflect on which key areas society needs to address to ensure the financial ecosystem of pharmaceutical R&D is fit for the future. The contents below expand on the key points raised and are summarised in Text box 13, built upon further in Annex C.

Stakeholder views on key areas for action:

- 1 Ensuring continued public investment in biomedical research to support pharmaceutical R&D
- 2 Increasing the availability of growth capital
- 3 Innovating in regulation- especially as it relates to clinical trials
- 4 Establishing innovative financial models to deal with the cost and pricing implications of new and more complex drugs
- 5 Building improved data architecture to inform more effective and efficient pharmaceutical R&D
- 6 Improving public perceptions of industry to ensure appropriate regulation while mitigating against over-regulation
- 7 Achieving sustained and enhanced commitment to collaboration, especially in information-sharing.

Text box 13. Making the financial ecosystem fit for the future – areas for action flagged by interviewees.

2.3.1. Continued public investment in biomedical research could help support pharmaceutical R&D pipelines

Several experts highlighted the importance of sustaining government commitment to funding research that ultimately informs pharmaceutical development with sufficient investment levels (Int2 Acad&Consult, Int4 Acad&Consult, Int5 R&D, Int6 Pol&Reg, Int7 Pol&Reg, Int10 Acad&Consult, Int11 Biotech, Int12 SVC, Int13 SVC, Int15 CVC, Int18 Acad&Consult, Int19 Pol&Reg, Int20 Biotech, Int23 Pol&Reg, Int24 Pol&Reg, Int25 Biotech, Int27 Pharm, Int29 NFP). However, the availability of private-sector funding cannot by itself create academic research and early translational research that leads to spin-outs and companies. Instead, public-sector investment is needed to generate private-sector innovation and investment (Int13 SVC, Int5 R&D). Experts also flagged the importance of creating frameworks to support public-sector research investments in translational research. Examples include frameworks for utilising integrated health systems and various types of data (Int19 Pol&Reg) and considering both industrial strategy and health policy to inform public-sector research investments (Int19 Pol&Reg, Int21 Pharm). Government support for biotechnology companies/SMEs is also needed to support their growth through direct financial support or tax credits and other incentives for innovation (Int22 Biotech).

Experts flagged some areas of market failures as particularly important for continuing public-sector commitments. According to one view:

‘With few exceptions, we believe that the financial ecosystem works well for medicines R&D. The exceptions are rare diseases and antimicrobial research, which do not generate enough financial incentives on their own to stimulate enough R&D to meet the needs of patients and the healthcare system. Government incentives are helpful in these cases and should be increased for rare diseases and implemented for antimicrobials. Governments should also continue to support basic R&D in academia, which can often create new avenues for medicines R&D.’ (Anonymous)

2.3.2. Greater availability of growth capital would enable biotechnology companies to develop their products or technologies further and mitigate against premature failure due to running out of capital

Stakeholders flagged the importance of larger growth funds to enable biotechnology companies to maximise chances of success and develop their products or technologies further (Int5 R&D, Int20 Biotech, Int22 Biotech/SVC, Int24 Pol&Reg). One expert noted that such growth funds would increase the biotechnology sector’s flexibility and opportunity to take more risks (Int20 Biotech). This interviewee also commented that growth capital could allow pharmaceutical companies who acquire biotechnology companies to remain more at ‘arm’s length’, encouraging biotechnology firms to continue developing their product/technology and bring in pharma expertise to clinical trials and approval stages where it is most needed (Int20 Biotech).

2.3.3. Innovative regulation could help keep up with changing science, technology and data landscapes

As discussed earlier (see Section 2.2.4), new regulatory frameworks and processes are needed to keep up with changing landscapes in science and technology. This is especially true in data and digital science, personalised medicine for segmented markets and innovative clinical-trial designs (Int5 R&D, Int6 Pol&Reg, Int16 Pharm, Int20 Biotech, Int30 NFP). Although innovative trial designs could help lower costs, government regulation, support and incentives will be essential to enable the use of innovative trial designs while ensuring safety and regulatory rigour (Int5 R&D, Int6 Pol&Reg, Int20 Biotech, Int16 Pharm). Regulation has a crucial role in making clinical trials cheaper, faster and easier to run while ensuring appropriate safeguards and sufficient trial diversity and representation of underrepresented groups (Int30 NFP).

2.3.4. Innovative financial models will be needed to ensure society can benefit from innovative drugs

As discussed in earlier sections, pharmaceutical R&D is becoming increasingly complex and costly (see Section 2.2.3). There is a need for more innovative and sustainable financial models for reimbursing highly innovative acute therapies (Int12 Biotech/SVC, Int20 Biotech, Int6 Pol&Reg, Int9 NFP, Int17 Acad&Consult, Int21 Pharm). According to one expert:

'In innovative financing, the advantage is that you can align incentives in a different way. There need to be incentives where people take risks in how to evaluate a product and study it. Then there could resultantly be an incentive to do the right trial and reduce unnecessary work while making sure that the study leads to valuable data for the product being studied.' (Anonymous).

In the absence of innovation in financial models, society's ability to absorb the costs of innovative drugs remains highly uncertain (Int15 CVC, Int19 Pol&Reg). The high price of personalised drugs has become and will remain an issue in countries with universal healthcare systems, especially those struggling to pay for expensive treatments (Int19 Pol&Reg). Innovative financial models are also needed to ensure innovation in areas traditionally less attractive to industry due partly to market viability concerns such as antimicrobial resistance (Int27 Pharm). This need also applies to historically underinvested areas such as prevention (Int7 Pol&Reg, Int21 Pharm), particularly as it can take many years and long-term investment to establish whether a preventative intervention is successful. Innovative financing is a derivative of better trial design, so changes in clinical trials would, according to one interviewee, also impact how R&D is financed (Int6 Pol&Reg).

2.3.5. An improved data infrastructure might enable more effective and efficient pharmaceutical R&D

Data-driven decision making is taking centre stage in multiple policy areas. In particular, diverse types of health data and real-world evidence are becoming increasingly important in pharmaceutical R&D, with the latter potentially requiring prolonged investment. Currently, passively collected data from electronic health records, claims or sensors (Int6 Pol&Reg) can yield patchy data that is not representative of the whole picture. There is a need to further develop data-science skills and infrastructure to support the level of data now being collected and use data to inform pharmaceutical R&D (Int6 Pol&Reg, Int27 Pharm). As the need for data increases, so does the need for data integration to prevent duplication of work. One interviewee gave the example of the FDA 505(b)(2) regulatory pathway that allows a pharmaceutical company to use data from a drug that failed or succeeded as part of a new application (Int10 Acad&Consult). Although a good idea in principle, the interviewee noted this initiative has not been entirely successful because of distrust in data from relatively unknown companies (Int10 Acad&Consult). Data integration would enable researchers and regulators to describe historical landscapes from clinical trials through the collation of longitudinal data (Int6 Pol&Reg). However, regulation around the use of real-world evidence and other large datasets will need careful governance to ensure some form of social agreement equipping the industry to utilise real-world evidence without infringing on people's rights (Int23 Pol&Reg, Int26 Pol&Reg).

2.3.6. Improved public perception of the pharmaceutical industry could help ensure appropriate regulation while mitigating against over-regulation

The pharmaceutical sector is often perceived as predominantly profit-driven at the expense of societal benefits to human health (Int3 CVC, Int21 Pharm), despite the benefits it generates. One expert noted that this perception risks potential over-regulation of the sector (Int21 Pharm), which

can be detrimental for pharmaceutical R&D more broadly (Int3 CVC). However, it is also critical to ensure that any changes in regulatory practices do not come at the expense of patient safety.

Greater transparency and improved communication about R&D's processes, costs and failures could help improve public perception of the pharmaceutical industry and overall understanding of pharmaceutical R&D (Int18 Acad&Consult). Companies do not want to be associated with perceived failures, which can lead to misunderstandings about drug pricing: the public is not privy to the costs associated with failure and may perceive the industry as entirely profit-driven (Int23 Pol&Reg). However, industry attitudes and roles to engagement in major public health challenges (as we have seen with COVID-19 and AMR) are also likely to influence public perceptions.

2.3.7. The commitment to enhanced collaboration is critical for making the pharmaceutical R&D financial ecosystem fit for the future, including enhanced information sharing

Although the importance of R&D collaboration has long been known, its necessity and benefits were most recently highlighted by the COVID-19 pandemic (Int10 Acad&Consult, Int12 Biotech/SVC). As described in previous sections, pharmaceutical R&D involves multiple actors participating at different stages of the R&D process. To develop safe, effective and affordable drugs for a sustainable system that benefits everybody, everyone needs to collaborate (Int12 Biotech/SVC, Int21 Pharm). According to some experts, several areas need enhanced collaboration, including information sharing (Int10 Acad&Consult, Int12 Biotech/SVC), as part of a collaboration framework rather than based simply on goodwill (Int12 Biotech/SVC). As one interviewee emphasised:

'The pandemic has helped facilitate the sense that we need to accommodate open collaborative models to support complex R&D in the future.' (Anonymous)

Appendix

Interviewees consulted

Table 2. Interviewees consulted.

Name of interviewee	Organisational affiliation	Stakeholder group	Location of organisation	Location where interviewee is based
Anonymous	Non-US University	Academic	Anonymised (non-US)	Anonymised
Joseph DiMasi	Tufts Centre for the Study of Drug Development	Academic	US	US
Kenneth Getz	Tufts Centre for the Study of Drug Development	Academic	US	US
Laura Magazzini	Institute of Economics, Sant'Anna School of Advanced Studies	Academic	Italy	Italy
Adrian Towse	Office of Health Economics	Academic and consulting	UK	UK
Colin Terry	Deloitte	Consultancy expert	Multinational	UK
Barbara Dalton	Pfizer Ventures	Funder (Corporate Venture Capital)	Multinational	US
Jeroen Bakker	Novo Holdings	Funder (Corporate Venture Capital)	Denmark	Denmark
Ilian Iliev	EMV Capital	Funder (Standalone Venture Capital)	UK	UK
Rene Kuijten	Life Science Partners	Funder (Standalone Venture Capital)	US, Germany, Netherlands	Netherlands
Ferenc Marofka	DG SANTE	International Policy Maker	Europe	Belgium
Fernando Galindo	OECD	International Policy Maker	Multinational	Paris
Anthony Humphreys	EMA	International regulator	Europe	UK
George Freeman	MP, UK	National Policy Maker	UK	UK
Matt Whitty	NHS England /Accelerated Access Collaborative	National Policy Maker	UK	UK
Amy Abernethy	FDA	National regulator	US	US

Catriona Manville	Association of Medical Research Charities	Not for profit	UK	UK
Susan Kohlhaas	Alzheimer's Research UK	Not for profit	UK	UK
William Skach	Cystic Fibrosis Foundation	Not for profit	US	US
Dilesh Doshi	Acadia Pharmaceuticals /Johnson & Johnson	R&D Innovators (Biotech and Pharma)	US (Acadia), Multinational (J&J)	US
Daniel Chain	TauC3 Biologics Limited	R&D Innovators (Biotech)	UK	UK
Jan van de Winkel	Genmab	R&D Innovators (Biotech)	Denmark HQ, Netherlands, US, Japan	Denmark
Jane Osbourn	Mogrify /Alchemab Therapeutics	R&D Innovators (Biotech)	UK	UK
Carlo Incerti	Forbion Capital Partners /Numab Therapeutics	R&D Innovators (Biotech) and Funder (Standalone Venture Capital)	Switzerland (Numab Therapeutics), Netherlands & Germany (Forbion)	Netherlands
Florent Gros	Handl Therapeutics and Earlybird Venture Capital	R&D Innovators (Biotech) and Funder (Standalone Venture Capital)	Multinational (Earlybird), Belgium (Handl)	Belgium
Vijay Karwal	CBC Group /Affamed Therapeutics	R&D Innovators (Biotech) and Funder (Standalone Venture Capital)	Hong Kong	Hong Kong
Chris Molloy	Medicines Discovery Catapult	R&D Innovators (networked initiative)	UK	UK
Andrew Williams	AstraZeneca	R&D Innovators (Pharma)	Multinational	UK
Anonymous	Novartis	R&D Innovators (Pharma)	Multinational	Anonymised
Judith Zuijderhoudt and Boris Azais	MSD/Merck	R&D Innovators (Pharma)	Multinational	Boris Azais (role covers Europe & Canada, based in Belgium), Judith Zuijderhoudt (Netherlands)
Mathieu Uhart	Sanofi	R&D Innovators (Pharma)	Multinational	France

Interview topic guides

Not-for-profit sector

- 1 When you look to the future, to the next ten years, what do you think the 3 biggest (i.e. most important and influential) factors that will impact on how medicines R&D is financed will be, and what impact will they have? (By this we mean influences on how R&D is financed we mean who funds, ability to fund, what they fund, how they collaborate)
- 2 In your view, in a historical lens, what have been the most significant changes over the past decade in the way that medicines R&D happens and what impact have they had (i.e. why do they matter)?
- 3 Has the way the charity/not for profit sector funds medicines R&D changed over time and how is it likely to change in the future in terms of their ability to fund, what they fund, how they capture returns, how they collaborate with other medicines R&D actors?
 - a Do you think not for profit funding for medicines R&D has increased or decreased over time /in your experience (and can you comment on this across countries/geographies briefly)? How do you see the future of not-for-profit sector investment in medicines R&D looking at and why?
 - b We are also interested in understanding whether research charities/not for profits are increasingly looking to get a return on their investment (e.g. royalties they can reinvest into other research funding programmes)? I.E. is how charities seek to capture value and the types of financial instruments they use to invest changing? Why?
 - c Have charity views on co-funding with industry changed?
- 4 How have the costs of medicines R&D changed over time and how do you think they will change in the future? Why – please explain the reasoning behind your answer. How might this impact on the charity/not for profit sector?
- 5 What are the key motivations/drivers of research charity decisions to invest in medicines R&D– i.e. what factors do they consider and how do you manage the trade-offs between different types of influencing factors?
 - a To clarify our question – we are trying to understand your views on the extent to which research charities consider societal impact, potential financial returns (e.g if IP is involved), probability of success and bigger strategic objectives into decisions about whether to invest into something or not, and how they balance these different considerations?
 - b Has this changed over time and is it likely to change in the future? Please explain the reasoning behind your answer?
- 6 Can public and third sector funders do anything differently in terms of how they invest to enhance the societal impact from their investments in the future?

- a We see some NGOs/research charities/not for profits monetising on investments (e.g. gaining and potentially selling royalty rights to reinvest in other R&D). Do you think this trend is likely to increase in the future and if so why (and does it apply across geographies)?
 - b To what extent do you think there is scope for public financing to extend into somewhat later stages of R&D – e.g. should governments invest longer, perhaps in collaboration with other investors (e.g. charities/not for profits, other)? And do you think this would have any impact on downstream impacts from innovation such as pricing negotiations?
- 7 When we started this interview, you mentioned some key influences on the future landscape? Having gone through the interview, are there any other important and influential changes/factors we will see that will influence the financing of medicines R&D?
- 8 And what are the biggest unknowns/ uncertainties about the future that will play a role and impact on the financial ecosystem going forward and why do they matter?
- 9 What do you think needs to change in relation to the present financial ecosystem for medicines R&D to make it more fit for the future?
- 10 Given the evolution of the financial ecosystem over time, what have been the biggest impacts on your sector to date and why and how so?
- 11 Is there anything that can be done in terms of how R&D is executed/done to make costs lower and to support drug affordability?

Pharmaceutical sector

- 1 When you look to the future, to the next ten years, what do you think the 3 biggest (i.e. most important and influential) changes or influencing factors that will impact on how medicines R&D is financed will be, and what impact will they have? By changes and influences we mean forces which will influence how finances R&D, what they finance and how?
- 2 In your view, in a historical lens, what have been the most significant changes over the past decade in the way that medicines R&D happens and what impact have they had (i.e. why do they matter)? Note that in this question we are interested in changes in how medicines R&D/innovation happens and not in financing issues exclusively.
- 3 Our analysis for this project suggests that SMEs/biotechs are increasingly trying to grow and move into later stage R&D and build capabilities for later stage R&D in-house (as opposed to licensing their assets to external organisations for further product development or as opposed to being acquired relatively early on).
 - a Does this resonate with your experience and if so why is this happening and do you see it continuing into the future?
 - b Do you think this biotech behaviour may impact on how financial value from medicines R&D is captured (i.e. who captures it and when it is captured along the R&D pathway)
- 4 Based on your views and/or experiences:
 - a What factors drive large pharma company decisions about whether to fund earlier stage R&D (i.e. pre-clinical trials) internally/in-house or to look externally (e.g. to SMEs/biotechs for example) to source innovation assets?
 - b When pharma decides to invest early (be it internally or through grants to other groups for example), do they already consider downstream non-lead indications/multiple indications when deciding on investment amounts?
 - c How have large pharma attitudes and practices related to internal versus external earlier stage R&D (pre trials) changed over time and why?
 - d And how are they likely to change in the future, and why?
- 5 How have the costs of medicines R&D changed over time and how do you think they will change in the future? Why – please explain the reasoning behind your answer.
- 6 When we look at the different types of investors into medicines R&D and the future: Our analysis suggests that VC spend on medicines R&D is likely to continue to grow rapidly in the future, government and NGO/not for profit spend on medicines related R&D has been relatively flat and relatively speaking is likely to lose share compared to the other sources of funding in the future. Biopharma R&D spend is growing moderately so likely to remain relatively stable in terms of relative contribution to the landscape in the future. Does that resonate with your views on the likely future investor landscape or not (10 year horizon), and if yes, what impact will this have on how the medical R&D landscape looks a decade from now? (If it does not resonate with your views, why not?)

- 7 To the extent that you are able to comment on this based on your experience and views, what has driven growth in the venture capital sector and what impact has it had on how the medical R&D innovation landscape looks like now and how it will look in the future?
- 8 Based on your insights and experience and when we look at the past rather than the future, has this mix of relative contributions from different types of investors into the R&D pathway for medicines changed significantly over time/ over the past 10 years (and if so, why, what has driven it)?
- 9 How do you think the motivations of different types of investors into R&D differ in terms of deciding on what to invest in and why; and has this changed over time and is it likely to change in the future? Please explain the reasoning behind your answer? To clarify our question – we are trying to understand your views on the extent to which different types of investors into R&D consider societal impact, potential financial returns, probability of success and bigger strategic objectives into decisions about whether to invest into something or not, and how they balance these different considerations?
- 10 We would like to better understand a bit more about WHEN and HOW you capture value from your investments
 - a How do you think about timelines for returns on investment (i.e. WHEN is some sort of pay out expected along the R&D pathway), when you invest in something at a specific stage of R&D? We are trying to understand what you see as end points for getting a return on your investments, in relation to specific stages of investment.
 - b Can you comment on how you capture value from your investments along different parts of the R&D pathway? In other words, what types of value transactions do you pursue in order to extract value from investments along the R&D pathway (i.e., not just at the commercialisation step). For example, to what extent is this through in-licensing, M&A, gaining further funding to do later stage R&D in house alone, or a growing recourse to establishing collaborations with different players (e.g. industry, not for profit, academia/ public research groups).
 - c Have the types of transactions you pursue these days changed in relation to the past? For example, do you use some types of transactions more or less than in the past?
- 11 When you look to the future, do you see returns on investment for pharma companies increasing, declining or remaining relatively constant – and why? Please can you explain the reasoning for your answer?
 - a Do you see some types of innovators taking comparatively bigger returns than in the past than others?
 - b Given your thoughts on future returns on investment, how do you think pharma strategies will change in the future and why?

- 12 When we started this interview, you commented on big changes which are likely to influence the future of medicines R&D finance. How certain are you that these changes will unfold? How likely is it that they will influence the future?
- 13 And what are the biggest unknowns/ uncertainties about the future that will play a role and impact on the financial ecosystem going forward and why do they matter?
- 14 What do you think needs to change in relation to the present financial ecosystem for medicines R&D to make it more fit for the future?
- 15 Given the evolution of the financial ecosystem over time, what have been the biggest impacts on the pharmaceutical industry to date?

Biotechnology sector

- 1 When you look to the future, to the next ten years, what do you think will be the biggest changes we will see which will influence how medicines R&D is financed and what impact will they have? (We are interested in understanding factors which you think will influence the financing of medicines R&D in the future; we are interested in the top 3 things you think matter)
- 2 And if we look to the past (e.g. past decade): In your view, what have been the most significant changes in the way that medicines R&D happens and what impact have they had (i.e. why do they matter)? In this question we are not asking about finance specifically but more generally on how the medicines R&D landscape has changed, for example in terms of the types of innovators and what they focus on, how they interact with each other (e.g. Are things large companies used to do internally now outsourced more to biotechs; do innovators tend to engage in transactions differently than before – for example, is there more or less focus on licensing, M&A, collaboration). We also of course welcome thought on any other key important changes over the past decade
- 3 Moving from ‘the big picture’ to a more specific question: Our analysis for this project suggests that SMEs/biotechs are increasingly trying to grow and move into later stage R&D and build capabilities for later stage R&D in-house (as opposed to licensing their assets to external organisations for further product development or as opposed to being acquired relatively early on).
 - a In your view, why is this happening, and do you see it continuing into the future?
 - b Do you think this biotech behaviour may impact on how financial value from medicines R&D is captured (i.e. who captures it and when it is captured along the R&D pathway – for example will biotechs capture comparatively more value in relation to large companies, will they seek a payout of some sort earlier in the R&D pathway)?
 - c Is there any geographical variation in this context in terms of the extent to which biotechs are pursuing these ‘go at it alone’ style strategies? Is it more common to some geographies than others?
- 4 How have the costs of medicines R&D changed over time and how do you think they will change in the future? Why – please explain the reasoning behind your answer. We are interested in understanding whether you think costs of R&D will grow or will innovators find efficiency gains which will reduce costs of R&D for example, and if so how?
- 5 Looking to the future, do you think we will see growth or decline in VC investment, government investment, not for profit investment, and corporate/pharma investment in R&D? Please explain your views and also whether you think this will differ across geographies (e.g. US, APAC, EU)

- 6 If we look to the past, and based on your insights and experience, has this mix of relative contributions from different types of investors into medicines R&D changed significantly over time/ over the past 10 years (and if so, why? what has driven it)?
- 7 Traditionally, public sector investors have been seen as focusing to a large extent on achieving societal impact when deciding whether to invest in medicines-related R&D while private investors (e.g. corporate investors, VCs) are seen as focusing more on financial returns and sometimes wider strategic objectives and probability of success. Do you think the factors that motivate different types of investors have changed over time and are likely to change in the future, and if so how? Please explain the reasoning behind your answer?
- a To clarify our question – we are trying to understand your views on how different types of investors balance considerations of societal impact, potential financial returns, probability of success and bigger strategic objectives into decisions about whether to invest into something or not, and whether this is changing for any types of investors?
- 8 In the context of a biotech company, we would like to better understand a bit more about WHEN and HOW you capture value from your investments / the investments you receive and from your R&D activity?
- a How do you think about timelines for returns on investment (i.e. WHEN is some sort of pay out from your activities expected along the R&D pathway), when you invest in something at a specific stage of R&D? We are trying to understand what you see as end points for getting a return on your investments, in relation to specific stages of investment. How long do you wait before you expect some sort of return and how does this relate to different stages of R&D?
 - b Can you comment on how you capture value from your investments along different parts of the R&D pathway? In other words, what types of value transactions do you pursue in order to extract value from investments at different stages of R&D (i.e., not just at the commercialisation step). For example, to what extent is this through in-licensing, M&A, gaining further funding to do later stage R&D in house alone, or a growing recourse to establishing collaborations with different players (e.g. industry, not for profit, academia/ public research groups)?
 - c Have the types of transactions you pursue these days changed in relation to the past? For example do you use some types of transactions more or less than in the past?
- 9 In terms of VCs specifically, we see VC investment growing rapidly in the past decade (globally, and especially rapid growth in APAC countries), we are seeing VCs also investing earlier with higher risk, and we are seeing larger deal values (i.e. growth is being driven by deal value over deal count).
- a To the extent that you are able to comment on this based on your experience and views, what has driven this growth and what impact has it had on how the medical R&D innovation landscape looks like now and how it will look in the future?

- b How easy/difficult is it for companies in the EU to access VC funding? How does this compare to the past? How does it compare to the situation in the US and APAC? What impact could this have in the future?
- 10 When you look to the future, do you see returns on investment for biotech companies increasing, declining or remaining relatively constant – and why? Please can you explain the reasoning for your answer?
- 11 What about large pharma companies? Do you see returns on their investment increasing, declining or remaining relatively stable, and why?
- 12 Having gone through the interview, do you still think these are the most important and influential changes we will see that will impact on the financing of medicines R&D? (And do you see any other important influences that you feel are likely to unfold (ie. that you feel relative certainty about)?
- a Is it relatively certain that they will happen?
- 13 And what are the biggest unknowns/ uncertainties about the future that will play a role and impact on the financial ecosystem going forward and why do they matter?
- 14 What do you think needs to change in relation to the present financial ecosystem for medicines R&D to make it more fit for the future? Please highlight your top thoughts.
- 15 Given the evolution of the financial ecosystem over time, what have been the biggest impacts on the biotech sector to date?

Standalone VC sector

- 1 When you look to the future, to the next ten years, what do you think the 3 biggest (i.e. most important and influential) changes or influencing factors that will impact on how medicines R&D is financed will be, and what impact will they have?
- 2 In your view, in a historical lens, what have been the most significant changes over the past decade in the way that medicines R&D happens and what impact have they had (i.e. why do they matter)?
- 3 Moving from big picture to a more specific question: Our analysis for this project suggests that SMEs/biotechs are increasingly trying to grow and move into later stage R&D and build capabilities for later stage R&D in-house (as opposed to licensing their assets to external organisations for further product development or as opposed to being acquired relatively early on).
 - a In your view, why is this happening and do you see it continuing into the future?
 - b Do you think this biotech behaviour may impact on how financial value from medicines R&D is captured (i.e. who captures it and when it is captured along the R&D pathway)
- 4 To the extent that you can comment on this, how have large pharma attitudes and practices related to doing earlier stage R&D (i.e. pre-clinical trials) internally versus looking to source innovation from external organisations changed over time, and how are they likely to change in the future, and why? Please explain the reasoning behind your thoughts in relation to the future outlook?
- 5 How have the costs of medicines R&D changed over time and how do you think they will change in the future? Why – please explain the reasoning behind your answer.
- 6 Looking to the future and to the diversity of investors into medicines R&D, our analysis suggests that VC spend on medicines R&D is likely to continue to grow rapidly in the future, government and NGO/not for profit spend on medicines related R&D has been relatively flat and relatively speaking is likely to lose share compared to the other sources of funding in the future. Biopharma R&D spend is growing moderately so likely to remain relatively stable in terms of relative contribution to the landscape in the future. Does that resonate with your views on the likely future investor landscape or not (10 year horizon), and if yes, what impact will this have on how the medical R&D landscape looks a decade from now? (If it does not resonate with your views, why not?)
- 7 And if we look to the past, based on your insights and experience, has this mix of relative contributions from different types of investors changed significantly over time/ over the past 10 years (and if so, why, what has driven it)?

- 8 What are the key motivations/drivers of your organisation's decisions to invest in medicines R&D– i.e. what factors do you consider and how do you manage the trade-offs between different types of influencing factors?
- a To clarify our question – we are trying to understand your views on the extent to which you consider societal impact, potential financial returns (e.g. if IP is involved), probability of success and bigger strategic objectives into decisions about whether to invest into something or not, and how they balance these different considerations?
 - b Has this changed over time and is it likely to change in the future? Please explain the reasoning behind your answer?
 - c How does risk appetite vary by stage of investment? More specifically, to what extent do assessments of probability of success (as opposed to other factors like potential for social impact or other strategic aims) influence decision-making about whether to invest in something at a particular stage in R&D (e.g. how early or late) and how to invest (e.g. grant, M&A, licensing, joint venture etc)?
 - d To the extent that you are familiar with this, how significantly has the overall success rate/probability of success for a drug development project changed over time and why?
- 9 We would like to better understand a bit more about WHEN and HOW you capture value from your investments?
- a How do you think about timelines for returns on investment (i.e. WHEN is some sort of pay out expected along the R&D pathway), when you invest in something at a specific stage of R&D? We are trying to understand what you see as end points for getting a return on your investments, in relation to specific stages of investment.
 - b Can you comment on how you capture value from your investments along different parts of the R&D pathway? In other words, what types of value transactions do you pursue in order to extract value from investments along the R&D pathway (i.e., not just at the commercialisation step). For example, to what extent is this through in-licensing, M&A, gaining further funding to do later stage R&D in house alone, or a growing recourse to establishing collaborations with different players (e.g. industry, not for profit, academia/ public research groups).
 - c Have the types of transactions you pursue these days changed in relation to the past? For example do you use some types of transactions more or less than in the past?
- 10 In terms of VCs specifically, we see VC investment growing rapidly in the past decade (globally, and especially rapid growth in APAC countries), we are seeing VCs also investing earlier with higher risk, and we are seeing larger deal values (i.e. growth is being driven by deal value over deal count)
- a To the extent that you are able to comment on this based on your experience and views, what has driven this growth and what impact has it had on how the medical R&D innovation landscape looks like now and how it will look in the future?
 - b VC investors across regions tend to like to invest in North American companies significantly more than into other regions, followed by Europe. (And European investors will more commonly invest in European companies than US investors will invest in

European companies; similarly APAC investors will invest more in APAC companies than North American or European investors will). How does this compare to the past? What are the implications for the future? What are your thoughts on the future landscape in this regard- for example how will European and APAC companies seeking VC investment fare if there is a preference for investing in the US?

- 11 When you look to the future, do you see returns on VC investment increasing, declining or remaining relatively constant – and why? Please can you explain the reasoning for your answer?
 - a Do you see some types of innovators taking comparatively bigger returns than in the past than others?
- 12 When we started this interview you mentioned some key influences on the future landscape? Having gone through the interview, are there any other important and influential changes/factors we will see that will influence the financing of medicines R&D?
- 13 And what are the biggest unknowns/ uncertainties about the future that will play a role and impact on the financial ecosystem going forward and why do they matter?
- 14 What do you think needs to change in relation to the present financial ecosystem for medicines R&D to make it more fit for the future?
- 15 Given the evolution of the financial ecosystem over time, what have been the biggest impacts on your sector to date?

Corporate VC sector

- 1 When you look to the future, to the next ten years, what do you think the 3 biggest (i.e. most important and influential) changes or influencing factors that will impact on how medicines R&D is financed will be, and what impact will they have?
- 2 In your view, in a historical lens, what have been the most significant changes over the past decade in the way that medicines R&D happens and what impact have they had (i.e. why do they matter)?
- 3 Moving from big picture to a more specific question: Our analysis for this project suggests that SMEs/biotechs are increasingly trying to grow and move into later stage R&D and build capabilities for later stage R&D in-house (as opposed to licensing their assets to external organisations for further product development or as opposed to being acquired relatively early on).
 - a In your view, why is this happening and do you see it continuing into the future?
 - b Do you think this biotech behaviour may impact on how financial value from medicines R&D is captured (i.e. who captures it and when it is captured along the R&D pathway)
- 4 Based on your views and/or experiences, what factors drive large pharma company decisions about whether to fund earlier stage R&D (i.e. pre-clinical trials) internally/in-house or to look externally (e.g. to SMEs/biotechs for example) to source innovation assets?
 - a How have large pharma attitudes and practices related to internal versus external earlier stage R&D (pre trials) changed over time and why?
 - b And how are they likely to change in the future, and why?
- 5 How have the costs of medicines R&D changed over time and how do you think they will change in the future? Why – please explain the reasoning behind your answer.
- 6 Looking to the future and to the diversity of investors into medicines R&D, our analysis suggests that VC spend on medicines R&D is likely to continue to grow rapidly in the future, government and NGO/not for profit spend on medicines related R&D has been relatively flat and relatively speaking is likely to lose share compared to the other sources of funding in the future. Biopharma R&D spend is growing moderately so likely to remain relatively stable in terms of relative contribution to the landscape in the future. Does that resonate with your views on the likely future investor landscape or not (10 year horizon), and if yes, what impact will this have on how the medical R&D landscape looks a decade from now? (If it does not resonate with your views, why not?)
- 7 Based on your insights and experience and when we look at the past rather than the future, has this mix of relative contributions from different types of investors into the R&D pathway for medicines changed significantly over time/ over the past 10 years (and if so, why, what has driven it)?

- a What are the key motivations/drivers of your organisation's decisions to invest in medicines R&D– i.e. what factors do you consider and how do you manage the trade-offs between different types of influencing factors?
 - To clarify our question – we are trying to understand your views on the extent to which you consider societal impact, potential financial returns (e.g. if IP is involved), probability of success and bigger strategic objectives into decisions about whether to invest into something or not, and how they balance these different considerations?
 - b Has this changed over time and is it likely to change in the future? Please explain the reasoning behind your answer?
 - c How does risk appetite vary by stage of investment? More specifically, to what extent do assessments of probability of success (as opposed to other factors like potential for social impact or other strategic aims) influence decision-making about whether to invest in something at a particular stage in R&D (e.g. how early or late) and how to invest (e.g. grant, M&A, licensing, joint venture etc)?
 - d To the extent that you are familiar with this, how significantly has the overall success rate/probability of success for a drug development project changed over time and why?
- 8 We would like to better understand a bit more about WHEN and HOW you capture value from your investments?
- a How do you think about timelines for returns on investment (i.e. WHEN is some sort of pay out expected along the R&D pathway), when you invest in something at a specific stage of R&D? We are trying to understand what you see as end points for getting a return on your investments, in relation to specific stages of investment.
 - b Can you comment on how you capture value from your investments along different parts of the R&D pathway? In other words, what types of value transactions do you pursue in order to extract value from investments along the R&D pathway (i.e., not just at the commercialisation step). For example, to what extent is this through in-licensing, M&A, gaining further funding to do later stage R&D in house alone, or a growing recourse to establishing collaborations with different players (e.g. industry, not for profit, academia/ public research groups).
 - c Have the types of transactions you pursue these days changed in relation to the past? For example, do you use some types of transactions more or less than in the past?
- 9 In terms of VCs specifically, we see VC investment growing rapidly in the past decade (globally, and especially rapid growth in APAC countries), we are seeing VCs also investing earlier with higher risk, and we are seeing larger deal values (i.e. growth is being driven by deal value over deal count)
- a To the extent that you are able to comment on this based on your experience and views, what has driven this growth and what impact has it had on how the medical R&D innovation landscape looks like now and how it will look in the future?
 - b VC investors across regions tend to like to invest in North American companies significantly more than into other regions, followed by Europe. (And European investors

will more commonly invest in European companies than US investors will invest in European companies; similarly APAC investors will invest more in APAC companies than North American or European investors will). How does this compare to the past? What are the implications for the future? What are your thoughts on the future landscape in this regard- for example how will European and APAC companies seeking VC investment fare if there is a preference for investing in the US?

- 10 When you look to the future, do you see returns on VC investment increasing, declining or remaining relatively constant – and why? Please can you explain the reasoning for your answer?
 - a Do you see some types of innovators taking comparatively bigger returns than in the past than others?
- 11 When we started this interview you mentioned some key influences on the future landscape? Having gone through the interview, are there any other important and influential changes/factors we will see that will influence the financing of medicines R&D?
- 12 And what are the biggest unknowns/ uncertainties about the future that will play a role and impact on the financial ecosystem going forward and why do they matter?
- 13 What do you think needs to change in relation to the present financial ecosystem for medicines R&D to make it more fit for the future?
- 14 Given the evolution of the financial ecosystem over time, what have been the biggest impacts on your sector to date?
- 15 Is there anything that can be done in terms of how R&D is executed/done to make costs lower and to support drug affordability?

Academics and consultants

- 1 When you look to the future, to the next ten years, what do you think the 3 biggest (i.e. most important and influential) changes or influencing factors that will impact on how medicines R&D is financed will be, and what impact will they have?
- 2 In your view, in a historical lens, what have been the most significant changes over the past decade in the way that medicines R&D happens and what impact have they had (i.e. why do they matter)?
- 3 Moving from big picture to a more specific question: Our analysis for this project suggests that SMEs/biotechs are increasingly trying to grow and move into later stage R&D and build capabilities for later stage R&D in-house (as opposed to licensing their assets to external organisations for further product development or as opposed to being acquired relatively early on).
 - a In your view, why is this happening and do you see it continuing into the future?
 - b Do you think this biotech behaviour may impact on how financial value from medicines R&D is captured (i.e. who captures it and when it is captured along the R&D pathway)
- 4 Based on your views and/or experiences, what factors drive large pharma company decisions about whether to fund earlier stage R&D (i.e. pre-clinical trials) internally/in-house or to look externally (e.g. to SMEs/biotechs for example) to source innovation assets?
 - a How have large pharma attitudes and practices related to internal versus external earlier stage R&D (pre trials) changed over time and why?
 - b And how are they likely to change in the future, and why?
- 5 Different studies have come up with highly varying estimates for the costs of R&D.
 - a Why do you think we see such a huge variety of estimates and ranges in the literature on the costs of drug development/medicines R&D? In your view, what can explain these ranges?
 - b Do you think we should be approaching methods for assessing the costs of R&D differently and if so how? (Are we considering the right units of analysis and methods)?
 - c How have the costs of R&D changed over time and how do you think they will change in the future? Why – please explain the reasoning behind your answer.
- 6 If we look to the future and to the diversity of investors into medicines R&D, our analysis suggests that VC spend on medicines R&D is likely to continue to grow rapidly in the future, government and NGO/not for profit spend on medicines related R&D has been relatively flat and relatively speaking is likely to lose share compared to the other sources of funding in the future. Biopharma R&D spend is growing moderately so likely to remain relatively stable in terms of relative contribution to the landscape in the future. Does that resonate with your views on the likely future investor landscape or not (10 year horizon), and if yes, what impact will this have on how the medical R&D landscape looks a decade from now? (If it does not resonate with your views, why not?)

- 7 Based on your insights and experience and when we look at the past rather than the future, has this mix of relative contributions from different types of investors into the R&D pathway for medicines changed significantly over time/ over the past 10 years (and if so, why, what has driven it)?
- 8 How do you think the motivations of different types of investors into R&D differ in terms of deciding on what to invest in and why; and has this changed over time and is it likely to change in the future? Please explain the reasoning behind your answer?
- a To clarify our question – we are trying to understand your views on the extent to which different types of investors into R&D consider societal impact, potential financial returns, probability of success and bigger strategic objectives into decisions about whether to invest into something or not, and how they balance these different considerations?
- 9 In terms of VCs specifically, we see VC investment growing rapidly in the past decade (globally, and especially rapid growth in APAC countries), we are seeing VCs also investing earlier with higher risk, and we are seeing larger deal values (i.e. growth is being driven by deal value over deal count).
- a To the extent that you are able to comment on this based on your experience and views, what has driven this growth and what impact has it had on how the medical R&D innovation landscape looks like now and how it will look in the future?
 - b VC investors across regions tend to like to invest in North American companies significantly more than into other regions, followed by Europe. (And European investors will more commonly invest in European companies than US investors will invest in European companies; similarly APAC investors will invest more in APAC companies than North American or European investors will). How does this compare to the past? What are the implications for the future? What are your thoughts on the future landscape in this regard- for example how will European and APAC companies seeking VC investment fare if there is a preference for investing in the US?
- 10 Can public and third sector funders do anything differently in terms of how they invest to enhance the societal impact from their investments in the future?
- a We see some NGOs/research charities/not for profits monetising on investments (e.g. gaining and potentially selling royalty rights to reinvest in other R&D). Do you think this trend is likely to increase in the future and if so why (and does it apply across geographies).
 - b To what extent do you think there is scope for public financing to extend into somewhat later stages of R&D – e.g. should governments invest longer, perhaps in collaboration with other investors (e.g. charities/not for profits, other)? And do you think this would have any impact on downstream impacts from innovation such as pricing negotiations?
- 11 When you look to the future, do you see returns on investment increasing, declining or remaining relatively constant for the different types of medicines R&D investors and if so why?

- a Do you see some types of innovators taking comparatively bigger returns than in the past, than other investors
 - b Given your thoughts on future returns on investment, how do you think pharma strategies will change in the future and why
- 12 When we started this interview you mentioned some key influences on the future landscape? Having gone through the interview, are there any other important and influential changes/factors we will see that will influence the financing of medicines R&D?
- 13 And what are the biggest unknowns/ uncertainties about the future that will play a role and impact on the financial ecosystem going forward and why do they matter?
- 14 What do you think needs to change in relation to the present financial ecosystem for medicines R&D to make it more fit for the future?

Policy-makers and regulators

- 1 When you look to the future, to the next ten years, what do you think the 3 biggest (i.e. most important and influential) changes or influencing factors that will impact on how medicines R&D is financed will be, and what impact will they have?
- 2 In your view, in a historical lens, what have been the most significant changes over the past decade in the way that medicines R&D happens and what impact have they had (i.e. why do they matter)?
- 3 Moving from big picture to a more specific question: Our analysis for this project suggests that SMEs/biotechs are increasingly trying to grow and move into later stage R&D and build capabilities for later stage R&D in-house (as opposed to licensing their assets to external organisations for further product development or as opposed to being acquired relatively early on).
 - a In your view, why is this happening and do you see it continuing into the future?
 - b Do you think this biotech behaviour may impact on how financial value from medicines R&D is captured (i.e. who captures it and when it is captured along the R&D pathway)
- 4 To the extent that you can comment on this and from your perspective, how have large pharma attitudes and practices related to doing earlier stage R&D (i.e. pre-clinical trials) internally versus looking to source innovation from external organisations changed over time, and how are they likely to change in the future, and why? Please explain the reasoning behind your thoughts in relation to the future outlook?
- 5 How have the costs of medicines R&D changed over time and how do you think they will change in the future? Why – please explain the reasoning behind your answer.
- 6 When we look to the future and to the diversity of investors into medicines R&D, our analysis suggests that VC spend on medicines R&D is likely to continue to grow rapidly in the future, government and NGO/not for profit spend on medicines related R&D has been relatively flat and relatively speaking is likely to lose share compared to the other sources of funding in the future. Biopharma R&D spend is growing moderately so likely to remain relatively stable in terms of relative contribution to the landscape in the future. Does that resonate with your views on the likely future investor landscape or not (10 year horizon), and if yes, what impact will this have on how the medical R&D landscape looks a decade from now? (If it does not resonate with your views, why not?)
- 7 And if we look to the past, and based on your insights and experience, has this mix of relative contributions from different types of investors changed significantly over time/ over the past 10 years (and if so, why, what has driven it)?

- 8 How do you think the motivations of different types of investors into R&D differ in terms of deciding on what to invest in and why; and has this changed over time and is it likely to change in the future? Please explain the reasoning behind your answer?
 - a To clarify our question – we are trying to understand your views on the extent to which different types of investors into R&D consider societal impact, potential financial returns, probability of success and bigger strategic objectives into decisions about whether to invest into something or not, and how they balance these different considerations?
- 9 Can public and third sector funders do anything differently in terms of how they invest to enhance the societal impact from their investments in the future?
- 10 When you look to the future, do you see returns on investment increasing, declining or remaining relatively constant for the different types of medicines R&D investors and if so why?
 - a Do you see some types of innovators taking comparatively bigger returns than in the past, than other investors
 - b Given your thoughts on future returns on investment, how do you think pharma strategies will change in the future and why
- 11 When we started this interview you mentioned some key influences on the future landscape? Having gone through the interview, are there any other important and influential changes/factors we will see that will influence the financing of medicines R&D?
- 12 And what are the biggest unknowns/ uncertainties about the future that will play a role and impact on the financial ecosystem going forward and why do they matter?
- 13 What do you think needs to change in relation to the present financial ecosystem for medicines R&D to make it more fit for the future?
- 14 Given the evolution of the financial ecosystem over time, what have been the biggest impacts on your sector to date
- 15 Is there anything that can be done in terms of how R&D is executed/done to make costs lower and to support drug affordability?