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Access to finance and barriers to growth in the innovative biopharmaceuticals sector

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Executive Summary

The European Federation of Pharmaceutical Industries and Associations (EFPIA) asked Charles River Associates (CRA) to investigate the extent to which there are barriers to the growth of biopharmaceutical companies in Europe and the extent to which companies of different sizes face different challenges in raising capital to fund research and development (R&D).

Although there is a large literature on the competitiveness and growth of micro and small- and medium-sized enterprises (SMEs) in Europe,¹ particularly those investing in early stage research, there has been little focus, to date, on how companies grow and whether similar challenges exist for innovative firms of a larger size, which are engaged in the far more costly later stages of product development.

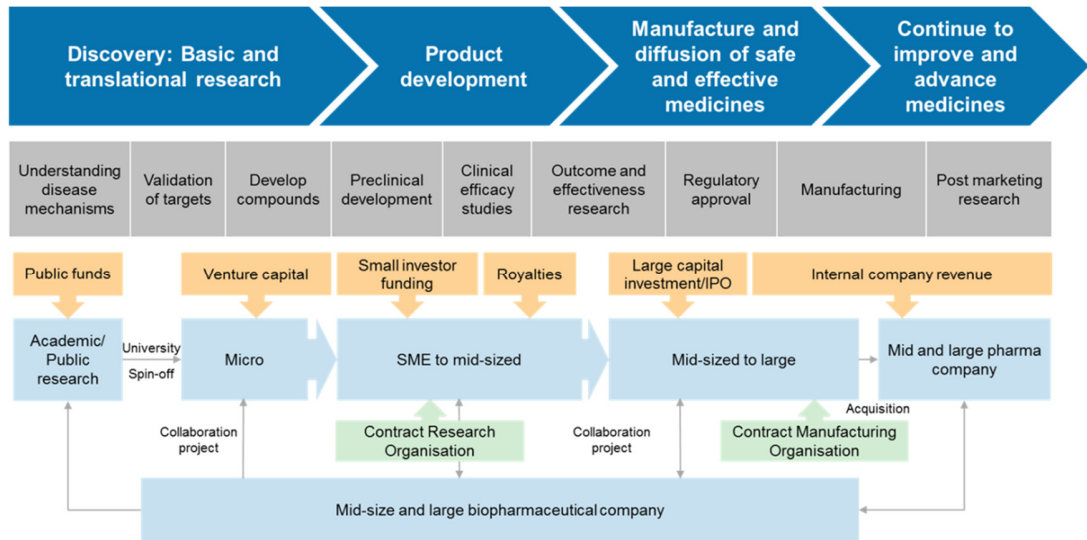
The biopharmaceutical sector and 'European based' companies

Figure 1 represents the processes involved in biopharmaceutical innovation, and illustrates how a variety of companies of different sizes and scopes link together over time to translate promising concepts for novel treatments of disease into safe and effective products, which are then commercialised, adding value to patients and society as a whole. The purpose of this study is to understand how biopharmaceutical companies involved in the value chain grow.

Within the innovation process, micro and SME companies grow as they progressively invest in later stages of development (the investment in early stage preclinical products typically involves investment of tens of millions of Euros, while phase III trials cost hundred millions of Euros), but larger companies grow by investing in a portfolio of products under development and an established portfolio of products in the market. Of particular interest to this study is whether the categories of finance available to companies of different sizes affect how they grow. In reality both the relationships between the companies with different roles and the business models along the chain, and the relationships between the different sources of financing and the different R&D activities, are far more dynamic and complex than can be shown here.

¹ The Commission defines micro companies as having fewer than 10 employees. Small and medium enterprises have between 10 and 250 employees. They should also have an annual turnover of up to €50 million, or a balance sheet total of no more than €43 million (Commission Recommendation of 6 May 2003). <http://ec.europa.eu/eurostat/web/structural-business-statistics/structural-business-statistics/sme>

Figure 1: The biopharmaceutical value chain



Source: CRA

Given that the aim is to look at whether the environment in Europe is encouraging growth in innovative companies, we have focused on companies primarily responsible for innovative product development. In reality many companies are highly international both in terms of the sources of their revenues and in where they locate functional activities. From an economic perspective, all companies that undertake activities in Europe contribute to the European economy; however, in this study we focus on companies with their commercial headquarters in Europe, and we define these as European based companies, although this is inevitably somewhat arbitrary for larger companies.

Is there a problem with the growth of European biopharmaceutical companies?

We have undertaken a comparative analysis of the EU based companies in this sector with companies of a similar size that are based in the US, aiming to understand more clearly what are the key success factors that underpin the superior achievements of the latter in terms of their organic growth from micro through SME stages to fully fledged fast growing, profitable R&D based international companies.

We based this analysis upon the data held in the EU R&D Scoreboard² database, which is published annually and provides a global view across all industry sectors, covering a range of business metrics, but which for ranking purposes uses annual R&D expenditure. We have abstracted from that database the companies in the biopharmaceutical sector.

² The EU Industrial R&D Investment Scoreboard provides economic and financial data and analysis of the top corporate R&D investors from the EU and abroad. It is based on company data extracted directly from each company's Annual Report. <http://iri.jrc.ec.europa.eu/scoreboard.html>

Looking at the sales turnover of these biopharmaceutical companies, it is clear that annual growth rates of European based companies are substantially below those of US based companies (except for the largest companies). Table 1 reports annual growth rates for four groups of companies based on annual turnover (< €50 million; > €50 million and < €300 million; > €300 million and < €4 billion; > €4 billion) we find growth rates for European companies are lower in each category.

Table 1: Average annual % turnover growth of different categories of biopharmaceutical company included in the EU R&D Scoreboard (2014) over the period 2011 to 2013

Turnover (€ million)	US	Europe
> €4,000	5.6	4.2
> €300 and < €4,000	30.2	6.4
> €50 and < €300	128.6	13.0
< €50	363.4	173.7

Source: European Commission World R&D Scoreboard

Looking in more detail at R&D spending, even the basic comparison of the number of companies of different size between the EU and the US shows significant differences in the scale of activities (Table 2). Although Europe seemingly has a similar number of biopharmaceutical companies investing between €100 million and €999 million and over €1 billion annually in R&D, there are significantly fewer companies in Europe investing in the range of €30-99 million.

Table 2: Number of biopharmaceutical companies of US and EU Origin by R&D spend category in the EU R&D Scoreboard

Annual R&D Expenditure (€ million)	US	Europe
Greater than €1,000m	10	9
Greater than €100 but less than €999m	17	19
Greater than €30m but less than €99m	72	38
Total	99	66

Source: European Commission World R&D Scoreboard

If we look in more detail at each category of company, the differences are even more significant.

- Companies based in Europe investing €100-999m per annum in R&D are significantly more mature as indicated by metrics such as R&D expenditure as a percentage of sales turnover and in terms of their long history. In the US, the level of R&D intensity (R&D as a percentage of turnover) was 104% compared to 17% for European companies (similar to companies investing over €1 billion). Clearly in the US there are many more high R&D intensity companies growing quickly, which, due to little or no revenue, have exceptionally high R&D intensity numbers and in consequence may be loss-making over many years.
- In the EU, there are fewer companies investing between €30m and €99m in R&D per annum than in the US, and those in the US have significantly higher levels of R&D intensity. Indeed, 66% (18) of the 27 US based companies had sustained losses in each of the four years over the period 2010-2013, while in the EU only 9% (2) of the 22 companies had sustained losses over the same period.

It is difficult to make these comparisons over time, in particular because the stock of companies in both the US and EU is constantly being eroded by numerous takeovers by big pharmaceutical companies, which assimilate them into their own organisations.³ However, our analysis suggests that while the performance of the largest firms (measured by sales or R&D expenditure) is similar in Europe to the US, the disparity between the performance of smaller companies in the US and those in Europe is becoming greater. Given the many existing definitions of companies, we are reluctant to suggest a new definition; however, given this difference in performance, it is useful to distinguish between larger biopharmaceutical companies and **mid-sized companies**, defined as those with turnovers between €50 million and €4 billion, or with annual R&D expenditures of between €30 million and €1 billion. We continue to use the EU Commission definitions and terminology for micro and SMEs.

Barriers to growth of biopharmaceutical companies in Europe

There are a number of explanations for the differences between the *modus operandi* of the European and US SME and mid-sized companies.

Although the quality and quantity of fundamental research is broadly similar in the EU and the US, the more successful ideas can be traced back to basic research in the US:

Although admittedly weak measures of innovative potential, in terms of the ultimate aim of bringing new medicines to the market and to patients, there are similar levels of publications and patents in the EU and US, and most interviewed participants recognised that the quality of the science and its commercial potential, insofar that it can be estimated, is similar on both sides of the Atlantic. We find little evidence to support the suggestion that the European science base is still catching up on fundamental advances from a chemical to a biologic basis for innovation. However, amongst our interviewees, there were some dissenting voices on this issue from private sector investors, who questioned whether the quality of European science was equivalent to that in the US. This perception is consistent with analyses that trace back

³ The companies included in EU R&D Scoreboard has also changed significantly over time, increasing from 1,000 in 2004 to 2,500 in 2014.

the source of innovative medicines to where the original research was undertaken. This shows that a smaller number of products have originated from research in the Europe compared to that in the US.

There are fewer leading academic bioscience centres of excellence and associated spin-off clusters in the EU, and many such centres appear culturally less inclined to seek useful applications for their basic research: Europe clearly has a strong science base; however, the translation of these ideas into useful therapeutic preclinical developments continues to be a challenge. There is recognition that Europe is weaker than the US in terms of academic entrepreneurship and the role of public-private clusters of companies around academic centres of excellence. Hence, although Europe is creating many spin-offs and start-ups, these are not being nurtured to the same degree as in the US. Equally for larger companies in Europe, the weaker links between academia and the industry could also be constraining their growth. The difficulties faced in converting ideas into development opportunities appears to be due to a number of factors, weaker levels of academic and business collaboration, lack of managerial and entrepreneurial skills and motivation amongst scientists and fewer well developed clusters.

There is a lack of private venture capital to fund the early loss-making development phases of proof of concept and essential safety testing in the EU but, and equally importantly, these weaknesses in European funding extend to other sources of funding and the later stages of product development: We find that the European venture capital (VC) market suffers from significant weaknesses in providing private investment for growth activities to the biopharmaceutical sector.

However, this is a broader problem than the weakness of the VC market, and there are reasons for concern about private equity, about access to capital markets, and that collaborations with large biopharmaceutical companies appear to be working less effectively in Europe than in the US.

Our analysis of the investment landscape shows that European faces serious challenges well beyond VC funding and the early stages of development. We note the following:

- Beyond funding by public sources, research foundations, disease sector charities, and public-private partnerships such as the EU Innovative Medicines Initiative (IMI), funding for preclinical and early stage capital is provided by business angels and individuals including family, friends and the founders themselves, as well as specialist venture capital funds. Funding from business angels is usually small and often invisible (in terms of national statistics), but this investment sector has grown in terms of the number of investors and amount of capital provided. The amount of capital invested by venture capitalists (VCs) to fund proof of concept and the preclinical and phase I clinical phases has displayed signs of weakness over many years, both in terms of the number of VC firms and the amount invested by them. The European market is characterised by a more risk averse attitude to high risk investments. In particular there is a lack of specialised VC firms in biotechnology and pharmaceuticals. The type of investment also differs: in Europe, VCs appear more likely to fund later phases of development. This is consistent with European VCs focusing on longer-term investment, but it is also

symptomatic of the market lacking alternative sources of funding for later stages of development, with the result that exit opportunities for VCs are limited (making their investment in the first place less attractive).

- Indeed, we note that private equity and mutual funds investments, which largely focus on financing late stage development, are weaker in Europe. European companies find it hard to finance activities via these instruments, as private equity firms have not established a strong presence in the market, and their exit opportunities are relatively weak in comparison to those in the US. Signs of US dominance are also found in the top mutual funds investors and their holdings. The alternative to raising VC risk financing and late stage development capital is by going public. This is the primary route to market followed by successful US mid-size companies, which launch IPOs on the US Nasdaq market. However, in Europe the market performance of the biotech index has been weak due a period of failed investments during the market boom in the late 1990s and early 2000s. The following 2008 economic crisis has further damaged confidence in all forms of EU investment, from which we are only now seeing signs of recovery. Despite this, companies have not been as inclined to list on European markets and their preferred alternative would almost always be to do so on US Nasdaq market, where sources of risk capital from well-informed specialist investment funds continue to flourish.
- Finally, investments from large international pharmaceutical companies remain an important source of funding whether through partnership, contracting or investment (many leading companies have set up their own venture funds for this purpose), from early stage preclinical research to full product development and product commercialisation. Numerous patent expiries leading to declining revenues have intensified competition between international companies on a global basis to capture the most promising new early phase projects through licensing contracts. Again we observe a greater amount of licensing activities and more positive collaboration in the US market than in the European market.

Public funding sources in Europe are providing investment support for companies, but this is focused on the earliest stages of their development and on particular types of companies: In the US and Europe, public funding of research and early stage development projects is provided by a range of institutions with different eligibility criteria. Many of the schemes require a collaboration with academics and public research institutes. In addition to programmes at the federal level in the US, or at the European Commission, there are national- or state-level programmes that also need to be taken into account. However, on the basis of the literature review and interviews undertaken in this study we conclude the following:

- The overall investment support for life sciences in the US is greater than that in Europe, but Europe is clearly increasing the investment it is making over time.
- Historically, US Government institutions have focussed investment upon early stage research, but they have progressively looked at how they can support translational science and in some therapy areas have supported later stages of clinical

development. It seems likely that the limitations on private funding in Europe have encouraged more widespread public support than in the US.

- European public institutions in aggregate, taking account of inputs at both the EU and national levels have played a larger role in providing funding directly to companies. However, there are limitations on the types of company eligible for these funds (with relative little rationale for these criteria). In both markets, there is a debate about whether to relax the rules for providing public funds to mid-sized companies for the later stages of development projects and some positive steps in this direction have been taken in Europe since the start of 2015.

Cost containment in Europe has significantly impacted mid-sized companies: Post the 2008 economic crisis, the downward pressure on all forms of public funding in the EU has become intense. As a consequence, biopharmaceutical innovators – regardless of their origin or size – have seen more interventions; and these delay market entry, reduce reimbursement status, and lower prices for innovative products compared to the pre-crisis era. There was a clear consensus, in the interviews, that cost containment in the European market has made commercialisation of products far more challenging and this has reduced the incentive to invest in R&D. It is not clear that this is a significant disadvantage for micro and SME European companies compared to US companies. However, long-established EU mid-sized companies have traditionally been able to fund R&D largely out of profits, derived to a substantial degree from the European market. A combination of intense generic competition and these cost containment pressures are placing the business models of EU mid-size companies under threat. As many older products have been displaced by cheaper generic products, and returns for newer product diminished due to health system cost containment, this industry segment has seen little growth in its home EU markets. Some have been able to compensate by extending sales outside the EU, and have sustained profitability through internal cost saving efficiencies to partially offset weakening revenues. Overall, however, this situation is eroding the capacity of these companies to sustain R&D investment, and they are seeking new sources of investment for key projects of high potential.

The case for further intervention in Europe

In this report we have classified, on the one hand, types of companies that participate in this market and, on the other, types of investors that fund them. Using this template we have sought to better understand where growth is being limited by lack of investment, and what remedies in terms of public policy, might be adopted to improve the situation.

Funding gaps are not in themselves a cause for policy intervention. If markets are working, the providers of capital (VC funds, private equity, financial markets, banks, and larger pharmaceutical companies) balance the risk and return from investing; and where investments offer a commercial return, funding will be made available (and, equally, where the investment is judged too risky for the potential return, funding will not). However, it is recognised that financing high risk investments can suffer from market failures – where the returns outweigh the potential risks, but nevertheless it is impossible to find external funding.

Many studies have identified that financing for micro and SME companies suffers from market failure (due to lack of track record, asymmetry of information between the company requiring

funding and the investor, and the weaknesses in the European VC industry), and therefore this justifies public support. This was the rationale for SME funding in the 7th Framework Programme for Research and Technological Development (FP7) and the European Investment Bank and the Commission's Risk Sharing Finance Facility (RSFF).

More recently, the Commission has gone further by introducing a new investment plan for Europe to support funding for SMEs and for mid-cap companies (defined as companies with up to 3,000 employees) through the newly established European Fund for Strategic Investment (EFSI). If we consider the recent changes to the rules on State Aid they also suggest that the market failures typically associated with the lack of finance for SMEs are much more widely applicable, and levels of R&D expenditure need to be taken into account. However, the current EU basis for defining which mid-cap companies might be eligible for access to funding under the proposed new EIB scheme appears to rest primarily upon the number of employees. As we have shown, there is a weak relationship between the level of direct employment and investment in R&D.

Our analysis indicates that companies with similar levels of employment that adopt different business models can have very different levels of turnover and investment in R&D, and face very different challenges in funding R&D. This suggests that the definition of SMEs and mid-caps based on levels of employment is arbitrary and often inconsistent with the *modus operandi* of the biopharmaceutical industry.

As set out in this report, the weaknesses in the growth of the European pharmaceutical industry goes beyond SMEs and encompasses a key sub-set of mid-size companies, which invest up to €1 billion each annually in R&D and have annual turnovers up to €4 billion. The weaknesses in the funding of European companies go well beyond weaknesses in the European venture capital industry and the earliest stages of product development. We have set out how the performance of private equity, mutual funds, access to financial markets, and the links between international pharmaceutical companies and smaller companies are weaker in Europe. Indeed, the lack of alternative sources of funding for the very expensive later stages of development reduce the exit options for VCs, exacerbating the lack of funding for early stages of development.

Given the changing portfolio of products and technologies, the asymmetry of information is likely to apply beyond SME, to mid-sized companies as well, making the importance of turnover to fund investment particularly important. This has created two types of problems affecting European growth:

- Established mid-sized companies: These companies usually have a long history of achievements as innovators in the biopharmaceutical sector. For the most part, because of the scope and scale of their businesses they have been able to fund complete late stage international development and commercialisation programmes for new medicines, albeit often within limited product portfolios. Over many decades they have achieved slow but steady growth by developing and commercialising valuable new medicines. They have upgraded their clinical and scientific R&D functions and manufacturing capabilities to remain internationally competitive, adopting the new bioscience based approach to innovation. In the broader context of the trend for much

research to be undertaken by university-linked micro and SME companies, they have been contributors to, rather than recipients of, joint public research funding schemes, such as the IMI. Now, however, there is a risk of them being unable to sustain growth through innovation, because of a combination of technological advances and changes in market circumstances – most notably, within the EU, resulting from six years of intense cost containment affecting European revenues (to which they are particularly exposed). Rather than investment in R&D being funded through external finance, there is considerable risk that R&D will be reduced and the appetite for risk diminished.

- A lack of companies growing from SMEs to mid-sized companies: We concur with the findings of previous studies that in comparison with the more dynamic US based micro and SMEs, Europe continues to show a much more limited development of successful companies. Insofar that some EU companies do have products that progress to the later phases of development, European companies are more likely to either sell or license their accumulated stock of intellectual property (patents and confidential 'know-how') to larger established biopharmaceutical companies. Our analysis shows that in sharp contrast to the US, it is rare to find examples of EU SME companies that evolve by an 'organic growth' route – through a combination of VC, dedicated biotech investment funds, or stage payment/option contracts with large biopharmaceutical companies – to engage in mid-to-late stage development activities. This issue is undoubtedly in part due to the weaknesses in the European venture capital industry, but it goes beyond this. Critically, it constrains continuing independent investment in the product life cycle at the point at which it is necessary to make a big step up in the investment commitment to enter a compound into a full development programme, involving international phase III clinical trials, the preparation of product license applications and investments in manufacturing capabilities. The difference between the US and European markets is starkly illustrated by the ability of the emerging US mid-sized companies to finance growing investment in phase III trials, with very high levels of R&D intensity and accumulating year-on-year losses for many years. This ability is unusual in the corresponding category of European based biopharmaceutical companies.

A high level assessment of the costs and benefits of increasing the flexibility of public support for later stage development projects for mid-sized companies is warranted:

- **Advantages for the European biopharmaceutical sector:** Public investment offers a different form of financing, allowing companies to use this as part of the financing package; the support of public investment acts as a certificate and improves access to other forms of finance.
- **Disadvantages for the European biopharmaceutical sector:** Although risk financing can be structured through loans that would be paid off with a return upon commercialisation of the product, it can be perceived as the public sector sharing the risk of product development. There is a chance that any public loan will displace private capital; if the loans are too attractive, this could lead to over-investment in some forms of high risk R&D in Europe, with a corresponding low return to society. Inevitably, investments by public organisations will have constraints – for example, regarding the location of activity, which might reduce the efficiency of the R&D process overall.

At the highest level, EU Commission policy looking towards 2020 will be determined by the need to restore economic growth by promoting and supporting industrial innovation, which inter alia will create high value and skilled employment and will restore tax revenues. The latest initiatives by the Commission and the European Investment Bank to strengthen innovation funding for mid-cap companies could if introduced effectively and in a timely manner make an important contribution to achieving this objective, but they need to take into account the challenges facing companies of different sizes and with different business models.

1. Introduction

The European Federation of Pharmaceutical Industries and Associations (EFPIA) asked Charles River Associates (CRA) to investigate the extent to which there are barriers to the growth of biopharmaceutical companies in Europe and the extent to which companies of different sizes face different challenges in raising capital to fund research and development (R&D). Specifically, we aim to do the following:

- Investigate the barriers to growth of biopharmaceutical companies in Europe, particularly the degree to which access to finance is a significant barrier to growth of companies in Europe as compared to the US and relative to other potential barriers to growth;
- Identify and classify current sources of funding to support R&D in Europe along the innovation value chain and contrast the sources of funding for companies in Europe to those available for companies of comparable size in the US;
- Set out the extent to which this justifies policy intervention from a health policy and from an industrial policy perspective.

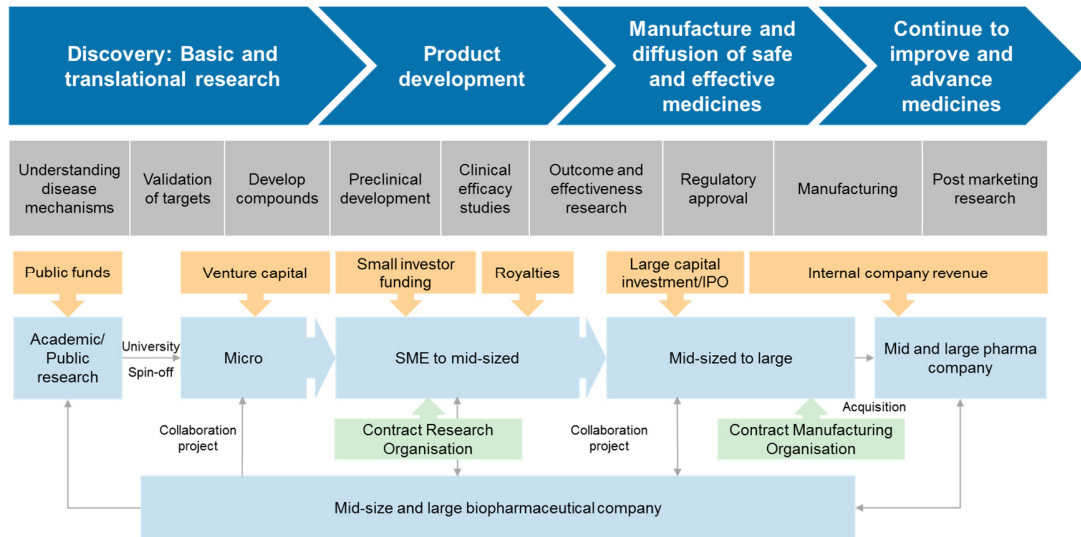
1.1. 'European' biopharmaceutical companies and existing definitions of company size

Figure 2 is a typical representation of the processes involved in biopharmaceutical innovation, and illustrates how a variety of companies of different size (defined below) and scope can link together over time to translate promising concepts for novel treatments of disease into safe and effective products, which can ultimately be commercialised, adding value to patients and society as a whole.

The purpose of this study is to understand how biopharmaceutical companies grow. Within the innovation process, the smallest companies (micro and SME) grow as they progressively invest in later stages of development (the investment in early stage preclinical products typically involves investment of tens of millions of Euros, while phase III trials cost hundred millions of Euros⁴) but larger companies grow by investing in a portfolio of products under development and an established portfolio of products in the market. Of particular interest to this study is whether the categories of finance available to companies of different sizes affect how they grow. Figure 2 is clearly a simplification, both in terms of the relationships between companies with different roles and business models along the chain and in terms of how different sources of financing are used for different types of R&D activities; these are far more dynamic and complex in reality.

⁴ The cost of developing a successful medicine has recently been updated and is now estimated as €2.6 billion. This includes the cost of failed investment and has been capitalised. 'Cost of Developing a New Drug', November 18, 2014. Tufts Center for the Study of Drug Development.

Figure 2: The biopharmaceutical value chain



Source: CRA

Our primary interest is in companies involved in the R&D of innovative pharmaceuticals. In reality, many companies partner with other players in the sector to undertake different activities in the industry value chain, and this outsourcing has become more important for the industry. We have focused on companies primarily responsible for innovative product development excluding:

- Companies focusing on the manufacture or sales of off-patent medicines (where levels of R&D intensity – R&D investment as a proportion of sales – are dramatically lower)
- Companies providing contract services to those with rights to develop the product (this includes contract research organisations (CROs) or contract manufacturing organisations (CMOs) and contracted salesforces).

Of course, at any point in time, we do not know what will happen to companies in the future. Therefore, our analysis includes companies that are undertaking R&D and will ultimately be acquired by another company or will sell the rights to develop the project to another company.

Finally, the study is about growth of *European* biopharmaceutical companies. Clearly most biopharmaceutical companies are global, undertaking different activities in different parts of the world. Any companies undertaking activities in Europe contribute to the European economy.⁵ However, for the purposes of this study we focus on companies with their commercial

⁵ The location of the commercial headquarters does not determine where R&D takes place. This report does not look at what determines R&D activities to take place in the EU. This is an equally important question but beyond the scope of this project.

headquarters in Europe; although this is inevitably somewhat arbitrary,⁶ it is helpful for our analysis of whether Europe is a conducive environment for R&D based companies.⁷

Finally, given that the objective of the study is to look at how companies grow over time, it is useful to categorise companies by size. There are many different definitions used to categorize companies, developed for a variety of different purposes. A common categorisation used by the European Commission divides companies by employee number and either turnover or balance sheet as follows:⁸

Table 3: Standard definition of company size used by the European Commission

Company Category	Employees	Turnover (€)	Balance sheet total (€)
Micro	< 10 employees	< 2 million	< 2 million
Small	10-49 employees	< 10 million	< 10 million
Medium-sized	50-249 employees	< 50 million	< 43 million
Large	> 250 employee	> 50 million	> 43 million

This is the categorisation used to define small- and medium-sized enterprises (SMEs).⁹

However, the European Commission is increasingly using the term *mid-cap*.¹⁰ A number of definitions are used by the European Commission or other European institutions:

⁶ Indeed, companies sometimes move their headquarters from one country to another with little change in the location of the majority of the company's activities.

⁷ This also means the sales might not be in Europe. For EU based companies, there is also much scope to grow by selling products to new customers outside of Europe in the US, Japan and middle-income countries (MICs). Broadening the base of a business by extending its global reach, through establishing higher revenue streams from outside of the EU, is a key strategy for achieving long-term sustainability, making it possible to overcome short-term shocks such as product failures, generic entry or sharp declines in national markets.

⁸ Eurostat, 'Small and medium-sized enterprises', European Commission, available at: http://epp.eurostat.ec.europa.eu/statistics_explained/index.php/Small_and_medium-sized_enterprises

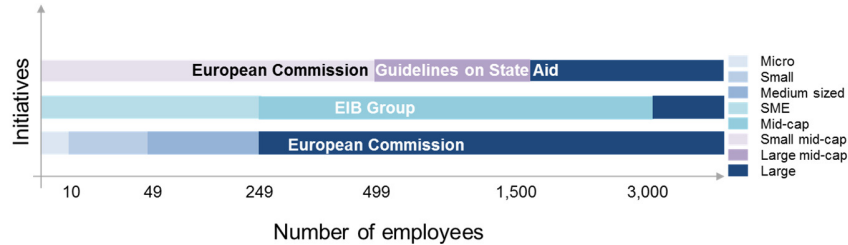
⁹ The Commission defines micro companies as having fewer than 10 employees. Small and medium enterprises have between 10 and 250 employees. They should also have an annual turnover of up to €50 million, or a balance sheet total of no more than €43 million (Commission Recommendation of 6 May 2003). <http://ec.europa.eu/eurostat/web/structural-business-statistics/structural-business-statistics/sme>

¹⁰ The Commission admitted there is no common EU definition of mid-cap companies. http://europa.eu/rapid/press-release_IP-14-2128_en.htm#_ftn1

- The European Investment Bank (EIB) Group categorises companies for financing purposes by number of employees in three groups: SME = 0-249, mid-cap = 250-3000 and large = more than 3000 employees.¹¹
- The European Commission’s Investment Plan for Europe, published in November 2014, targets mid-cap companies, which were defined as those employing between 250 and 3,000 employees, as per EIB’s classification.^{12,13}
- In a separate document, the Commission Guidelines on State Aid, companies are categorised as *small mid-caps* (meaning an undertaking whose number of employees does not exceed 499) and *innovative mid-caps* (up to 1,500 employees and with R&D and innovation costs representing 10% of total operating costs).¹⁴
- Elsewhere, the term large mid-cap projects has also been used, but without a strict definition.¹⁵

Although the above-mentioned initiatives and classifications are all devised and/or used by the European Commission (EC), they offer different categorisations of companies by employee numbers (shown in Figure 3).

Figure 3: Differences in definition of company size by employee numbers in European Commission initiatives



Source: CRA analysis based on European Commission sources

11 European Investment Bank (2015), ‘Products’, available at: <http://www.eib.org/products/blending/innovfin/products/index.htm>

12 This is made more complicated with *medium-sized* sometimes being used interchangeably with *midcap* (see <http://www.eib.org/projects/priorities/sme/>).

13 ‘Communication from the Commission to the European Parliament, the Council, the European Central Bank, the European Economic and Social Committee, the Committee of the Regions and the European Investment Bank: An Investment Plan for Europe’, Brussels, 26 November 2014, COM(2014) 903 final

14 ‘State aid: Commission adopts new rules on risk finance – frequently asked questions’, Brussels, 15 January 2014.

15 ‘Draft Opinion of the Committee on Industry, Research and Energy for the Committee on Economic and Monetary Affairs on the proposal for a regulation of the European Parliament and of the Council on the European Fund for Strategic Investments and amending Regulations’
http://www.europarl.europa.eu/meetdocs/2014_2019/documents/itre/pa/1051/1051424/1051424en.pdf

Throughout the report, we use these definitions but investigate other potential measures of size that could be equally relevant for examining barriers to growth. First, categories could be based on market value (how much it would cost to acquire the company), which is the more common use of the term mid-cap in financial and academic articles. This could be a useful measure as it reflects access to financial markets.^{16,17} Additionally, categories could be based on sales turnover, as this represents a proxy for internal funding capability, or the assets of the company, which could be a proxy for internal resources. Finally, companies could be categorised based on the level of investment in R&D.¹⁸ The categorisation of companies is clearly useful in helping to analyse how innovative activity associated to firms grows over time. We discuss the different categorisations in chapter 2 of this report.

1.2. The existing literature on growth of biopharmaceutical companies

The development of new medicines is carried out by a wide variety of different types of companies (often working together), ranging from large multinational companies to small and micro-sized enterprises (as defined above). Depending on their size, companies have developed very different business models regarding how they research, develop and bring new medicines to market. There are many reports describing the business models of large global biopharmaceutical companies and many reports describing SMEs, but few reports have focused on how companies grow from being an SME into a larger company and if there are barriers to growth for firms of different sizes.

The existing research, which categorises companies by market capitalisation, focuses on describing their R&D priorities and pipeline and how this is evolving.¹⁹ The research provides a good description of companies' R&D expenditures, R&D intensity, and geographic dispersion

16 This is potentially confusing given the use of the term mid-cap by European institutions. However, mid-cap is often based on market capitalisation, with a mid-cap company defined as one with a market capitalisation between \$2 and \$10 billion. This is calculated by multiplying the number of a company's shares outstanding by its stock price.

17 Classification by market cap can be less stable as it is usually calculated by the percentages of total stocks, large-cap being equal to 70% of total market, mid-cap being equal to the next 20% of the market and small-cap representing the balance. Based on this definition, in 2013, European and UK companies were defined as follows: large-cap > \$9 billion; \$1.7 billion < mid-cap < \$9 billion; and small-cap < \$1.7 billion. Morningstar (2013), 'Investing in small-, mid- and large-cap stocks', available at: <http://www.morningstar.co.uk/uk/news/105769/investing-in-small--mid--and-large-cap-stocks.aspx>.

18 The R&D Scoreboard also considers R&D intensity – the percentage of sales invested into R&D. They distinguish between High R&D intensity sectors (R&D intensity above 5%), Medium-high R&D intensity sectors (between 2% and 5%), Medium-low R&D intensity sectors (between 1% and 2%) and Low R&D intensity sectors (less than 1%). Given that nearly all pharmaceutical companies are high R&D intensity, this is not a useful categorisation.

19 Yoruk, D. E., Mitra, J. (2009) 'Mid-pharma: How big is it and where is it going?' Innogen Working Paper No. 81. It is possible to draw conclusions about growth from this literature. For example, if we perform a regional comparison of average growth across all categories, we notice the following: Japanese companies experience the highest growth at 81.1% (Note: based only on two observations); US based companies follow with approximately 60% average growth (one negative outlier at -2.6%); and EU companies have the lowest average growth rate at approximately 54% (one outlier at 4%).

of R&D centres; however, it does not look at how smaller companies grow into or out of this category or whether there are significant barriers to growth.

There have been a number of studies looking at the structure of the industry and comparing companies based in Europe to those based in the US. Indeed, a series of papers commissioned or written by the Commission between 2007-2009 found that²⁰

- Europe and the US had a similar number of biotech companies (2,163 compared to 1,991), but the European companies were generally smaller in size.
- The median number of employees of private biotechnology companies (those not listed on the stock market) was 12 in Europe and 28 in the US. This was attributed to the lower median age of European private companies (10 years compared to 12 in the US).

The authors concluded that at the aggregate level, the US biotech industry consists of roughly the same number of companies as the European industry, but the difference is clear: ²¹ the US biotech industry employs twice as many people as Europe's; spends three times more on R&D; and generates twice as much revenue in total.

Although the European Commission has not recently published any reports focusing specifically on the structure of the European biopharmaceutical sector, independent assessments suggest that the differences between the European and US industry continue. This is most evident in EY reports on the biopharmaceutical industry.²²

Table 4: Comparison of EU/US biotech included in EY's Beyond Borders 2013

	Europe	US
Number of companies (Public and private)	1,964	2,175
Number of employees	51,570	100,100
Market cap (\$ billion)	\$79.8	\$360.3

Source: EY Beyond borders 2013

These have consistently reported that the value, number of employees, and amount of R&D invested is far higher in the US than in Europe.

²⁰ 'Competitiveness of the European biotechnology industry', Tomas Jonsson, European Commission, Enterprise and Industry DG drawing on Bio4EU.

²¹ 'The financing of biopharmaceutical product development in Europe'. Study on the competitiveness of the European biotechnology industry, 2009.

²² For 27 years, Ernst & Young has examined the structure of the biotech sector using a database of financial statements including public and private companies.

The EU R&D Scoreboard (which we further analyse later in the report) provides a commentary on the differences between the Europe and the US biopharmaceutical sector. The authors find the therapeutic biotechnology subsector is dominated by the US: eight of the top ten companies in terms of R&D growth and profitability are based in that country. However, they also conclude that there are a number of examples of EU companies that show both high performance and the ability to grow to a sustainable size through well-chosen collaborations.²³

Even though little research has focused on the structure of the European industry, there has been considerable research on the micro and SME companies and the degree to which funding acts as a barrier to growth.²⁴ A number of reports commissioned by the European Commission have examined funding. Although many different ways of raising capital for drug development are identified (including public grants, forming alliances with larger pharmaceutical companies, attracting venture capital (VC), out-licensing drug candidates, Initial Public Offerings (IPOs) and follow-on offerings and bank loans), the research has focused (perhaps not surprisingly, given the focus on the smallest companies) on funding by VCs.

The weakness of the European VC market has been identified as a significant problem in a series of studies.²⁵ Indeed, most recognise the concept of a funding gap for smaller companies in the European biopharmaceutical sector. The European Commission in 2007 identified three gaps:

- First funding gap: the funding of micro (academic spin-offs) and SMEs leading to a credible intellectual property package and evidence of potential for development in preclinical testing. Typical funding sources include seed capital from grants, founders, business angels and VC investments.
- Second funding gap: the funding of clinical trial phases I and II. Typical funding sources include VC funds, corporate VC, government-backed investment funds, licensing and collaborations.
- Third funding gap: the funding of clinical trials in phase III, authorisation and marketing. Typical funding sources include VC funds, corporate VC, government-backed investment funds, licensing, collaborations, buyouts, hybrid capital (mezzanine), and public equity (IPO).

23 'The EU R&D Scoreboard: 'The 2013 Industrial EU R&D investment Scoreboard'.

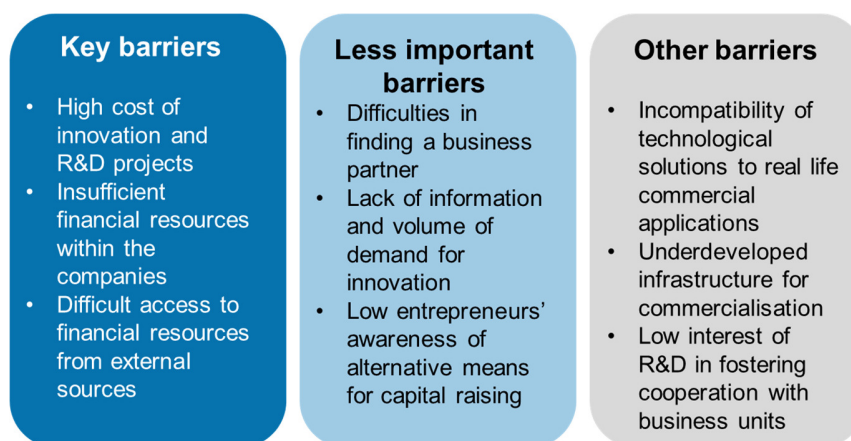
24 This is not unique to the biopharmaceutical sector. In a 2013 survey of all SMEs, access to finance was the second most importance barrier to growth. European Commission and ECB, SMEs' Access to Finance Survey 2013 Analytical Report (14 November 2013).

25 European Commission (2009), 'The financing of biopharmaceutical product development in Europe'. The Framework Contract of Sectoral Competitiveness Studies; Behrens et al. (2012), 'Specific managerial human capital, firm age, and venture capital financing of biopharmaceutical sector venture: A contingency approach, Journal of High Technology Management Research; Hamilton (2011), 'Trends in Mid-Stage Biotech Financing', Tuck School of Business at Dartmouth; Catalonia Bio (2014), 'Global pharma and biotech M&A report – 2014', available at: <http://cataloniabio.org/wp-content/uploads/2.pdf>

In terms of the underlying cause of any funding gap, according to this literature, smaller firms as opposed to larger ones are likely to encounter more difficulties as a result of imperfect and asymmetric information in their need for risk capital, to carry out the innovation process, and are likely to find it harder to coordinate and network successfully.²⁶ They also suffer from resource constraints, insufficient collateral, and lack of a track record. These potential 'market imperfections' justify public intervention in entrepreneurial financing.

In addition to the studies focusing on the European situation, there have been a number of national studies investigating the factors affecting growth of companies. These indicate that public funding for research is insufficient for the establishment of a strong biotech industry.²⁷ Other studies have examined the importance of the labour market, in addition to capital markets constraints, and the importance of bio clusters.²⁸

Figure 4: Hierarchy of factors affecting the growth of biopharmaceutical companies



Source: Martin, M., 2013. *The Barriers to Growth of Biotechnology Companies in Emerging Economies; Regional Case Study Analysis. International Journal of Economic Sciences, 11(1): 21–39.*

In more recent years, the focus has been on testing the belief that funding has become a more significant challenge since the financial crisis. A number of studies have focused on whether the financial crisis has limited the amount of funding available and made investors more risk averse (particularly as European biotechnology financing dropped dramatically from 2007 to 2008 due to the financial crisis). These difficulties have been used to justify a number of different public interventions at the European and member state level. For example, in 2007,

²⁶ University Manheim (2005), 'Innovation market failures and state aid: developing criteria – A report prepared for DG Enterprise and Industry European Commission'.

²⁷ 'A case study on obstacles to the growth of biotechnology'. *Technological Forecasting & Social Change*, Nuno Arantes-Oliveira.

²⁸ 'A comparative study on biotechnology companies in Denmark and Sweden: Why do they perform differently.'

EIB and the European Commission launched a Risk Sharing Finance Facility (RSFF) to boost investment in R&D projects in Europe that have a higher than average risk profile.

In the great majority of these papers, the focus has been describing the challenges faced by micro and SME size companies, particularly those investing in early stage research. There has been, to date, little focus on how firms grow and whether similar or additional problems exist for larger firms or firms focused on later stages of development. That is the purpose of this study.

1.3. The study approach

To investigate whether there is a problem with growth of European biopharmaceutical companies and if so, the factors that act as a barrier to growth, we have undertaken a number of tasks:

- Literature review: We reviewed 35 papers looking at existing trends in the European industry, comparing the European based industry to that in the US, and determining whether there are problems with financing innovation.
- Data analysis: To examine the structure of the EU industry, we analysed data in the EU R&D Scoreboard. This provides economic and financial data for 2,500 companies analysing the top corporate R&D investors from the EU and abroad. The Scoreboard is published annually, and we used data R&D drawn from the latest available companies' accounts, i.e. usually the fiscal year 2013 or 2013/14.
- Comparison of funding sources in Europe and the US: Using public sources, we compared the eligibility of different types of company for funding from different public sources of funding support, and validated the role of these schemes in the interviews described below.
- Interviews: We held 16 interviews with companies of different sizes and various providers of private funding (from venture capital to investment banking) and sources of public funding (including DG Research, the European Investment Bank, the European Investment Fund). These interviews were undertaken on an anonymous basis and we only distinguish between the types of company and organisation when reporting the views expressed.

1.4. Structure of report

The rest of the report is structured as follows:

- In chapter 2, we review evidence regarding the growth of the European biopharmaceutical industry, the merits of different categorisations of size, and the extent to which there is evidence of a problem with growth of European biopharmaceutical companies.
- In chapter 3, we consider the possible barriers to growth and if inadequate sources of finance is a significant barrier to growth in Europe for different categories of company.
- In chapter 4, we consider whether the funding gaps identified represent a market failure that provides a justification for intervention and the policy alternatives.

2. Is there a problem with the growth of European biopharmaceutical companies?

Although all stakeholders would agree that sustainable growth is important – leading ultimately to profitable returns to investors, employment and valuable products for patients and health systems, and other desirable socio-economic contributions – growth can have quite different meanings depending on the context. Growth could mean an increase in

- total employment of the industry
- the contribution of the industry to the European economy (perhaps measured by gross value added)
- industry revenues or profitability.

However, for the purposes of this study we are interested in company growth – that is, whether companies are growing from micro to SME and ultimately into larger companies and, in so doing, increasing their employee numbers, their turnover, and in particular their investment in R&D.

2.1. How do we measure growth?

There are clearly many different ways that companies can grow – and it could be argued that there is not a typical way that biopharmaceutical companies grow. Acquiring the scientific evidence of proof of the therapeutic concept and a sound product patent position are seen as the two key milestones for a biopharmaceutical company, but even then there will be a period when losses continue, accumulating year-on-year the need to use funding sources, without any offsetting revenues from product sales.

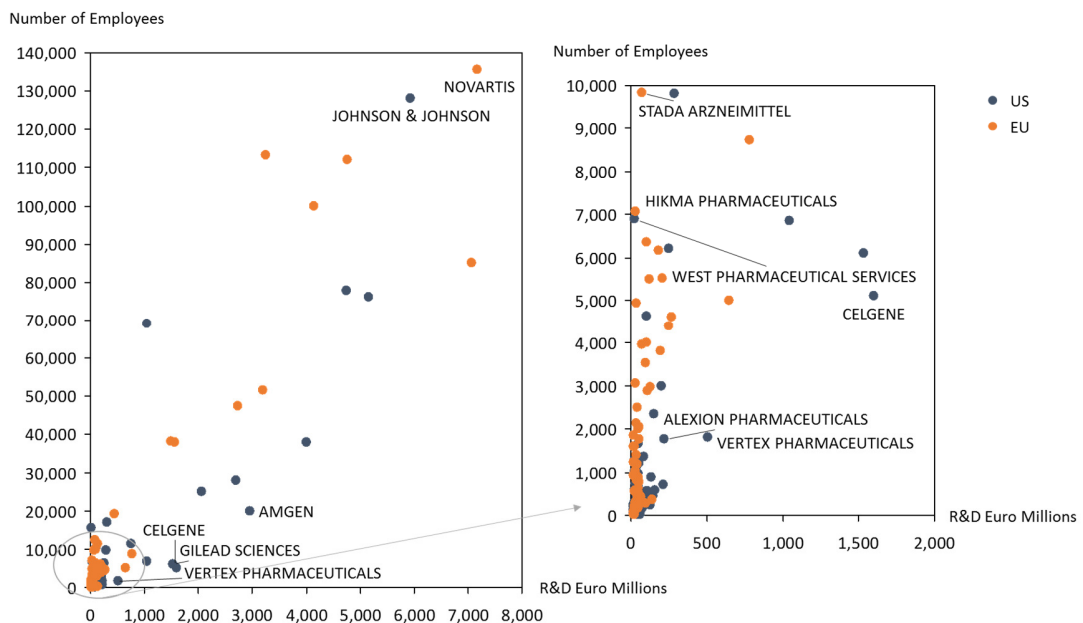
The earliest forms of modest revenues for such companies could be from contract sales of specialist 'platform' technology 'know-how' to other R&D based companies and/or through payments for exclusive licensing options from larger companies based upon agreed milestone progress payments. Many companies in this early phase inevitably have relatively short lives, because commonly they fail to achieve early milestone targets. SMEs that have overcome the early barriers, having completed promising preclinical programs, face different choices when contemplating the next steps. There are essentially three options:

- Sell the business as a whole to a larger company that has all the capabilities to integrate any candidate products into their much larger R&D portfolio and do a full international clinical development programme. In this case, we would stop observing the company as a free-standing entity.
- Enter into a formal licensing arrangement with a larger company, which for exclusive marketing rights to sell the product will agree to share the costs of the full clinical development programme. Some companies continue to grow, successfully using this business model to manage a number of such partnership arrangements in parallel with different major companies.

- Raise the much larger capital required for a full clinical development programme, for example, by floating the company with an IPO on NASDAQ in the US or on AIM or the main London Stock Exchange in the UK. The different sources of funding will be discussed in detail in the next chapter.

In reality, these options are not mutually exclusive, and in practice many companies grow by following a combination of these growth paths. Depending on whether the companies undertake different activities in-house, contract out or partner with other companies for different activities will have a significant impact on employment.²⁹ Obviously, companies undertaking more of the activities in-house will have a larger number of employees than those that contract out (even though the economic activity created could be the same). To the extent that the business models being used in Europe are different to those in the US, or that the maturity of companies differs, this will not be a reliable measure of innovative activity. As illustrated below, although for larger companies the correlation is clear, there is a weak correlation between the level of employment and the level of innovative activity (as measured by R&D spending) in both European companies and US companies.

Figure 5: The correlation between employment and investment in R&D



Source: European Commission 2014 World R&D Scoreboard

²⁹ The EU R&D Scoreboard: The 2013 Industrial EU R&D investment Scoreboard provides a very useful description of how four companies have undertaken partnership agreements. They look at Abcam, MorphoSys, Oxford Nanopore and Regeneron Pharmaceuticals. These four examples illustrate the different ways in which smaller biotechs can grow to a size where they are self-sustaining.

If we consider firms that employ around 3,000 employees, we find very different levels of R&D spending (from €40 million to €200 million) and turnover (from €600 million to €1.5 billion).

Given the use of the term mid-cap it is tempting to look at companies in terms of market capitalisation. That is how much they are valued according to the price of their shares. There are a number of weaknesses with this approach. It is very difficult to disentangle companies that work in different sectors (this is also true for sales but to a lesser degree), the value changes considerably when there is stock market volatility (as in the last financial crisis), and this can only be applied to public companies. Therefore, we do not see this as a viable method to look at biopharmaceutical growth.

Equally, we could look only at turnover or revenue growth. For companies with products on the market, this would be indicative of their success (and linked to the value they create for the economy). However, this has a clear limitation for companies who are yet to bring products to the market or where their portfolio of commercialised products is maturing. In the next section we compare the growth of US and European based companies directly in terms of sales turnover and then look more closely at the pattern of R&D spending.

2.2. Current landscape of biopharmaceutical companies (EU vs US)

We first look at the structure of the European and the US based industries in terms of sales turnover. To investigate this we have used data collected within the European R&D Scoreboard to directly compare the European and the US originated pharmaceutical companies. Out of 2,500 companies in total, 256 are life sciences companies. Each of these has been associated to a country based on the location of its headquarters. Drawing on company financial accounts, the Scoreboard reports investment in R&D,³⁰ net sales, cap expenditure, profitability and the number of employees.

There are clearly some significant advantages in using an existing dataset of this kind. It has consistent data published over a long period of time, and it includes publicly and privately listed firms. However, it also has limitations: the minimum level of R&D investment is €15.5 million (€22 million for life sciences companies), effectively excluding small and micro companies, and it only captures some of the metrics about the firm's financial performance.

Growth in sales turnover by size of company

Looking at the composition of companies by turnover, we have banded companies into less than €50 million, €50 million to €300 million, €300 million to €4 billion, and greater than €4 billion.

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Research and Development (R&D) investment in the Scoreboard is the cash investment funded by the companies themselves. It excludes R&D undertaken under contract for customers such as governments or other companies. It also excludes the companies' share of any associated company or joint venture R&D investment.

Table 5: Number of companies included in the 2014 World R&D Scoreboard by turnover

Turnover (million)	US	Europe	Japan
> €4,000	13	11	6
> €300 and < €4,000	20	38	18
> €50 and < €300	24	16	2
< €50	65	12	2
Total	122	77	28

Source: European Commission 2014 World R&D Scoreboard

If we look at the sales over time, we can look at the growth year-on-year.

Table 6: Average annual % turnover growth of different categories of biopharmaceutical company included in the EU R&D Scoreboard (2014) over the period 2011 to 2013

Turnover (Euro million)	US	Europe
> €4,000	5.6	4.2
> €300 and < €4,000	30.2	6.4
> €50 and < €300	128.6	13.0
<€50	363.4	173.7

Source: European Commission 2014 World R&D Scoreboard

Looking at the sales turnover of the biopharmaceutical companies, it is clear that annual growth rates of European based companies are substantially below those of US based companies (except for the largest companies).

R&D spending by size of company

If the opportunity and capabilities of European companies were the same as in other markets, such as the US, we might expect to see the same distribution of spending on R&D in Europe as in the US. We have divided the companies into three groups based on R&D expenditure distinguishing between companies with investment in R&D of

- less than €100 million
- greater than €100 million and less than €999 million
- greater than €1 billion.

As is clear from Table 7, although Europe has a similar number of companies investing more than €1 billion and slightly more investing between €100 million and a €1 billion, the most significant difference, in terms of absolute numbers, is the number of companies investing more than €30 million but less than €100 million.

Table 7: Number of companies included in the EU R&D Scoreboard

R&D spending (million)	US	Europe	Japan
> €1,000	10	9	4
€100-999	17	19	6
€30-99	72	38	15
Total	99	66	25

Source: EU R&D Scoreboard

R&D intensity is the percentage of sales that are devoted to R&D.³¹ In Table 8,9,10 we examine this for the three R&D bands respectively. For the largest category, the level of R&D intensity is quite similar (unsurprisingly around the industry average), and although the max is higher in the US (resulting from one company), we conclude R&D intensity is similar in large European headquartered companies when compared to US headquartered companies. Given that these are global pharmaceutical companies, often investing in a wide variety of locations around the world, perhaps this is not surprising.

Table 8: R&D intensity for companies with R&D spending over €1 billion

	Average	Min	Max
Europe	18%	14%	22%
US	21%	14%	34%

Source: EU R&D Scoreboard

When we look at the middle category (greater than €100 million but less than €999 million), however, the structure of the European and US industries differs quite significantly. The European large mid-caps companies have a level of R&D intensity similar to the largest

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This analysis clearly has some weaknesses: (1) It is unclear if the R&D activities are undertaken in the EU or in the US, (2) R&D intensity could be higher because of higher R&D or because the companies are systematically smaller in the category.

companies. This suggests they are mature companies, funding R&D from their revenue stream. There is a larger variance in R&D intensity (compared to the larger companies) but the maximum is only 28%. In contrast, the US companies have a much higher level of R&D intensity, on average investing more in R&D than they have revenue. This suggests companies that are still growing significantly, and they are relying on other source of finance to pay for the R&D investment.

Table 9: R&D intensity for companies with R&D spending over €100 million and less than €999 million

	Average	Min	Max
Europe	17%	5%	28%
US	104%	5%	570%

Source: EU R&D Scoreboard

When we turn to the smallest category, the differences between Europe and US continue. In this category, Europe clearly has some high intensity investors (although significantly less than in the US) but the US has a higher average, and a significantly larger range.

Table 10: R&D intensity for companies with R&D spending over €30 million and less than €99 million

	Average	Min	Max
Europe	101%	3%	384%
US	188%	0%	1015%

Source: EU R&D Scoreboard

In the appendix to this paper, we have analysed how firms grow over time and move between categories. We examined the constituents of the R&D Scoreboard over the last four years, and we found that although the proportion of companies moving from one category to another is similar in Europe and the US, the performance of the companies over time differs dramatically. The US small mid-caps R&D companies were much more likely to sustain losses. Indeed, 66% (18) of 27 US small R&D companies had sustained losses each of the four years (2010-2013), while in the EU only 9% (2) of the 22 companies had sustained losses each of the four years (2010-2013). It is also notable that all of the US companies are publicly listed, whereas a significant number (4) of the European companies were privately held.

Based on simple comparison of turnover and R&D spending there are significant differences between companies based in Europe and the US:

- Companies based in Europe investing €100-999m per annum in R&D are significantly more mature as indicated by their R&D expenditure as a percentage of sales and in terms of their long history. In the US, the level of R&D intensity (R&D as a percentage

of turnover) was 104% compared to 17% for European companies (similar to companies investing over €1 billion). Clearly in the US there are many more high R&D intensity companies growing quickly, which, because they have little revenue, are loss-making and have exceptionally high R&D intensity numbers.

- In the EU there are fewer companies investing between €30m and €99m in R&D per annum than in the US, and those in the US have significantly higher levels of R&D intensity. Indeed, 66% (18) of the 27 US based companies had sustained losses in each of the four years over the period 2010-2013, while in the EU only 9% (2) of the 22 companies had sustained losses over this period.

The evidence suggests that Europe has not grown biopharmaceutical companies as successfully as the US. Given the many existing (and contradictory) definitions of companies, we are reluctant to suggest a new definition; however, given this difference in performance, it is useful to distinguish between larger biopharmaceutical companies and **mid-sized companies**, defined as companies with turnover between €50 million and €4 billion or R&D spending of between €30 million and €1 billion. We continue to use the EU Commission definitions and terminology for smaller companies.

2.3. Views from the interviews

We asked a range of different stakeholders whether they perceive a problem in the European industry in terms of the growth of biopharmaceutical companies. There is a general recognition among the stakeholders who took part in the interview programme that growth of companies in Europe is weak compared to the US. Throughout the discussions, participants highlighted the limited numbers of success stories involving European originated companies. It was seen as more likely that micro and SME European companies would be acquired by larger players (and earlier in their development) or that companies that did try to develop organically would have a slower progression than similar companies in the US. It is useful to distinguish between three broad groups of stakeholders participating in our interview programme, who discussed the limited growth in Europe as follows:

- *Views from the industry:* There is a unanimous perception among companies of different sizes that the opportunity for companies to grow in Europe is more limited than in the US.
 - Micro and SMEs voiced concerns about the chance of survival in the European market. They pointed to the greater number of companies being sold to large pharmaceutical and biotech companies in Europe. In some cases, these smaller companies only sell the rights to one of their technologies, but even in these cases they were concerned this reduced their chance of survival and growth. Attempts to mitigate this have also led to over-reliance on partnership with other companies for development, and reduced individual growth. Overall, these companies view the challenge to grow organically as significantly greater compared to their US counterparts.
 - Similarly, mid-sized companies recognised that successfully growing as a European company was more challenging than as a company based in the US

market. However, there is an indication that international growth and expansion has been equally challenging for all firms regardless of their originating country.

- The largest companies also recognised that growing an SME in Europe was challenging, particularly when products were approaching Phase II and Phase III; and that smaller companies were more likely to be taken over by larger companies in Europe.
- *View from the private investors:* There is a consistent view across different private investors, including business angels, private equity firms, and banking and financial analysts, that European biotech companies grow more slowly compared to US ones. This view was shared independently of whether the investors were in the US or Europe. All participants in this category highlighted the substantially lower number of small- to mid-sized companies in Europe involved in IPOs, which give companies under financial constraints the necessary resources to grow without compromising independence or survival in the market.
- *View from the public investors:* Perhaps unsurprisingly, public organisations involved in supporting European biopharmaceutical industry (including EIB, DG Research) believed their intervention was key to overcoming the problem facing companies growing in the EU. Most of the European Commission initiatives to invest in small companies are, according to these participants, a measure to help overcome the barriers to turning European science into a proof of concept and commercialisation. Public investors have recently recognised an increasing need for growth stimulation for mid-sized companies and responded by creating projects open to these companies (Innovative Medicines Initiative 2).

2.4. Conclusion

Although there is broad consensus that Europe lags the US in terms of developing new biopharmaceutical companies, data on this is actually scarce. On average, companies are larger in the US, with higher sales and greater levels of investment. This has clearly been the case for many years. However, by directly comparing the level of turnover and the investment in R&D we can observe a number of issues:

- Apart from the largest companies (with turnover in excess of €4 billion) the growth rate of European companies is substantially lower.
- There are significantly fewer companies in Europe investing €30-99 million in R&D, and the companies investing €100-999 million are significantly more mature as indicated by lower % of R&D and in terms of age.
- We can observe many more high intensity companies growing quickly in the US while still relying on external funding.

Although much of the literature has focused on the SME category, it seems clear from this analysis that there are significant problems regarding the growth of mid-sized biopharmaceutical companies in Europe. Although it is complicated to make comparisons over time (for example, because the coverage of the EU R&D Scoreboard has changed), if anything the difference between the US and Europe is getting larger.

3. Barriers to growth of biopharmaceutical companies in Europe

This chapter considers the range of potential barriers to growth, and the extent to which inadequate sources of private or public finance represent a significant barrier to the growth of different size companies in Europe, and thereby helps to explain the differences between the European and US industry observed in the previous chapter.

3.1. The range of possible explanations

In the last chapter, we set out the quantitative and qualitative evidence that the structure of the biopharmaceutical industry originating in Europe differs from that in the US, and this evidence indicates that there are barriers to growth. However, there are a number of explanations for these observations:

- Hypothesis 1: The science base in Europe has not created the same number or quality of opportunities for companies to develop.
- Hypothesis 2: The environment to nurture development opportunities is weaker in Europe.
- Hypothesis 3: Companies have not been able to finance the development of products from private sources (and hence have licensed assets to larger companies or been sold to companies who can find financing).
- Hypothesis 4: Public sources are not providing sufficient support for companies at the crucial stages of their development.
- Hypothesis 5: The proximity to the US market provides an advantage for US originated companies.

3.2. Hypothesis 1: The science base in Europe has not created the same number or quality of opportunities for companies to develop

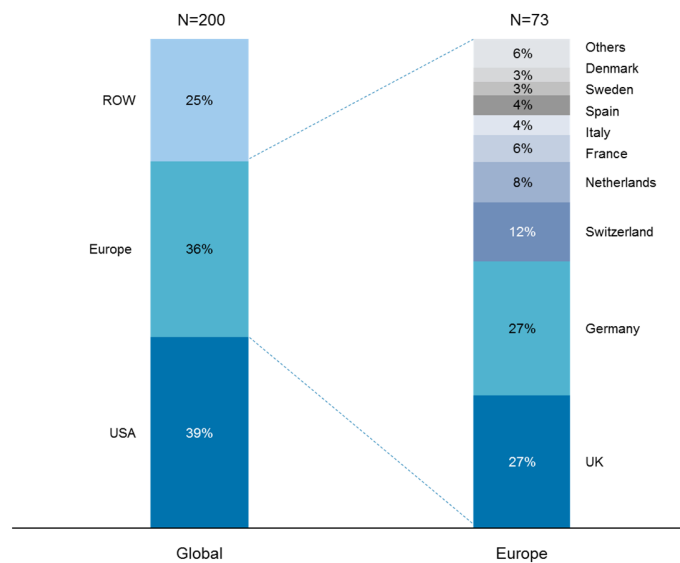
The differences in structure could all result from a smaller number of commercial opportunities in Europe. There are a number of potential reasons why opportunity could be lower in Europe: (1) the quality of the science, (2) a lack of local academic and/or publicly supported centres of excellence to educate and provide highly specialised training for the skilled workers at all levels required to compete in the innovation process, (3) the environment, i.e. lack of incentives for academic spin-outs from universities or for entrepreneurial activity, (4) because Europe is still catching up, as the bio-revolution in drug development started in the US earlier.

To test this hypothesis, it is useful to examine the European industry's performance in terms of scientific output (publications by universities, the resulting patents, the extent of collaboration between academia and business, and the products that were originally developed by EU institutions). Many papers in the past have done this, so we briefly summarise the information here.

Comparing the academic output of the EU vs the US

Europe and the US have historically been hubs for excellent academic institutions including leading biomedical universities, which perform all types of research including fundamental, applied and translational.³² Referring to rankings of biomedical institutions by the number of primary research articles they publish in Nature journals, we note that the number of leading biomedical universities in Europe and the US has remained balanced, with the US displaying some superiority in numbers. The most recent data (seen in Figure 6) shows that from the worldwide pool of the top 200 leading universities, 36% of these are based in Europe as opposed to 39% in the US.³³ In 2012, the same ranking showed Europe and the US at a 40% share each. However, there is still strong presence in Europe in the top 10 classification, where we find institutions such as the Max Planck Society in Germany (4th), the National Centre for Scientific Research in France (7th) and the University of Cambridge in the UK (10th). This was confirmed in the discussions with European and US companies, who reported that the scientific basis in Europe is strong, leading to many US biotech companies utilising scientists from this region.

Figure 6: Proportion of biotechnology research institutions ranked in the top 200 publishing institutions, by country in 2013



Source: CRA analysis using Nature Publishing Index - 2013 Global Top 200

³² Fundamental: research that aims to create new knowledge on how biomolecular processes work in the body; Applied: research conducted on the application of new knowledge with the aim to investigate and improve the understanding or processes in diseases; Translational: multidisciplinary form of research that bridges the gaps between fundamental and applied science, translating knowledge into applications.

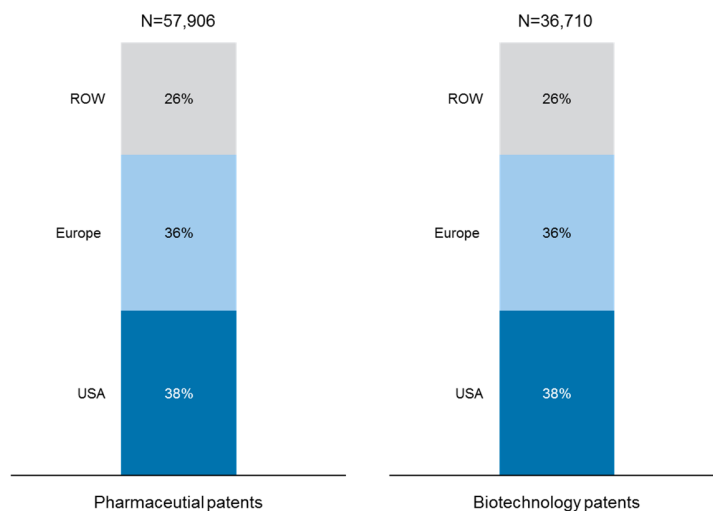
³³ Nature Publishing Index (2014), 'Nature Publishing Index – 2013 Global Top 200', available at: <http://www.natureasia.com/en/publishing-index/global/>.

However, as illustrated in Figure 6, there is considerable disparity across European countries, with Germany and the UK having the two biomedical academic hubs, at 27% of all European top 200 institutions each. This issue was raised in interviews with private and public investors who voiced the concern that science is sparse in Europe beyond a narrow set of countries.

Despite the inventive activity being somewhat larger in the US, Europe performs well in terms of patents³⁴

In academic literature, patent publications are often used as a proxy for innovative activity.³⁵ Annual data on patent publications by origin country of applicant is available through World Intellectual Property Organisation (WIPO) across a range of industries. If we compare both biotechnology and pharmaceutical patent publications in 2013 across Europe, the US and Rest of World (here: Australia, Canada, China and Japan), we see similar performance in pharmaceutical and biotech as in Figure 7.³⁶ Despite the US leading by a small amount, Europe shows good performance in translating raw science into patents, with 36% of patents in both sectors originating in the region.

Figure 7: Proportion of biotechnology and pharmaceutical patent applications in 2013



Source: World Intellectual Property Organization (2014), 'Data Center'

Europe appears therefore to be performing well. Indeed, this view was supported by different stakeholders in the interviews, where we heard that not only is the level and quality of academic research comparable between the EU and the US, it could even be said that the quality of research is better in the EU as it is more focused on translational science.

34 Innovation differs from invention in that innovation refers to the use of a better and, as a result, novel idea or method, whereas invention refers more directly to the creation of the idea or method itself.

35 Pakes (1984), 'Patents, R&D and the stock market rate of return', National Bureau of Economic Research.

36 World Intellectual Property Organization (2014), 'Data Centre', available at: <http://ipstats.wipo.int/ipstatv2/>.

However, there are some clear limitations to the use of patent data as a proxy for successful science. First, the proxy used in the analysis above is patent application numbers, which is a good measure of scientific activity but not of quality, as the rate of success is not accounted for. Patent publications or patent citations are equally limited as a proxy, as these are again an indicator of quantity; a larger number is not necessarily proportional to a greater value of patents.³⁷ Lastly, in any attempt made to assess scientific and innovative activity, it is crucial to make the distinction between invention and innovation, the latter requiring a successful commercialisation of a scientific idea.³⁸ Therefore, a large number of patents does not adequately indicate the success and quality of the science but rather its novelty.

The changing from a chemical to bio based innovation model

There is a hypothesis that given that the roots of the biologic revolution were in the US, this indicates that although the science may be of equal quality in the US and in Europe, it was more relevant in the US and more closely associated to opportunities for drug development.³⁹ However, we find that performance in terms of academic publications and patents (for either pharmaceutical or biotech) has remained the same for some time.

Although on some measures Europe has comparable quality and quantity of patentable science, the evidence of this ultimately leading to new medicines is weak

Academic research has examined the geographical origin of new medicines and shows that over the time period 1998-2007 the origin of new therapeutic biologics was dominated by US biotechnology companies and US universities partnered with them. Only 21% of the new biological medicines in the markets traced back to European companies and universities.⁴⁰ Therefore, even though Europe shows a strong academic research base, in terms of commercialisation and new treatments delivered to patients the US is significantly more successful. However, there are caveats that should be mentioned regarding this research. First, this analysis is focused solely on the origin of the patents but fails to account for all the contributions that may have been made to the final discovery by previous inventions and scientific articles. In addition, in cases where researchers belonged to more than one institution a judgement call was made in deciding which one was responsible for the discovery. In more general terms, the study may be biased: it focuses on drugs approved by the US Food and Drug Administration (FDA) for the US market, perhaps creating a small bias towards science

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- 37 Abrams et al. (2013), 'Understanding the link between patent value and citations: creative destruction or defensive disruption?', University of Pennsylvania.
- 38 Ruttan (1959), 'Usher and Schumpeter on invention, innovation, and technological change', *The Quarterly Journal of Economics* 73 (4).
- 39 In reality, the basic science was developed both in the US and in Europe. 'The origins of the biopharmaceutical industry in the US date to the late 1970s and the discovery of the recombinant DNA technique by Cohen and Boyer in 1973 at Stanford and the University of California at San Francisco (UCSF) and Kohler and Milstein's discovery of monoclonal antibodies at Cambridge (UK) in 1975'.
- 40 Kneller (2010), 'The importance of new companies for drug discover: origins of a decade of new drugs', *Nature Reviews Drug Discovery* (9), November 2010.

that has originated in the US rather than in Europe. Additionally, the study has not been updated, so it is possible that this could have changed over the last five years.

Conclusion on hypothesis 1

Although admittedly weak measures of innovative potential, in terms of the ultimate aim of bringing new medicines to the market and patients, the levels of publications and patents are similar; and most interview participants recognised that the quality of the science and its commercial potential, insofar that it can be estimated, is similar on both sides of the Atlantic. We find little evidence to support the suggestion that the European science base is still catching up on the fundamental change from chemical to biologics, and after thirty years the argument is becoming less convincing. However, there were some dissenting voices on this subject from the private investment sector, which questioned whether the quality of European science was equivalent to that of the US. This is consistent with research that traces back to the source of innovative medicines, to see where the original research was undertaken; a smaller number of products have originated from research in Europe than from that in the US.

3.3. Hypothesis 2: The environment to nurture development opportunities is weaker in Europe

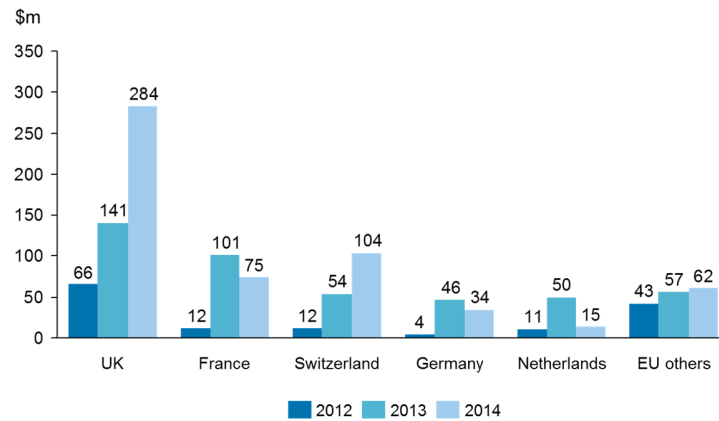
Even if the science provides the same opportunities, it requires spin-offs or companies to work closely with academia for these ideas to be turned into commercial opportunities. Recent data shows that that European companies are not developing these opportunities to the same extent as US companies.

There is evidence of weaker valuing of R&D in Europe compared to the US

A recent study uses seed and series A financing⁴¹ data to provide an indication of success in commercialisation or valuing of R&D and finds that the US biotech sector leads the way by a large amount. In Europe, the UK shows the best commercialisation potential, followed by the Switzerland, France and Germany. The amount of seed investment during the past three years across European countries is shown in Figure 8, and suggests that the UK received half of the seed and series A investment in Europe in the past two years.⁴²

41 A Series A round is the name typically given to a company's first significant round of venture capital investment.

42 Zipkin, M. (2015), 'Europe waking to the American dream', BioCentury Innovations.

Figure 8: Seed and Series A investment in European countries

Source: Owen-Smith et al. (2015)

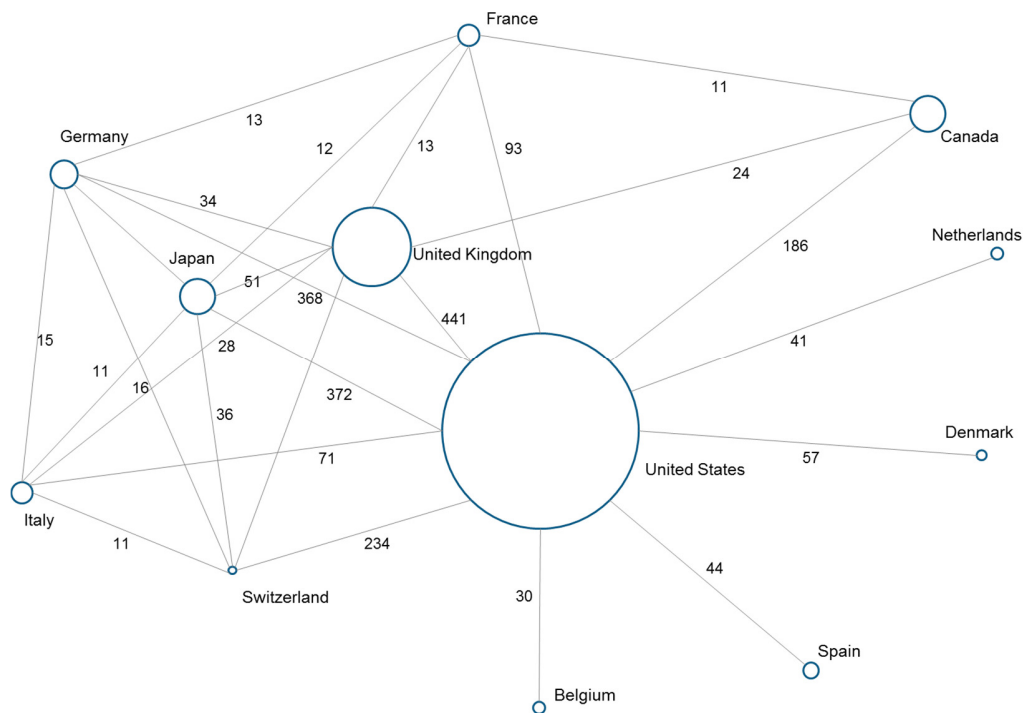
Recent reports find that the UK market environment is closer to the US one and creates a more favourable structure and ecosystem to nurture early stage innovations. It has been suggested that the reasons are varied but include the regulatory environment for setting up companies and shareholder rules.

There is greater scientific cooperation between academic and commercial organisations in the US, leading to product development

To perform successful applied research and early stage development, often academic institutions collaborate with small to large companies to transform patented ideas through expensive development programmes into approved medicines. In Europe, past research has found that the region is characterised by specialisation and less diversity in research performed by public institutions, including universities. The latter tend to mainly develop local collaborations with small firms that have a similar scientific focus, whereas cross-national cooperation is limited and involves only large pharmaceutical companies. In stark contrast, as shown in Figure 9, in the US the collaboration between private companies and public research organisations such as universities and is observed across multiple areas and regions creating a robust network of public and private players leading to much closer integration of basic science and clinical development. This collaboration in combination with other positive factors has promoted a better commercialisation of academically originated research, mainly through the founding of biotechnology firms.⁴³

⁴³ Owen-Smith et al. (2002), 'A comparison of U.S. and European University-Industry Relations in the Life Sciences', *Management Science* 48(1).

Figure 9: Cross national networks of R&D involving public institutes and private firms



Source: Owen-Smith et al. (2002)

This trend has continued in similar fashion during the past decade. A recent study by the European Commission on university-business cooperation (UBC) in the EU found that despite the perceived benefit of UBC by stakeholders involved (academic institutions including staff and private businesses), such activity remains limited in the region. Out of 14 countries studied, only 5 had a high level of UBC collaboration in conducting R&D, namely the UK (highest), Ireland, Germany, Finland and Sweden, and the rest was assessed as medium level. The extent of UBC is even lower in activities related to commercialisation of R&D, in average levels; the only countries with high activity being the UK and Ireland.⁴⁴

Looking more specifically at the number of partnerships between big pharma and academic institutions, a similar picture can be observed, as in Table 11. This list shows that there is still a considerable lack of interaction between businesses and universities in Europe, with only 6 out of the top 20 being a European partnership.⁴⁵

⁴⁴ European Commission DG Education and Culture (2013), 'The State of University-Business Cooperation across countries', available at: <http://www.ub-cooperation.eu/index>.

⁴⁵ A number of studies have looked into this in detail; for example, the OECD found that more than 80% of Spanish firms have never collaborated with a university. OECD (2010). 'OECD Territorial Reviews: Venice, Italy 2010', available at: <https://books.google.co.uk/books?isbn=9264083529>

Table 11: 20 Major alliances between pharma and academia in 2012

Pharmaceutical company	University (and other partners)
Sanofi	University of San Francisco, Brigham and Women's Hospital/Harvard Medical School
Johnson & Johnson	The University of Queensland
Eli Lilly, Merck, Pfizer	University Hong Kong, University Singapore
Elan	Cambridge University
Novo Nordisk	(1) Oxford University (2) JDRF
Bristol-Myers Squibb	Vanderbilt University
Novartis	University of Pennsylvania
Merck	California Institute of Biomedical Research
GlaxoSmithKline (GSK)	Yale University
AstraZeneca	Broad Institute, Massachusetts, a consortium of US universities
AstraZeneca, Boehringer Ingelheim, GSK, Janssen, Merck, Pfizer	University of Dundee
Abbott, AstraZeneca, Bayer, Eli Lilly, GlaxoSmithKline, Merck, Sanofi	Texas A&M University, Weill Cornell Medical College, Bill & Melinda Gates Foundation
AstraZeneca, Genentech, Merck	The University of Washington
Accuray	University of Heidelberg
Bayer HealthCare	University of California, San Francisco
Roche, Eli Lilly, Servier, Janssen Pharmaceuticals, Pfizer	King's College London
UCB	Oxford University

Source: *Fierce Biotech 2012* ⁴⁶

⁴⁶ Toor, S. and McBride, R. (2012) '20 Major Pharma-Academic Alliances in 2012', available at <http://www.fiercebiotech.com/slideshows/20-major-pharma-academic-alliances-2012>.

Although typically associated with early stages of development, partnerships remain important for company growth as they allow companies to share the responsibility and risk. The lack of collaboration is partially caused by a lower number of commercially astute scientists in Europe compared to the US

Bringing a new idea through preclinical and then into clinical development requires collaboration between scientists and businesses. This could be through academic spin-offs. The average percentage of tertiary graduates whose degree is in science and manufacturing seems to be higher in Western Europe (France, Germany, Netherlands, Switzerland and the UK) than in the US, which suggests that Europe should see a greater number of biopharmaceutical start-ups.⁴⁷ However, an estimate of the total number of biotech start-ups in 2013 found 39 in the US, six times greater than the 6 observed in Europe.⁴⁸ This phenomenon supports the view that the diversity of both scientific and managerial expertise in European scientists is insufficient for creating biopharmaceutical start-ups. In Europe there is a shortage of biotech management expertise, and it takes time to find the right executive team, thus leading to a very reduced and inefficient talent pool.

Indeed, participants in our interviews mentioned that there is a considerable lack of entrepreneurship and business management expertise in science and academia in Europe. European academic institutions teach more traditional notions of risk and entrepreneurship and do not nurture the same 'risk-taking' attitude as their US counterparts. Research has established that the notion of entrepreneurship within universities has been historically more prominent in the US than in Europe. For example, in Germany there is a lingering perception of risk associated with start-ups, caused in large part by the high failure rates of biotech start-ups that were backed by the government in the '90s without professional investor screening.⁴⁹ Only in recent years have universities in Europe started to actively encourage academic entrepreneurs. An example, also mentioned in interviews, is Imperial Innovations, stemming from Imperial College London and aiming to commercialise research from the golden triangle comprising of Cambridge, Oxford, and London.^{50,51,52}

47 JLL (2014), 'Life Sciences Cluster Report Global 2014', available at: <http://www.jll.com/Research/2014-global-life-sciences-report-JLL.pdf?654be919-aef1-45a0-bef3-ab01d0a4ece6>

48 Timmerman, L (2013). 'The Biotech Startup Class of 2013: Don't Worry, It's a Short List', available at: <http://www.xconomy.com/national/2013/11/18/biotech-startup-class-2013-dont-worry-short-list/2/>

49 Zipkin, M. (2015), 'Europe waking to the American dream', BioCentury Innovations.

50 Franzoni, C. and Lissoni, F. (2009) 'Academic entrepreneurs: critical issues and lessons for Europe', in Varga, A. (ed.) *Universities, Knowledge Transfer and Regional Development: Geography, Entrepreneurship and Policy*. Edward Elgar, Cheltenham, UK; Northampton, MA, USA. pp. 163–190

51 Erdos, K. (2010). 'The Academic Entrepreneur: Myth or Reality for Increased Regional Growth in Europe?', available at: <http://www.sre.wu.ac.at/ersa/ersaconfs/ersa10/ERSA2010finalpaper1451.pdf>

52 Imperial Innovations (2015), 'About Us', available at: <http://www.imperialinnovations.co.uk/about/>

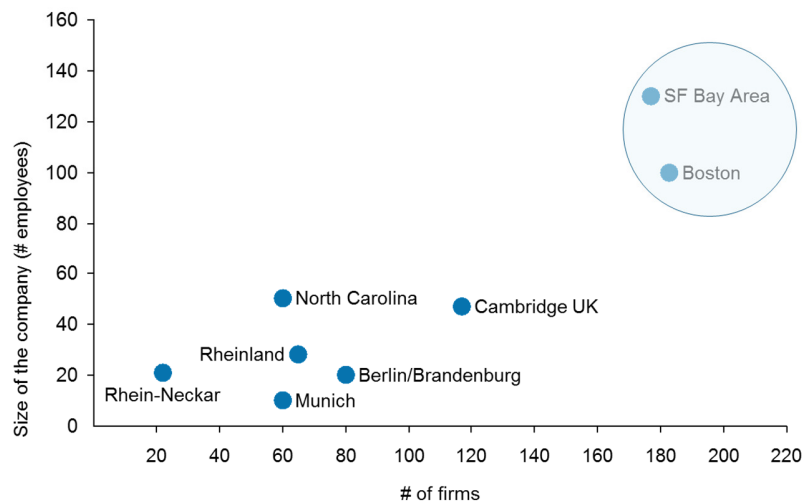
The clustering effect fosters a more favourable and stronger environment for science in the US compared to Europe

Clustering was highlighted in the CRA interview programme and has clearly been the focus of much academic research. It was seen as important due to its role in:

- knowledge spillovers
- creating cultural and physical proximity
- improving the link between academia and business by creating a platform where all different stakeholders from the academic scientist to the manager, investors and policymakers can meet.

This is an area where Europe has experienced limited development compared to other regions such as the US, which has some of the most renowned high-tech clusters. In Europe, most scientific work is attributed to individual long-standing research and academic centres, but there is some limited evidence of close links to companies and their research labs. This is illustrated in Figure 10, which indicates that European clusters are considerably smaller and less mature than US leading ones such as the San Francisco Bay Area and Boston, Massachusetts, clusters.⁵³

Figure 10: The size maturity of clusters (as proxied by number of firms and the average number of employees) in the US and Europe



Source: CRA analysis based on European Commission (2011)⁵⁴

⁵³ Zechendorf, B. (2011), 'Regional biotechnology – The EU biocluster study', *Journal of Commercial Biotechnology* 17(3).

⁵⁴ European Commission (2011), 'Regional Biotechnology: Establishing a methodology and performance indicators for assessing bioclusters and bioregion', DG Research.

- One of the most mature clusters in Europe is the Oxford Biotech Cluster in the UK, with 163 companies in 2012, a growth of approximately 14% since 2008, and around 10% of all companies in the cluster had been there for 20 years or more. Part of this cluster are academic institutions as well as some investors such as banks and VCs. This cluster has some successful biotech companies, such as Circassia, Optibiotix, and Midatech, which, with the support of the cluster, have listed in the stock markets.^{55,56} Another European example is Vlaams Instituut voor Biotechnologie (VIB), a biotech cluster and support network that promotes collaboration of biotech companies and researchers in the Flanders region. This network has provided good support to members in accessing skilled workforce and finance from public sources, the European Research Council and private venture capital firms. It has been successful in setting up more than 200 companies including for example Ablynx, ActoGeniX, and Devgen.⁵⁷ Although there is positive activity, it is scattered in the region, and as one of the interviewees mentioned, the EU in comparison to the US remains very 'tribal', and dilution is a risk for performance and innovation. The sector and governments need to encourage cooperation across institutions rather than competition'. There is a general recognition among the interviewees that despite some evidence of European success, the US has been able to create larger, more mature and more numerous biotech clusters that enjoy better access to excellent science with some of the leading academic institutions based in a cluster, such as Harvard and MIT in Boston.
- US clusters are also characterised by a greater offering and larger variety of VC enabling start-ups to easily attract venture capital and investment funds (as discussed in the next section). This is also due to a more favourable geographic distance to main financial centres such as Boston. It is noted that in the US, the majority of investments are to companies based in regional ecosystems that are highly integrated with local high profile universities.⁵⁸
- Organic growth of US clusters has been fostered by a combination of academia and well-functioning and risk-taking capital markets in close proximity and not as a 'plan' devised by the government. Europe has the potential to develop these hubs, but the process will be long to achieve a replica of the US cluster organic evolution.

Return on investment in the past decade in life sciences in Europe, coupled with the oversupply of resources, may partially suggest a lack of good ideas

Overall, the interview programme suggested that the science base in Europe is strong and does not constitute a growth barrier for companies, but some investors also highlighted that confidence had been dented by the performance of the last few years. Only in recent years has

55 Oxford Biotech Network official website (2015), available at: <http://www.obn.org.uk/>.

56 LiftStream (2012), 'Oxford Biotech Cluster', available at: <http://www.liftstream.com/oxford-biotech-cluster.html#VMEZSSusVBk>.

57 VIB (2014), 'Annual Report: From Science to Value', available at: <http://www.vib.be/en/about-vib/annual-report/2014/Pages/default.aspx>.

58 Zipkin, M. (2015), 'Europe waking to the American dream', BioCentury Innovations.

the pharmaceutical sector delivered a more positive outlook to investors and better stock evaluations, leaving behind years of poor late and early stage product pipelines, decreases in cash generation, and unsatisfactory dividends.⁵⁹ A view voiced by a financial analyst, during the discussion with us, emphasised that this historical return on investment suggests that there is an oversupply of money and a lack of good ideas. This is a view in isolation, but it raises the theory that if investors recognise an appealing scientific idea, the appetite to invest will emerge.

Conclusion on hypothesis 2

Europe clearly has a relatively strong science base. However, there is a recognition that Europe is weaker than the US in terms of the entrepreneurship of academics and the role of clusters. Hence, although Europe is creating many spin-offs and start-ups these are not being nurtured. It has been suggested that this could be compensated for by closer cooperation between existing companies and academia. However, we find little evidence for this and the contrary appears to be true.

It does seem that companies set up to develop opportunities for biologics in the US more quickly than in Europe. Academics have identified that institutional features of the US academia-industry environment, as well as the possibility that US academics could establish companies while retaining their academic positions, was important in encouraging knowledge flows and rapid commercialisation. Whereas many US start-ups originated in the 1970s, Europe only saw the growth of such companies in the 1990s.⁶⁰

Evidence and theory suggests that the lack of commercialisation of science in Europe is due, in part, to the poor academic and business collaboration, limited managerial and entrepreneurial skills of scientists, and less favourable clusters in Europe compared to the US, rather than to a lack of good scientific ideas.

3.4. Hypothesis 3: Companies have not been able to finance the development of products from private sources

In the previous two sections we have focused primarily on whether the structure of the European industry means that there are simply fewer SMEs and hence it is inevitable that we cannot observe them develop and grow into mid-sized companies. Equally, the problem could be due to lack of finance to fund investment in R&D, which could affect SME growth or equally explain why mid-sized companies are not investing in Europe in the same way as in the US.

As set out in chapter 2, the funding needs vary considerably along the development process; during research and early development the cost is in the millions or tens of millions. For example, it would be typical for a phase I programme to look for funding of €20-25 million. As the product enters later stages of clinical development and larger trials are involved, the costs

59 Stovall, S. (2012), 'European pharma industry seen 'rising from the ashes in mid-2012', available at: <http://blogs.wsj.com/health/2012/01/05/european-pharma-industry-seen-rising-from-the-ashes-in-mid-2012/>.

60 Xia, T. and Roper, S. 'Worlds Apart? A Comparison of the New Product Development Strategies of Biopharmaceutical Firms in Europe and the USA', Working Paper No. 101, September 2008.

multiply, with phase III trials potentially costing many millions for one asset. Although this varies depending on the disease category, it was estimated that the typical cost for phase III is €100-€300 million. Therefore, unsurprisingly the sources of funding vary depending on what the companies are doing and the extent to which they have an existing revenue base to fund R&D.

Generally, it was agreed in the interviews that it was most relevant to focus on four types of investors: business angels (for initial start-ups); VC, private equity and specialist mutual funds; capital markets; and collaborations with large pharmaceutical companies and licensing. For each of these we consider the evidence on the state of the European market and how it compares to the US market.

There has been considerable growth in EU early stage investment instruments, but this remains only a fraction of the amount invested in the US

New start-ups that have no cash flow seek external funding for preclinical development or phase I development, which according to stakeholders are the least expensive stages of development. Despite it being difficult to draw a line on funding needed for the preclinical development for one molecule in isolation, as these costs contribute towards the development of several compounds, recent studies have estimated this at \$5 million.⁶¹ With respect to phase I, research studies have estimated the out of pocket cost at a range of estimates: \$15 million (Paul et al., 2010), \$20 million (DiMasi et al., 2003) and \$31 million (Adams and Brantner, 2010).⁶² Being the least expensive stages of development, these are more commonly financed, at least initially, by business angels and the Triple F or Friends, Family and Fools. Many of the interviewed companies expressed the importance of the Triple F in enabling the start of new projects in combination with presence from business angels.

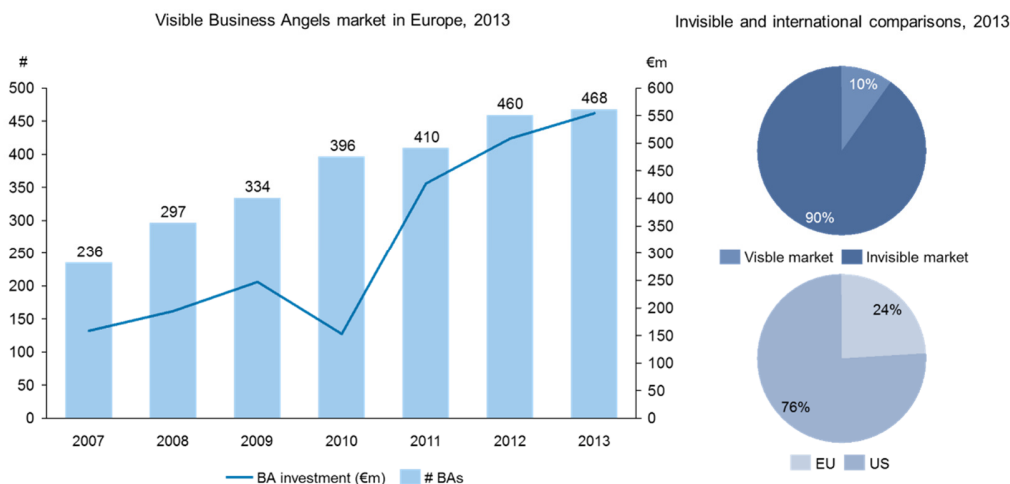
In Europe, investment from business angels has grown dramatically in both absolute number of angel investors and the amount of investment. As shown in Figure 11, since 2007 there has been a steady growth in both these indicators – with the exception of 2010 investment, as a result of the turmoil caused by the financial crisis. In total, in 2013 the amount of investment reported is just short of €0.5 billion. Despite the impressive growth, this is not a substantial total, particularly for expensive R&D investments. However, as displayed by the right-hand side of Figure 11, this amount represents only the visible market investments, which constitute 10% of the overall amount of €5.54 billion. When comparing the total market to the US, we note that European business angels invest only about a quarter of the combined investment in Europe and the US.⁶³

61 Paul et al. (2010), 'How to improve R&D productivity: the pharmaceutical industry's grand challenge', *Nature Reviews* 9.

62 DiMasi et al. (2003), 'The price of innovation: New estimates of drug development costs', *Journal of Health Economics* 22; Paul et al. (2010), 'How to improve R&D productivity: the pharmaceutical industry's grand challenge', *Nature Reviews* 9, March 2010; Adams and Brantner (2010), 'Spending on new drug development', *Health Economics* 19(2).

63 Please note that the above data includes all sector investment with ICT and biotech and healthcare representing the main areas of concentration.

Figure 11: The state and development of business angel investment across markets



Source: CRA analysis based on EBAN data⁶⁴

Venture capital

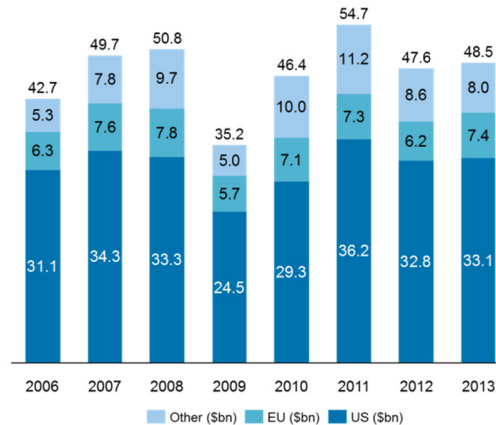
When companies require larger financial resources to fund their phase I and phase II R&D, European companies report that bank debt or IPO options for capital are unlikely to succeed due to lack of predictable revenues. VCs were mentioned as a main available source of capital.

There has been a lot of research on the European VC market. Early research on the state of biotechnology and funding in Europe showed that European companies are half as likely to raise capital from VCs as their US counterparts.⁶⁵ Over the years, other research has looked at VC investments worldwide and noted that the US is by far the market with the largest overall investment as shown in Figure 12.⁶⁶ The amount of VC invested indicates that there is less capital available and obtainable for European firms, a view that resonates with the perception and experience of all the stakeholders we have interviewed. In addition, although in absolute terms the capital invested by VC firms in Europe is considerable, some interviewees believe that what is lacking is for this capital to be allocated to biotech and pharmaceutical.

⁶⁴ The European Trade Association for Business Angels, Seed Funds and Early Stage Market Players, accessed at: http://ec.europa.eu/growth/tools-databases/smaf/business-angels/index_en.htm.

⁶⁵ EuropaBio (2006), 'Biotechnology in Europe: 2006 comparative study', available at: <http://www.europabio.org/index.htm>.

⁶⁶ EY (2014), 'Adapting and evolving: Global venture capital insights and trends 2014'.

Figure 12: Global annual venture capital investment, 2006 - 2013

Sources: EY (2014), 'Adapting and evolving'

We note that the financial crisis led to an overall decrease in VC investment, illustrated by the dip in 2009. However, due to a lower risk appetite in Europe, recovery in Europe has been a slower than in the US up to 2013, indicating that investors have moved to less risky investments which require less capital and shorter time horizons.⁶⁷ This is evidenced not only by the value of VC investment but also by the growth in number of deals from 2009 to 2012, which have increased by only 13% in Europe and by 53% in the US.⁶⁸

The weakness of European VC markets is exacerbated by the chronic lack of specialised life science investors who are capable of informed decisions and increased willingness to invest

The most pressing issue according to all the key stakeholders involved is the lack of mature specialised VCs in the European market, which have the potential to make more informed and efficient investments. Interviewees suggested that in the US there is a larger number of life science dedicated VCs, whereas in Europe there are only a few companies of this kind and less than five significant players such as GIMV in Germany and Sofinnova in France. Indeed, looking at the most active and largest life sciences VCs, globally, we find that European representation in the top 15 has remained very weak, with only one company out of 15, namely

⁶⁷ Van Beneden, 'Economic trends in European venture capital.' *Nature*.

⁶⁸ Rooney (2013), 'Venture Capital in the US and Europe compared', available at: <http://blogs.wsj.com/tech-europe/2013/07/31/venture-capital-in-the-u-s-and-europe-compared/>.

Sofinnova in France, in the 2008 ranking, later replaced by Novo A/S⁶⁹ of Denmark in the 2013 list.^{70,71}

This was seen as particularly important due to the value of an informed investor. The greater presence of specialised investors is important not only because of the exclusive allocation of funds in life sciences but also because the willingness to invest increases with information, regardless of the available financing. In turn, this is seen as causing risk aversion, a weakness most European investors display, according to the interviews. The risk averse European attitude, caused also by lack of specialisation, is detrimental for investment in the life sciences sector, which has risk at its core. Thus, as voiced by interviewees, in the US, VCs make larger and riskier investments, which in turn lead to more success.

Traditionally, VC investment is focused on earlier stages of development, but traits are changing and vary across regions, causing more severe problems in particular areas

Generally, VCs are considered key to the advancement of Phase I and II, each estimated at a range of:⁷²

- phase I: \$15 million (Paul et al., 2010), \$20 million (DiMasi et al., 2003) and \$31 million (Adams and Brantner, 2010)
- phase II: \$30 million (DiMasi et al., 2003), \$42 million (Paul et al., 2010) and \$111 million (Adams and Brantner, 2010)

On the other hand, phase III, at a cost range from \$78 million (Adams and Brantner, 2010), \$111 million (DiMasi et al., 2003) to \$158 million (Paul et al., 2010), is significantly more expensive, and as a result VCs play a smaller role. A recent study on the trends of early versus late stage investment confirms that both life sciences VCs and particularly biotechnology VCs invest more resources in early than in late stage investment (shown in Figure 13). The most recent data point that refers to the first quarter of 2014 shows that early stage investment constituted approximately 73% of total biotech VC investment.⁷³

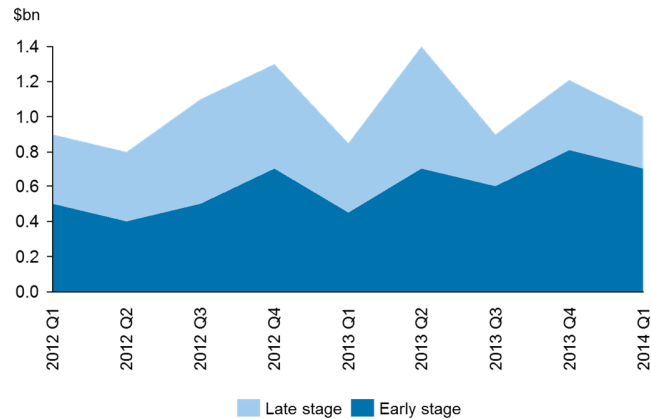
69 Please note this is the venture capital fund established by big pharma company Novo Nordisk.

70 FierceBiotech (2008), 'Top Venture Capital Firms', available at: <http://www.fiercebiotech.com/special-reports/top-venture-capital-firms>.

71 FierceBiotech (2013), 'The top 15 biotech VC firms', available at: <http://www.fiercebiotech.com/special-reports/top-15-biotech-vc-firms>.

72 DiMasi et al. (2003), 'The price of innovation: New estimates of drug development costs', *Journal of Health Economics* 22; Paul et al. (2010), 'How to improve R&D productivity: the pharmaceutical industry's grand challenge', *Nature Reviews* 9, March 2010; Adams and Brantner (2010), 'Spending on new drug development', *Health Economics* 19(2).

73 PwC (2014), 'Biotech deals rising', available at: http://www.pwc.com/en_US/us/health-industries/publications/assets/pwc-pharma-money-tree-q1-2014.pdf.

Figure 13: VC Biotechnology funding by stages, 2012 - 2014

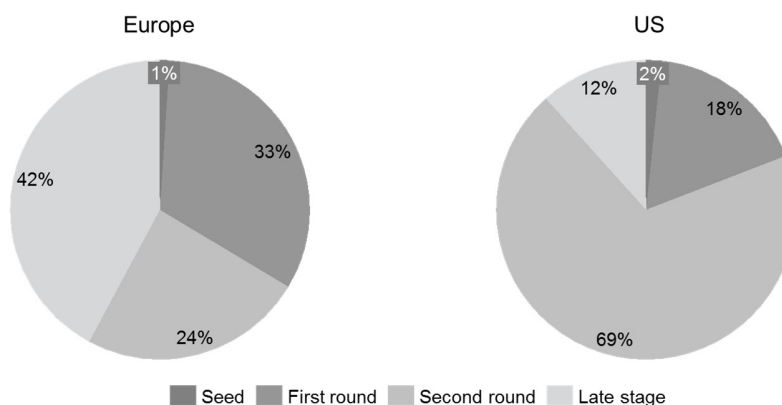
Source: PwC (2014), 'Biotech deals rising'

However, we note differences in the spread between early and late stage investment when we compare Europe to the US. As shown in Figure 14, VCs in the US concentrate their investment in early stage first and second round investments rather than later stages of development, as opposed to Europe, where the VC investment is spread between early stage first and second round and late stage development.⁷⁴ Although this suggests VCs play a role later in the development process in Europe, it is important to note that

- Europe displays a larger focus on late stage investment as, traditionally, EU national markets have only a few VCs, and these almost exclusively invest in local companies and tend to support throughout the development stages. For instance, in Germany there are only two main VCs that have invested in life sciences. They have invested approximately €1 billion. These VCs are marked by a long history of nurturing local biotech companies.
- Another view is that availability of financial organisations and instruments is significantly limited in Europe compared to the US. Thus, VCs contribute to other stages of development, usually financed in the US by other types of companies such as mutual funds and private equities (further elaboration in the next section). Thus, despite the more equal spread between stages, this is indicative of a lack of other financial instruments – and therefore exit options for the VCs – in the European market.

74

Dow Jones Venture Source, available at: <https://infoqr.am/Europe-Vs-US-Investment-by-Deal-Stage>.

Figure 14: Investment by deal stage in Europe vs the US, 10-year average

Source: Dow Jones Venture Source

Private equity and specialist mutual funds

For the biggest investments, private equity firms and mutual investment funds become the likely sources of finance. It was recognised by interviewed stakeholders that these sources might not offer greater amounts of funding but are often a more reliable source of finance for Phase II and III of R&D. This observation is supported in the investment literature, which has seen these investment vehicles become major investors of risk capital for later stages of development.⁷⁵ Indeed, studies have shown that private equity firms invest in Phase II and III trials via some typical financing instruments such as⁷⁶

- Project financing for a particular molecule that has completed Phase I clinical trials
- Revenue interest financing companies which may involve some products in the markets or products at later stages of development. This is usually not available to biotech companies in Phase II trials (or earlier in the development) due to the high clinical and regulatory risk.

Past research has raised concerns regarding the availability of private equity capital in the European market. EU based firms have experienced difficulties in raising sufficient capital, and they raise considerably less than US biotech enterprises. As early as 2006, a study by EuropaBio showed that biotech companies based in Europe can access a fifth of the private equity finance of their US counterparts and that the differences in availability of and access to capital for biotech enterprises in Europe and the US suggest that the European biotech industry 'shows signs of chronic underfunding'.⁷⁷ More recent data confirms that European countries have less private equity activity than the US. Figure 15 shows that the US is the top performer

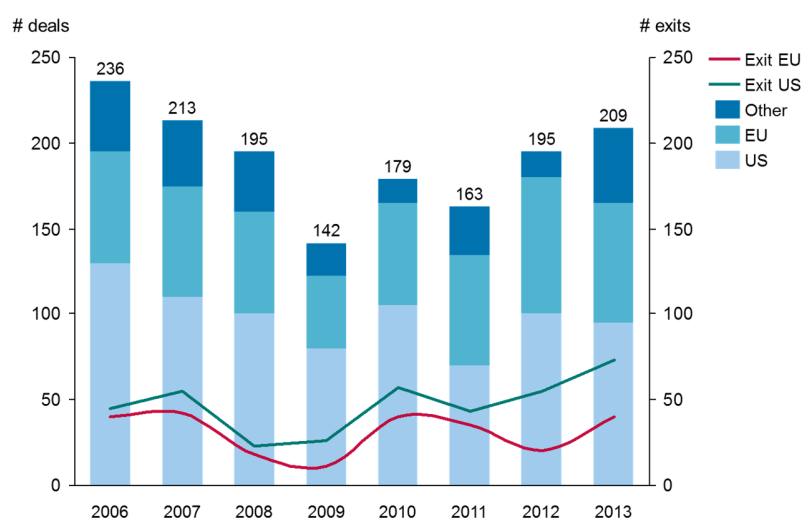
⁷⁵ Ford and Nelsen (2013), 'The view beyond venture capital', *Nature*, available at: <http://www.nature.com/bioent/2013/131201/full/bioe.2013.15.html>.

⁷⁶ Hamilton (2011), 'Trends in mid-stage biotech financing', Tuck School of Business at Dartmouth.

⁷⁷ EuropaBio (2006), 'Biotechnology in Europe: 2006 comparative study', available at: <http://www.europabio.org/index.htm>.

in terms of number of deals completed in each given year and that its growth has been higher than that of Europe since the dip in 2009 that was due to the financial crisis. On the other hand, the same study shows that exit opportunities have also been greater in the US, which could be a cause for the lower extent of deals in the EU.^{78,79} Indeed, all the stakeholders in the interview programme supported these observations and voiced the need for more private equity investment for later stage development in the European market.

Figure 15: Global private equity deal count and number of exits



Source: CRA analysis based on Bain & Company data (2014)

Another private investment vehicle used in later stage development and risk financing is mutual funds. Compared to private equity, these are broader in scope and securities included, as they invest not only in private entities but also in stocks, bonds and money market instruments. In Europe, there is a large and well-established base of mutual funds, but this has for a long time lagged behind the US market.⁸⁰ The same pattern is reflected in the health and biotechnology mutual funds market, as ranked by investment research agencies such as Zacks, Morningstar and Yahoo Finance. This shows 100% dominance from US based funds at the top end. Based on the top three performers in biotech mutual funds, ranked by Zacks, we perform an analysis of their geographical location and that of their holdings. As shown in Figure 16, the top three

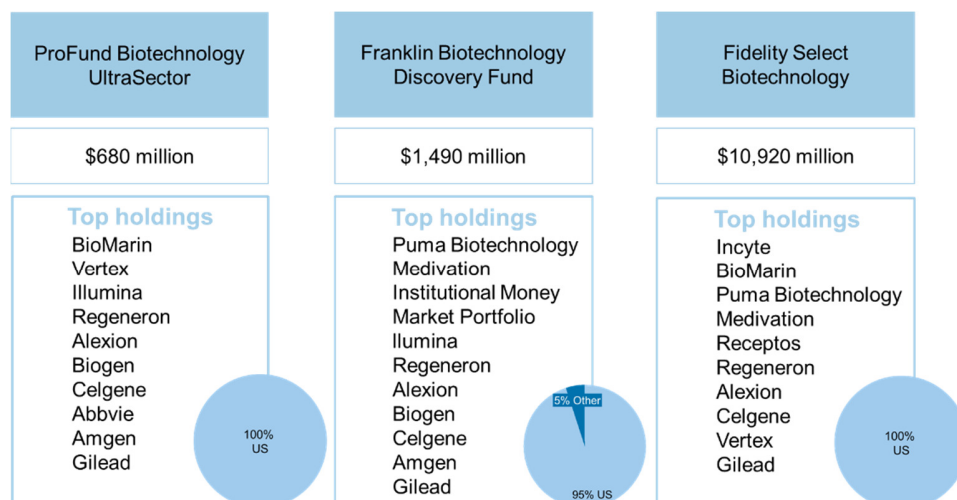
⁷⁸ Bain & Company (2014), 'Global healthcare private equity report 2014', http://www.bain.com/Images/BAIN_REPORT_Global_healthcare_private_equity_report_2014.pdf.

⁷⁹ Please note that this refers to the total number of deals in the overall healthcare industry and this is used as a proxy for pharmaceutical and biotechnology deals.

⁸⁰ Otten and Schweitzer (2002), 'A comparison between the European and the US mutual funds industry', *Managerial Finance* 28(1).

biotech funds all originate in the US, and the top 10 companies in their holdings are almost exclusively US based biotechs as well.^{81,82}

Figure 16: Top biotechnology mutual funds, total net assets and top holdings, 2014



Source: CRA analysis based on Zacks and Marketwatch data

During the discussions with the interviewees, these findings on the state of European mutual funds and private equity investment were echoed by all the participants. They suggest that the late stage risk financing market is less developed in Europe, and more private equity and mutual funds investments need to be available to offer better exit opportunities to earlier investors. This suggests that the traditional weakness attributed to the venture capital market is much wider, affecting private equity and mutual fund investment, and therefore represents a weakness for investing beyond phase I and early phase II trials.

Capital markets and IPOs

The next option for a company attempting to raise finance is to list its shares on an exchange. Capital market should provide an opportunity for life sciences companies to undertake an Initial Public Offering (IPO). The current state of the capital markets and the opportunities offered for companies to go public are defined by a series of events:

- The biotech sector experienced a boom in investment in the late 1990s; this was associated to the perceived potential of genetic sequencing to produce a new era of personalised medicine. Many argue this resulted in a biotech bubble which later failed to deliver.

81 Zacks (2013), '3 top ranked biotech mutual funds surging higher', available at: <http://www.zacks.Zakom/stock/news/110282/3-top-ranked-biotech-mutual-funds-surging-higher>.

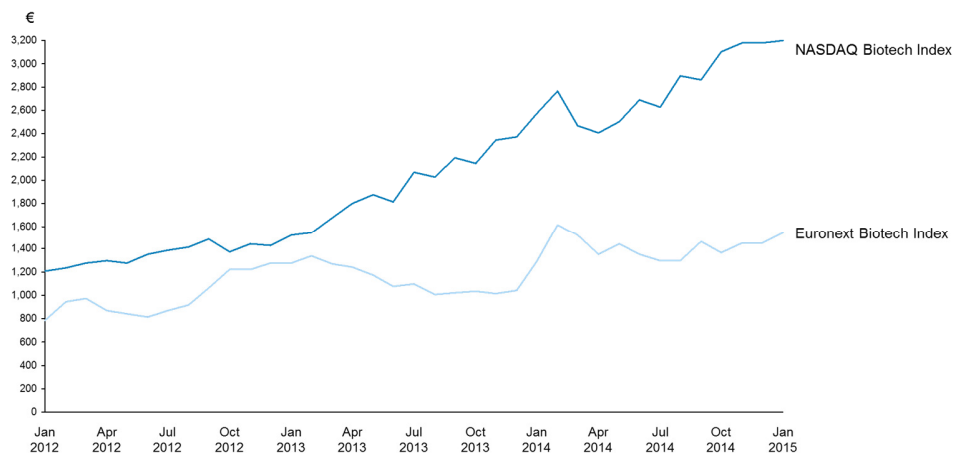
82 Marketwatch data (2015), 'ProFund Biotechnology UltraSector', available at: <http://www.marketwatch.com/investing/fund/bipix>; Marketwatch data (2015), 'Franklin Biotechnology Discovery Fund', available at: <http://www.marketwatch.com/investing/fund/fbdix>; Marketwatch data (2015), 'Fidelity Select Biotechnology', available at: <http://www.marketwatch.com/investing/fund/fbiox>.

According to financial analysts, the impact of this has been to change market sentiment and lead to a more conservative market by culture in Europe than in the US.

- Since then, the US market has had a greater level of IPO activity and has created more success stories, building investor confidence. There is a chronic lack of evidence of success in Europe, which leads to further risk averseness and less investment in the market.
- The financial crisis at the end of the 2000s negatively impacted both the amount of capital and investors' confidence in capital markets. The US has experienced a much faster recovery compared to Europe.
- Europe is also a more fragmented market, where countries display very different characteristics. For instance, Germany, in particular, has not recovered since the aftermath of the dot-com boom. Even though existing German tech stocks have grown considerably, there has not been a single biotech IPO on the Frankfurt exchange.

Looking at the valuation of biotechnology companies in recent years in the US versus European markets, the weakness in the European performance is clear. Figure 17 shows the value of the NASDAQ Biotech Index value against Euronext Biotech Index value for the same time period; we note that the US market outperforms the European market in biotechnology stock performance by some margin. This negatively impacts investor confidence, willingness to list in Europe as opposed to the US, and ultimately the IPO feasibility and activity.

Figure 17: NASDAQ Biotech and Euronext Biotech Index value, 2012 - 2015



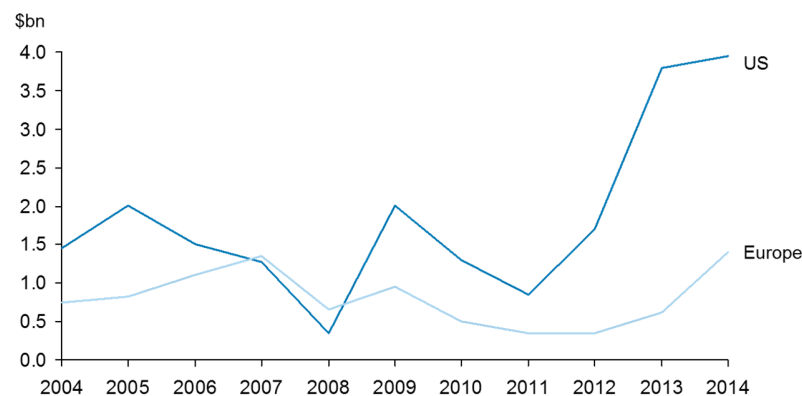
Source: CRA analysis based on index value on Yahoo Finance

If we assess the IPO deals in recent years we find that in the EU there were only 19 deals, valued at €148 million, versus 14 deals, valued at \$852 million, in the US in 2012; and 14 deals,

valued at €119 million, (EU) versus 54 deals, valued at \$8,647 million, (US) in 2013.⁸³ This again illustrates the lack of risk appetite and consequently low valuations that are seen as characteristic of the European markets.

Further evidence of the immaturity of European markets is found by comparing the number of deals in the EU versus the US during the past 10 years. We note that generally, the European market underperforms the US market and that conditions have worsened in recent years. Figure 18 shows that since the dip in 2008 due to the financial crisis, the European market has recovered very slowly, whereas the US market has experienced more severe fluctuations but displays significant improvement in activity since 2011.

Figure 18: Biotech deal volumes in Europe versus the US, 2004 - 2014



Source: CRA analysis based on Dealogic

As indicated by Figure 18, 2014 was marked by high activity in IPO in the life sciences sector. Despite both Europe and the US showing a good market recovery, the US led by some margin in terms of the amount of capital raised. Until November 2014, biotech companies raised \$4 billion in 43 IPOs in the US, against \$1.4 billion raised from 28 IPOs in Europe for the same time frame.

European companies, faced with difficult market conditions and lack of investor confidence in Europe, often opt to list in the US markets. Due to these conditions there have been instances when European biotech companies have opted to list in the US, such as the UK based GW Pharmaceutical. After years of stagnating values on London's Alternative Investment Market (AIM)⁸⁴ the company decided in favour of a dual listing on NASDAQ in 2013, and has since

83 PwC (2014), 'IPO Watch Europe: 2013', available at: <http://www.pwc.co.uk/assets/pdf/ipo-watch-europe-2013.pdf>; PwC (2014), '2013 Annual US Capital Markets Watch', , available at: http://www.pwc.ru/en_RU/ru/capital-markets/publications/assets/us_ipo_watch_2013.pdf. Please note that the US numbers refer to healthcare deals but in the report it is mentioned that that these are almost exclusively biotech for the given years

84 Aim is the international market for companies trading in the London Stock Exchange to give smaller companies the opportunity to raise capital in a regulated market.

experienced an approximately tenfold increase from the initial \$8.90 offer price.^{85,86} This view was largely supported in interviews, but participants acknowledged that there are advantages to listing on domestic markets, such as physical proximity and no cultural and language barriers. Indeed, we should recognise that the last year was more successful in terms of European IPOs. Circassia, an anti-allergy UK based specialist, listed on the London Stock Exchange for £200 million, one of the largest IPOs of the year.⁸⁷

Collaborations with large pharmaceutical companies and licensing

The gap in funding from financial services providers experienced by companies could also be filled by the involvement of big and well established biopharmaceutical companies. The interviewees reported that large biopharmaceutical companies have been playing an increasingly important role in funding R&D undertaken by small companies. This occurs in Europe as well as in the US, but it appears that US companies are more active than those in Europe.

Venture Funding

Some large pharmaceutical companies have set up venture funds to invest in other life science companies.⁸⁸ Interviewed stakeholders expressed interest in obtaining funding from venture capital companies associated within large biopharmaceutical companies. Indeed, there seems to be good opportunity to do so – the top 20 pharmaceutical VC funds have a combined capital of over \$3.5 billion and in 2013 made over 258 investments.⁸⁹ Within the portfolio of the three venture funds (Roche Venture Fund, Novartis Venture Funds, and Novo Ventures) an analysis of active investments in 2013 shows that an overwhelming majority are located in the US (see Figure 19). These three venture funds had a combined number of 99 active investments: 32 in Europe and more than double (67) in the US.

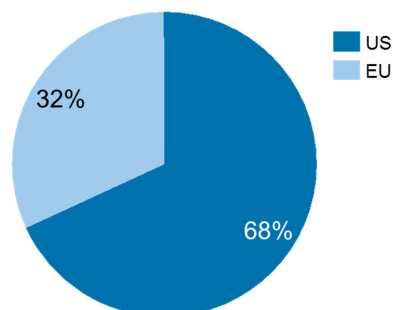
85 Nasdaq (2013), 'GW Pharmaceuticals prices at IPO \$8.90', available at: <http://www.nasdaq.com/article/gw-pharmaceuticals-prices-ipo-at-890-below-expectations-cm242701>.

86 Ward (2014), 'Europe struggles to catch US biotech bulls', Financial Times.

87 Ward and Aglionby (2014), 'Circassia raises £200m in biotech IPO', Financial Times.

88 Timmerman (2011), 'Merck Joins the Big Pharma VC Party Setting Up \$250M Biotech Investment Fund', available at: <http://www.xconomy.com/national/2011/09/15/merck-joins-the-big-pharma-vc-party-setting-up-250m-biotech-investment-fund/>.

89 Genetic Engineering and Biotechnology News (2013), 'Top 20 Corporate Venture Funds', available at: <http://www.genengnews.com/insight-and-intelligence/top-20-corporate-venture-funds/77899832/?page=2>.

Figure 19: Companies with top 3 big pharma venture funding in 2013

Source: CRA analysis of venture funding portfolios

Strategic Alliances

Over the last ten years, large pharmaceutical companies have focused on the development of strategic alliances with smaller pharmaceutical companies.^{90,91} For the big pharmaceutical company, this provides an opportunity to focus efforts and funding on products close to commercialisation. For the smaller biopharmaceutical company, a partnership can provide much 'in kind' or monetary resource.^{92,93}

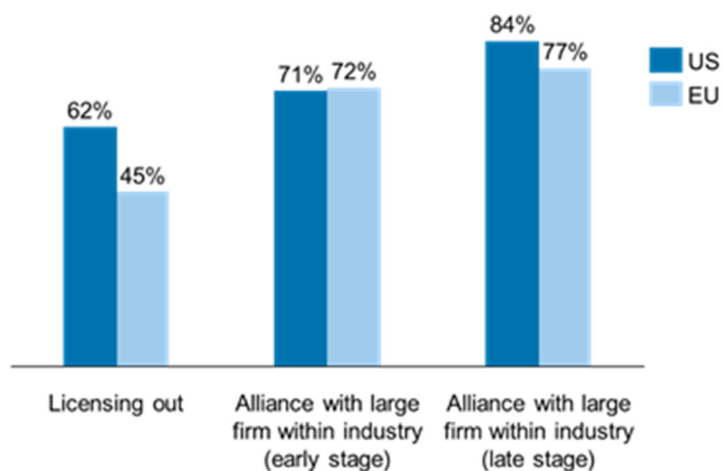
Collaboration or Co-development is where a large biopharmaceutical shares some of the responsibility of drug development and then reaps a share of future rewards.⁹⁴ An analysis comparing alliances for early and late stage product development in 999 US and 1,099 European biopharmaceutical companies, it was observed that the percentage of early stage alliances with large counterparts was comparable between US and European companies.⁹⁵

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- 90 Audretsch, D.B., & Feldman, M.P. (2003) Small-firm strategic research partnership: The case of biotechnology. *Technology Analysis and Strategic Management* 273-288.
- 91 Chang, K. (2008). The strategic alliance of the biotechnology firm. *Applied Economics*, 3089-3100.
- 92 Bytes, B. (2013) 'Pharma Biotech mergers: the potential and the problems', available at: <http://www.oxbridgebiotech.com/review/business-development/pharma-biotech/>
- 93 LaMattina, J. (2014). 'The Symbiotic Relationship of Big Pharma and Biotech', available at: http://www.bilcare.com/insight/white_paper_Symbiotic_Relationship.htm
- 94 For example, the Celgene and MorphoSys collaboration to jointly develop and promote a compound for multiple myeloma undergoing Phase I and II development is an interesting example. Celgene paid MorphoSys €70.8 million up-front for a 50% share of profits. MorphoSys (2013). 'MorphoSys and Celgene Create Strategic Alliance to Advance CD38 Cancer Program MOR202 for Patients with Multiple Myeloma', available at: <http://www.morphosys.com/pressrelease/morphosys-and-celgene-create-strategic-alliance-advance-cd38-cancer-program-mor202-patients-multiple>
- 95 Xia, TJ & Roper, S. (2008) 'Working paper: Worlds apart? A comparison of the NPD strategies of biopharmaceutical firms in Europe and the US'. Warwick Business School.

However, a significantly greater percentage of alliances for late stage development were found in US companies. This is illustrated in Figure 20.

Basic Licence: In this case, large biopharmaceutical companies provide a one-off upfront payment for a compound. This contract could include optional royalties.⁹⁶ The same study by Xia & Roper (2008) found that a larger percentage of US than European firms licence out products (see Figure 20).⁹⁷

Figure 20: Comparison of strategic alliances between the US and Europe



Source: Xia, T. J. and Roper, S. (2008)⁹⁸

There are a number of possible factors that result in stronger collaborations between large biopharmaceutical companies in the US than in the EU. Any investment or strategic alliance decision must make business sense to all parties involved. In particular, the 'big pharma' counterpart must find the collaboration fitting to its current business strategy.⁹⁹ Thus, that there is less collaboration in the EU than in the US may reflect that EU projects are insufficiently attractive to potential partners because of their poor quality and/or misaligned disease focus.¹⁰⁰ Assuming that science in Europe and science in the US are in fact of comparable

96 One example is the recent transaction where Roche purchased licencing rights to compound targeting pseudomonas aeruginosa for an upfront payment of CHF35 million which if commercialised successfully would require a further CHF465 million to Polyphor. Roche (2013), 'Media Release: Roche and Polyphor join efforts to combat multi-drug-resistant bacterial infections', available at: <http://www.roche.com/media/store/releases/med-cor-2013-11-04.htm>

97 Ibid.

98 Ibid.

99 Fischette, C. (2004). 'What does big pharma want from biotech?', available at: http://www.asiabiotech.com/publication/apbn/08/english/preserved-docs/0810/0552_0567.pdf

100 Ibid.

attractiveness, the more complex and fragmented European regulatory processes might discourage big companies from seeing sufficient market potential for creating alliances within Europe. Even when large biopharmaceutical companies are keen to collaborate with EU companies, the poor coordination between the numerous clusters in Europe obstructs knowledge sharing and an effective platform for partners to identify one another.¹⁰¹

Conclusion on hypothesis 3

We find that the European VC market suffers from significant weaknesses in providing private investment for growth activities to the pharmaceutical and biotechnology sector. However, this is a broader problem than the VC market, and there are reasons for concern about private equity, about access to capital markets, and that collaborations with large biopharmaceutical companies appear to be working less effectively in Europe than in the US.

An analysis of the investment landscape shows that problems persist well beyond the early stages of development. We note the following:

- Beyond funding by public sources, research foundations, disease sector charities, and public-private partnerships such as the EU Innovative Medicines Initiative (IMI), funding for preclinical and early stage capital is provided by business angels and individuals including family, friends and the founders themselves, as well as specialist venture capital funds. Funding from business angels is usually small and often invisible (in terms of national statistics) but this investment sector has grown in terms of the number of investors and amount of capital provided. The amount of capital invested by VCs to fund proof of concept and the preclinical and phase I clinical phases has displayed signs of weakness over many years, both in terms of the number of VC firms and the amount invested by them. The European market is characterised by a more risk averse attitude to high risk investments. In particular there is a lack of specialised VC firms in biotechnology and pharmaceuticals. The type of investment also differs: in Europe, VCs appear more likely to fund later phases of development. This is consistent with European VCs focusing on longer-term investment, but it is also symptomatic of the market lacking alternative sources of funding for later stages of development, with the result that exit opportunities for VCs are limited (making their investment in the first place less attractive).
- Indeed, we note that private equity and mutual funds investments, which largely focus on financing late stage development, are weaker in Europe. European companies find it hard to finance activities via these instruments, as private equity firms have not established a strong presence in the market and their exit opportunities are relatively weak in comparison to those in the US. Signs of US dominance are also found in the top mutual funds investors and their holdings. The alternative – to raise risk financing and late stage development capital by going public – is another strategy for both companies and their earlier investors. However, in Europe the market performance of

¹⁰¹ EU FP7 (2012) 'Deliverable 8.6: Report on best practices industry-university models for collaborative management of IP rights in blue technology', available at: http://microb3.eu/sites/default/files/deliverables/MB3_D8_6_PU.pdf

the biotech index has not been very strong, partly due to the failed investments during the market boom and the following stream of failures as well as a very slow recovery from the recent financial crisis. Despite signs of recovery, companies have not been as inclined to list on European markets, and their preferred alternative would almost always be to list on US markets such as NASDAQ, where valuations have been a lot higher in recent years.

- Finally, investments from large international pharmaceutical companies remain an important source of funding whether through partnership, contracting or investment (many companies have set up venture funds for this purpose) from early stage preclinical research to full product development and product commercialisation. Numerous patent expiries have intensified competition between international companies on a global basis to capture the most promising early phase projects through licensing contracts. Again we observe a greater amount of licensing activities and more positive collaboration in the US market than in the European market.

3.5. Hypothesis 4: Public sources are not providing sufficient support for companies at the crucial stages of their development

In addition to the use and availability of private sources of funding for R&D, it is clearly possible that differences in public funding help to explain differences in growth between US and European companies.¹⁰² In order to assess this we have looked at the different sources of funding at national, regional and European level, contrasted this with the US, and drawn on the interviews with different stakeholders.

In Europe, government R&D financing initiatives and programmes are not spread equally across countries and do not have the potential to make a significant contribution to expensive R&D stages

At a national level, the five largest pharmaceutical markets in the EU – namely France, Germany, Italy, Spain and the UK – have in place country programmes and financing support for R&D activities of pharmaceutical and biotech companies. Some of the main initiatives are summarised in Figure 21; these range from approximately €300 million in Spain to over €800 million in Germany, and focus on the following:¹⁰³

- The French National Research Agency provides financing for both basic and applied research across industries and across recipients. Despite this being open to all types of companies, the grants provided are very small scale, ranging from €320,000 to €880,000, and would make a significant impact only to small players.
- In Germany, the Federal Ministry of Education and Research (BMBF) launched the Pharmaceuticals Initiative for Germany in order to give new impetus to Germany's

¹⁰² Cockburn and Henderson (2001), 'Publicly funded science and the productivity of the pharmaceutical industry', National Bureau of Economic Research: Innovation Policy and the Economy 1.

¹⁰³ Please note that this is not an exhaustive list of national programmes of public funding for R&D activities in the pharmaceutical sector but represents some of the most significant activities.

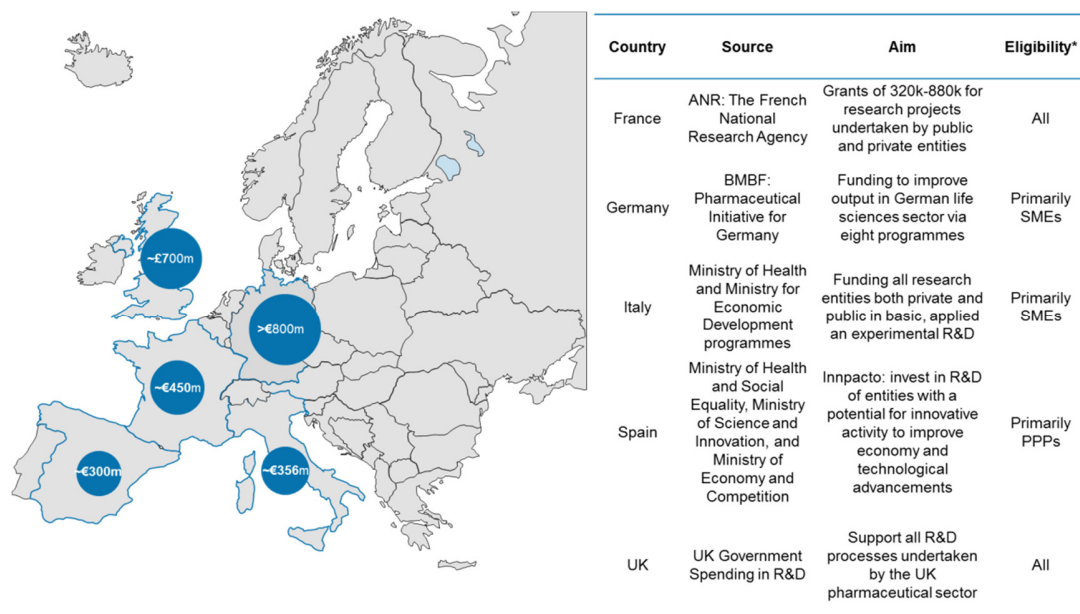
biotechnology and pharmaceuticals industries. Overall funding is over €800 million. It finances projects that range from €10 million to over €350 million¹⁰⁴ across single or multiple companies and institutions. Despite very significant contribution from the government and support for a large range of industry players, the scale of investment is typically too small to help mid-sized and large companies finance later stages of development.

- Italy is an important market for life sciences in Europe, with well-established companies based in the country, but government support in financing the sector is low. Public sources include a National Innovation Fund established by the Ministry for Economic Development, which provides R&D grants of up to €3 million to SMEs,¹⁰⁵ and other Ministry of Health initiatives that provide approximately €350 million in total annual funds.
- Similarly, the Spanish public financing of R&D is limited, with approximately €300 million invested annually across all R&D activities and life sciences companies. These are grants given by the different Ministries and the INNFACTO initiative and are primarily directed to partnership with academic consortia.
- In the UK, the government has progressively increased the funding it provides to UK pharmaceutical businesses. However, at approximately €700 million per year provided as R&D financing across all players in the life sciences sector, the typical funding does not have the potential to make the required impact and positive contribution to the larger players in the industry.

104 This is one of the largest funding schemes encountered at a national level, but the financing is used for a number of research projects across a number of industry players in the National Genome Research Network (research conducted in cardiovascular diseases, cancer, neuronal diseases and infections and inflammations).

105 Fondo per l'innovazione (2012), available at:
http://www.umbriainnovazione.it/portaldato/umbriainnovazionefile/OUI_BIT_03_bandi.pdf.

Figure 21: Public funding for pharmaceutical R&D activities, EU5 countries



Source: CRA analysis based on different sources^{106,107,108,109,110}

Note: * Eligibility here only refers to firm size; SMEs defined as per European Commission classification

These national programmes represent a positive effort by governments and other public organisations to make a contribution toward R&D activities and innovation. However, even though the investments are a considerable amount in aggregate, typically each is too small to fund the later stages of R&D. Indeed, during the discussion, interviewees did not regard national public contributions as representing an important channel for funding R&D.

106 Federal Ministry of Education and Research in Germany, 'The Pharmaceuticals Initiative for Germany', available at: <http://www.bmbf.de/en/10540.php>.

107 National Audit Office (2013), 'Research and Development funding for science and technology in the UK', available at: <http://www.nao.org.uk/wp-content/uploads/2013/07/Research-and-development-funding-for-science-and-technology-in-the-UK1.pdf>.

108 Agence Nationale de la Recherche (2014), '2013 Annual Report', available at: http://www.agence-nationale-recherche.fr/fileadmin/documents/2013/AR_ENG/WebReader.html.

109 El farmacéutico (2011), 'El gobierno invierte 327 millones en un plan sectorial para la industria farmacéutica', available at: http://www.elfarmacéutico.es/noticias/cronicas/el-gobierno-invierte-327-millones-en-un-plan-sectorial-para-la-industria-farmacéutica#.VMqX0_7kdCc; Ministerio de Economía y Competitividad (2014), 'CDTI invierte 72 millones de euros para 141 proyectos de I+D I empresarial', available at: <http://www.idi.mineco.gob.es/portal/site/MICINN/menuitem.edc7f2029a2be27d7010721001432ea0/?vgnnextoid=2fb3ce1c1e17a410VgnVCM1000001d04140aRCRD&vgnnextchannel=4346846085f90210VgnVCM1000001034e20aRCRD>

110 Istat (2012), 'Ricerca e sviluppo in Italia'.

Some regional organisations offer further R&D financing support, but this is largely directed to SMEs

There are a number of regional initiatives – one of the best known being the Vlaams Instituut voor Biotechnologie (VIB) – that offer support to life sciences companies. For instance, VIB is a research institute and cluster in the Flanders region of Belgium working in partnership with four Belgian universities (UGent, KU Leuven, University of Antwerp and Vrije Universiteit Brussel). The institute receives approximately €44 million in funding from the Flemish government (2011) and generates another €32 million by other sources (2011) to invest in VIB administrative costs and R&D activities in spin-off companies and SMEs in the region.¹¹¹

The VIB has co-funded several spin-off companies from the partner universities. VIB activities include not only conducting research and building proprietary platforms but also offering the spin-offs with business and managerial advice and support in attracting national and international investors. The VIB has co-funded together with VC firms a total of nine spin-offs. Another four companies, within the Green Biotech Cluster in Ghent, have been co-funded in cooperation with other non-venture capital.¹¹²

The institute also serves as a platform where university based research cooperates with larger and more established pharmaceutical and biotech companies, such as the collaboration of Oxford BioMedica and VIB research on the further preclinical evaluation of MoNuDin for the treatment of amyotrophic lateral sclerosis (ALS). This collaboration also received further funding of £255,000 from the MND Association.¹¹³

Further, the VIB has supported successful spin-offs, such as the flu vaccines pioneered by researchers at VIB and Ghent University, which were developed by the British-American biotech company Acambis.¹¹⁴ The company together with the vaccine rights were bought by Sanofi-Aventis in 2008.¹¹⁵

The evidence shows that VIB has successfully financed R&D in university spin-offs and other SMEs and supported their collaboration with larger companies, but it does not provide the same beneficial 'cluster' conditions and financing for mid-sized or large biopharmaceutical companies.

111 VIB (2012), 'Finance', available at: <http://www.vib.be/en/about-vib/annual-report/2013/financial/Pages/default.aspx>.

112 VIB (2014), 'VIB start-ups', available at: <http://www.vib.be/en/business-opportunities/spinoffs/Pages/default.aspx>.

113 VIB (2010) 'VIB – KU Leuven and Oxford Biomedica announce collaborative research project for treatment of ALS', available at: <http://www.vib.be/en/news/Pages/Oxford-Biomedica-and-VIB-K.U.Leuven-announce-collaborative-research-project-for-treatment-of-ALS.aspx>.

114 VIB (2007), 'Universal flu vaccine tested successfully on humans', available at: <http://www.vib.be/en/news/Pages/Universal-flu-vaccine-tested-successfully-on-humans-.aspx>.

115 Financial Times (2008), 'Acambis seals Sanofi-Aventis deal', available at: <http://www.ft.com/cms/s/0/f6afc32e-5a79-11dd-bf96-000077b07658.html#axzz3Q6pvZrQS>.

European Commission initiatives

The European Commission has established a number of initiatives in cooperation with different organisations and Member States (MS) to provide support and particularly funding to encourage R&D. The EC-level innovation initiatives were recognised by all stakeholders in the interview programme as a key source of funding for R&D and innovation activities in the region. The Framework Programmes for Research and Technological Development, abbreviated FP1 through FP7 with 'FP8' being named 'Horizon 2020', are funding programmes created by the European Union/European Commission to support and foster research in the European Research Area (ERA). The two most recent programmes are as follows:

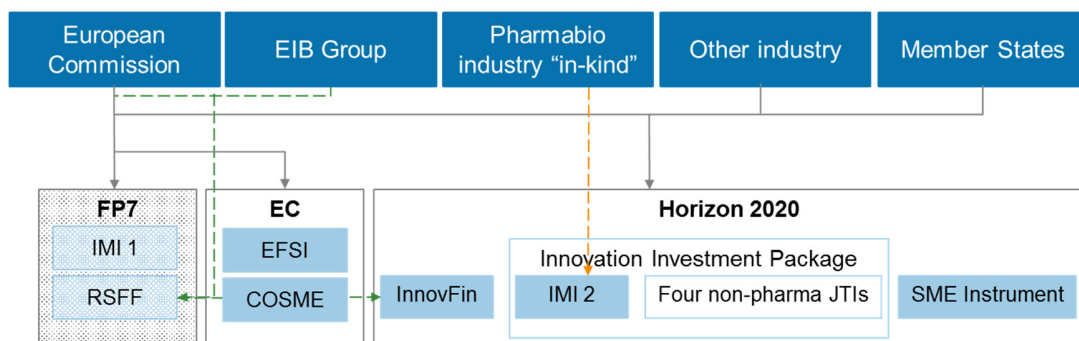
- The *7th Framework Programme for Research and Technological Development (FP7)* ran from 2007 to 2013 in support of research across industries in Europe and was generally funded through instruments and specific targeted research projects. The total contribution of over €50 billion was mainly provided in the form of grants given to different public and private companies, universities and research institutions, other organisations or consortia to co-fund R&D. The majority of the FP7 programmes were implemented under its cooperation block. This provides funding for research activities in transnational consortia of industry and academia in innovation intensive industries such as health, biotech, energy and space.¹¹⁶
- *Horizon 2020* is the eighth and current phase of the EU's Framework Programmes for Research and Technological Development. It is implemented by the European Commission as well as various agencies such as the European Research Council (ERC) Executive Agency or the Executive Agency for Small and Medium-sized Enterprises (EASME) as part of a seven-year programme from 2014 to 2020. The initiative intends to invest approximately €80 billion – a notable increase from its predecessor FP7 – via research partnerships with industries including pharmaceuticals, aerospace, automotive and electronics.¹¹⁷

As mentioned, these initiatives target innovative industries across European countries. However, for the purpose of this analysis, we will focus on programmes and collaborations with particular relevance for the pharmaceutical industry, which are shown in Figure 22 below.

116 European Commission (2007), 'FP7 in Brief', available at: http://ec.europa.eu/research/fp7/pdf/fp7-inbrief_en.pdf.

117 European Commission (2014), 'Horizon 2020', available at: <http://ec.europa.eu/programmes/horizon2020/en/h2020-sections>.

Figure 22: European-level funding initiatives for pharmaceutical companies



	Initiative	Time	Amount (€)	Contribution (€)	Eligibility*
1.	FP7	2007-2013	50 billion	EC	
a.	IMI 1	2007-2013	2 billion	FP7 = 1 billion EFPIA = 1 billion	SMEs
b.	RSFF	2007-2013	11 billion	EC = 1 billion EIB = 10 billion	All
2.	Horizon 2020	2014-2020	80 billion	EC	
a.	SME Instrument	2014-2020	3 billion	Horizon 2020	SMEs
b.	IMI2	2014-2024	3.276 billion	EC = 1.638 billion EFPIA = 1.425 billion Other industry = 213 million	Turnover ≤ €500m
c.	InnovFin	2014-2020	24 billion	Horizon 2020 = 2.7 billion EIB Group = over 21 billion	All
3.	European Commission	2014-2020	Various	EC and partners	
a.	COSME	2014-2020	2.3 billion	European Commission	SMEs
b.	EFSI	2015-2017	21 -> 315 billion	EC = 16 billion EIB = 5 billion	All

Source: CRA analysis based on European Commission sources

Notes: * Eligibility here only refers to firm size; SMEs defined as per European Commission classification; EIB: European Investment Bank; FP7: The 7th Framework Programme for Research and Technological Development; IMI: Innovative Medicines Initiative; RSFF: Risk Sharing Finance Facility; JTI: Joint Technology Initiatives; EFSI: European Fund for Strategic Investments

Within the current research framework programme, a number of specific instruments and initiatives are worth highlighting which are of particular relevance to the biopharmaceutical sector and biotech companies.

- Pharmaceutical specific:** The Innovative Medicines Initiative (IMI), previously under the FP7, is currently implemented as part of the Horizon 2020 framework programme. This represents a European-wide public-private partnership (PPP) between the European Commission and the innovative industry represented by EFPIA and aims to encourage the development of innovative medicines and improve patient access in areas of an unmet

medical or social need. The first phase of the programme (IMI 1) from 2007 to 2013 had a budget of €2 billion. Building on the successes and lessons learnt under IMI 1, the second generation programme (IMI 2) was started in 2014. Currently the largest PPP in life sciences in the world, it has a budget of approximately €3.3 billion for a ten-year period. This programme aims to provide funding and facilitate collaboration between companies and institutions involved in healthcare research, including universities, larger pharmaceutical companies, SMEs, as well as patient organisations and medicines regulators. Companies that apply for funding must join a consortium formed of public research organisations and other non-profit academics institutions, and have no guarantee of getting a grant. Under IMI 1, SMEs (the European definition) could benefit from EU funding in line with IMI funding rates (75% of direct eligible costs linked to research activities + 20% of overhead cost). Since IMI 2, this has been reformed and all companies with up to €500 million turnover can apply for funding. Funding rates are now aligned with Horizon 2020 regulation and are set to fund 100% of direct eligible research costs + 25% overheads or real cost.¹¹⁸ Large pharmaceutical companies (members of EFPIA) serve as funding contributors to the IMI programme and are not recipients of any of its funding. They may be involved in the projects also by making contributions, such as donating their researchers' time or providing access to research facilities or resources.¹¹⁹ So far, 135 SMEs have been involved in IMI's 46 ongoing projects, representing 15% of IMI funding beneficiaries, and these have benefited from 18.4% of IMI's budget under the first 8 Calls.¹²⁰ The majority of these are biotech companies; of the rest, most are IT / data management companies.

- *Cross-industry small scale SME funding:* The SME Instrument is a dedicated fund under Horizon 2020 that supports innovation projects in SMEs. The programme has a €3 billion budget for the period 2014-2020, and offers the SMEs with close-to-market innovations grants of different sizes and purposes, from €50,000 grants for feasibility assessments to grants of €0.5 million to €2.5 million for innovation development and demonstration purposes. It is important to note that these grants are relatively low scale and that the initiative is applicable to SMEs only.¹²¹ Running alongside the SME instrument is the COSME programme for the Competitiveness of Enterprises and Small and Medium-sized Enterprises (SMEs) with a planned budget of €2.3 billion.¹²² The COSME budget will fund guarantees and counter-guarantees for financial intermediaries (e.g. guarantee

118 Proposal for a Council Regulation on the Innovative Medicines Initiative 2 Joint Undertaking

119 Innovative Medicines Initiative official website - information available at: <http://www.imi.europa.eu/content/home>.

120 Innovative Medicines Initiative official website - Small and medium-sized enterprises (SMEs), accessible at: <http://www.imi.europa.eu/content/smes>

121 European Commission (2014), 'Horizon 2020: The SME Instrument', available at: <http://ec.europa.eu/programmes/horizon2020/en/h2020-section/sme-instrument>.

122 European Commission – DG Enterprise & Industry, available at: http://ec.europa.eu/enterprise/initiatives/cosme/index_en.htm

organisations, banks, leasing companies) to help them provide more loan and lease finance to SMEs. This facility will also include securitisation of SME debt finance portfolios.

- *Risk financing in cooperation with the EIB Group:* The European Commission has cooperated with European Investment Bank (EIB) and the European Investment Fund (EIF) to provide a platform for financing to innovative companies. The EIF provides equity financing through financial intermediaries, whereas the EIB provides direct debt financing to companies. We note that while this programme has a broader scope in terms of companies it provides financing to, in terms of size it has budgetary limitations for pharmaceutical and biotechnology companies as the finance resource pool is spread across all industries:
 - Under the FP7, the European Commission and the EIB Group teamed to set up the Risk Sharing Finance Facility (RSFF) and the Risk Sharing Instrument (RSI), which were developed to provide improved access to debt financing to innovative companies on the principle of risk sharing. The initiative deployed €2 billion, equally invested in the programme by the European Commission and EIB Group, in the forms of direct lending to innovative companies of different sizes, lending for capacity extension of financial intermediaries, and investment in other European projects such as the Joint Technology Initiatives (JTIs).¹²³ In the pharmaceutical sector, this initiative funded companies' R&D activities, such as a €30 million loan to PharmaMar to advance trials of Aplidin antitumor drug and a €30 million loan to the MED-Invest consortium (five SMEs) for technology development.¹²⁴
 - InnovFin is the successor of Risk Sharing Instrument (RSI), which was developed under FP7, and is the new generation of financial instruments and advisory services developed by the European Commission under Horizon 2020 to help innovative firms access finance more easily. The total budget of €24 billion will be invested in the seven-year period 2014-2020 via the EIF and the EIB to fund small,

¹²³ European Commission (2008), 'Banking on Research, Banking for Research, Risk-Sharing Finance Facility', available at: http://ec.europa.eu/invest-in-research/pdf/download_en/rssfb_brochure.pdf.

¹²⁴ RSFF (2011), 'Investing in European research and innovation', available at: ftp://ftp.cordis.europa.eu/pub/news/research-eu/docs/focus-10_en.pdf.

medium and large companies that develop innovative technologies. The range of financial products offered includes the following:^{125,126,127}

- Large, medium and mid-cap financing via direct EIB loans of €7.5 million to €300 million as in the EIB-UCB deal presented in Box 1
- Mid-cap growth finance available to all mid-caps and SMEs via direct EIB loans of €7.5 million to €25 million
- Mid-cap guarantees offered by EIB as contingent loans of €7.5 million to €25 million and delivered through financial intermediaries
- SME guarantees and counter-guarantees on debt financing of between €25,000 and €7.5 million offered to small mid-caps and SMEs and implemented by the EIF through financial intermediaries.

The role of InnovFin in funding the mid-cap segment is illustrated in Box1.

- The most recent initiative undertaken by the European Commission and EIB Group emerged from the Investment Plan for Europe devised and announced by the new European Commission Presidency. An integral part of this plan is the establishment of the European Fund for Strategic Investments (EFSI) to encourage growth and revive investment in strategic projects around Europe. Detailed information on the scheme is provided below:^{128,129}
 - *Targeted companies and sectors:* The scheme will focus on some sectors of the European economy including strategic infrastructure, education, research and innovation, environmental sustainability and smaller businesses.
 - *Funds:* The strategic partnership is forecasted to launch by the end of July 2015 and will be established within the existing EIB Group structures.

125 European Commission (2014), 'Horizon 2020: InnovFin – EU Finance for Innovators', available at: <http://ec.europa.eu/programmes/horizon2020/en/news/innovfin-%E2%80%93-eu-finance-innovators-new-financial-instruments-help-innovative-firms-access-finance>.

126 In this programme companies are classified by size as follows: large = over 3,000 employees; large mid-cap = 499 to 3,000 employees; small mid-cap = up to 499 employees.

127 EIB Group firm size categorisation for financing purposes by number of employees: SME = 0-249; Small Mid-Cap = 250-499; Large Mid-Cap = 500-2999; Large = 3000 and more. Information from EIB Group website, available at: http://www.eib.org/attachments/documents/innovfin_mgf_flysheet_en.pdf

128 EIB (2015), 'Investment Plan for Europe', available at: <http://www.eib.org/about/invest-eu/index.htm>.

129 EUR-Lex (2015), 'Communication from the Commission to the European Parliament, the Council, the European Central Bank, the European Economic and Social Committee, the Committee of the regions and the European Investment Bank – An Investment Plan for Europe', available at: <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM:2014:903:FIN>.

Initial investment in the scheme will be €21 billion, which is intended to unlock additional investment of €315 billion over 2015-2017. A contribution of €16 billion comes from the EU budget in the form of a guarantee, and €5 billion is from the EIB's own reserves. Some of this represents a re-purposing of money initially allocated to Horizon 2020.

- *Funding:* The EU guarantee will be backed up by existing EU funds from the existing margins of the EU budget (€2 billion), the Connecting Europe Facility (€3.3 billion) and the Horizon 2020 programme (€2.7 billion).
- *Project selection:* The Task Force set up by the partnership will identify investment projects and inform and monitor progress regularly. The EIB Group will ensure transparency so the EFSI pipeline proceedings will be visible and available to all potential investors including MS, banks, etc. However, there will be no guarantee that all the EFSI pipeline projects will receive additional funding.
- *Focus on SMEs and mid-caps:* In addition to the focus on specific sectors for growth including digital, infrastructure and energy, the EFSI Task Force regarded investment in SMEs and mid-caps key. These companies are still constrained by limited access to finance, as significant early-stage risks discourage private investment even when long-term benefits are large. Out of the initial €21 billion, long-term sector investments will receive €16 billion (to raise €240 billion), while SMEs and mid-caps will receive €5 billion (to raise €75 billion). The expected multiplier effect of 1:15 in real investment is due to the initial risk-bearing capacity.

Box 1: InnovFin funding through the Large Projects instrument: the UCB case

In 2014, InnovFin provided a first of its kind direct risk finance for RDI activities to a 'larger' company, namely to the pharmaceutical company UCB. In this pilot project, the €75 million is provided by EIB funds to finance a selected number of UCB compounds and is structured in the form of a risk sharing agreement. This is phased funding and monitored biannually with payments defined by milestones as follows:

- If UCB missed development milestones, the company is not liable for payment towards EIB, which would lead to a proportion of the debt being written off.
- If a milestone in the development of a compound is reached, UCB provides EIB with a payment.
- Should one of the financed molecules go to commercialisation, payments will be made to EIB.

In principle, this agreement differs from a conventional EIB loan as the ability to repay the debt is based on the assessment of molecules rather than UCB's general credit rating. However, the decision and selection of company is based on criteria that includes:

- Credit: any prior the transaction history between EIB and the company
- Profitability of molecules: assessment of the molecules to finance in terms of the disease area and the potential for a global market reach
- Alignment of interests: primarily in encouraging innovation and performing R&D activities in Europe (this is not tracked by EIB but proof of performance to be provided).

The aim of the scheme is to encourage innovation in Europe, as a pilot project. If it proves successful, similar programmes could be implemented with other companies in the life sciences sector.

The InnovFin large projects instrument is intended to improve the timing of access to finance and to accelerate innovative activities.

Source: CRA analysis from different sources^{130,131}

As a whole, EU public funding for research and innovation has grown considerably over the past decade, and the EU has provided much needed support to SMEs in all innovative sectors (including biotech). Specific instruments and initiatives such as the RSFF or IMI are seen as

130 European Commission (2014), 'A breakthrough operation in the world of finance and research', available at: http://europa.eu/rapid/press-release_BEI-14-137_en.htm?locale=FR.

131 Horizon 2020 Projects (2014), 'EIB and UCB partner to develop new medicines', available at: <http://horizon2020projects.com/sc-health/eib-and-ucb-partner-to-develop-new-medicines/>.

successful, and these programmes have continued to benefit from greater sources of funding. This has helped largely public research organisations and universities but also many SMEs including small biotech companies.¹³² In light of the continued difficulty of companies to access the debt and equity markets to encourage more private investment, the new framework programme (Horizon 2020) has made improved access to finance one of its key priorities especially for SMEs and has also expanded the criteria so that more companies are eligible for funding (including mid-caps and 'larger' companies). However, this involves fewer direct grant funding and more intervention in the forms of risk sharing (for loans and guarantees) and providing risk finance (equity).

Comparison of the role of public funding in Europe and the United States

To compare the European to the US environment, it is useful to look at the main sources of support and what types of activity they are used for. We look first at the National Institutes of Health (NIH) and then at US public funding overall.

The NIH provides substantial contributions to the US industry, but European Commission initiatives play a more important role in the constraints of the European market

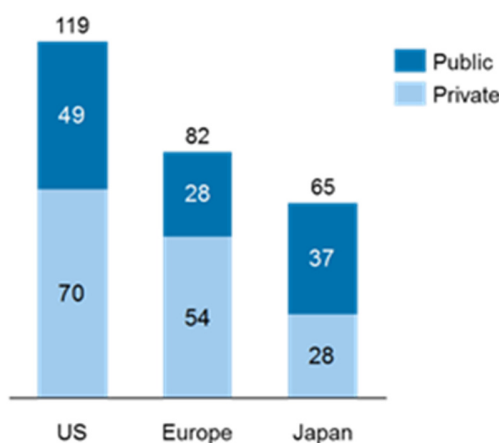
The US government is the world's leading funder of global health research and development. In 2012, the public sector in the US spent up to \$48.9 billion in biomedical R&D representing 40.9% of the total expenditure in biomedical research at a national level. In contrast, Europe's share of public spending on biomedical R&D stood at 34.3% of total spending, with \$28.1 billion of expenditure.¹³³ These figures demonstrate that the US has been significantly more active in funding biomedical research in both absolute and relative terms.¹³⁴

132 For example Apitope, which has received €6 million to develop a therapeutic vaccine for Grave's disease as part of the FP7 programme. Freeman, Z. (2014) 'Discussing European funding and Horizon 2020 in the Commons', accessible at : <http://blog.bioindustry.org/2014/07/17/discussing-european-funding-and-horizon-2020-in-the-commons/>

133 Chakma, J. et al. (2014). 'Asia's ascent – global trends in biomedical R&D expenditures', *New England Journal of Medicine* 370(1): 3-6.

134 Moses III (2015), 'The Anatomy of Medical Research: US and International Comparisons', *The Journal of the American Medical Association* 313 (2).

Figure 23: Biomedical R&D expenditures by the public sector and private industry in the United States, Europe & Japan, \$ billion



Source: Chakma (2014)

Financial support for biomedical in the US is largely driven by three agencies: NIH, United States Agency for International Development (USAID), and the United States Department of Defense (DoD) – which are responsible for US government funding for global health R&D.¹³⁵ According to a report on global health research, the US government has invested more than \$12.7 billion over the past 10 years in developing new vaccines, drugs and diagnostics.¹³⁶

In 2012, NIH funding accounted for \$30.9 billion of the R&D investment in the United States. It is reported that US government funding made some contribution to the development of 48% of all drugs approved by FDA and 65% of drugs that have received priority review between 1988 and 2005.¹³⁷ More than 80% of NIH funding is targeted to extramural research, which involves more than 200,000 scientists and other research personnel affiliated with more than 3,100 organisations nationally and internationally. Most of this funding goes to support long-term investments in fundamental biomedical research but also increasingly supports translational research. Of its budget, 36% was allocated to clinical research.¹³⁸

NIH programs also seek to stimulate and complement private-sector medical research and development. As part of the NIH road map created in 2003, novel partnerships between public and private sectors have been developed to accelerate movement of scientific discoveries by

¹³⁵ Global Health Technologies Coalition (GHTC), Policy Cures (2012) *Saving Lives and Creating Impact: Why Investing in Global Health Research Works* from the Global Health Technologies Coalition (GHTC).

¹³⁶ Global Health Technologies Coalition (GHTC), Policy Cures (2012) *Saving Lives and Creating Impact: Why Investing in Global Health Research Works* from the Global Health Technologies Coalition (GHTC).

¹³⁷ Sampat, B. N., Lichtenberg, F. R., 'What are the respective roles of the public and private sectors in pharmaceutical innovation?' *Health Affairs* (Millwood) 2011, 30(2):332-9.

¹³⁸ Zerhouni, E. A. (2005), 'US biomedical research: basic, translational, and clinical sciences', *JAMA*, 294(11):1352-1358.

way of greater collaboration between public and private research bodies. The National Center for Advancing Translational Sciences (NCATS) was established by NIH in December 2011 to transform the translational science process by encouraging collaborations among government, academia, industry and non-profit patient organisations. Since then, a number public-private partnerships and joint ventures have been created to increase collaborative research:

- NCATS has developed *Discovering New Therapeutic Uses for Existing Molecules*, a collaborative programme with \$20 million to fund cooperative agreement research grants to help re-engineer the research pipeline by pairing public and private researchers with a selection of pharmaceutical industry agents.
- NIH's National Center for Research Resources administers the Clinical and Translational Science Awards, which fund a national consortium of medical research centres that train physicians in the drug development process.
- The *Accelerating Medicines Partnership* is a \$230 million joint venture between the NIH and 10 biopharmaceutical companies to transform the current model for developing new diagnostics and treatments.¹³⁹
- The *Biomarkers Consortium* is a PPP between NIH, FDA and Pharmaceutical Research and Manufacturers of America (PhRMA) to facilitate the discovery, development and validation of biomarkers using new and existing technologies.
- Other collaboration projects have been designed to help accomplish specific government missions. For example, GSK has entered into a potential \$200 million antibiotics pact with the Biomedical Advanced Research and Development Authority (BARDA) to develop drugs to fight antibiotic resistance and bioterrorism.

However, some of these programmes have clear limitations to the level of public funding available to research institutions including companies. For example, NCATS's Clinical and Translational Science Awards, which support a broad range of resources for clinical research including clinical trials, has a maximum annual allowable budget request of 3.0% of the annual NIH funding base of all participating institutions, and the maximum annual allowable budget request cannot exceed \$25.0 million total costs (direct and indirect costs).¹⁴⁰ Additionally there is an authorisation limit which specifies that support for clinical trials through pilot projects and within training programs to trials is only until the end of Phase IIA.¹⁴¹

In addition to NIH, the Department of Health and Human Services' Small Business Innovation Research (SBIR) programme and Small Business Technology Transfer programme provide financial assistance to small companies attempting to advance their initial discoveries to commercial development. Funds are obtained by allocating a certain percentage of the total extramural (R&D) budgets of the 11 federal agencies whose extramural research budgets are

139 National Institutes of Health - Accelerating Medicines Partnership, accessible at: <http://nih.gov/science/amp/index.htm>

140 NCATS - FAQs About CTSA RFA-TR-14-009, accessible at: <http://www.ncats.nih.gov/files/ictsa-webinar-slides.pdf>

141 NCATS About the CTSA Program, accessible at: <http://www.ncats.nih.gov/research/cts/ctsa/about/about.html>

more than \$100 million. Approximately \$2.5 billion is awarded through this programme each year. The DoD is the largest agency in this programme, with approximately \$1 billion in SBIR grants annually.¹⁴² The SBIR programme agencies award monetary contracts and/or grants to companies with no more than 500 employees for projects in phases I and II of a three-phase programme.¹⁴³ As part of Phase III (the stage at which a small business pursues commercialisation objectives), no additional SBIR funding may be awarded and 'the small business must find funding in the private sector or other non-SBIR federal agency funding'.

Similarly, the FDA encourages the use of Cooperative Research and Development Agreements (CRADAs) to foster PPPs in targeted areas of interest to the agency.¹⁴⁴

Initiatives are taking place at the state level as well. The Texas Emerging Technology Fund, for example, is designed specifically to help companies finance proof-of-concept research. The fund invests in biologic sciences and biotechnology as well as engineering, materials science, and information technology, and has committed funding to individual companies ranging from \$500,000 to \$10 million.¹⁴⁵ These programmes look relatively similar to the national programmes found in the EU.

In general, government funding for biomedical research in the US is significant and larger than in the EU. The vast majority of NIH funding supports research conducted in universities and the private sector through the NIH Office of Extramural Research. In FY 2013, roughly 81% of the NIH budget funded extramural research through research grants, research training, and research and development contracts. Since 2003, public funding has increasingly been targeted at PPP between the NIH, FDA and private industry to speed up the search for treatments; however, the level of public research in late stage clinical development and product development remains limited in comparison to the EU.

Is public funding more or less important for European companies?

There has been a great amount of research on the differences and role of public funding for new product development activities in the life sciences across regions, but few studies have directly compared the European to the US environment. One study – on the range of factors that impact new product development in Europe vs the US – raises the issue of government and public funding in general as an important determinant.¹⁴⁶ This study suggests that since the contribution of US government funding has been very generous but less directive than in

142 'Small Business Innovation Research', U.S. Department of Defense.

143 SBIR-Participating Agencies, U.S. Small Business Administration website, accessed 28 November 2014.

144 Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation (2009), Breakthrough Business Models: Drug Development for Rare and Neglected Diseases and Individualized Therapies: Workshop Summary. Washington, DC: National Academies Press (US); 2, Current Model for Financing Drug Development: From Concept Through Approval, available from: <http://www.ncbi.nlm.nih.gov/books/NBK50972/>

145 Ibid.

146 Xia and Roper (2008), 'Worlds apart? A comparison of the NPD strategies of biopharmaceutical firms in Europe and the US', Warwick Business School Small and Medium Sized Enterprise Centre, Working Paper No. 101.

Europe. In general, companies in the EU are more likely to have received funding support from the government, while US companies are funded mainly from private finance sources. The study found that 65.8% of firms in the European sector have received government funding compared to 46.7% in the US. However, the authors point out that the causality of this is difficult to determine. It could be that the lack of private funding alternatives in Europe has led to more government funding initiatives or vice versa. Furthermore, these results do not suggest that the total amount of contribution from the European public sector is more substantial in absolute terms.

Conclusion on hypothesis 4

Comparing public support in the US and Europe is complicated; it is spread across a range of institutions with different eligibility criteria. Many of the schemes require collaboration between private companies, academics and public research institutes, making it difficult to determine the allocation of funding provided to commercial activities. In addition to programmes at the federal level in the US or at the European Commission level, there are national or state level programmes in Europe and US respectively that also need to be taken into account. However, on the basis of the evidence collected and interviews undertaken we conclude the following:

- The overall investment support for life sciences in the US is greater than that in Europe, but Europe is clearly increasing the investment it is making over time.
- Historically, the US has provided most of its support for early stage research but has progressively looked at how it can support translational science, and in some therapy areas has supported later stages of clinical development. It seems likely that the limitation on private funding in Europe has encouraged wider support than is necessary in the US.
- Europe has played a larger role in providing funding directly to companies. In both markets, there is a debate about whether to relax the rules for providing public funds to larger companies and later stages of development.

3.6. Hypothesis 5: The proximity to the US market provides an advantage for US originated companies

The final hypothesis is that although the scientific opportunities are similar in Europe and it would be possible to finance and bring them to commercialisation, SMEs and mid-sized companies that originate in the US have an advantage because of their proximity to the US market. For this reason we are more likely to see the development of mid-sized companies in the US and more likely to see companies with promising assets in Europe be sold or license out their promising assets.

There is wide agreement that although the European market is clearly strategically important, the US market is commercially more attractive due to its overall size (even if its rate of growth has slowed), the speed to market, and the uptake of innovative medicines. Therefore, for a product to be commercially successful it will be important for it to launch in the US. However, this market is potentially available to both US and European originated companies, so for this hypothesis to be valid, it must be the case that accessing the US market is easier for US originated companies. There could be a number of reasons for this:

- It is easier to get FDA approval if the company is located in the US or a greater proportion of late stage development has been undertaken in the US.
- Ensuring market access through efficient contracting and marketing is easier if the company is located and managed in the US.

In reality, the products licensed by the European Medicines Agency (EMA) and FDA are broadly similar, and great efforts have been made to have a similar process on both sides of the Atlantic. There is evidence that the FDA is on average faster than the EMA and this is particularly the case for innovative products.¹⁴⁷ However, we can find no evidence that success at the FDA is affected by whether the company is US or European originated.

During the interviews, we discussed with SMEs and mid-sized European companies the extent to which commercialisation would be easier if they had been located in the US (and the degree to which this influenced either funding or the likelihood they will ultimately be purchased or license out their promising assets to a US company or global pharmaceutical company). There was support that commercialisation in the US is challenging for European SMEs, and this was one of the justifications for licensing. This was less the case for mid-sized European companies that are mature and often have US affiliates. On the other hand, US mid-sized companies can realistically commercialise the product in the US and then look to develop their commercialisation capabilities in Europe over time.

However, it was also argued that although there is an advantage for US SMEs commercialising their products in the US, this advantage has decreased with time. Given the focus on specialist and hospital initiated products, the importance of salesforces has reduced the need for a large US infrastructure if a company wanted to commercialise independently. At the same time, the availability of contract salesforce on both sides of the Atlantic again makes this argument appear less compelling.

If this was the case, we might expect to see European SMEs being taken over by US or international companies but rarely by mid-sized European companies without a US marketing capability. Looking at the small European companies that have left the EU R&D Scoreboard (although admittedly a small sample), this does not appear to be the case.

Post the 2008 economic crisis, the downward pressures on all forms of public funding in the EU has become intense. As a consequence, biopharmaceutical innovators, regardless of their origin or size, have seen more interventions, which delay market entry, reduce reimbursement status, and lower prices for innovative products compared to the pre-crisis era. There was a clear consensus from the interviews that cost containment in the European market has made commercialisation of products far more challenging, and this has reduced the incentive to invest in R&D. It is not clear that this is a significant disadvantage for European micro companies and SMEs compared to US companies. However, mid-sized companies have traditionally been able to fund R&D largely out of profits, derived to a greater extent from the European market. A combination of intense generic competition and the cost containment pressures are placing

¹⁴⁷ 'Approval rating: how do the EMA and FDA compare?' an article by Marc Beishon adapted from R. R. Shah, S. A. Roberts and D. R. Shah (2013), *Br J Clin Pharmacol* 76:369–411 'Time to approval (days) for tks in the EU and US'.

this business model under threat. As many older products have been displaced by cheaper generic products and returns for newer product diminished due to health system cost containment, this industry segment has seen little growth in its home EU markets. Some have been able to compensate by extending sales outside the EU and sustain profitability through internal cost-saving efficiencies to partially offset weakening revenues. However, overall this situation is eroding their capacity to sustain R&D investment, and they are seeking alternative sources of investment for key projects of high potential.

Conclusion on hypothesis 5

We therefore conclude that proximity to the US market advantages US SMEs and acts as a barrier to growth in Europe, but this appears less important than access to finance. This does not mean that the market opportunity in Europe is not affecting R&D. There was a clear consensus from the interviews that cost containment in the European market has made commercialisation of products more challenging and this has reduced the incentive to invest in R&D. It is not clear that this is a significant disadvantage for European companies compared to US companies. However, the significant cost containment over the last five years has had a proportionally larger impact on European mid-sized companies, reducing the revenues that historically they would have used to finance R&D, and diminishing their ability to invest in R&D unless they use other sources of finance.

4. The case for further intervention

In the preceding chapters we have set out the evidence of a growth problem in the European market and discussed the potential barriers that are the underlying cause. In this chapter we consider the economic case for further policy intervention and particularly the case for providing greater public support to mid-sized R&D companies for the cost of developing medicines.

4.1. Evidence of market failure¹⁴⁸

That the structure of the US industry differs from that of the EU industry and the pattern of funding differs between the US and the Europe are interesting observations, but funding gaps are not in themselves a cause for policy intervention. That requires evidence of market failure.

If markets are working, the providers of capital (venture capital funds, private equity, financial markets, banks and larger pharmaceutical companies) balance the risk and return from investing; and where investments offer a commercial return, funding will be made available (and, equally, where the investment is judged too risky for the potential return, funding will not). However, it is recognised that financing high risk investments can suffer from market failures – where the returns outweigh the potential risks, but nevertheless it is impossible to find external funding. Indeed, as set out by the Commission: *‘Identified funding gaps have been interpreted as a ‘market failure’. However, it is very difficult to say whether the companies that are trying to raise capital actually ‘deserve’ more capital or if they are simply not able to present projects that are worth investing in. In this perspective, the market is working to its perfection’.*¹⁴⁹

There is an existing consensus that funding for SME suffers from market failure. This was the rationale for SME funding in the 7th Framework Programme for Research and Technological Development (FP7) and the European Investment Bank and the Commission’s RSFF. The market failures associated to funding R&D fall into a number of categories:^{150,151}

148 In this section we focus on types of R&D and types of company. Equally the case for supporting research and development of particular types of product is already made. For products for which there is no commercial opportunity, but society would value their development. For example, antibiotics or medicines for rare diseases: there is an economic argument for investment of public money (although there are clearly other, and potentially preferable, solutions to this problem).

149 ‘The financing of biopharmaceutical product development in Europe’, The Framework Contract of Sectoral Competitiveness Studies – ENTR/06/054 Final report.

150 We are not concerned here with fundamental research. There is an academic and institutional consensus that this represents a clear market failure. As this research often develops new ideas or thinking that are not directly patentable, these represent a public good. This is often described as ‘Inappropriability’ of the profit stream from research, leading to a divergence between public and private returns on investment. Without investment from governments there would be too little investment in research. This is the justification for much of the investment by NIH in the US and DG Research in Europe. This research primarily takes place in academic institutions. Czarnitzki and Hottenrott, ‘Financing Constraints for Industrial Innovation: What do we know?’, Expert Group on Impact of R&D Tax Incentives, DG Research, European Commission.

151 ‘SME Access to External Finance’ BIS Economics Paper No. 16, January 2012.

- Imperfect or asymmetric information: There is an asymmetry of information between the lender and the business. These companies understand much better than potential lenders the nature of the risk associated to the investments they are undertaking, and it is difficult for the lender to distinguish between high and low risk entrepreneurs without incurring significant costs. This asymmetry of information means that it will be difficult for companies to find funding by borrowing from banks or raising money on capital markets.¹⁵²
- There is an undersupply of finance to young high-growth potential businesses due to the divergence of private and social benefits from investing in these businesses. This is because investing in early stage innovative businesses can lead to a number of positive spillover effects through innovation and knowledge transfers to other parts of the economy, which private investors do not take into account when making decisions to invest in venture capital.
- Some papers argue that early stage SMEs may have insufficient information regarding the different sources of funding (although most markets would solve this problem through lenders and investors marketing their services).

There is agreement that smaller firms are more likely to face financing constraints, as they usually cannot provide as much overall collateral value compared to larger, more capital intensive firms. Problems of asymmetric information are more severe for younger firms that have not established long and stable relationships with their banks. Without intervention, SMEs that lack track record would find it difficult to raise debt or equity finance, even though this would be socially beneficial. It is usually assumed that larger companies do not suffer from the same problems, as they have track records, have collateral, and are building on previous innovation (and may therefore be considered less risky).

Turning to mid-sized companies in the biopharmaceutical sector, who would typically be involved in the later stage of product development of medicines (although many are still involved in early stages), there are clearly some arguments that do not apply. These firms should be aware of the different funding options in the market. However, there are clearly a number of arguments suggesting that the market failures that apply to SMEs (in the biopharmaceutical industry and in other industries) continue to apply to these larger, mid-sized, biopharmaceutical companies:

- Pharmaceutical companies' portfolios are made up of numerous projects, each with a defined lifespan. It is common for products to fail; and even when they succeed, after a period of time the company will invest in a new set of projects potentially in different

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For example, Commission established a new framework for state aid for research and development and innovation. The state aid promotes risk capital investments in young innovative enterprises in their first years of existence to help them overcome initial cash shortages. The new guidelines also include a light assessment procedure with a number of elements such as a higher investment threshold of €1.5m per SME over a 12- month period. Below this ceiling the Commission accepts that a market failure is assumed to exist (European Commission 2007).

therapeutic areas. Given the pressures on companies to develop novel treatments, it is much less the case that established firms can innovate by building on their previous innovations. The move from a chemical to a bio innovation mode has exacerbated the difficulty of building on past innovations. This suggests the asymmetry of information may persist as companies get bigger.

- Although spillovers are associated with early stage research, the social benefits are due to information spillovers between companies. This is the justification for investing in clusters. The importance of locating within clusters is clearly important for SMEs, but it has a growing importance for mid-sized pharmaceutical companies, as illustrated by their increasing location near to scientific clusters.
- Established firms are able to use sales turnover or revenue to fund R&D, overcoming any problem associated with asymmetric information. However, with significant cost containment, the revenues to pay for research are significantly reduced. The fact that mid-sized companies have in the past funded R&D from revenues also means that a relationship between mid-sized companies and potential investors is unlikely to exist.
- There is research that suggests the existence of asymmetrical information has more to do with the type of R&D than the size of the company. It distinguishes between firms that are doing routine R&D to strengthen their established product lines and firms investing in more fundamental R&D projects aiming at more radical market innovations. According to this distinction, the former firms are less likely to face financial constraints on their activities than the latter firms.
- High-tech industries are a special case. Investment in innovative industries compared to other types of investments is characterized by a high degree of asymmetric information between the parties involved. Complexity and specificity of innovation projects make it difficult for outsiders to judge their potential value. Moreover, firms may be reluctant to reveal details of the projects to potential investors for competition reasons.

There is therefore an economic argument that the market failures typically associated with financing of SMEs applies to significantly larger companies – mid-sized companies – in the biopharmaceutical market. In the same way that the fragmentation of the VC industry exacerbates the problem for SMEs, the weaknesses in other forms of funding, more relevant for later stages in the product development process, are a potential problem for larger companies.

Looking to the academic literature, this would seem a controversial conclusion. However, referring to recent European Commission decisions, it would appear to be consistent, to a degree, with the direction of current policy, and its rationale. As set out in the introduction of the new Investment Plan for Europe, there is a need to support risk finance for SMEs and for mid-cap companies (defined as companies with up to 3,000 employees), to help them overcome capital shortages. According to the Task Force that the EC set up, SMEs and mid-cap companies are constrained by limited access to finance, as significant early stage risks discourage private investment even when long-term benefits are large. Thus, too little is spent on innovative SMEs and mid-caps leading to a strong economic case for targeted public

intervention.¹⁵³ The Investment Plan for Europe aims to overcome the current market failures in SMEs and mid-caps by ¹⁵⁴

- **Addressing market gaps:** 'by taking on some of the risk, we can help increase promoters' appetite to invest. The EIB will provide loans and will in turn be covered by the EU budget guarantee'.
- **Mobilising private investment** 'and other relevant public funding. As there is abundant liquidity in the market, sound projects will be able to attract funding from private investors'.

Additionally, if we consider the recent changes to the rules on State Aid, they also suggest a recognition that the market failures typically associated to financing of SMEs are more widely applicable. The new guidelines conclude the following:¹⁵⁵

- Small midcaps: 'Extending the scope of eligible undertakings under a risk finance measure to include small mid-caps may be justified in so far as it provides an incentive to private investors to invest in a more diversified portfolio with enhanced entry and exit possibilities'.
- Innovative midcaps: 'Mid-caps, in certain circumstances, could also face financing constraints comparable to those affecting SMEs. Such may be the case for mid-caps carrying out R&D and innovation activities alongside initial investment in production facilities, including market replication, and whose track record does not enable potential investors to make relevant assumptions as regards the future market prospects of the results of such activities'.

Although this is directionally similar to our conclusions, the definition of eligible mid-caps continues to focus primarily on the number of employees. As we have shown, there is a weak relationship between the level of direct employment and the investment in R&D. Companies with similar levels of employment, adopting different business models, can have very different levels of turnover and investment in R&D, and face very different challenges funding R&D. This suggests that the definitions of SMEs and mid-caps based on employment are arbitrary and often inconsistent with the structure of the pharmaceutical industry.

As set out in the report, the shortcomings in the growth of the European pharmaceutical industry go beyond SMEs and include companies investing up to €1 billion on R&D and with turnover up to €4 billion. The weaknesses in the funding of European companies go well beyond the deficiencies in the European venture capital industry and the earliest stages of product development. We have set out how the performance of private equity, mutual funds,

153 European Commission (2015), 'Special Task Force (Member States, Commission, EIB) on investment in the EU', available at: http://ec.europa.eu/priorities/jobs-growth-investment/plan/docs/special-task-force-report-on-investment-in-the-eu_en.pdf.

154 EIB (2015), 'Investment Plan for Europe', available at: <http://www.eib.org/about/invest-eu/index.htm>.

155 European Commission (2014), 'Guidelines on State aid to promote risk finance investments'.

access to financial markets, and the links between international pharmaceutical companies and smaller companies are weaker in Europe. Indeed, the weak alternative sources of funding for later stages of development reduce the exit options for venture capitalists, exacerbating the lack of funding of early stages of development.

Given the changing portfolio of products and technologies, the asymmetry of information is likely to apply beyond SMEs to mid-sized companies as well, making turnover to fund investment particularly important. This has created two types of problems affecting European growth:

- **Established mid-sized companies:** These companies usually have a long history of achievements as innovators in the biopharmaceutical sector. For the most part, because of the scope and scale of their businesses they have been able to fund complete late stage international development and commercialisation programmes for new medicines, albeit often within limited product portfolios. Over many decades they have achieved slow but steady growth by developing and commercialising valuable new medicines. They have upgraded their clinical and scientific R&D functions and manufacturing capabilities to remain internationally competitive, adopting the new bioscience based approach to innovation. In the broader context of the trend for much research to be undertaken by university-linked micro and SME companies, they have been contributors to, rather than recipients of, joint public research funding schemes, such as the IMI. Now, however, there is a risk of them being unable to sustain growth through innovation, because of a combination of technological advances and changes in market circumstances – most notably, within the EU, resulting from six years of intense cost containment affecting European revenues (to which they are particularly exposed). Rather than investment in R&D being funded through external finance, there is considerable risk that R&D will be reduced and the appetite for risk diminished.
- **A lack of companies growing from SMEs to mid-sized companies:** We concur with the findings of previous studies that in comparison with the more dynamic US based micro and SMEs, Europe continues to show a much more limited development of successful companies. Insofar that some EU companies do have products that progress to the later phases of development, European companies are more likely to either sell or license their accumulated stock of intellectual property (patents and confidential 'know-how') to larger established biopharmaceutical companies. Our analysis shows that in sharp contrast to the US, it is rare to find examples of EU SME companies that evolve by an 'organic growth' route – through a combination of VC, dedicated biotech investment funds, or stage payment/option contracts with large biopharmaceutical companies – to engage in mid-to-late stage development activities. This issue is undoubtedly in part due to the weaknesses in the European venture capital industry, but it goes beyond this. Critically, it constrains continuing independent investment in the product life cycle at the point at which it is necessary to make a big step up in the investment commitment to enter a compound into a full development programme, involving international phase III clinical trials, the preparation of product license applications and investments in manufacturing capabilities. The difference between the US and European markets is starkly illustrated by the ability of the emerging US mid-sized companies to finance growing investment in phase III trials, with very high levels of R&D intensity and accumulating year-on-year losses for many years. This ability is

unusual in the corresponding category of European based biopharmaceutical companies.

The European Commission criteria that determine eligibility for public support for innovative investment have become more flexible (now including companies larger than SMEs and noting the importance of R&D intensity) but still appear too narrowly focused on companies with a given number of employees, rather than targeted to the challenges facing the European based pharmaceutical industry.

4.2. The costs and benefits of intervention

A high level assessment of the costs and benefits of increasing the flexibility of public support for later stage development projects for mid-sized companies is warranted:

- **Advantages for the European biopharmaceutical sector:** Public investment offers a different form of financing, allowing companies to use this as part of the financing package; the support of public investment acts as a certificate and improves access to other forms of finance.
- **Disadvantages for the European biopharmaceutical sector:** Although risk financing can be structured through loans that would be paid off with a return upon commercialisation of the product, it can be perceived as the public sector sharing the risk of product development. There is a chance that any public loan will displace private capital; if the loans are too attractive, this could lead to over-investment in some forms of high risk R&D in Europe, with a corresponding low return to society. Inevitably, investments by public organisations will have constraints – for example, regarding the location of activity, which might reduce the efficiency of the R&D process overall.

At the highest level, EU Commission policy looking towards 2020 will be determined by the need to restore economic growth by promoting and supporting industrial innovation, which inter alia will create high value and skilled employment and will restore tax revenues. The latest initiatives by the Commission and the European Investment Bank to strengthen innovation funding for mid-cap companies could if introduced effectively and in a timely manner make an important contribution to achieving this objective, but they need to take into account the challenges facing companies of different sizes and with different business models.

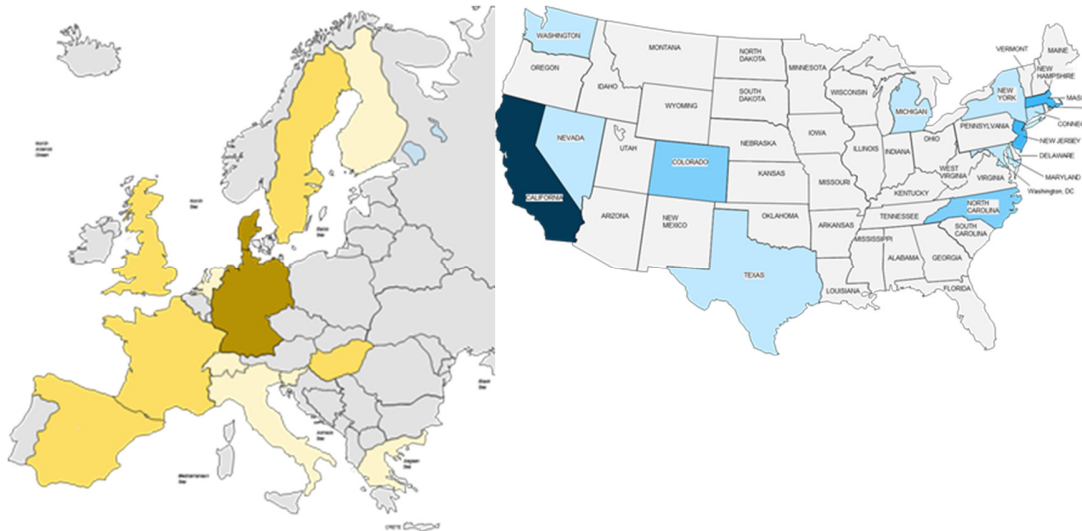
Appendix: Comparing the paths of European and US companies

To compare the evolution of European and US R&D based companies we have analysed companies from 2010 and examined whether these companies continue to invest a similar level of R&D, have been taken over by other companies, have ceased to exist, or have grown so that they are included in a different category of company.

Comparing European to US companies investing between €30 and €100 million

There were 27 companies in Europe compared to 38 companies in the US. In terms of location, the European firms are in the recognised bio-hubs and the US companies are predominantly in California.

Figure 24: Location of small mid-cap companies (€30-99 million)



Notes: light yellow = 1 company, medium yellow = 2 companies, gold = 3 companies; light blue = 1 company, medium blue = 2-4 companies; dark blue = 9 companies

Looking at what happened to these companies:

- Out of 27 European companies investing €30 to 99 million per year in 2010, 22 remain. The other 5 either were acquired by a larger pharma company (Dako, Crucell, NeuroSearch), merged with another biopharma (Intercell), or ceased to exist because of clinical trial failures (Antisoma). Four of the companies (Qiagen, Almirall, Krka and Orion Oyj) invested over \$99 million.
- Out of 38 US companies that invested €30-99 million in R&D, 9 (24%) merged or were acquired by another company.

Comparing European to US companies investing between €100 and €999 million

There were 13 such companies in Europe compared to 23 in the US. In terms of location, similarly to the small category, the European firms are in the recognised bio-hubs and the US companies predominantly in California.

Figure 25: Location of large mid-cap companies (€100-999 million)



Notes: light yellow = 1 company, medium yellow = 2 companies, gold = 3 companies; light blue = 1 company, medium blue = 2-4 companies; dark blue = 9 companies

Looking at what happened to these companies:

- Out of 13 European companies that invested €100-999 million in R&D in 2010, 10 (76%) existed in 2013.
- Out of 23 US companies investing €100-999 million in R&D in 2010, only 16 (69.5%) existed in 2013.

More general observations

- All of the US companies are publicly listed, whereas 4 of the European companies were public.
- The US small R&D companies were much more likely to sustain losses. Indeed, 66% (18) of 27 US small R&D companies sustained losses each of the four years (2010-2013). In the EU, only 9% (2) of the 22 companies sustained losses each of the four years (2010-2013).