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European Federation of Pharmaceutical  
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# Factors affecting the location of biopharmaceutical investments and implications for European policy priorities

## Final Report

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## Table of contents

Abbreviations .....	i
Executive summary .....	1
<b>1. Introduction .....</b>	<b>5</b>
1.1. Background .....	5
1.2. Methodology .....	7
1.2.1. Literature review .....	7
1.2.2. Data analysis .....	8
1.2.3. Interview programme .....	9
1.3. Structure of this report .....	9
<b>2. Trends in investment in R&amp;D, clinical trials, and different types of manufacturing .....</b>	<b>10</b>
2.1. Trends in R&D expenditure .....	10
2.2. The location of clinical trials .....	15
2.3. The location of investigational and commercial manufacturing .....	19
2.4. Foreign direct investment and exports .....	22
2.5. Summary .....	24
<b>3. Factors driving the location of biopharmaceutical R&amp;D and investigational and commercial manufacturing .....</b>	<b>26</b>
3.1. Research hubs .....	26
3.2. Clinical trials .....	31
3.3. Investigational and commercial manufacturing sites .....	38
3.4. Summary .....	49
<b>4. Attracting greater biopharmaceutical inward investment in Europe .....</b>	<b>52</b>
4.1. Addressing Europe's relative decline in attractiveness as a centre for biopharmaceutical investment .....	53
4.2. Responding to the impact of new therapeutic solutions on dynamics and location of investment, using ATMPs and digital technologies as examples .....	60
4.3. Learning from COVID-19 and managing risk and the external environment .....	69
Appendix .....	74

## Table of figures

Figure 1: Pharmaceutical companies' R&D expenditure is growing in all major markets, but fastest in the US and China.....	12
Figure 2: The US and China represent a growing share of biopharmaceutical R&D investments made in major markets.....	13
Figure 3: Pharmaceutical R&D employment has grown at a much faster rate in China than in other major markets.....	14
Figure 4: US continues to outcompete Europe, China and Japan as the most attractive location for industry-sponsored clinical trials*.....	16
Figure 5: The location of Advanced Therapy Medicinal Products (ATMP) clinical trials differ from the overall geographic pattern of biopharma clinical trial activity.....	18
Figure 6: Relative growth in pharmaceutical manufacturing (including APIs and generics) is greatest in China.....	21
Figure 7: The number of facilities capable of producing ATMPs is highest in the US.....	22
Figure 8: Europe as a region still attracts more pharmaceutical greenfield FDI projects than the US or China.....	23
Figure 9: Europe has retained its position as the biggest exporter of pharmaceuticals compared to the US, China and Japan over the last decade.....	24
Figure 10: The US and China are the top performers in more investment performance metrics than Europe, exhibiting stronger growth trends.....	25
Figure 11: The majority of large multinational pharmaceutical companies now have an R&D centre in China.....	29
Figure 12: There has been strong growth in the number of clinical trials employing digital technologies or virtual interactions.....	35
Figure 13: The location of clinical trial sites and commercial sales of first cell therapies are similar.....	38
Figure 14: The decision of where to locate manufacturing activities depends on which type of activity is being undertaken.....	40
Figure 15: Summary of factors driving the location of biopharmaceutical investments.....	51
Figure 16: NIH spending per capita is greater in the strongest US bioclusters.....	54
Figure 17: Horizon 2020 research spending in Europe is not concentrated in Member States with high R&D activity.....	55
Figure 18: Individual European clusters are outcompeted by those in the US based on presence of major biopharmaceutical companies.....	56
Figure 19: There is a degree of interconnectivity in the value chain for ATMPs, between research, clinical development and manufacturing.....	61
Figure 20: Europe's strongest biopharma R&D centres do not rank highly on digital competitiveness.....	68

## Table of tables

Table 1: Guidance regarding regulatory requirements for local clinical trial evidence appears to be relatively uniform .....	32
Table 2: Global pharmaceutical companies typically conduct R&D across a range of major markets, including their headquarter location.....	58
Table 3: Kearney FDI Confidence Index rankings show investors remain most confident in the US market.....	74
Table 4: Sixteen biopharmaceutical investment case studies were reviewed during the interview programme .....	75

## Abbreviations

AMR	antimicrobial resistance
API	active pharmaceutical ingredient
ATMP	advanced therapy medicinal product
CAGR	compound annual growth rate
CDMO	contract development and manufacturing organisation
CH	Switzerland
CHMP	Committee for Medicinal Products for Human Use
CMC	chemistry, manufacturing and controls
CMO	contract manufacturing organisation
CRO	contract research organisation
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FDI	foreign direct investment
HTA	health technology assessment
IMP	investigational medicinal product
IP	intellectual property
NGO	non-governmental organisation
NIH	National Institutes of Health
R&D	research and development
RWE	real-world evidence
UK	United Kingdom
US	United States
WHO	World Health Organization

## Executive summary

The European Federation of Pharmaceutical Industries and Associations ('EFPIA') asked Charles River Associates to research the factors affecting the location of biopharmaceutical investments in Europe relative to other global regions (with a particular focus on the United States (US), Japan, China):

- Distinguishing between investment drivers and patterns in the location of research hubs, clinical trial sites, investigational manufacturing and commercial manufacturing
- Accounting for the impact of evolving technologies and the implications of these for industry's investments
- Relating theory to real-life, recent investment decisions

This was achieved through a literature review at global, regional and national levels focused on trends but also the impact of the recent COVID-19 pandemic; a long-term analysis of investment data patterns; and an interview programme with senior executives from 15 pharmaceutical companies focused on actual recent major investment decisions.

### Box 1: Summary of key findings

- Twenty years ago, the amount of investment made by pharmaceutical companies in R&D in the US and Europe differed by only €2 billion; in 2020, the difference had increased to almost €25 billion, with Europe increasingly lagging behind.
- China is emerging as an increasingly competitive region for companies to locate their activities; this is evidenced through the establishment of regional research hubs, increased clinical trial activity, and rapid growth in manufacturing capacity.
- Areas of weakness in Europe's competitiveness include a siloed approach to policymaking and missed opportunities with new therapeutic solutions, such as Advanced Therapy Medicinal Products and the digital transformation.
- The revision of the EU pharmaceutical legislation currently falls short of protecting and future-proofing Europe's life science sector.
- In this report we identify seven new areas of policy focus to help Europe reverse its relative decline in attractiveness and keep up with the impact of new therapeutic solutions and risks presented by the evolving geopolitical environment.

### *Europe's relative decline in attractiveness as a centre for biopharmaceutical investment*

Pharmaceutical research and development (R&D) expenditure in the US in 2020 exceeded that in Europe by over €20 billion. This gap is widening: twenty years ago, in 2002, the difference was only €2 billion. China exhibits much stronger growth: between 2010 and

2020, private R&D expenditure in China grew by 540%.<sup>1</sup> The establishment of regional research hubs in China is likely not occurring in a material way at the expense of investment in Europe; however, from a European Union (EU) perspective, it is notable that the choice of greenfield regional research hubs in Europe, for example by non-European companies, is focused primarily on markets such as Switzerland and the United Kingdom (UK). This drives our first main recommendation:

- 1. Incentivise the development of truly world-class innovation hubs.** The leading research centres (Boston and San Francisco in the US), in addition to having proximity to world-class academic institutions, also receive considerable policy and funding focus. California, New York and Massachusetts rank as the states receiving the most funding from the National Institutes of Health.<sup>2</sup> Research spending in Europe is significantly more uniform, and the countries with the highest spending per population are not the centres of innovation. For example, the European Commission should consider more strategic allocation of resources to foster growth of world-leading research centres.

Another growing source of pharmaceutical innovation continues to be early-stage, emerging companies. The share of European-headquartered emerging biopharma companies has been declining over the last 10 years, with the US dominating in terms of number of companies and their contribution to the global pipeline, and China growing rapidly at a rate of 456% between 2016 and 2021.<sup>3</sup> Our second main recommendation is:

- 2. Enhance end-to-end capabilities and funding of disruptive pharma innovation.** This has a spillover effect: a critical driver of most new investments is the location and performance of existing R&D or manufacturing footprints. As emerging US- and China-headquartered companies continue to grow into medium- and large-sized enterprises, it is likely that they will invest in Europe, but their investments will be more heavily directed towards the US and China than to Europe (i.e. close to their home base). Although positive trends can be observed in some Member States in supporting the growth of companies, there could be benefit from adopting a more pan-EU policy and funding strategy to accelerate these efforts.

#### *The impact of new technologies on dynamics and location of investment*

The changing nature of science and healthcare needs to be taken into account to fully understand recent global trends in pharmaceutical industry investment. In this report we focus, based on feedback from our interviews, on Advanced Therapy Medicinal Products (ATMPs) and on the digital transformation in life sciences as example of new therapeutic solutions. While Europe produces more scientific publications on ATMPs than any other

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1 See Figure 1 of this report.

2 NIH Awards by Location & Organization. Available at: <https://report.nih.gov/award/index.cfm#tab1> [Accessed October 2022]

3 IQVIA Institute for Human Data Science (2022) Available at: <https://www.iqvia.com/insights/the-iqvia-institute/reports/emerging-biopharma-contribution-to-innovation> [Accessed July 2022]

region,<sup>4</sup> the clinical trial activity is twice as high in the US and almost three times as high in China.<sup>5</sup> Around half of the world's ATMP manufacturing facilities are in the US.<sup>5</sup> A general weakness in Europe for pharmaceutical innovation is in the translation of scientific concepts into commercial products; this has particular ramifications for ATMPs. Our research has led to two main recommendations:

3. **Rethink policies along the supply chain to attract ATMP investment in Europe.** Given the complexity of the technology and the precision involved, the ATMP value chain is more interconnected than for small molecules and biologics. Attracting early research that is then translated into therapies that can reach patients requires an innovation-oriented access environment, not just an academic ecosystem with strong centres of excellence. For ATMPs, this access environment, in which companies can be sure to achieve an appropriate return on investment, then also acts as a magnet for attracting manufacturing activities, because for ATMPs “the process is the product”. The old approach of siloed policymaking focused on innovation, manufacturing and healthcare sustainability does not work.
4. **Support innovation by implementing early access mechanisms, including generation and use of real-world evidence.** Given the challenges with evidence development, ATMPs for instance are more likely to launch with limited Phase II/III data and subsequently generate real-world evidence (RWE). Europe needs to create an environment that is more conducive to ATMP development, by supporting generation and use of RWE and acceptance of RWE by payers and health technology assessment (HTA) bodies through appropriate pricing and market access routes.

Digital transformation in life sciences is also increasingly impacting all pharmaceutical business functions, health systems, and all aspects of the pharmaceutical value chain. Pharmaceutical companies increasingly look towards countries where there is a supportive digital ecosystem. Currently the US is far ahead of Europe in terms of digital infrastructure, interconnectedness and interoperability. Thus we recommend the following:

5. **Boost EU digital transformation and support development of digital capabilities.** To enable digitalisation, for example through automation of value chains or virtual clinical trials, pharmaceutical companies are being drawn towards locations with a workforce that is well-versed in digital technology and where the broader ecosystem is digital-ready. The EU's top-ranking biopharma clusters, however, rank poorly on digital competitiveness.<sup>6</sup> Europe could take a more proactive role in upskilling the scientific workforce in digital technologies and accelerating the digitalisation of health systems.

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4 Loche, A. et al. (2021) A call to action: Opportunities and challenges for CGTs in Europe. Available at: <https://www.mckinsey.com/industries/life-sciences/our-insights/a-call-to-action-opportunities-and-challenges-for-cgts-in-Europe> [Accessed June 2022]

5 CRA analysis of data retrieved in July 2022 from GlobalData.com

6 IMD World Digital Competitiveness Centre (2022) World Digital Competitiveness Ranking 2022. Available at: <https://www.imd.org/centers/world-competitiveness-center/rankings/world-digital-competitiveness/> [Accessed October 2022]



*Learning from crises like the COVID-19 pandemic and managing risk and the external environment*

Pharmaceutical investments, although undertaken with a long-term outlook, are not unaffected by major disruptive events such as the COVID-19 pandemic, the war in Ukraine, tensions over global trade, the climate emergency and the recent global energy crisis. The COVID-19 pandemic has had the most tangible impact on industrial policy thus far, with increased attention being paid to the resilience of pharmaceutical supply chains and calls for localisation of manufacturing. Our final recommendations are as follows:

- 6. Foster adoption of sustainable procurement and pricing policies for innovation.** There is a danger that industrial policy becomes focused on the most novel technologies and relocating manufacturing of off-patent medicines, and the need for a sustainable market is overlooked. Ongoing investment in manufacturing and the development of medicines needs to be supported by policymakers and governments, for example through sustainable pricing policies and a robust and stable intellectual property environment; this has implications for types of innovation receiving public support, procurement, and the trade-off between investing in mature and future technologies.
- 7. Develop a longer-term, collaborative method for encouraging growth in Europe's attractiveness for biopharmaceutical investments.** The increase or perceived increase in risk in the global environment resulting from recent geopolitical challenges has implications for where companies are placing their investments. This could affect the attractiveness of Europe, both positively and negatively. Europe needs to establish an effective process for implementation of the Pharmaceutical Strategy (its first in over 50 years since the first pharmaceutical legislation was implemented in the EU) with ongoing dialogue regarding how the environment will change over 5-, 10- and 20-year timescales, and the expected and actual impact of policy changes, and ensuring a focus and impact on innovation as well as production.

## 1. Introduction

Charles River Associates ('CRA') was commissioned by the European Federation of Pharmaceutical Industries and Associations ('EFPIA') to undertake an analysis of global trends in biopharmaceutical research and development (R&D), with a separate focus on research and clinical trials, and the manufacturing of innovative medicines. The aim was to understand the factors behind changes in Europe's attractiveness as a location for biopharmaceutical companies to invest compared to that of the United States, Japan and China. The aim of the analysis was to consider if there are policy lessons and recommendations for boosting Europe's attractiveness.

### 1.1. Background

Europe is a leading centre for biopharmaceutical innovation and manufacturing. Looking across Member States, we can find activity across every country and the industry makes a significant contribution to employment and economic activity.

The subject of this study is what drives investment location and the performance of Europe relative to other global regions and how this has changed. This is not a new area for research. Many studies have been undertaken by academics, on behalf of the European Commission and on behalf of the industry, over the last twenty years. However, the environment continues to evolve as a result of new technologies, the changes in the industry business model, global policy changes affecting innovation, and events such as the COVID-19 pandemic, leading to new questions about the location of pharmaceutical value chain. Moreover, there has been an increasing desire by European governments for R&D investment and job growth. As set out recently by the European Commission in the Pharmaceutical Strategy, location is an important policy debate.<sup>7</sup>

The relative decline in Europe's attractiveness as a centre for innovation and manufacturing has been a concern for many years, with a series of studies at the beginning of the century.<sup>8</sup> This analysis was subsequently updated during the Pharmaceutical Sector Inquiry and periodically over the last decade. In some cases, studies have looked specifically at biopharmaceuticals, and in other cases, more generally across sectors but highlighting biopharmaceuticals.<sup>9,10</sup> The general conclusion is that Europe has underperformed when compared to the US and growth in other regions. This is evident from statistics on the percentage of global new treatments that are of European origin, the region's share of

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<sup>7</sup> European Commission (2020) Pharmaceutical Strategy for Europe. Available at: [https://health.ec.europa.eu/system/files/2021-02/pharma-strategy\\_report\\_en\\_0.pdf](https://health.ec.europa.eu/system/files/2021-02/pharma-strategy_report_en_0.pdf) [Accessed July 2022]

<sup>8</sup> "Innovation in the pharmaceutical sector". A report by Charles River Associates for DG Enterprise, 2004. <https://media.crai.com/sites/default/files/publications/innovation-in-the-pharmaceutical-sector.pdf>. Indeed. The recognition of the issue occurred much earlier still. In its 1994 Communication on the Outlines of an Industrial Policy for the Pharmaceutical Sector in the European Community, the European Commission stated that the pharmaceutical "industry is a substantial asset for growth and employment in the European Union" and that "there are signs that the competitiveness of the Community industry is yielding in comparison with its main competitors".

<sup>9</sup> Study on the relationship between the localisation of production, R&D and innovation activities ANNEX 2: Data analysis report. 2014. A report undertaken on behalf of European Commission

<sup>10</sup> IDEA Consult and VDI Technologiezentrum on behalf of the European Commission (2018) R&D and Innovation Activities in Companies Across Global Value Chains.

global R&D, the investment in early phases of product development, the number of patents, and employment in R&D.<sup>11</sup>

There are many surveys gathering investor sentiment on the location of investments. It is possible to look historically at the annual Kearney Foreign Direct Investment (FDI) Confidence Index from 2005 to present.<sup>12,13,14</sup> These surveys show that a number of factors are important for attracting investment: a stable political situation; strong commitment and legislative framework for intellectual property and regulatory incentives; strong and effective anti-corruption policies; a strong science-based educational model; world-class university life sciences centres of excellence and associated private sector biopharma clusters; a strong national medicines regulatory agency that is up to speed on advanced medicines and diagnostics regulation; and ease of moving capital into and out of the country. By looking at rankings over time, we can also observe the evolving competitive dynamics between Europe, the US and China. China's rise to the top of investment attractiveness rankings is evident over the last two decades, although notably with a gradual drop in global ranking from number two in 2016 to number 10 in 2022 (Appendix Table 3: ).<sup>14,15</sup> However, these long-standing reports contain very little specific information on the pharmaceutical sector. More recently, a number of studies have focused on factors affecting market attractiveness in Europe. One such study collated 21 different indicators to develop an index of market attractiveness including the political, social and economic environments, the industrial investment context, life science innovation and the healthcare investment environment.<sup>16</sup>

Another way to look at location has been to focus on the location of the headquarters of companies involved in the pharmaceutical sector.<sup>17</sup> Although this is not based on activities within the region but their headquarters, it supports that Europe has fallen behind but that the picture depends on the type of technology. The most recent European Union (EU) Industrial R&D Investment Scoreboard found that "EU companies grew R&D at a slightly higher pace than their US counterparts, but their overall level of R&D remains well behind that of the US companies (half the US level of R&D investment). In biotechnology, the R&D growth of the US companies was remarkably higher; in 2020 they outperformed their EU

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11 EFPIA has previously highlighted this in "Would the last pharmaceutical investor in Europe please turn the lights out". 3 January 2020

12 Kearney (2005) FDI Confidence Index. Available at: <https://www.kearney.com/documents/291362523/291366906/FDICI-2005.pdf> [Accessed June 2022]

13 Kearney (2012) FDI Confidence Index 'Cautious Investors Feed a Tentative Recovery'. Available at: [https://www.kearney.com/documents/291362523/291366906/Cautious\\_Investors\\_Feed\\_a\\_Tentative\\_Recovery-FDICI+2012.pdf](https://www.kearney.com/documents/291362523/291366906/Cautious_Investors_Feed_a_Tentative_Recovery-FDICI+2012.pdf) [Accessed June 2022]

14 Kearney (2022) FDI Confidence Index 'Optimism Dashed'. Available at: <https://www.kearney.com/foreign-direct-investment-confidence-index/2022-full-report> [Accessed June 2022]

15 Kearney (2016) FDI Confidence Index 'FDI on the Rebound?'. Available at: <https://www.kearney.com/foreign-direct-investment-confidence-index/2016-full-report> [Accessed June 2022]

16 Attracting Life Science Investments in Europe. An Initiative of the BIOMED Alliance, EUROPABIO & JOHNSON & JOHNSON. 22 June 2021  
[https://www.janssen.com/emea/sites/www.janssen.com\\_emea/files/life\\_science\\_attractiveness\\_july.pdf](https://www.janssen.com/emea/sites/www.janssen.com_emea/files/life_science_attractiveness_july.pdf)

17 European Commission. The 2021 EU Industrial R&D Investment Scoreboard. Available at: <https://iri.jrc.ec.europa.eu/scoreboard/2021-eu-industrial-rd-investment-scoreboard> [Accessed June 2022]

counterparts in terms of R&D investment (11 times larger) and number of companies (166 vs 20) and, to a lesser extent, with higher R&D intensity (30.6% vs 26.5%).”<sup>18</sup>

Equally, the policy factors affecting location have long been debated. It is sometimes argued that the problem in Europe is not that the decline in competitiveness has been unreported or the underlying cause undiagnosed, or even that Europe lacks the resources to compete on innovation (with 16 of the world’s top 50 life science universities and many of the leading companies based in Europe). Rather, it is the lack of coherence in the policy response. The current agenda has been set by the EU Commission 2020 ‘Pharmaceutical Strategy for Europe’ document.<sup>19</sup> While the Pharmaceutical Strategy for Europe has the dual objective of promoting access to medicines for all European patients and boosting the competitiveness of the pharmaceutical industry, the latter appears to receive less attention. A vibrant innovative ecosystem in Europe will lead to better access to medicines for patients and, ultimately, better health outcomes for all European citizens.

This report seeks to provide an up-to-date assessment of our current understanding of the drivers of investment location, distinguishing between R&D hubs, clinical trial location and types of manufacturing. It also, where appropriate, uses examples of specific types of new technology – digital technology and Advanced Therapy Medicinal Products (ATMPs) – and draws specific lessons for investment in these technologies. To the extent possible, we take into account recent economic and geopolitical events (including COVID-19 and European geopolitical crisis – the ‘Russia-Ukraine’ crisis). Finally, we consider the implications, relate theory to real-life investment decisions, and provide recommendations on European policies to attract more research, clinical trials, and manufacturing investments in the future.

## 1.2. Methodology

To understand historical and recent trends in R&D and manufacturing investment and consequently to consider potential policy reforms needed in Europe to improve its attractiveness as a location to invest, our research involved three key steps:

- A literature review of recent government and non-government policy and academic literature on the issue at global, European, and country-specific levels
- An analysis of long-term trends in the location of global biopharmaceutical R&D and manufacturing activity over the past 20 years
- An interview programme with senior executives from major biopharmaceutical companies focused on actual recent major investment decisions and the factors that affected the decisions

### 1.2.1. Literature review

For the literature review, we assessed governmental, non-governmental, industry and academic literature on factors affecting location of investments, focusing on studies

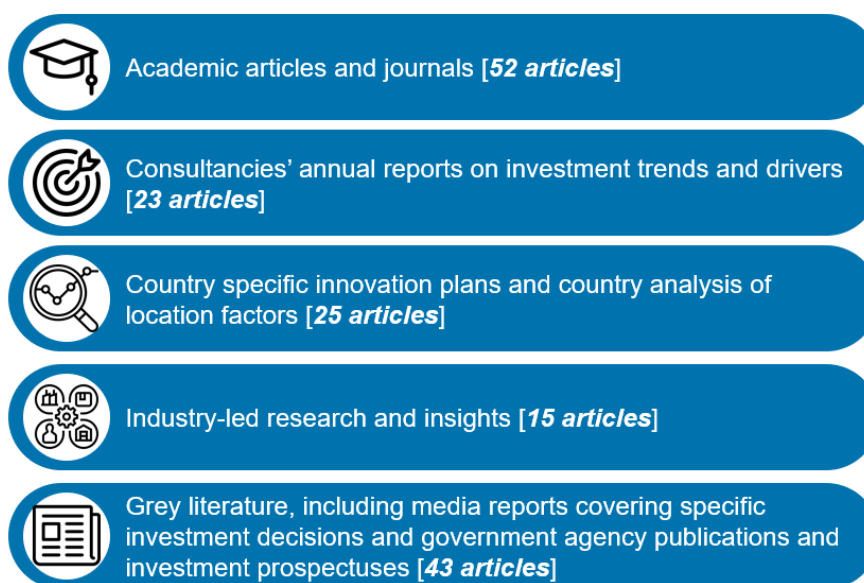
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<sup>18</sup> European Commission. The 2021 EU Industrial R&D Investment Scoreboard. Available at: <https://iri.jrc.ec.europa.eu/scoreboard/2021-eu-industrial-rd-investment-scoreboard> [Accessed June 2022]

<sup>19</sup> European Commission. 2020. A pharmaceutical strategy for Europe. Available at: [https://ec.europa.eu/health/medicinal-products/pharmaceutical-strategy-europe\\_en](https://ec.europa.eu/health/medicinal-products/pharmaceutical-strategy-europe_en) [Accessed June 2022]

published over the last five years. This encompassed a range of published studies, including annual qualitative surveys of executive decision makers within companies, statistical analyses and models of investment trends, and hybrid approaches. The literature review included global studies as well as specific analyses of the market attractiveness of Europe as a region, individual European countries, and the US and China. The search used combinations of the following terms: 'factors affecting location', 'market attractiveness', 'drivers of foreign direct investment', and 'pharmaceutical industry'. This review was followed by a more targeted search into literature focused separately on location of research hubs, clinical trials, and manufacturing facilities.

The literature review covered academic and governmental policy reports, non-governmental organisation (NGO) publications and grey literature, including:



### 1.2.2. Data analysis

In parallel to the literature review, quantitative historical data were collected to understand patterns of investment and relate these to the drivers of location choice identified in the literature review. The data were sourced from open-access international databases, numerous government and expert reports, and industry-published statistics. Where possible, the data were validated and quality-checked with relevant experts before incorporation into the analysis. The data collected included a range of indicators on Europe's performance in terms of attracting R&D, clinical trials and manufacturing:

- Expenditure on R&D and manufacturing
- Clinical trial locations
- Location of manufacturing focus on ATMPs as an example of a new therapeutic solution
- Level of employment in R&D and manufacturing
- Foreign direct investment and exports

### 1.2.3. Interview programme

As described above, there have been many surveys asking company executives to rank the factors explaining the location of investments. The approach taken in this project was to look at actual decisions and try to tease apart the company specific and environmental factors. Interviews were conducted with key decision makers from pharmaceutical companies. The interviews were structured around specific recent examples of major investments made by pharmaceutical companies in Europe and other regions (Table 4 see Appendix Table 4). In total, 15 one-hour interviews were conducted between June and July 2022. The interviews provided insight on the factors affecting real investment decisions involving pharmaceutical companies' research and manufacturing facilities. Particular attention was paid to any specific circumstances or decision drivers mentioned in press releases related to the investment, as well as the type of technology involved and the location of the company's headquarters.

We draw on the insights from all of these discussions throughout the report, and also have six specific case-study examples based on publicly available information. To draw lessons from these we combine information available in the public domain as well as aggregate findings obtained from the literature review, data analysis, and interview programme, rather than reflecting a particular company's perspective on a specific investment decision.

## 1.3. Structure of this report

The structure of this report is as follows:

- Chapter 2 examines the trends in investment in R&D, clinical trials and types of manufacturing, taking a twenty-year time horizon.
- Chapter 3 considers what we know about the different drivers that influence companies' decisions to invest in R&D and manufacturing in specific locations and how these factors can explain the observed trends of global investment activity. It then considers if these changes are due to the nature of new technology or geopolitical events.
- Chapter 4 assesses potential policy solutions to boost Europe's attractiveness as a location for biopharmaceutical companies to invest in R&D, clinical trials, and manufacturing, and critiques the extent to which the current EU policy direction achieves these objectives.

## 2. Trends in investment in R&D, clinical trials, and different types of manufacturing

To understand where investments in R&D, clinical trials and manufacturing of investigational medicinal products (IMPs) and commercial products are occurring, it is useful to start with broad statistics focusing on each component individually. In this chapter, we set out to compare trends across the US, Europe (EU + United Kingdom (UK) + Switzerland), Japan and China.

### 2.1. Trends in R&D expenditure

Given the headwinds facing the global economy, the increase in global R&D investment is dramatic, with an expected growth rate of 4.2% per year to reach \$233 billion in 2026.<sup>20,21</sup> There is, however, evidence that R&D investments are shifting out of Europe and into the US, and that the European pharmaceutical industry is facing increasing competition from China and other emerging economies.<sup>22</sup> To test this, it is useful to compare private R&D investments in each of these regions. For this report, we define R&D investment data as including basic and translational research, as well as developmental activities such as clinical trials undertaken by private companies, which include contract research organisations (CROs) and contract manufacturing organisations (CMOs). There are a number of issues with comparing data on this basis:

- The coverage depends on the companies that are members of the relevant trade associations.<sup>23,24</sup> Indeed, coverage changes over time as companies enter or leave these associations.
- Due to differing statistics reported, comparisons of R&D investment in relevant geographical areas are needed.
- Definitions vary between countries and over time. Data may be based on tax accounting (ideal case) or company estimates (where different approaches may be

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20 EvaluatePharma (2021) World Preview 2021, Outlook to 2026 report. Available at: <https://www.evaluate.com/thought-leadership/pharma/evaluate-pharma-world-preview-2021-outlook-2026> [Accessed August 2022]

21 The 15 largest pharmaceutical companies invested a record \$133 billion in 2021 in R&D expenditure, an increase of 44% since 2016. Available at: <https://www.iqvia.com/insights/the-iqvia-institute/reports/global-trends-in-r-and-d-2022>

22 European Parliamentary Research Service (2021) European pharmaceutical research and development: Could public infrastructure overcome market failures? Available at: [https://www.europarl.europa.eu/thinktank/en/document/EPRS\\_STU\(2021\)697197](https://www.europarl.europa.eu/thinktank/en/document/EPRS_STU(2021)697197) [Accessed June 2022]

23 Trade associations represent different numbers of pharmaceutical companies: EFPIA 39 members, PhRMA 33 members, JPMA 74 members, RDPAC 44 members [as of June 2022]. Although other trade associations cover a wider set of companies, these do not report R&D expenditure data.

24 It is important to note the difference in the methodology to collect data on R&D investments. For example, PhRMA collects data from PhRMA member companies, while EFPIA relates to the R&D carried out in each country. In Europe, some countries reported the same level of R&D investment in the last six years (e.g. France, Netherlands, Sweden) which potentially under- or overestimate the actual level of investments in R&D in Europe.

used). There are also issues regarding the accounting for R&D; for example, R&D expenditure for a product that failed may or may not be allocated to the year when it occurred.

- Fluctuations in exchange rates and inflation need to be taken into account when making a comparison across countries and over time.

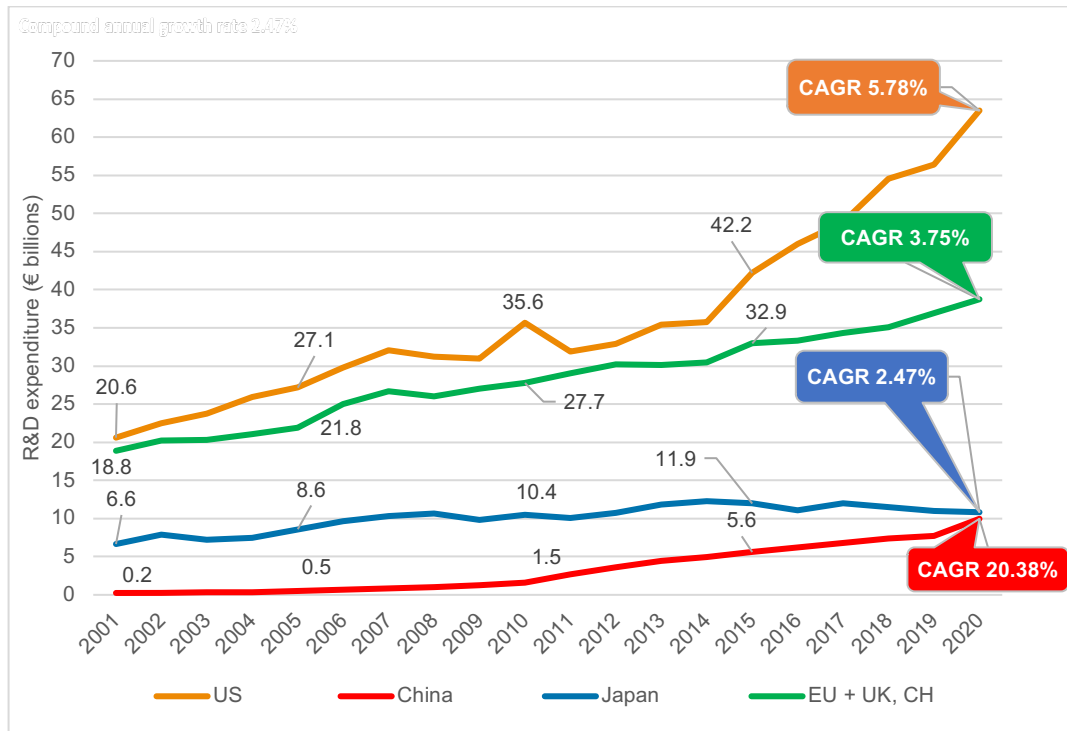
R&D investment data collected annually by major pharmaceutical industry associations and converted into euros is presented in Figure 1 below. This graph shows the US leading in aggregate terms. However, in terms of compound growth, China leads, albeit with much lower absolute numbers and a much larger population. Although in absolute terms Europe remains ahead of China, the growth rate of R&D expenditure in China far exceeds that of Europe over this period. R&D growth in China appears to have slowed from 2016 onwards (36% average annual growth rate between 2010 and 2015 compared to 10% average annual growth rate between 2016 and 2020); yet it is still occurring at a considerably faster rate than in Europe, where the average annual growth rate between 2010 and 2020 was only 3.7%.

Continued strong growth in the US is evident in Figure 1, which shows the expenditure of surveyed members of PhRMA, in which membership has also increased over time. Particularly rapid growth in US expenditure from 2014 onwards may also be viewed as a reaction to stifled R&D investment during a conservative slowdown from 2008 to 2014 in response to the financial crisis (which did not seem to have the same impact in Europe). Nevertheless, it is clear that the US continues to attract considerably more pharmaceutical R&D investment than other regions, including Europe.

These data can also be viewed as each region's share of the combined R&D expenditures from the four regions (Figure 2). Of the total R&D investments made in the US, Europe, China and Japan in 2020, 31% occurred in Europe. This has declined steadily over the last twenty years, down from 41% in 2001. Over the same period, China's share has grown from 1% to 8%. There is no evidence that expenditure in China is occurring at the expense of investment into Europe. Indeed, expenditure in Europe continues to grow, but at a much slower rate; this leads to Europe having a diminishing share of total global pharmaceutical R&D investment.

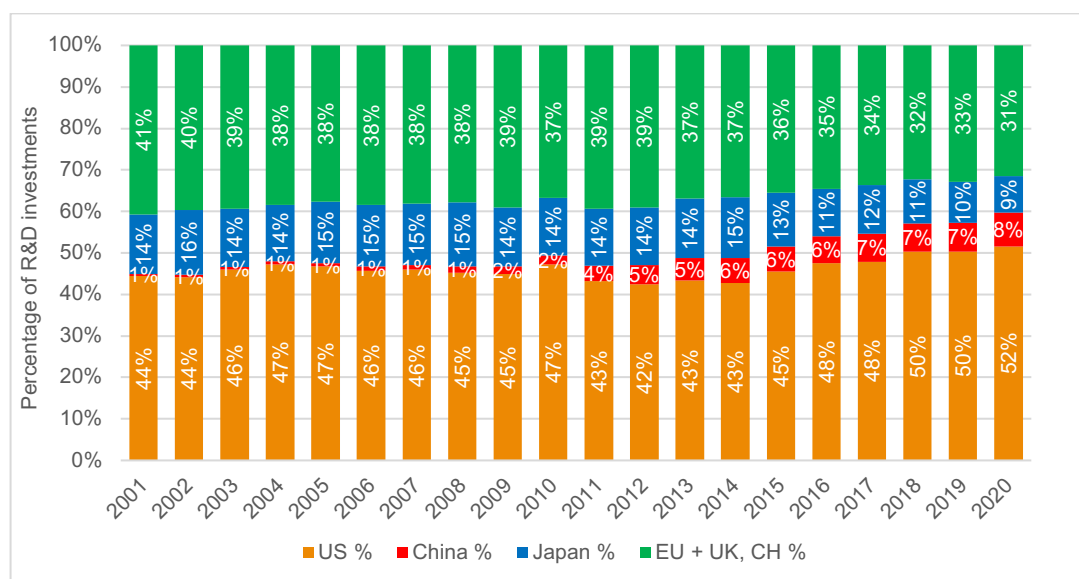


**Figure 1: Pharmaceutical companies' R&D expenditure is growing in all major markets, but fastest in the US and China**



\*CAGR (compound annual growth rate) is the average rate of growth between two given years

**Figure 2: The US and China represent a growing share of biopharmaceutical R&D investments made in major markets**



Source: Various<sup>25</sup>

Another way to look at activity is to consider the level of employment in the pharmaceutical sector in each region. Although there are also issues here in comparing data between regions, it is possible to compare R&D employment over time, to a certain degree.<sup>26</sup> This is illustrated in Figure 3 below. According to available data, the number of pharmaceutical R&D employees in China (as stated in the China Statistical Yearbook)<sup>27</sup> has increased by over 800% since 2001, although growth has stabilised from 2014 to the present. In contrast, employment in Europe has increased by only 30% over the same period. Although metrics for measuring pharmaceutical R&D employment differ in each country, we can nonetheless conclude from the data that China is experiencing a significant increase in R&D employment over the last two decades, overtaking Europe in 2012 and now rivalling the level of employment in the US. When looking at Figure 1 and Figure 3, we observe that R&D expenditure per employee is significantly lower in China compared to that of Europe and

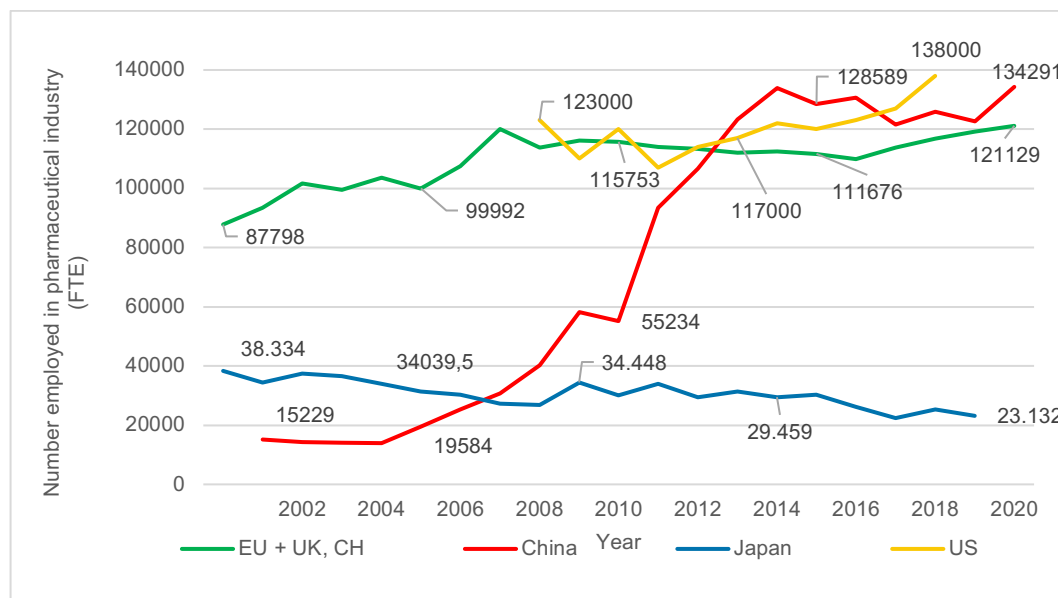
<sup>25</sup> US source: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Survey; China source: Chinese Statistical Yearbook; Japan source: Japan Pharmaceutical Manufacturers Association, R&D Expenditures of the Pharmaceutical Industry; Europe source: European Federation of Pharmaceutical Industries and Associations, the Pharmaceutical Industry in Figures. All currencies converted to Euros with ECB 2020 exchange rates to control for fluctuations in relative currency value over time.

<sup>26</sup> We have defined the pharmaceutical industry as using NACE code C21 (Manufacture of basic pharmaceutical products and pharmaceutical preparations). NACE codes are standard classification for businesses, which allow consistent analysis across EU countries. R&D personnel include all persons employed directly within R&D, as well as persons supplying direct services (such as managers, administrative staff and clerical staff). This is aligned with the Frascati Manual 2015 – the internationally recognised methodology for collecting and using R&D statistics. Available at: <https://www.oecd.org/sti/frascati-manual-2015-9789264239012-en.htm>

<sup>27</sup> China Statistical Yearbook is provided by the National Bureau of Statistics of China. The statistical data covers all state-owned and non-state-owned enterprises with annual sales revenue above 5 million CNY. As these enterprises represented the main industrial components, it is credible that they reflect the main condition and progress of R&D investment in China's pharmaceutical industry.

the US; however, we can infer that the capacity for and the capability of conducting large-scale R&D have increased in China, indicating its increasing attractiveness as a base for pharmaceutical companies to locate their research activities.

**Figure 3: Pharmaceutical R&D employment has grown at a much faster rate in China than in other major markets**



Source: Various<sup>28</sup>

It is also instructive to look at the composition of the industry. Although an imperfect proxy, the EU R&D scoreboard looks at the performance of companies based on the location of their headquarters. This is particularly concerning for the development of smaller companies in Europe. Investment in early-stage companies in Europe is lagging behind that of the US and China. When comparing data from 2015 to 2017 with data from 2018 to 2020, the average early-stage funding in Europe increased by 13% (\$14.1 million to \$20.6 million), while in the US and China it grew by 17% (\$22.5 million to \$36 million) and 18% (\$28.3 million to \$46.2 million), respectively.<sup>29,30</sup> In absolute terms, the majority of innovation coming from early-stage companies continues to originate in the US (46%), followed by Europe (20%), but strong growth has been observed in China.<sup>31</sup> Between 2018

<sup>28</sup> US source: National Science Foundation; China source: National Statistics Office, China Statistical Yearbook; Japan source: Japan Pharmaceutical Manufacturers Association; Europe source: European Federation of Pharmaceutical Industries and Associations, the Pharmaceutical Industry in Figures. FTE = full-time equivalent.

<sup>29</sup> McKinsey & Company 2021. Can European biotechs achieve greater scale in a fragmented landscape? Available at: <https://www.mckinsey.com/industries/life-sciences/our-insights/can-european-biotechs-achieve-greater-scale-in-a-fragmented-landscape> [Accessed June 2022]

<sup>30</sup> McKinsey & Company 2021. Infographic: Capital landscape for European biotechs is maturing, but it continues to trail the United States. Available at: <https://www.mckinsey.com/industries/life-sciences/our-insights/infographic-capital-landscape-for-european-biotechs-is-maturing-but-it-continues-to-trail-the-united-states>

<sup>31</sup> IQVIA Institute for Human Data Science 2022. Available at: <https://www.iqvia.com/insights/the-iqvia-institute/reports/emerging-biopharma-contribution-to-innovation> [Accessed July 2022]

and 2020, 7 of the 10 largest biopharma Initial Public Offerings originated from China.<sup>32</sup> Between 2020 and 2021, there was a notable rise in the number of Chinese institutions ranking in the top 10 global R&D institutes, from only one in 2020 (the Chinese Academy of Sciences – CAS) to four institutions in 2021.<sup>33</sup>

It would be interesting to break down R&D spending into spending on particular types of technology, including new therapeutic solutions such as ATMPs, artificial intelligence (data exists on its fast growth rate but not its location)<sup>34</sup> and digital therapeutics, but this has thus far not been possible.

## 2.2. The location of clinical trials

Although R&D investments include those made by pharmaceutical companies in clinical trials, it is nevertheless useful to consider in more detail the locations of clinical trial activity differentiated by types of clinical trials.

There are various data sources that can be used to compare clinical trials globally. This includes the World Health Organization's (WHO) International Clinical Trials Registry Platform (ICTRP), which contains information from the European Union Clinical Trials Register (EU-CTR), the National Institutes of Health (NIH)'s ClinicalTrials.gov, and commercial data sources such as GlobalData. There are challenges in attributing clinical trials to countries and regions:

- Inclusion of trials that have only started recruiting, are already completed, or have had results reported
- Accounting for multinational studies with many different countries involved
- Incomplete datasets

Although these registries do not provide comprehensive results of clinical trials, a trend analysis can still be undertaken (if the inclusion criteria are taken into account). To make this comparison, we have focused on [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov), and specifically on industry-sponsored trials.<sup>35</sup> Although this database goes back over many years, only since 2007

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<sup>32</sup> McKinsey & Company 2021. The dawn of China biopharma innovation. Available at: <https://www.mckinsey.com/industries/life-sciences/our-insights/the-dawn-of-china-biopharma-innovation> [Accessed June 2022]

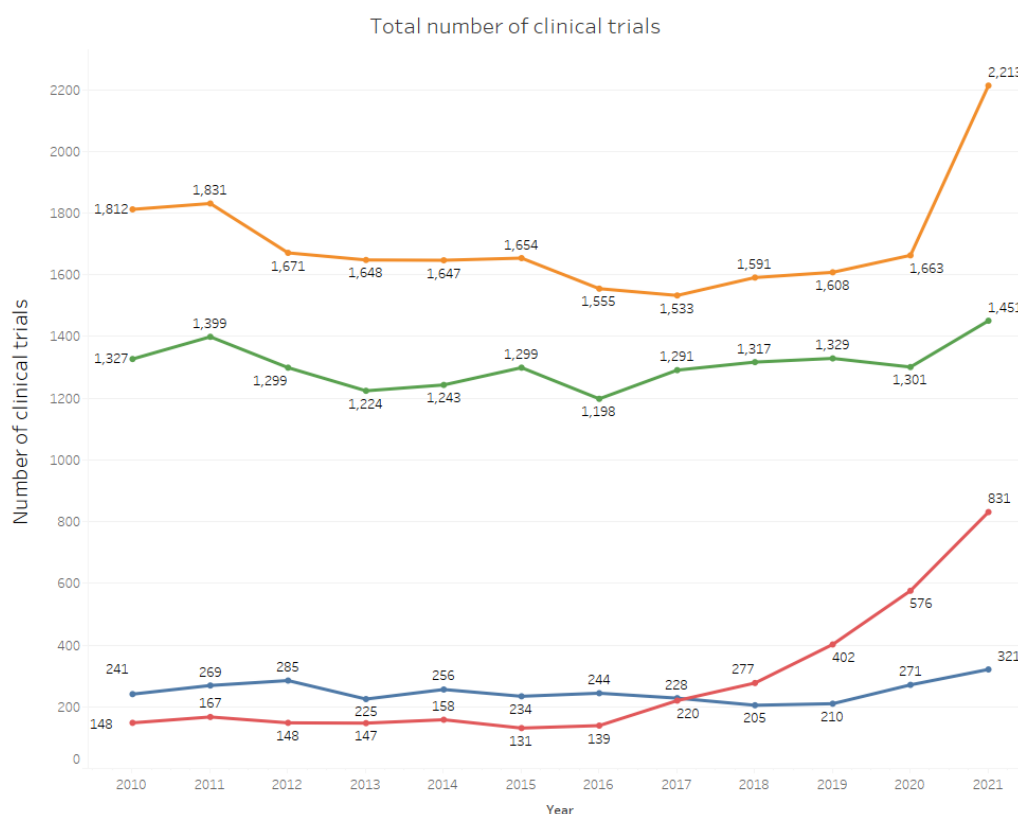
<sup>33</sup> Nature Index institution rankings 2022. Available at: <https://www.nature.com/nature-index/annual-tables/2022/institution/all/all/global> [Accessed September 2022]

<sup>34</sup> <https://www.pharmaceutical-technology.com/analysis/pharma-ai-investment/>. There are estimates of public investment in this area. For example, it is reported that annual investment of the EU in AI is €1bn, compared to €5.1bn invested annually by the US and €6.8bn by China. <https://euobserver.com/digital/154861>

<sup>35</sup> ClinicalTrials.gov is a web-based resource that provides patients, their family members, healthcare professionals, researchers and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. The website is maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH).

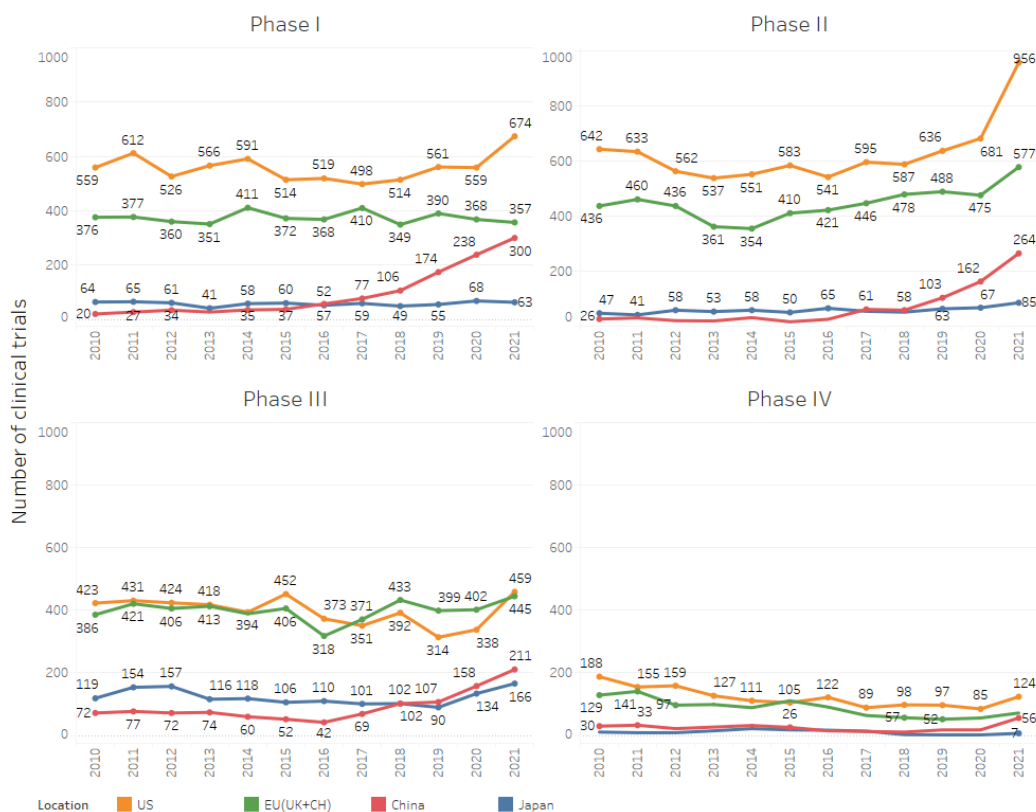
have companies been required to include clinical trials in it.<sup>36</sup> Therefore our analysis is based on the last 10 years. These data show that the US continues to outcompete Europe, China and Japan as the most attractive location for industry-sponsored clinical trials (Figure 4). This is consistent across all phases of clinical development. As with research expenditure (Figure 1), Europe still attracts more industry clinical trial investment than China; however, industry investment in China, where clinical trial activity has historically been largely government-led, is growing at a rapid pace across all phases of development – particularly for Phase 1 studies. While Japan has historically attracted more industry-sponsored clinical trials than China, China has overtaken it in the number of clinical trials conducted per year since 2017. Strong growth in recent data is also likely to be partly due to the COVID-19 pandemic. Industry clinical trial activity was generally maintained throughout the pandemic, to which the industry has adapted by developing new approaches to enable research to continue. This is discussed further in the next chapter.<sup>37</sup>

**Figure 4: US continues to outcompete Europe, China and Japan as the most attractive location for industry-sponsored clinical trials\***



<sup>36</sup> NIH US National Library of Medicines, ClinicalTrials.gov FDAAA 801 and the Final Rule. Available at: [https://www.clinicaltrials.gov/ct2/manage-recs/fdaaa#:~:text=To%20Top-Which%20Trials%20Must%20Be%20Registered%20on%20ClinicalTrials.gov%3F\\_as%20of%20December%2026%2C%202007](https://www.clinicaltrials.gov/ct2/manage-recs/fdaaa#:~:text=To%20Top-Which%20Trials%20Must%20Be%20Registered%20on%20ClinicalTrials.gov%3F_as%20of%20December%2026%2C%202007) [Accessed June 2022]

<sup>37</sup> <https://www.iqvia.com/insights/the-iqvia-institute/reports/global-trends-in-r-and-d-2022> [Accessed July 2022]



Source: Various<sup>38</sup> \*It is important to note that our numbers of clinical trials are lower compared to other research papers<sup>39</sup> or published data by WHO.<sup>40</sup> CRA focused only on industry-sponsored trials having a status of recruiting, active or completed, compared to other analysis which counted all registered clinical trials. We also excluded trials with an unknown status or non-applicable study phase.

We also considered whether the pattern of clinical trial locations varies for different types of technology, focusing on the trends for ATMPs as an example of a new therapeutic solution. The key difference observed is the competitiveness of the Asia-Pacific region (used as a proxy for China, where data are not available) in attracting ATMP clinical trials relative to the US (Figure 5). The number of trials conducted in the US and Asia-Pacific region grew by 70% and 67%, respectively, between 2014 and 2021. Meanwhile, the number of ATMP trials in Europe appears lower and stagnant despite overall growth of the

38 CRA analysis on data extracted from clinicaltrials.gov. CRA included interventional, industry-funded studies (recruiting, active not recruiting and completed) from 01/01/2010 to 31/12/2021. Observational studies and studies with expanded access were excluded from the analysis. Countries included are the US, China, Japan, all EU countries including the UK, CH, Norway, and Iceland.

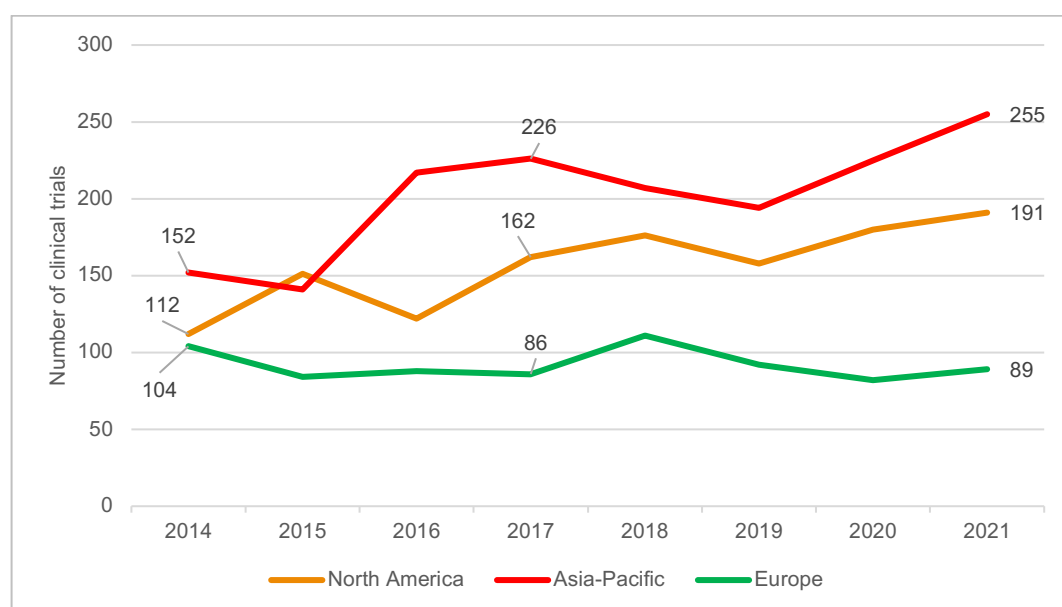
39 George, M., Selvarajan, S., Dkhar, S. & Chandrasekaran, A. (2013) Globalization of clinical trials – where are we heading? *Current Clinical Pharmacology*. 8(2): 115–123.

40 WHO Number of clinical trial registrations by location, disease, phase of development, age and sex of trial participants (1999–2021) Available at: <https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/number-of-trial-registrations-by-year-location-disease-and-phase-of-development>, [Accessed June 2022]

global clinical development pipeline.<sup>41</sup> This observation is consistent with those in the literature; the Alliance for Regenerative Medicine found that three times as many ATMP trials were initiated in North America than in Europe between 2014 and 2018, and that during this time there was a marked increase in North America (36%) and Asia (28%), but not in Europe (<2%).<sup>42</sup>

This contrasts with the trends observed in Figure 4 and indicates that while Europe continues to be an attractive location for pharmaceutical companies to conduct clinical trials for more traditional medicinal technologies, this is not the case for all new therapeutic solutions, including but not limited to ATMPs. It is also incongruous with Europe's relative strength in ATMP academic research: between 2017 and 2019, the lead authors of around 120,000 papers published in ATMP publications were affiliated with a European institution. In the US and China, equivalent figures were 72,000 and 100,000, respectively.<sup>43</sup> In Chapter 3, **Error! Reference source not found.** we explore the reasons behind these contrasting patterns of investment.

**Figure 5: The location of Advanced Therapy Medicinal Products (ATMP) clinical trials differ from the overall geographic pattern of biopharma clinical trial activity**



41 ASGCT (2021) Gene, Cell, & RNA Therapy Landscape. Available at: <https://asgct.org/global/documents/asgct-pharma-intelligence-quarterly-report-july-20.aspx> [Accessed July 2022]

42 Alliance for Regenerative Medicine (2019) Clinical Trials in Europe: Recent Trends in ATMP Development. Available at: <https://alliancerm.org/indication-data/clinical-trials-in-europe/> [Accessed July 2022]

43 Loche, A. et al. (2021) A call to action: Opportunities and challenges for CGTs in Europe. Available at: <https://www.mckinsey.com/industries/life-sciences/our-insights/a-call-to-action-opportunities-and-challenges-for-cgts-in-Europe> [Accessed June 2022]

Source: GlobalData<sup>44</sup>

### 2.3. The location of investigational and commercial manufacturing

We next consider investment in the manufacturing of innovative medicines.<sup>45</sup> We are interested in IMPs, commercial manufacturing, and, to a lesser extent, active pharmaceutical ingredient (API) manufacturing. An IMP is defined as a medicine used in a clinical trial;<sup>46</sup> commercial manufacturing is manufacturing of regulatory approved medicines; and an API is any substance, or mixture of substances, intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product.<sup>47</sup> There are even greater challenges in making like-for-like comparisons across regions than there are with R&D investments:

- *Inconsistent metrics:* Unlike investment in R&D, where comparisons are long-standing, there has been less effort to standardise measurements across regions. There are a number of potential definitions that could be useful, such as gross investments in tangible goods in the EU, investments in private non-residential fixed assets in the US and investment in fixed assets in China. These varying definitions make comparison challenging:
  - In the EU, gross investment in tangible goods is defined as investment during the reference period in all tangible goods. Included are new and existing tangible capital goods, whether bought from third parties or produced for own use (i.e. capitalised production of tangible capital goods), and having a shelf life of more than one year. This also includes non-produced tangible goods such as land.<sup>48</sup>
  - In the US, the Bureau of Economic Analysis defines fixed assets as those used continuously in production for an extended period of time, and generally

<sup>44</sup> CRA analysis on data extracted from GlobalData.com. CRA analysed cell and gene therapy clinical trials in North America, Asia-Pacific and Europe between 2014 and 2021. The analysis included completed, ongoing not recruiting, ongoing recruiting, ongoing recruiting by invitation, and planned clinical trials. Suspended, terminated and withdrawn clinical trials were excluded. The analysis included all sponsor types (company, government, individual, institution).

<sup>45</sup> EMA defines innovative medicine as a medicine that contains an active substance or combination of active substances that has not been authorised before. Available at: <https://www.ema.europa.eu/en/glossary/innovative-medicine> [Accessed July 2022]

<sup>46</sup> EMA Investigational medicinal product. Available at: <https://www.ema.europa.eu/en/glossary/investigational-medicinal-product> [Accessed July 2022]

<sup>47</sup> The EudraGMDP Glossary. Available at: [http://eudragmdp.ema.europa.eu/help\\_public/content/v3\\_0\\_user\\_manual/glossary.htm](http://eudragmdp.ema.europa.eu/help_public/content/v3_0_user_manual/glossary.htm) [Accessed July 2022]

<sup>48</sup> Eurostat Glossary: Gross investment in tangible goods – SBS. Available at: [https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Glossary:Gross\\_investment\\_in\\_tangible\\_goods\\_-\\_SBS](https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Glossary:Gross_investment_in_tangible_goods_-_SBS) [Accessed July 2022]



defines consumer durables as tangible products that can be stored or inventoried and that have an average shelf life of at least three years.<sup>49</sup>

- *Incompleteness*: Moreover, the data have many limitations. In Europe, several smaller countries do not report data to Eurostat for confidentiality reasons, and in the US, data is collected only at the level of chemical industry. Therefore, these reports are inconsistent across different regions and, as a result, we cannot aggregate them to obtain insight on regional shares.
- *Level of granularity*: Given the different drivers, we wanted to understand investment location for both IMPs and commercial manufacturing; however, our sources do not typically break down data on manufacturing investments by types of manufacturing. Similarly, the sources used did not provide a breakdown of commercial product manufacturing by API manufacturing versus formulation and commercial production.
- *Coverage*: Although there are measures of investment in each market, coverage varies for the total pharmaceutical and biotech sector. There are ambiguities as to whether API production is included in this sector or rather in the chemical sector statistics.

In order to compare between regions, we have therefore used the best data that exist in the region<sup>50</sup> and accept that while we cannot directly compare aggregate statistics, we can compare trends. If we compare relative patterns of growth within each region over time, we find that in Europe, investments in pharmaceutical production have increased at an annual average rate of 10.9% per year (Figure 6), with a sharp notable decline from 2018 to 2019, which potentially could be explained by delayed data reporting to Eurostat. The pattern observed in the US is constant, with a 5.1% average annual growth rate between 2005 and 2019, and a sharp 16% increase observed from 2018 to 2019.<sup>51</sup>

At the same time, manufacturing investments in China have grown on average 19% each year, a rate significantly higher than that observed in Europe and the US.<sup>52</sup> This is consistent with observations in the literature, that over the past 20 years, industry offshoring strategies for small molecules, and especially for generics, have shifted all but the most

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49 The Bureau of Economic Analysis (BEA). Available at: [https://apps.bea.gov/iTable/index\\_FA.cfm](https://apps.bea.gov/iTable/index_FA.cfm) [Accessed July 2022]

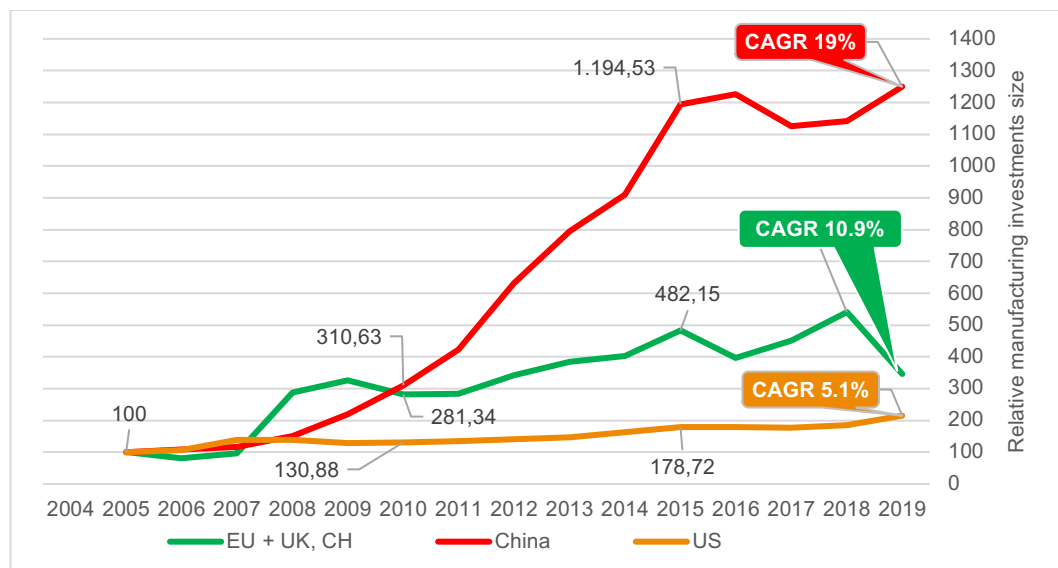
50 CRA used Eurostat data on gross investment in tangible goods for Europe; the US Bureau of Economic Analysis. Used Non-residential Detailed Estimates – Investments, Chemicals sector, capital expenditure data; China Statistical Yearbooks 2003–2019. Investments in Fixed for manufacturing medicines for China.

51 CRA analysis of US Bureau of Economic Analysis. Used Non-residential Detailed Estimates – Investments, Chemicals sector, Investment in Private Nonresidential Fixed Assets (Updated 19 August 2021). Available at: <https://apps.bea.gov/national/FA2004/Details/Index.htm> [Accessed June 2022]

52 CRA analysis of China Statistical Yearbooks 2003–2019.

challenging or sensitive API manufacturing out of the US and Europe into jurisdictions with lower costs and taxes.<sup>53, 54</sup>

**Figure 6: Relative growth in pharmaceutical manufacturing (including APIs and generics) is greatest in China<sup>55</sup>**



Source: CRA analysis of various sources<sup>56</sup>  
 \*CAGR (compound annual growth rate) is the average rate of growth between two given years

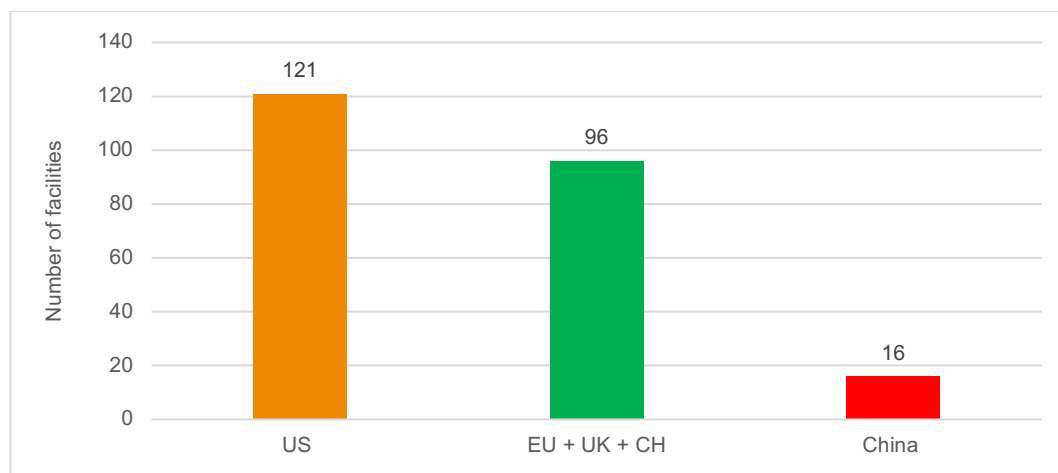
We are also interested in manufacturing activity broken down by types of technology, and more specifically the impact of new therapeutic solutions (using ATMPs as an example) on the location of investment. Given the lack of granularity on investment data and the fact that ATMPs are still an emerging technology, it is more informative to look at investments in the facilities capable of producing these products in the future, rather than historical investments. We observe that the US and Europe (including the UK and Switzerland) are two leading regions (Figure 7), and that China has relatively far fewer production facilities.

<sup>53</sup> Woodcock, J. (2019) Safeguarding Pharmaceutical Supply Chains in a Global Economy. Available at: <https://www.fda.gov/news-events/congressional-testimony/safeguarding-pharmaceutical-supply-chains-global-economy-10302019> [Accessed June 2022]

<sup>54</sup> European Parliamentary Research Service (2021) European pharmaceutical research and development: Could public infrastructure overcome market failures? Available at: [https://www.europarl.europa.eu/thinktank/en/document/EPRS\\_STU\(2021\)697197](https://www.europarl.europa.eu/thinktank/en/document/EPRS_STU(2021)697197) [Accessed June 2022]

<sup>55</sup> To account for the different definitions and that the data are not directly comparable, we have indexed each series at 2005.

<sup>56</sup> CRA used Eurostat data on gross investment in tangible goods for Europe; the US Bureau of Economic Analysis. Used Non-residential Detailed Estimates – Investments, Chemicals sector, capital expenditure data; China Statistical Yearbooks 2003–2019. Investments in Fixed for manufacturing medicines for China.

**Figure 7: The number of facilities capable of producing ATMPs is highest in the US**

Source: GlobalData [as of June 2022]

## 2.4. Foreign direct investment and exports

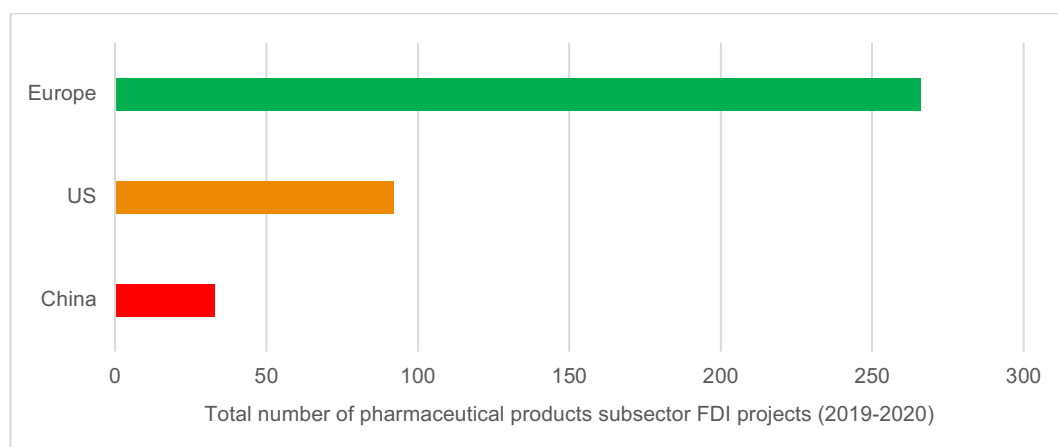
Another perspective on investment is to look at foreign direct investments (FDI), which are made by entities outside of the country. There are annual reports that apply a range of sophisticated methodologies based upon FDI data, surveys, and numerous social, technological, and economic indices to compare countries. In the 2019 World Economic Forum (WEF) Global Competitiveness Report, the key output is summarised in the form of a table ranking the Global Competitiveness of national economies.<sup>57</sup> The first conclusion to be drawn from this analysis might be that size does not matter. The top 10 countries in rank order are: Singapore, the US, Hong Kong, the Netherlands, Switzerland, Japan, Germany, Sweden, the UK, and Denmark. However, this is non-specific to pharmaceutical industry investment, as these reports typically do not break down data by industry.

Evidence for the pharmaceutical industry shows a similar pattern. Between January 2014 and December 2019, Western Europe received more than a third (36.12%) of all global pharmaceutical investments, with the UK attracting the most FDI projects (22.12%), followed by Germany (17.37%) and France (11.7%). In 2020, most sectors saw a decline in FDI as a result of the COVID-19 pandemic, including the pharmaceutical industry. Interestingly, Western Europe emerged as the leading region for attracting FDI in 2020, with an increase in greenfield FDI projects from 2019, while Asia-Pacific and North America saw a decrease.<sup>58</sup> However, when looking at individual countries rather than regional aggregates, the US stands out as a clear leader (Figure 8 **Error! Reference source not found.**). Notably, most of the 92 FDI projects in the US in 2020 came from European-based companies (Germany: 20, UK: 18, Switzerland: 10).

<sup>57</sup> World Economic Forum (2019) The Global Competitiveness Report 2019. Available at: [https://www3.weforum.org/docs/WEF\\_TheGlobalCompetitivenessReport2019.pdf](https://www3.weforum.org/docs/WEF_TheGlobalCompetitivenessReport2019.pdf) [Accessed June 2022]

<sup>58</sup> Karadima, S. (2022) FDI in pharmaceuticals: The state of play. Available at: <https://www.pharmaceutical-technology.com/analysis/fdi-pharmaceuticals-state-of-play-investment/> [Accessed June 2022]

**Figure 8: Europe as a region still attracts more pharmaceutical greenfield FDI projects than the US or China**



Source: Adapted from Karadima, S. (2022)<sup>59</sup>

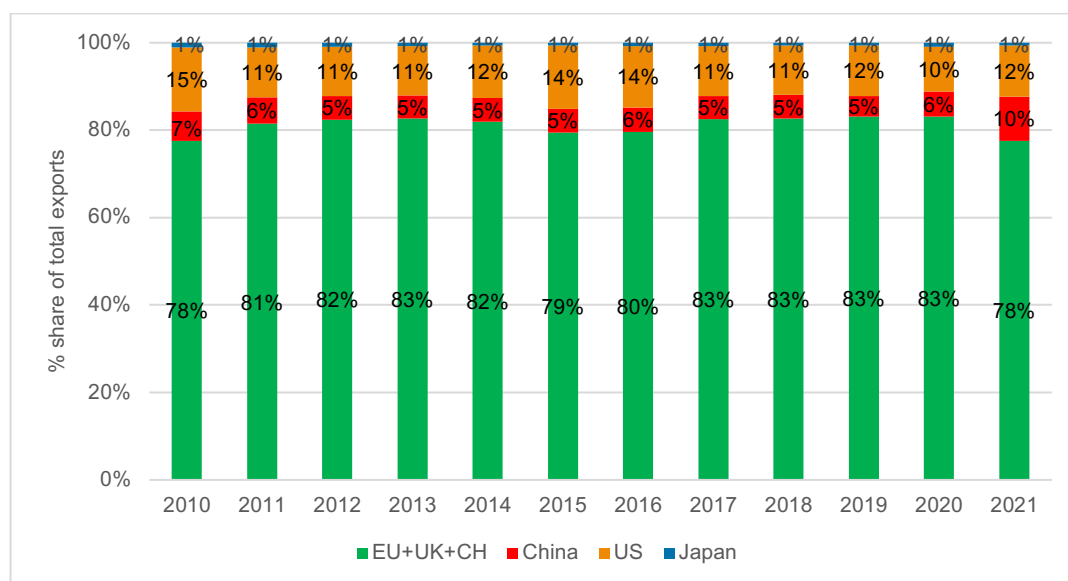
When separating the FDI data by business function, the ranking of countries changes: China was the leading destination in 2020 for R&D.

A final way to look at location is to look at trade. This is clearly a proxy; while we might expect countries attracting considerable investment to export to other markets, in reality, large regions that are mostly self-sufficient may have higher levels of investments. In terms of trade, EU exports and imports of medicinal and pharmaceutical products grew between 2010 and 2021, with the net combined exports of the EU, the UK and Switzerland (CH) reaching €281 billion in 2021. Looking at the total value of pharmaceutical exports from major markets (EU, US, China, Japan), this represents a 78% share (Figure 9). This share has remained relatively stable over time. Even the COVID-19 pandemic, which affected trade in many other products, did not cause a fall in exports or imports of medicinal and pharmaceutical products. When compared to other regions, the EU is by far the largest exporter of such products.

59

Karadima, S. (2022) FDI in pharmaceuticals: The state of play. Available at: <https://www.pharmaceutical-technology.com/analysis/fdi-pharmaceuticals-state-of-play-investment/> [Accessed June 2022]

**Figure 9: Europe has retained its position as the biggest exporter of pharmaceuticals compared to the US, China and Japan over the last decade**



Source: UNCTAD<sup>60</sup>

## 2.5. Summary

The long-term trends in location of R&D, clinical trials and manufacturing should not come as a surprise. It has been well documented in many reports over the last 20 years. The amount of annual investment in Europe is growing less quickly than the US, and China has seen a dramatic increase in investment over the same period. However, the sub-trends presented in this chapter are some of the important ones that are worth noting before we attempt to explain the pattern of investment and consider the policy ramifications. Although Europe is not yet so far behind in terms of absolute values, the downward trend already taking place relative to the US and China – both regions that experience stronger growth in multiple areas and possess more indicators in the “strongest performance” category – is alarming (Figure 10). The picture for Europe is a loss of market share to the US and China on most metrics, incongruous with some of its strengths, including hosting the majority of academic research activity for ATMPs (not reflected in corresponding clinical trials) and possessing the lion’s share in pharmaceutical exports (perhaps reflecting historical location decisions). In many other areas, such as attracting pharmaceutical company R&D activity, clinical trials and manufacturing, the US leads and China is growing rapidly. Understanding what drives these trends is paramount and serves as the basis of Chapter 3 of this report.

<sup>60</sup> UNCTAD data were used (Exports: medicinal and Pharmaceutical Product). All currencies converted to Euros with ECB 2020 exchange rates to control for fluctuations in relative currency value over time.

**Figure 10: The US and China are the top performers in more investment performance metrics than Europe, exhibiting stronger growth trends**

Indicators		Ranking			
		Europe	US	China	Japan
Investment in R&D	Total private investment	Light Green	Dark Green ▲	Light Green ▲	Light Orange
	Employment	Light Green	Dark Green	Dark Green	Light Orange ▼
	Early funding support	Light Orange	Dark Green	Light Orange	Light Orange
	ATMP basic research	Dark Green	Light Green	Light Orange	Light Orange
Investment in clinical trials	Industry-sponsored trials	Light Green	Dark Green	Light Green ▲	Light Orange ▲
	ATMP clinical trials	Light Orange	Light Green	Dark Green	Light Orange
Investment in manufacturing	Total manufacturing investment	Light Green	Light Green ▲	Dark Green ▲	Light Orange
	ATMP manufacturing	Light Green	Dark Green	Light Orange	Light Orange
Foreign Direct Investment and exports	Foreign direct investment	Light Green	Dark Green	Light Orange	Light Orange
	Exports	Light Green ▲	Light Green	Light Green ▲	Light Orange

Key:   
■ = strongest performance ▲ = growth of ≥20% in last five years   
■ = moderately strong performance ▼ = decline of ≥20% in last five years   
■ = comparably weak performance

Source: CRA analysis of data described in Chapter 2 of this report.

**Box 2: Summary of key findings**

- Recent trends in multiple indicators show a decline of Europe’s overall attractiveness as a location for pharmaceutical companies to invest, with prior areas of strength (in research, clinical trials and manufacturing) now failing to keep up with the pace of progression in other regions.
- Pharmaceutical industry R&D investment is growing at a slower rate in Europe than in the US, and China has seen a dramatic increase in investment over the same period.
- While Europe continues to be an attractive location for pharmaceutical companies to conduct clinical trials for more traditional medicinal technologies, this is not the case for new therapeutic solutions, including but not limited to ATMPs.
- Consistent with observations that high-volume manufacturing is increasingly offshored to lower-cost markets, the growth rate of pharmaceutical manufacturing investment in China is double what it is in Europe and quadruple the growth rate in the US.
- The US is the leading country for attracting pharmaceutical FDI; however, when looking specifically at pharmaceutical R&D FDI projects, China is now in the lead.

### 3. Factors driving the location of biopharmaceutical R&D and investigational and commercial manufacturing

In this chapter, we consider how we can explain the trends observed in the previous chapter, drawing on the existing literature on the factors driving the location of pharmaceutical industry investments and the interviews undertaken with decision makers. Here, we first briefly summarise the literature to date for pharmaceutical research, clinical trials, and manufacturing, and then focus in more detail on new issues regarding the impact of recent global shocks and new technology. The case studies are based only on public information.

It is clear from the existing literature and interviews that the factors driving the location of research hubs, clinical trials, and manufacturing differ considerably.

#### 3.1. Research hubs

One way to understand the patterns of spending on R&D investment is to consider the location of research hubs.

##### *Characteristics of research hub investment decisions*

Research centres or hubs are often concentrated campuses focusing on a specific area of scientific exploration. This is distinct from clinical trials activity, which is often spread across leading hospitals and academic centres. Major companies will have a relatively small number of research hubs; for example, Pfizer lists eight research centres, while GSK lists 10.

Given the relatively small number of research hubs, the decision regarding a hub's location is a significant strategic choice, often made at a Board level, representing a long-term commitment to the market and the structure of the company. The literature and interviews suggest that internal factors primarily dictate the decision on where to locate biopharmaceutical research activities, both implicitly (e.g. company culture and strategy) and explicitly (e.g. evaluation of the location and performance of existing sites).<sup>61,62,63</sup> For example, location of new research centres is often based on how these fit with existing commitments to regional markets. A European hub will often replace an existing European hub. So, for pharmaceutical companies, their existing geographic footprint in terms of R&D hubs is the starting point for any decision regarding the choice between Europe, the US, China and Japan.<sup>64</sup>

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61 Bramley-Harker, E. et al. (2007) Key Factors in Attracting Internationally Mobile Investments by the Research-Based Pharmaceutical Industry. London, UK: NERA Economic Consulting.

62 Rozek, R.P. (2011) Risk and Regulatory Factors Affecting Location Decisions by Research-Based Pharmaceutical Companies. *European Journal of Risk Regulation*. 2(1): 92–103.

63 Rangan, S. (2000) Search and Deliberation in International Exchange: Microfoundations to Some Macro Patterns. *Journal of International Business Studies*. 31(2): 205–222.

64 Ruane, F.P. and Zhang, X. The Determinants of Location Choices by Pharmaceutical MNEs in Europe. Available at: <https://www.etsg.org/ETSG2008/Papers/Ruane.pdf> [Accessed June 2022]

For emerging start-up companies, there is not necessarily a proactive decision on where to start activities. Still, the location may often be a passive result of where the innovation ecosystem is more conducive to the spin-out of companies from universities, for example, or where a wealth of venture capital funding is available. Without an established footprint, we expect the location of biotech start-ups to be driven by the external factors summarised below.

Studies indicate that quality of the scientific ecosystem takes precedence over cost for research hub location decisions. Both surveys with decision makers and economic analyses indicate that co-location with world-leading academic centres of excellence, research scientists and skilled research staff are key drivers of location, and in many cases, there are only a relatively small number of world-class locations.<sup>65,66</sup> Ability for these centres of academic excellence to collaborate with industry and translate academic research into successful candidates for the clinic is also key.

Cost is consistently ranked as one of the least important factors in research location decision-maker surveys.<sup>67,68</sup> This balance of factors is evident in the recent decision to establish a major research hub in London, UK, where the cost of labour and production are high, but access to world-leading scientists and skilled staff acted as sufficiently attractive incentives (Box 3).

### Box 3: Case study | Investment in London's "Knowledge Quarter"

In 2020, MSD announced that London had been selected as the location for their new Discovery Research Centre, and they would be investing over \$1.3 billion in its development.<sup>69</sup> The new research hub will be located opposite London King's Cross railway station, one of the UK's largest transport hubs. This site was attractive for multiple reasons:<sup>70</sup>

- Primarily, it allows proximity to highly qualified research staff. London has a number of world-leading universities, is densely populated, and is regarded as a desirable location to live, making recruiting and retaining the right talent easier in an increasingly competitive labour market.
- It also facilitates access to potential collaborators. The UK's science and research capabilities are strong and have been for decades, being home to two

65 Bramley-Harker, E. et al. (2007) Key Factors in Attracting Internationally Mobile Investments by the Research-Based Pharmaceutical Industry. London, UK: NERA Economic Consulting.

66 Guimón, J. (2008) Government strategies to attract R&D-intensive FDI. *The Journal of Technology Transfer*. 34(4): 364–379.

67 Michaelis, C., King, K. and Radevsky, A. (2010) Qualitative research into businesses' Research and Development (R&D) decision-making processes, UK: Databuild Research and Solutions Ltd for HM Revenue and Customs.

68 Rodgers, P. et al. (2019) Exploring the determinants of location choice decisions of offshored R&D projects. *Journal of Business Research*. 103: 472–483.

69 MSD Our new London Discovery Research Centre site. Available at: <https://www.msd.com/stories/our-new-london-discovery-research-center-site/> [Accessed June 2022]

70 Information from interview programme with MSD representative, June 2022.



of the world's top five universities for life sciences.<sup>71</sup> Locating by a major London transport hub also facilitates connections to other collaborators in Europe and the rest of the world.

- London also offers practical benefits, such as having English as the local language (which for a US company helps with transferability of labour within the company) and accessibility and connectivity (with links to the academic triangle of Cambridge-Oxford-London, and direct flights possible to and from the US).

Source: Press releases and interview programme

Clusters also play an important role. Research clusters are likely a result of companies all gravitating towards these centres of expertise,<sup>61,62</sup> and a driver for further inward investment due to the knowledge spillover benefits and “place-to-be effect”.<sup>72</sup>

The literature on factors attracting R&D investments suggests that there has been little change over previous decades in what drives companies to invest in a location for a research hub. Our interview programme largely confirmed this; however, one additional driver is emerging: the digital infrastructure. Digital transformation in the pharmaceutical industry is complex, especially in large companies with established infrastructure. To modernise processes and keep pace with the digital evolution of the industry, particularly post-COVID-19, pharmaceutical companies look towards countries with a supportive digital ecosystem. This requires access to a rich talent pool of people and organisations who are highly trained in digital skills and data handling, digital communication infrastructure and data sharing capabilities, and presence of companies specialised in data who can act as support services to the pharmaceutical industry in automating parts of the research process (and subsequent value chain).<sup>73</sup>

#### *Understanding global trends in location of research hubs: explaining China*

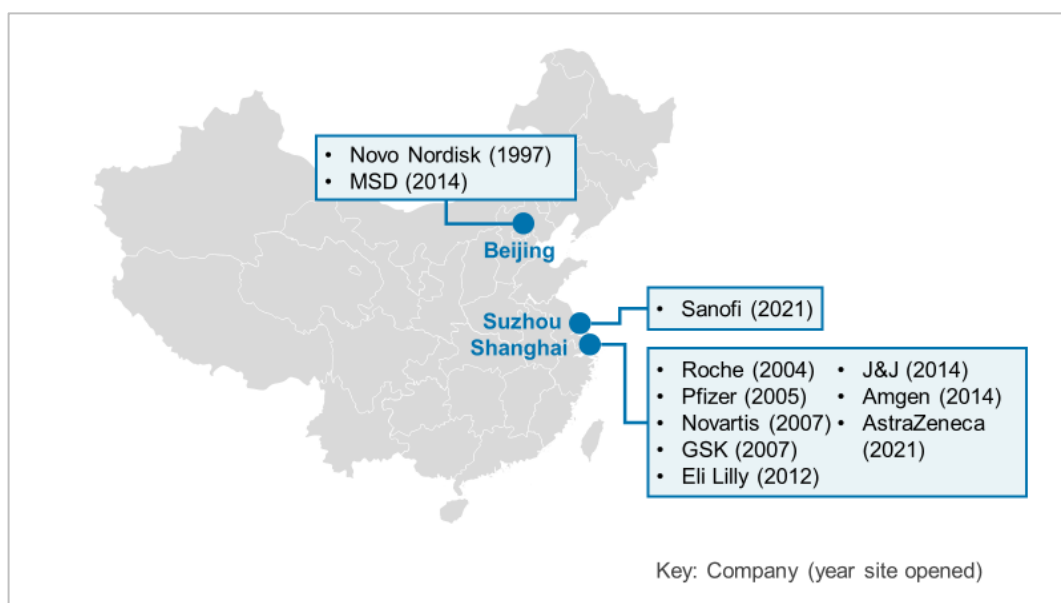
The explanation above would suggest that the location of R&D hubs would change only slowly over time; however, in reality, we have observed a series of significant decisions to open research hubs in China, mostly in Shanghai. The first global pharmaceutical company to establish a major research facility in China was Novo Nordisk in 1997, and now 11 of the top 15 global pharmaceutical companies have a significant research hub in mainland China (Figure 11).

71 HM Government Life Sciences Vision 2021. Available at: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/1013597/life-sciences-vision-2021.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1013597/life-sciences-vision-2021.pdf) [Accessed June 2022]

72 Erken, H. and Kleijn, M. (2008) Location factors of international R&D activities: an econometric approach. *Economics of Innovation and New Technology*. 19(3): 203–232.

73 Information from interview programme with pharmaceutical company representatives, June–July 2022.

**Figure 11: The majority of large multinational pharmaceutical companies now have an R&D centre in China**



Sources: Company websites and press releases<sup>74</sup>

This would appear inconsistent with the view regarding the location of R&D hubs. There are several reasons for this:

- China has dramatically improved its position in terms of scientific infrastructure, over the last 15 years. In 2000, US universities awarded twice as many doctorates in STEM fields (18,289) as Chinese universities (9,038). But by 2007, the order had reversed, and China began outpacing US universities. In 2010, 34,801 STEM doctorates were awarded by Chinese universities, compared to 26,076 by American universities. In 2019, Chinese universities produced 49,498 PhDs in STEM fields, while US universities produced 33,759.<sup>75</sup> In 2021, according to Nature Index, which ranks institutions by their scientific output, four out of 10 top global R&D institutes were located in China, with the Chinese Academy of Science

<sup>74</sup> <https://www.roche.com/innovation/structure/rnd-locations/pharma-shanghai;>  
[http://www.china.org.cn/english/scitech/147304.htm;](http://www.china.org.cn/english/scitech/147304.htm) [https://www.thepharmaletter.com/article/novartis-to-open-new-r-d-facility-in-china-with-100-million-investment;](https://www.thepharmaletter.com/article/novartis-to-open-new-r-d-facility-in-china-with-100-million-investment) <https://www.inj.com/media-center/press-releases/johnson-johnson-innovation-launches-asia-pacific-innovation-center-and-announces-new-alliances;>  
[https://www.merck.com/news/merck-establishes-new-msd-rd-asia-headquarters/;](https://www.merck.com/news/merck-establishes-new-msd-rd-asia-headquarters/)  
[https://www.yicai.com/news/sanofi-unveils-first-global-research-institute-in-china-to-develop-innovative-drugs;](https://www.yicai.com/news/sanofi-unveils-first-global-research-institute-in-china-to-develop-innovative-drugs) [http://www.chinadaily.com.cn/bizchina/2007-07/03/content\\_908686.htm;](http://www.chinadaily.com.cn/bizchina/2007-07/03/content_908686.htm)  
[https://focus.cbbc.org/astrazeneca-makes-shanghai-a-global-rd-centre/#.Yqr\\_anbMKUk;](https://focus.cbbc.org/astrazeneca-makes-shanghai-a-global-rd-centre/#.Yqr_anbMKUk)  
[https://www.amgen.com.cn/en/media/amgen\\_asia\\_research\\_development\\_center.html;](https://www.amgen.com.cn/en/media/amgen_asia_research_development_center.html)  
[https://www.fiercebitech.com/biotech/lilly-to-shutter-u-s-china-r-d-centers;](https://www.fiercebitech.com/biotech/lilly-to-shutter-u-s-china-r-d-centers)  
<https://www.novonordisk.com/science-and-technology/research-and-technology-centres.html> [Accessed June 2022]

<sup>75</sup> CSET Data Brief China is Fast Outpacing U.S. STEM PhD Growth 2021. Available at: <https://cset.georgetown.edu/publication/china-is-fast-outpacing-u-s-stem-phd-growth/> [Accessed June 2022]

taking the number one position on this list of top R&D institutes.<sup>76</sup> This showed a significant change from 2020, when only one Chinese institute reached the top 10 global R&D institutes list.<sup>77</sup>

- China is now a market that is seen to warrant or require a regional research centre. The opening of such a centre in China does not represent a move away from other regions, but the need for a new regional centre. Clearly, this is partly due to the growth of the Chinese economy and the growing importance of the Chinese pharmaceutical market. China's pharmaceutical market has been constantly growing in recent years. It is estimated to reach \$161.8 billion by 2023 and take a 30% share of the global market.
- China is strengthening its intellectual property (IP) laws in order to strengthen and support the pharmaceutical industry. Many of China's laws governing patents, trademarks, copyrights and other areas have recently been amended or are in the process of being amended, and it is acknowledged that the pharmaceutical industry will be a beneficiary of these changes.<sup>78</sup>

This would suggest that investments in China are not at the expense of investment in European research hubs, but rather indicate the development of a regional R&D hub in an increasingly important global market. However, the issue for the EU is that when choices regarding the location of new research hubs in Europe come along, the choice is focused on markets such as Switzerland and the UK, unless there are existing R&D hubs in EU markets.<sup>79</sup>

#### *The impact of new technology: learnings from ATMP research*

In the last chapter, we set out how some new therapeutic solutions, particularly ATMPs, appear to differ from overall trends. There is significant literature on the difference in the R&D process between ATMPs and other therapeutic areas – with distinct challenges in pre-clinical development, the clinical development programme, vector development and manufacturing, and patient-specific drug product manufacturing. Some of the complexities and differences are related to the nature of ATMPs relative to conventional medicines, whereas others arise from the rarity of the target patient population. This results in a subtle change in the factors driving a company's decision on where to locate research activities.<sup>80</sup>

- The strength of the overall innovation ecosystem, while important for all research activities, becomes more important for new emerging therapeutic solutions, such

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76 Nature Index 2022 tables: Institutions. Available at: <https://www.nature.com/nature-index/annual-tables/2022/institution/all/all/global> [Accessed September 2022]

77 FierceBiotech The top 10 global R&D institutes of 2021. Available at: <https://www.fiercebiotech.com/biotech/top-10-global-rd-institutes-2021> [Accessed September 2022]

78 China: Patent Law Amendment brings sea change to pharmaceutical patent regime; Available at: <https://www.allenoverly.com/en-gb/global/news-and-insights/publications/china-patent-law-amendment-brings-sea-change-to-pharmaceutical-patent-regime> [Accessed June 2022]

79 Information from interview programme with pharmaceutical company representatives, June–July 2022.

80 Information from interview programme with pharmaceutical company representatives, June–July 2022.

as ATMPs. Incubators and accelerators and access to funding are increasingly relevant for taking innovative (and potentially high-risk) scientific concepts forward.

- A company's existing R&D footprint plays less of a role in driving the decision, as ATMP facilities tend to be distinct from small molecules and biologics. The location of existing research staff is still somewhat relevant if there is considered the potential of retraining and redeploying staff, but the source of talent to drive the research programmes is largely considered to depend on the extent to which local universities are producing expert researchers.

It is clear that the US market is leading the development of ATMPs, but China appears to have a significantly higher share of R&D investments in this area, while Europe lags further behind. There are two potential reasons for this: the higher investments could represent the new area where strategic hubs are being decided (i.e. it is a timing issue rather than specific to the technology), or China has an advantage over Europe in these technologies.

In the literature, a number of reasons are used to explain the performance of China:<sup>81</sup>

- The result of STEM investment targeted in this area. According to the Chinese Academy of Sciences analysis, China generated 24,199 publications and 4,850 patent applications related to ATMPs between 1988 and 2017, ranking second after the US, which generated 36,901 publications and 14,573 patent applications.
- The regulatory environment is seen as supportive. In 2003, China became the first country worldwide to approve gene therapy. Although there are concerns about the lack of clear and strict regulatory frameworks, the series of regulatory reforms implemented by the government over the last 20 years is seen as encouraging progress.<sup>82</sup> In 2017, the National Development and Reform Commission (NDRC) issued the "13<sup>th</sup> Five-Year Biological Industry Development Plan", which stressed that the development of stem cell and CAR-T industry should be one of the main focuses in the next five years.
- There has been a push to encourage collaborations between multinational companies and their Chinese counterparts.

### 3.2. Clinical trials

There is common agreement that the factors affecting investment in research hubs and clinical trials are distinct. It is also important to differentiate between the different stages of clinical trials. The early stages have relatively few patients and are often more likely to be held in a relatively small number of locations. For phase III clinical trials, much larger patient populations are needed, and this is likely to mean more clinical centres in more countries. Indeed, for rare conditions, it may be necessary to conduct clinical trials across regions in order to find the required number of patients. It should also be noted that clinical trials are

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<sup>81</sup> Boodhoo, A. (2021) How China is making progress in cell and gene therapy. Available at: [https://www.ey.com/en\\_gl/life-sciences/how-china-is-making-progress-in-cell-and-gene-therapy](https://www.ey.com/en_gl/life-sciences/how-china-is-making-progress-in-cell-and-gene-therapy) [Accessed July 2022]

<sup>82</sup> Wang, Y. et al. (2022) An Overview of Cell and Gene Therapy Development in China. *Human Gene Therapy*. 33(1–2): 14–24.

often undertaken by contract research organisations (CROs), which have a significant role in the decision-making process.

#### *External factors affecting the location of clinical trial sites*

In terms of the main factors driving clinical trial location there appears a consensus that for the long, expensive development phases, it is essential to work with leading hospitals with world-class specialists in key disease areas, who conduct trials based upon the appropriate diagnostics methods and standard of care.<sup>83</sup>

Additional regulatory and practical considerations also apply, such as ease of trial approval, ease of patient recruitment, good clinical practice regulations with related inspections, and potential medicine regulators' preference for locally generated data.<sup>61,62,83</sup> While most regulators do not impose formal requirements for a specific proportion of clinical trial evidence to come from local populations, in practice regulators exhibit a preference for this, and applications for new drugs relying solely on data from a narrow range of countries require a defensible explanation from the submitting company (Table 1). However, there is evidence that flexibility is increasing for new technologies in rare diseases; for example, the European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) advisory committee recently recommended approval of gene therapy Upstaza for the treatment of aromatic L-amino acid decarboxylase (AADC) deficiency, largely based on the results of three clinical trials conducted in Taiwan, where the gene therapy was first developed.<sup>84</sup> This contrasts with the US Food and Drug Administration (FDA)'s recent rejection of Eli Lilly's PD-1 inhibitor Tyvyt based on clinical trial data generated solely in China, requesting that an additional multiregional trial be conducted.<sup>85</sup>

**Table 1: Guidance regarding regulatory requirements for local clinical trial evidence appears to be relatively uniform**

Location	Regulatory authority	Requirements
European Union	European Medicines Agency (EMA)	Guidelines indicate that a substantial proportion of the evidence in marketing authorisation dossiers is to be gathered in European populations. Guidance defines characteristics of a medicine's likely sensitivity to ethnic factors. <sup>86</sup>
United States	Food and Drug Administration (FDA) CDER/CBER/CDRA	Under 21 CFR 312.120 regulations, marketing approval of a new drug based solely on foreign

<sup>83</sup> Gehring, M. et al. (2013) Factors influencing clinical trial site selection in Europe: the Survey of Attitudes towards Trial sites in Europe (the SAT-EU Study). *BMJ Open*. 3(11): e002957.

<sup>84</sup> APM HealthEurope EMA acceptance of largely Taiwanese data for PTC's Upstaza partly down to ethnicity-neutral nature of gene therapy 2022. Available at: <https://www.apmhealthurope.com/story.php?objet=79823> [Accessed June 2022]

<sup>85</sup> Cancer Network FDA's ODAC Cites Need for Additional Research for Sintilimab Combo for Frontline NSCLC 2022. Available at: <https://www.cancernetwork.com/view/fda-s-odac-cites-need-for-additional-research-for-sintilimab-combo-for-frontline-nsclc> [Accessed July 2022]

<sup>86</sup> EMA Available at: [https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-5-r1-ethnic-factors-acceptability-foreign-clinical-data-step-5\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-5-r1-ethnic-factors-acceptability-foreign-clinical-data-step-5_en.pdf) [Accessed June 2022]

		clinical data is possible. <sup>87</sup> However, a common assumption applied in practice is that at least 20% of the clinical data should be gathered in US patients. <sup>88</sup>
<b>Japan</b>	Pharmaceuticals and Medical Devices Agency (PMDA)	If a product is likely to be affected by ethnicity, data generated in Japanese populations is required. If it is unlikely to be affected by ethnicity, this does not apply. <sup>89</sup>
<b>China</b>	State Administration for Market Regulation (SAMR)	If a product is likely to be affected by ethnicity, data generated in Chinese populations is required. If it is unlikely to be affected by ethnicity, this does not apply. <sup>90</sup>

Sources: Regulatory guidance

However, much of the literature recognised that there is also strategic commercial consideration in determining the location of clinical trial programmes. They are often spread across many OECD (Organisation for Economic Co-operation and Development) countries to provide a platform for international uptake. Having strong links to top clinical research centres locally which understand the new medicine is seen as a considerable asset. Logically, a major commercial market may be an attractive location for a clinical trial because of the advantages associated with familiarising clinical key opinion leaders with a new product pre-launch to support its rapid uptake post-marketing authorisation.<sup>91</sup> Furthermore, the Helsinki Declaration revision of 2013 stipulates patients participating in a clinical trial must retain post-trial access, which is now factored into decisions on where to initiate clinical trials.<sup>92</sup>

Commercial conditions may also indirectly influence the ability for a high-quality trial to be conducted. A restrictive pricing and access environment for innovative therapies can stagnate the standard of care in a market, as physicians may be treating patients with older, low-cost therapies rather than newer, high-cost therapies. From a clinical standpoint, this may be considered the most appropriate comparator for a clinical trial in the same therapy area. This could prevent a company from conducting a clinical trial in such a market in the

87 FDA Available at: <https://www.fda.gov/files/about%20fda/published/FDA-Acceptance-of-Foreign-Clinical-Studies-Not-Conducted-Under-an-IND--Frequently-Asked-Questions.pdf> [Accessed June 2022]

88 IQVIA Global approaches to drug development: when ex-US clinical data can support US drug approvals. Available at: <https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/global-approaches-to-drug-development.pdf> [Accessed June 2022]

89 <https://www.clinicalleader.com/doc/meeting-clinical-trial-data-requirements-in-asian-markets-0001> [Accessed June 2022]

90 Morgan Lewis (2018) China national drug administration sets guidelines for overseas drug trial data. Available at: <https://www.morganlewis.com/pubs/2018/08/china-national-drug-administration-sets-guidelines-for-overseas-drug-trial-data> [Accessed June 2022]

91 Bramley-Harker E., et al. (2007) Key Factors in Attracting Internationally Mobile Investments by the Research-Based Pharmaceutical Industry. London: NERA Economic Consulting.

92 Iunes, R. et al. (2019) Who should pay for the continuity of post-trial health care treatments? *International Journal for Equity in Health*. 18:26.

future because the outdated clinical guidelines used may not reflect what a comparator arm needs to be in an innovative clinical trial.<sup>93</sup>

Potentially this provides an explanation that reconciles the conflict in the literature, where statistical analyses show correlation between price regulations and location of clinical trials,<sup>94,95</sup> whereas many qualitative decision-maker interviews suggest that – although important – price regulation is not a key driver when deciding on location of clinical trials.<sup>96,97,98</sup> For example, it may be true that changes to price regulations in a country would not impact a company's near-term clinical trial location decision. However, over the long term, poor market conditions could impact the clinical standard of care and in five to 10 years could become a reason why that country is not a suitable location for clinical trials.

#### *Understanding global trends in clinical trial activity*

It is clear that Europe has been losing market share in terms of the location of clinical trials. According to GlobalData, Europe accounted for a 19.3% share of global clinical trial activity in 2020, a decrease of 6.3% compared with a 25.6% average over the last 10 years.<sup>99</sup> A number of reasons for this are stated in the existing literature:<sup>100</sup>

- The pool of eligible patients
- The speed of approvals
- Presence of disease-management networks
- Development of other geographical areas
- Costs and government financial incentives, although these were seen as relatively less important

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93 Information from interview programme with pharmaceutical company representatives, June–July 2022.

94 Golec, J. and Vernon, J.A. (2010) Financial effects of pharmaceutical price regulation on R&D spending by EU versus US firms. *Pharmacoeconomics*. 28(2): 615–628.

95 Eger, S. and Mahlich, J. C. (2014) Pharmaceutical regulation in Europe and its impact on corporate R&D. *Health Econ Rev.* 4:23.

96 Bramley-Harker, E. et al. (2007) Key Factors in Attracting Internationally Mobile Investments by the Research-Based Pharmaceutical Industry. London, UK: NERA Economic Consulting.

97 Information from interview programme with pharmaceutical company representatives, June–July 2022.

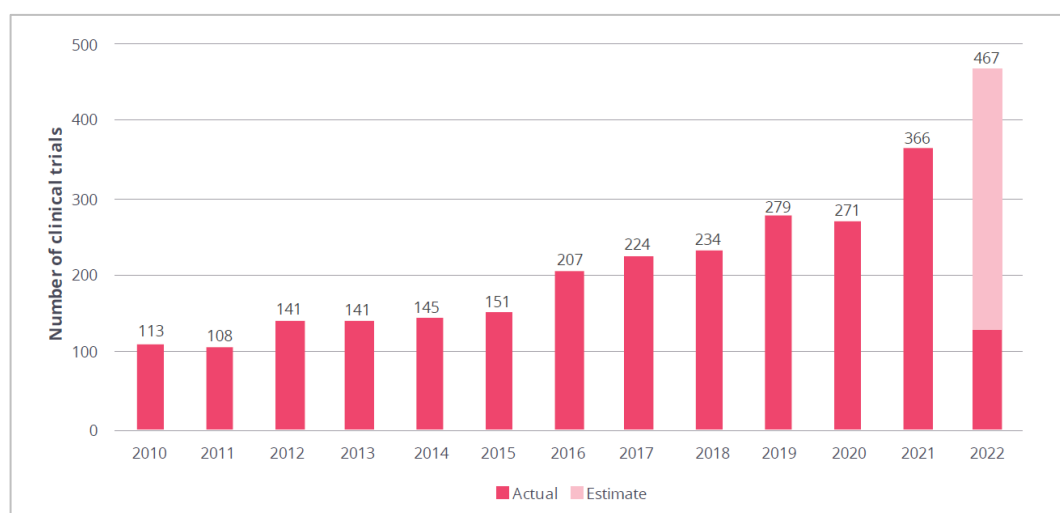
98 IQVIA (2022) Attracting Investment in Clinical Development. Available at: <https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/iqvia-attracting-investment-in-clinical-development.pdf>

99 Europe accounts for 19.3% share of global clinical trial activity in 2020. Available at: <https://www.clinicaltrialsarena.com/clinical-trials-analysis/europe-accounts-for-19-3-share-of-global-clinical-trial-activity-in-2020/> [Accessed June 2022]

100 Gehring, M., Taylor, R. S., Mellody, M., Casteels, B., Piazzi, A., Gensini, G., & Ambrosio, G. (2013). Factors influencing clinical trial site selection in Europe: the Survey of Attitudes towards Trial sites in Europe (the SAT-EU Study). *BMJ Open*, 3(11): e002957. Available at: <https://bmjopen.bmj.com/content/3/11/e002957>

Clinical trials have historically been concentrated around the clinical site, typically an academic or general hospital, employing experienced investigators and site staff. However, this could be changing with innovation. The increasing adoption of new technologies like artificial intelligence, big data analytics, blockchain, clinical trial payments, and patient engagement solutions, among others, have significantly contributed to the market growth (Figure 12). The COVID-19 pandemic has also improved the adoption of virtual clinical trials. There have been a number of interesting initiatives relating to the use of these technologies in clinical trials in Europe; for example, the Innovative Medicines Initiative (IMI)'s 'Trials@Home' project, which aims to conduct a pan-EU pilot on innovative, technology-led, decentralised clinical trial designs.<sup>101</sup> However, in overall adoption of digital health technologies, Europe has lagged behind other regions, such as the US, which is perceived to be at the forefront of the digital healthcare revolution,<sup>102</sup> putting Europe a step behind in attracting modern clinical trials.

**Figure 12: There has been strong growth in the number of clinical trials employing digital technologies or virtual interactions**



Sources: Trialtrove® (Pharma Intelligence), March 2022. Trialtrove consolidates data from over 58,000 distinct trial intelligence sources.

More generally, the COVID-19 pandemic had an impact on the location of clinical trials. While Europe initially observed a smaller negative impact than the US, there is evidence that the US has rebounded more quickly.<sup>103</sup>

#### *The impact of new technology: learnings from ATMP clinical trials*

As observed in the last chapter, the location of clinical trials for ATMPs diverges from the general pattern of global clinical trial investments, with the highest proportion of trials occurring in Asia, followed by the US, and then Europe, which has substantially fewer

101 Trials@Home Available at: <https://trialsathome.com/> [Accessed July 2022]

102 Keen, C. E. (2018) The USA's digital healthcare revolution. Available at: <https://healthcare-in-europe.com/en/news/the-usa-s-digital-healthcare-revolution.html> [Accessed July 2022]

103 Lasch, F. et al. (2022) The Impact of COVID-19 on the Initiation of Clinical Trials in Europe and the United States. *Clinical Pharmacology & Therapeutics*. 111(5): 1093–1102.



(Figure 5). To understand this trend, a number of reasons have been suggested in the literature:

- *The importance of R&D support:* China's leadership in ATMP clinical trial research has been largely government-driven (three quarters of Chinese gene therapy trials are non-industry sponsored).<sup>104</sup> Biotech was prioritised in the Chinese government's Five-Year Plans and subsequently built upon by a series of policies and funding to create an ATMP research ecosystem that brings together government, industry, academics, hospitals and investors. In the US, access to more venture capital also supports greater translation of ATMP research into commercial development, as 85% of ATMP assets launched to date have not originated in a large pharmaceutical company.<sup>105</sup>
- *Regulator acceptance of clinical trial design:* Due to the novelty of the technology and the number of rare diseases that lack therapeutic alternatives, there are not always established pathways for ATMP clinical development.<sup>106</sup> This results in the regulatory environment weighing more heavily on a decision on where to conduct trials for ATMPs versus traditional therapies. There is also increasing reliance on virtual decentralised clinical trial models to recruit a wider pool of patients in rare diseases,<sup>107</sup> although historically there has been some reluctance to accept these models in Europe.<sup>108</sup> Despite being the first country worldwide to approve a gene therapy, in 2003, China initially lacked a clear and comprehensive regulatory framework for these therapies, which is thought to have damaged its attractiveness for future development investment. Triggered by their therapeutic potential and the rapid growth of the market, the government then conducted a range of regulatory reforms to promote the development of ATMPs in China.<sup>109</sup>
- *The role of specialist centres:* There are multiple hospitals in China sponsoring CAR-T trials, with the four most prominent being Shenzhen Geno-Immune Medical Institute, Beijing Boren Hospital, Chinese PLA General Hospital (in Beijing) and

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104 Clinical Trials Arena (2021) The changing dynamics of gene therapy research: 2001–2021. Available at: <https://www.clinicaltrialsarena.com/comment/gene-therapy-research/> [Accessed July 2022]

105 McKinsey & Company (2021) A call to action: Opportunities and challenges for CGTs in Europe. Available at: <https://www.mckinsey.com/industries/life-sciences/our-insights/a-call-to-action-opportunities-and-challenges-for-cgts-in-europe> [Accessed July 2022]

106 Ilieva, K. Borissov, B. and Toumi, M. (2020) Gene therapy randomised clinical trials in Europe – a review paper of methodology and design. *J Mark Access Health Policy*. 8(1): 1847808.

107 Raconteur. How Covid-19 rocked rare disease communities 2021. Available at: <https://www.raconteur.net/healthcare/covid-rare-disease-impact/> [Accessed July 2022]

108 De Jong, A. J. et al. (2022) Opportunities and Challenges for Decentralized Clinical Trials: European Regulators' Perspective. *Clinical Pharmacology and Therapeutics*. 112(2): 344–352.

109 Wang, A. et al. (2022) An Overview of Cell and Gene Therapy Development in China. *Human Gene Therapy*. 33(1–2): 14–24.

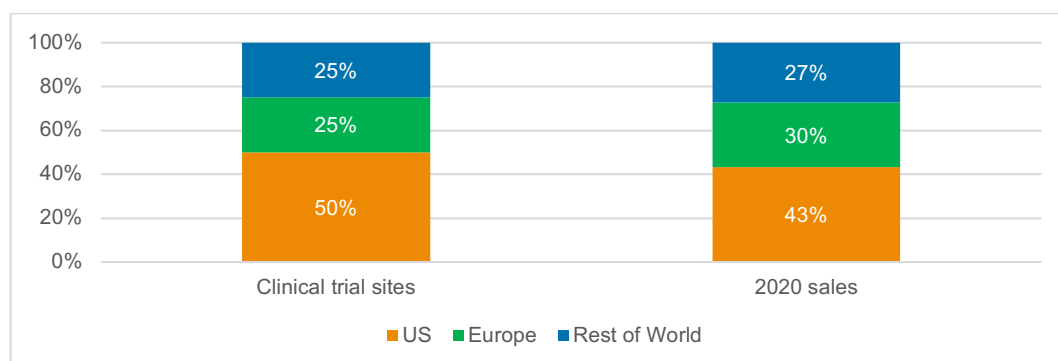
Southwest Hospital (in Chengdu, Sichuan).<sup>110</sup> The active role of hospitals in sponsoring trials appears lesser in the US<sup>111</sup> and Europe.<sup>112</sup>

- *Degree of patient centricity:* A patient-centric approach to healthcare delivery is critical to the successful uptake of ATMPs and thus forms a larger part of the decision of where to locate clinical development activity.

The pricing environment may also be more significant in locating new therapeutic solutions, such as ATMP, because they are perceived as riskier investments. One way to look at this is to consider CAR-T cell therapies that were first launched in 2017. By comparing the location of the pivotal trial sites to the eventual commercial sales in each region, we see a similar pattern. The US accounted for 50% of trial site locations in the JULIET Phase 2 trial, and in 2020 the US represented 43.2% of global sales at that point (Figure 13), while 25% of trial sites were in Europe, and Europe represented 29.5% of global sales in 2020. A challenging commercial environment may also impact post-launch clinical research, and send a signal to other developers: with Glybera, the first gene therapy approved in Europe, in 2012, poor commercial uptake of the drug post-launch led to its eventual withdrawal from the European market and termination of the European Phase IV studies that the EMA had required.<sup>113,114</sup> Subsequently, between 2012 and 2020, Europe's share of global gene therapy clinical trials fell from 30.5% to 19.3%.<sup>115</sup>

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- 110 Boodhoo, A. (2021) How China is making progress in cell and gene therapy. Available at: [https://www.ey.com/en\\_my/life-sciences/how-china-is-making-progress-in-cell-and-gene-therapy](https://www.ey.com/en_my/life-sciences/how-china-is-making-progress-in-cell-and-gene-therapy) [Accessed July 2022]
- 111 Kassir, Z. et al. (2020) Sponsorship and Funding for Gene Therapy Trials in the United States. *JAMA*. 323(9): 890–891.
- 112 Catapult. The Cell and Gene Therapy Catapult UK clinical trials database. Available at: <https://ct.catapult.org.uk/clinical-trials-database> [Accessed July 2022]
- 113 MIT Technology Review (2016) The World's Most Expensive Medicine Is a Bust. Available at: <https://www.technologyreview.com/2016/05/04/245988/the-worlds-most-expensive-medicine-is-a-bust/> [Accessed July 2022]
- 114 Labiotech (2017) Goodbye Glybera! The World's First Gene Therapy will be Withdrawn. Available at: <https://www.labiotech.eu/trends-news/unique-glybera-marketing-withdrawn/> [Accessed July 2022]
- 115 Clinical Trials Arena (2021) Europe accounts for 19.3% share of global clinical trial activity in 2020. Available at: <https://www.clinicaltrialsarena.com/clinical-trials-analysis/europe-accounts-for-19-3-share-of-global-clinical-trial-activity-in-2020/> [Accessed July 2022]

**Figure 13: The location of clinical trial sites and commercial sales of first cell therapies are similar**



Source: clinicaltrials.gov and EvaluatePharma, accessed July 2022.

### 3.3. Investigational and commercial manufacturing sites

Manufacturing facility investment decisions differ from research hub decisions in that they are made more frequently, as companies aim to upscale and upgrade their production capacity and capabilities to manage evolving demand, access new markets and manage the evolution of their portfolio. However, there are still long-term commitments that are, therefore, often strategically important. It is also important to distinguish between the commercial manufacturing of medicines and the manufacturing for supply of IMPs for clinical studies.

IMP and commercial manufacturing have different characteristics which may impact what makes a particular location more or less attractive for investment:

- *Scale*: Products going through clinical development are produced in much lower quantities and have more predictable demands for the specific clinical studies than commercial products being produced for global delivery to patients, for which the demand may vary extremely in the first years of being marketed and afterwards based on various factors (e.g. as a result of epidemics or pandemics in extreme circumstances, or more commonly as a result of changes in competition in the market, or unanticipated off-label use).
- *Need for revision and flexibility*: During the development process, there is a need to produce sufficient volume for the clinical trials but also to investigate and overcome the challenges affecting commercial production. Any changes in the production process affect the regulatory process.

API and manufacturing associated with formulation and finishing also have different characteristics, largely related to the degree of outsourcing and how production can be undertaken most efficiently, as does whether the product is on- or off-patent.

The type of manufacturing affects the strategic choice of which parts of the manufacturing process to undertake and where to partner with other companies, for example through contract manufacturing organisations (CMOs) and contract development and manufacturing organisations (CDMOs), as illustrated in Figure 14, and the location decision.

- *IMP versus commercial production*: Pharmaceutical companies often outsource IMP manufacturing to CDMOs; commercial manufacturing is more likely to occur

in-house using a pharmaceutical company's own manufacturing sites and capacities where the manufacturing can be combined with other products in the portfolio using similar or the same equipment to use capacity effectively.<sup>116</sup>

- *API versus formulation and finishing:* Over the last 20 years we have seen companies continue to outsource the production of large-scale raw materials and APIs to specialised companies. In fact, the growth of the CMO/CDMO market is expected to outpace the growth of the overall pharmaceutical industry between now and 2025, with the majority of outsourcing to CDMOs occurring at the API production stage rather than at finished product manufacturing or packaging.<sup>117</sup> Outsourcing of production is particularly prevalent in the Asia-Pacific region, where it is estimated that the CDMO market will be worth over \$80 billion by 2025 (versus \$34 billion and \$23 billion in North America and Europe, respectively).<sup>118</sup> This is particularly driven by outsourcing API manufacturing to countries such as China and India as a result of low labour and production costs.<sup>119</sup> Although data are not yet available, we might expect the COVID-19 pandemic, the energy crisis and environmental or transport-related aspects to impact companies' attitudes towards outsourcing.
- *Generic versus on-patent medicines:* Although there is a common perception that API manufacturing is not undertaken in Europe, this is confusing the manufacturing of innovative medicines with off-patent medicines. For generics, Europe is highly dependent on Asia; in terms of APIs and precursors, European direct and indirect dependency is estimated to be around 74%.<sup>120</sup> However, for innovative medicines, a 2020 survey of 16 EFPIA member companies reported that 64% of APIs are still manufactured in Europe, with 15% manufactured in North America and only 11% in both China and India combined.<sup>121</sup> The majority of European chemical APIs use raw materials manufactured in Europe (64%), but there is also dependency on India and China (29% of raw materials) and the US (5%).

This shows that European production remains an important element for the research-based companies, at least in ensuring the quality and sustainability of European medicine supply chains, but remains interwoven with the global supply chain.

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116 Information from interview programme with pharmaceutical company representatives, June 2022.

117 PwC (2019) Current trends and strategic options in pharma CDMO market. Available at: <https://www.pwc.de/de/gesundheitswesen-und-pharma/studie-pharma-cdmo-market.pdf> [Accessed July 2022]

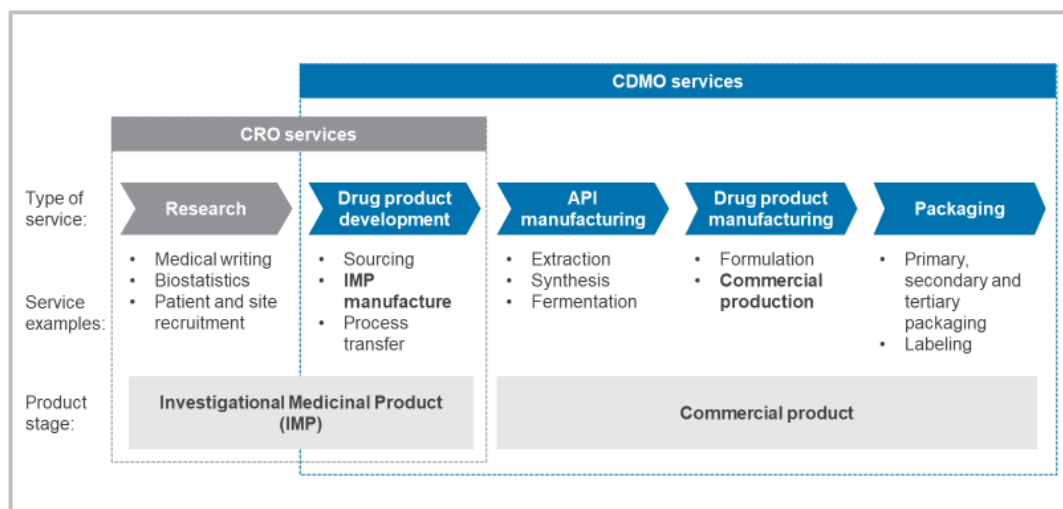
118 <https://www.grandviewresearch.com/industry-analysis/pharmaceutical-contract-manufacturing-market> [Accessed July 2022]

119 IQVIA (2020) EU Fine Chemical Commercial KPI. Available at: [https://efcg.cefic.org/wp-content/uploads/2021/06/20201211\\_IQVIA-for-EFCG\\_Executive-summary.pdf](https://efcg.cefic.org/wp-content/uploads/2021/06/20201211_IQVIA-for-EFCG_Executive-summary.pdf) [Accessed July 2022]

120 IQVIA (2020) EU Fine Chemical Commercial KPI. Available at: [https://efcg.cefic.org/wp-content/uploads/2021/06/20201211\\_IQVIA-for-EFCG\\_Executive-summary.pdf](https://efcg.cefic.org/wp-content/uploads/2021/06/20201211_IQVIA-for-EFCG_Executive-summary.pdf) [Accessed July 2022]

121 EFPIA (2021) Drug Shortages in Europe: 2nd EPFIA member companies survey investigating the role of API as a possible root-cause for drug shortages.

**Figure 14: The decision of where to locate manufacturing activities depends on which type of activity is being undertaken**



Source: Adapted from PwC (2019)<sup>122</sup>

In-house manufacturing remains important, especially for research-based manufacturers to gain knowledge and the ability to share and understand the processes, particularly for commercial production, and companies are unlikely to entirely outsource production. We can see this when looking at the number of sites owned by major pharmaceutical companies with many marketed products: while Pfizer only has eight major research centres, it lists 35 manufacturing sites across six continents.<sup>123</sup> Given the complexity and vulnerability of global supply chains, it is imperative that a company's global network of manufacturing plants enable it to reliably meet demand and support business growth. The location of these plants is therefore something under frequent review and consideration.<sup>124</sup>

#### *Factors affecting the location of manufacturing investments*

As with R&D, manufacturing decisions are not made from a blank page; internal company considerations strongly influence the decision on manufacturing location for both IMP and commercial manufacturing.<sup>125</sup> In fact, multinational companies expand their existing production sites up to six times as often as they establish new facilities, likely as this involves fewer costs and relocation of existing resources.<sup>126</sup> Internal company-driven factors can also be relevant at the final decision-making step: even if a location is deemed attractive for cost, quality, reliability or market-driven reasons as well as demand, lack of

<sup>122</sup> PwC (2019) Current Trends and Strategic Options in the Pharma CDMO Market. Available at: <https://www.pwc.de/de/gesundheitswesen-und-pharma/studie-pharma-cdmo-market.pdf> [Accessed July 2022]

<sup>123</sup> Pfizer. Available at: <https://www.pfizercentreone.com/manufacturing-network> [Accessed July 2022]

<sup>124</sup> ReliablePlant, Pfizer announces plans to reconfigure its global plant network. Available at: <https://www.reliableplant.com/Read/24643/Pfizer-reconfigure-plant-network>

<sup>125</sup> Information from interview programme with pharmaceutical company representatives, June–July 2022.

<sup>126</sup> Guimón, J. (2008) Government strategies to attract R&D-intensive FDI. *The Journal of Technology Transfer*. 34(4): 364–379.

internal capabilities or resources to exploit these conditions may nullify its attractiveness.<sup>127</sup> This inevitably means there is considerable inertia, and moving away from an existing location of manufacturing needs to be justified. Often the decision to move away is attributable to long-term negative drivers away from the existing site (such as trade barriers, and inflexibility to expand locally) rather than positive drivers associated with a new potential site (such as lower labour costs).<sup>128</sup>

Looking at the external environment, the consensus in the literature is that the overall cost plays a bigger role for commercial manufacturing than for manufacturing of IMPs. This was corroborated by our interview programme.

Literature from the 1990s onwards also emphasises that taxation is a critical cost factor for manufacturing investments; from both statistical analysis and qualitative interviews, it is clear that high tax rates act as a major deterrent for manufacturing investments.<sup>129,130</sup> Typically ranking second is labour flexibility, which allows companies to move more easily to new activities, and is viewed as more important than the cost of labour itself.<sup>129</sup> As a stand-alone metric, some modelling has suggested labour cost does not significantly impact manufacturing location choice as it can be balanced with productivity.<sup>131</sup> Transport costs are less important still, as they generally account for a small proportion of the overall cost of production. However, this may change in the future. Cost factors are collectively considered more critical by our interviewees for large-scale commercial manufacturing with evolving demands than for small-scale IMP manufacturing.

For commercial manufacturing, it is still seen as imperative that locations meet quality levels, mainly in terms of availability of a skilled workforce, compliance with internationally recognised regulatory standards (such as good manufacturing practices and inspections) and infrastructure (such as reliable power and water supply, and access to support services).<sup>129,132</sup>

For IMP manufacturing, the need for high quality and efficient processes that allow fast speed to market largely dominates over cost. The key drivers reported by our interviewees overlap more with research activities than with commercial manufacturing, namely the need for access to highly qualified staff to drive process development.<sup>133</sup> The impact of this is

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127 Theyel, G., Hofmann, K. and Gregory, M. (2018). Understanding Manufacturing Location Decision Making: Rationales for Retaining, Offshoring, Reshoring, and Hybrid Approaches. *Economic Development Quarterly*. 32(4): 300–312.

128 Information from interview programme with pharmaceutical company representatives, June–July 2022.

129 Rozek, R.P. (2011) Risk and Regulatory Factors Affecting Location Decisions by Research-Based Pharmaceutical Companies. *European Journal of Risk Regulation*. 2(1): 92–103.

130 Devereux, M.P. and Griffith, R. (1998). Taxes and the location of production: evidence from a panel of US multinationals. *Journal of Public Economics*. 68(3): 335–367.

131 Guimón, J. (2008) Government strategies to attract R&D-intensive FDI. *The Journal of Technology Transfer*. 34(4): 364–379.

132 United Nations Conference on Trade and Development (2011). Investment in Pharmaceutical Production in the Least Developed Countries: A Guide for Policymakers and Investment Promotion Agencies. Available at: [https://unctad.org/system/files/official-document/diaepcb2011d5\\_en.pdf](https://unctad.org/system/files/official-document/diaepcb2011d5_en.pdf) [Accessed June 2022]

133 Information from interview programme with pharmaceutical company representatives, June–July 2022.

evident from recent IMP manufacturing facilities established by major pharmaceutical companies, which tend to locate in areas of concentrated academic expertise (Box 4).

**Box 4: Case study | Investment to bridge development and manufacturing for clinical trials**

In 2020, Merck KGaA announced a €250 million investment in Switzerland, aiming to bridge biotech development and manufacturing for clinical trials in order to support growth and progression of Merck's biologic pipeline and get medicines to patients earlier.<sup>134</sup> Particularly for biologics, which are more complex to produce than small molecules, this choice of location enables the facility to access high-quality staff in two ways:

- Close proximity to Merck's existing manufacturing site in Corsier-sur-Vevey, Switzerland. This allows ease of transfer of internal knowledge and expertise.
- Switzerland is perceived to have high-quality infrastructure for complex manufacturing and is globally renowned in life sciences, with over 45,000 life sciences employees in the country.<sup>135</sup> Switzerland was also ranked first in the Global Talent Competitiveness Index (GTCI) in 2020, demonstrating its strong talent base.<sup>136</sup>

The importance of tax rates, labour skill, regulations and quality infrastructure can explain the development of clusters where many companies have located manufacturing activities. In Ireland, for example, despite being one of the smallest countries in the EU by geographic area, all of the world's top 10 pharmaceutical companies have operations, and there are 90 pharmaceutical and biopharmaceutical plants throughout the country.<sup>137</sup> This is attributed to consistent low corporate taxation, low labour costs and high workforce skills.<sup>138</sup> Once established, the benefits of a cluster become self-justifying. The benefits to a company in joining a cluster include the existing stock of skilled staff and the established infrastructure, such as availability of manufacturing support service firms. Co-location with the chemical industry can offer efficiency benefits, as can co-location with the source of raw materials.<sup>139</sup> This gravitational pull effect can be observed when clusters' attractive

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134 FiercePharma (2020) Merck KGaA antes up €250M to bridge R&D with manufacturing. Available at: <https://www.fiercepharma.com/manufacturing/merck-kga-a-antes-up-eu250m-to-bridge-r-d-manufacturing> [Accessed July 2022]

135 Interpharma, Switzerland as a pharma hub. Available at: <https://www.interpharma.ch/themen/starke-wirtschaftliche-rahmenbedingungen/pharmastandort-schweiz/?lang=en> [Accessed July 2022]

136 Hobson Prior (2020) Why are there so many pharmaceutical companies in Switzerland? Available at: <https://www.hobsonprior.com/blog-post/2020-8/why-are-there-so-many-pharma-companies-in-switzerland> [Accessed July 2022]

137 Hobson Prior (2020) Why are there so many pharmaceutical companies in Switzerland? Available at: <https://www.hobsonprior.com/blog-post/2020-8/why-are-there-so-many-pharma-companies-in-switzerland> [Accessed June 2022]

138 Siedschlag, I., Yan, W. and Driffield, N. (2021) Enhancing the Attractiveness of the Island of Ireland to High-Value Foreign Direct Investment. ESRI Research Series 133. Available at: <https://www.esri.ie/publications/enhancing-the-attractiveness-of-the-island-of-ireland-to-high-value-foreign-direct> [Accessed June 2022]

139 Ruane, F.P. and Zhang, X. The Determinants of Location Choices by Pharmaceutical MNEs in Europe. Available at: <https://www.etsg.org/ETSG2008/Papers/Ruane.pdf> [Accessed June 2022]

conditions remain stable over time and companies continue to benefit from co-location; Ireland, for example, was home to only two biologics manufacturing sites in 2003, and by 2020 this had increased tenfold to 20 sites.<sup>137</sup> Modelling also indicates that companies are more likely to expand production at sites that are located in a cluster with other companies.<sup>140</sup> We now see the attractiveness of the Irish cluster extending beyond European and US-based companies and also attracting investment from Chinese-based companies (Box 5) due to the quality, stability and reliability of the business environment.

#### **Box 5: Case study | Foreign direct investment into Ireland cluster**

In 2018, the first major FDI greenfield pharmaceutical manufacturing project from China was announced by WuXi Biologics, a major Chinese contract manufacturing organisation. The location chosen was Dundalk, Ireland.<sup>141</sup> Looking to expand operations outside of China, Europe was the initial region of choice (although operations are also expected in North America from 2024).<sup>142</sup> Considering the potential locations within Europe, Ireland was most attractive to WuXi Biologics for a number of reasons:<sup>143</sup>

- As a Chinese company with no experience of European business operations, the presence of all of the top 10 global pharmaceutical companies in Ireland increases confidence to invest.
- The existing cluster also means support service firms are nearby and easily accessible to support establishment and operation of the site.
- An English-language-speaking business environment is more accessible to Chinese-speaking headquarter staff than an alternative European language.
- Proximity and ease of movement to the rest of the EU allows access to the European market; good transport links to China facilitate interaction with headquarters.
- The 12.5% corporate tax rate helps to de-risk investment, which as the first ex-China greenfield project could be considered high-risk.
- Existence of a sizeable and highly qualified labour pool allows rapid recruitment and start-up of operations.
- The Irish government provides strong support through the Industrial Development Agency (IDA) Ireland, for example through pre-purchase and preparation of the site by IDA Ireland before sale to WuXi.

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140 Ruane, F.P. and Zhang, X. The Determinants of Location Choices by Pharmaceutical MNEs in Europe. Available at: <https://www.etsg.org/ETSG2008/Papers/Ruane.pdf> [Accessed June 2022]

141 The Irish Times (2021) Wuxi Biologics Ireland in €679.6m gain after restructuring. Available at: <https://www.irishtimes.com/business/health-pharma/wuxi-biologics-ireland-in-679-6m-gain-after-restructuring-1.4699274> [Accessed June 2022]

142 Wuxi Global Network. Available at: [https://www.wuxibiologics.com/locations-facilities/#Global\\_Network](https://www.wuxibiologics.com/locations-facilities/#Global_Network) [Accessed June 2022]

143 Information from interview programme with WuXi representative, June 2022.



There are also potential drawbacks to locating in a cluster. For example, companies in a cluster may lose staff to other firms, potentially resulting in a wage ‘bidding war’ between co-located companies,<sup>144</sup><sup>64</sup> but the upside of knowledge availability is typically stronger.

*Understanding global policy trends: localisation of manufacturing*

As a potential disruptor to the cluster model, in recent years an increasing number of countries have considered manufacturing localisation policies. These policies can favour domestic manufacturing at the expense of products from other countries (‘forced localisation’). Policies can take multiple forms:<sup>145</sup>

- Intellectual property (IP)-based rules that support speed and breadth of IP protection and ability to defend it
- Regulatory rules that impact the speed and approval in regulatory submissions
- Reimbursement, pricing and procurement rules
- Absence of trade barriers such as import or export bans for components, raw and the final material, favour of a locally produced alternative (for generics only) or discriminatory taxation policies

Until recently, localisation policy debate and implementation has primarily occurred with governments aiming to drive localisation for perceived economic or health system benefits. This was applied by China, with the ‘Made in China 2025’ strategy aiming to increase local manufacturing of innovative pharmaceutical and medical devices in China, supporting a lower time to access and increased availability of innovative drugs.<sup>146</sup> Innovative medicines produced locally benefit from a number of policies, including reduced corporate tax rates<sup>147</sup> and priority regulatory review.<sup>148</sup> We can observe increased pressures for reshoring or localisation in the EU Member States, which risk harming Europe’s global competitiveness, given the potential for retaliation or reciprocal measures from other economies.<sup>149</sup> To date, the EU has supported global supply chains, and successfully defended against the implementation of forced localisation policies, most recently in Turkey, with the World Trade

144 Ruane, F.P. and Zhang, X. The Determinants of Location Choices by Pharmaceutical MNEs in Europe. Available at: <https://www.etsg.org/ETSG2008/Papers/Ruane.pdf> [Accessed June 2022]

145 Perspectives on Trade 2017 Trade Barriers Report: Government Procurement. Available at: <https://trade.djaghe.com/?p=3911>

146 Institute for Security & Development Policy. Made in China 2025. Available at: <https://isdp.eu/content/uploads/2018/06/Made-in-China-Backgrounder.pdf>

147 PugatchConsilium (2016) Separating Fact from Fiction – How Localization Barriers Fail Where Positive Non-discriminatory Incentives Succeed. Available at: [https://www.pugatch-consilium.com/reports/Localization%20Paper\\_US\\_FINAL.pdf](https://www.pugatch-consilium.com/reports/Localization%20Paper_US_FINAL.pdf)

148 ITIF (2019) China’s Biopharmaceutical Strategy: Challenge or Complement to U.S. Industry Competitiveness? Available at: <https://itif.org/publications/2019/08/12/chinas-biopharmaceutical-strategy-challenge-or-complement-us-industry>

149 EFPIA (2020) COVID-19 Key Messages regarding International Trade. Available at: <https://www.efpia.eu/media/554474/covid-19-and-international-trade.pdf> [Accessed July 2022]

Organization (WTO) ruling against forced localisation measures in July 2022 being upheld.<sup>150</sup>

Although the localisation debate started in the EU with the discussion on drug shortages, it has accelerated as a result of a crisis situation (initially the Iceland volcano eruption, followed by the COVID-19 pandemic), as countries seek localisation as an empirical means to protect supply continuity in case of global supply chain disruption. Although in 2021 the Biden Administration withdrew the proposal,<sup>151</sup> forced localisation was politically backed in the US in 2020 with the Trump administration's 'Buy American' Executive Order for purchases of essential medicines, requiring that these be removed from the coverage of any international free trade agreements.<sup>152</sup> Similar debates can be observed in Russia, Brazil, Turkey and China. In the EU, the European Parliament has highlighted the importance of a more proactive EU policy on reshoring the pharmaceutical industry to mitigate concerns around supply security, focusing on generic API.<sup>153</sup>

#### *The impact of new technology: learnings from continuous manufacturing*

Crisis situations like the COVID-19 pandemic have also accelerated other manufacturing trends. Well-established techniques in other industries (e.g. food and vitamins) such as continuous manufacturing have often been cited as another solution for increasing the strength of pharmaceutical supply chains, and the pandemic has reinvigorated this.<sup>154</sup> Furthermore, there is the development of the harmonised standard for filing under the International Council for Harmonisation (ICH Q13 guideline). Continuous manufacturing contrasts with traditional batch manufacturing in that the production of APIs or drugs occurs in a continuous flow rather than in stop-start multi-step batches.<sup>155</sup> Furthermore, it can decrease the environmental footprint by enabling smaller factory sizes, using less territory and energy, as well as reducing unproductive cleaning cycles. Even smaller quantities can be manufactured, and alternative facility setups can be used, such as containers.

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150 European Commission (2022) Press release: "EU wins WTO case against Turkey's discriminatory practices on pharmaceuticals". Available at: [https://ec.europa.eu/commission/presscorner/detail/en/IP\\_22\\_4670](https://ec.europa.eu/commission/presscorner/detail/en/IP_22_4670) [Accessed July 2022]

151 The National Law Review, "Buy American" Update: Essential Medicines May Continue to Come From Abroad (For Now). Available at: <https://www.natlawreview.com/article/buy-american-update-essential-medicines-may-continue-to-come-abroad-now>

152 Perspectives on trade. Trump's Buy American Order for Medicines. Available at: <https://trade.djaghe.com/?p=6547>

153 Policy Department for External Relations Directorate General for External Policies of the Union. Post Covid-19 value chains: options for reshoring production back to Europe in a globalised economy. Available at: [https://www.europarl.europa.eu/RegData/etudes/STUD/2021/653626/EXPO\\_STU\(2021\)653626\\_EN.pdf](https://www.europarl.europa.eu/RegData/etudes/STUD/2021/653626/EXPO_STU(2021)653626_EN.pdf)

154 Pharmaceutical Technology. Continuous manufacturing builds on hype but adoption remains gradual. Available at: <https://www.pharmaceutical-technology.com/analysis/continuous-manufacturing-builds-on-hype-but-adoption-remains-gradual/>

155 FDA. Modernizing the Way Drugs Are Made: A Transition to Continuous Manufacturing. Available at: <https://www.fda.gov/drugs/news-events-human-drugs/modernizing-way-drugs-are-made-transition-continuous-manufacturing>

The pandemic increased the debate on continuous manufacturing, although a trend was already evident with major pharmaceutical companies such as Novartis, Johnson & Johnson, Amgen, and Eli Lilly making use of the technology for parts of their manufacturing processes.<sup>156</sup> Although this may not affect location decisions for some companies – Pfizer, being one of the first companies to venture into continuous manufacturing technology, chose to upgrade their existing site in Germany rather than adopt a different location strategy (Box 6) – for others continuous manufacturing enables all stages of the production chain (Figure 14) from raw material through to packaging to occur at a single site, so we would expect this to influence investment decisions.<sup>156</sup>

#### **Box 6: Case study | Investment in continuous manufacturing plant in Germany**

Pfizer was an early adopter of continuous manufacturing technology, opening the world's first continuous manufacturing facility for the pharmaceutical industry in Freiburg, Germany, in 2017.<sup>157</sup> The main decision for the company to make was whether to invest in this type of technology or not, rather than where would be a viable place to do so. As continuous manufacturing sites produce finished products, existing reliable Pfizer manufacturing sites with the capabilities of launching new products and in locations where there would be unrestricted access to global markets were the main contenders for locating the new technology. By avoiding a greenfield investment, efficiencies were gained from leveraging the utilities, infrastructure and labour skill at the existing site.<sup>158</sup>

Therefore, some shortening of the industry value chain appears inevitable.

#### *The impact of new technology: learnings from ATMP manufacturing*

Relative to other technologies, manufacturing of certain new therapeutic solutions, particularly ATMPs, is complex, high-risk, more time-sensitive, and smaller-scale. This is particularly the case for ex vivo products, given the need to manufacture for individual patients using their source material, leading to additional cost and a need for advanced technical expertise and support. The consistency of manufacturing quality is also more critical: while new drug reviews by regulators typically focus 80% on clinical factors and 20% on chemistry, manufacturing and controls (CMC) factors, for ATMPs this ratio is reversed. Currently, this may be driven in part by the unknowns in the new technology.<sup>159</sup> For these and other new technologies, the concept of “the process being the product” is even more true, and therefore manufacturing quality needs to stay consistent from Phase 1 through to commercial rollout. The location of the source of raw materials for ATMPs must also be considered, as the value chains need to be structured differently:

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156 World Economic Forum (2021) Top 10 Emerging Technologies of 2021. Available at: [https://www3.weforum.org/docs/WEF\\_Top\\_10\\_Emerging\\_Technologies\\_of\\_2021.pdf](https://www3.weforum.org/docs/WEF_Top_10_Emerging_Technologies_of_2021.pdf)

157 Healthcare Industry BW, Industry 4.0: Pfizer opens continuous manufacturing plant in Freiburg. Available at: <https://www.gesundheitsindustrie-bw.de/en/article/news/industry-40-pfizer-opens-continuous-manufacturing-plant-in-freiburg>

158 Information from interview programme with Pfizer representative, June 2022.

159 Deloitte (2020) Cell and gene therapies: Delivering scientific innovation requires operating model innovation. Available at: <https://www2.deloitte.com/us/en/insights/industry/life-sciences/operating-models-for-gene-cell-therapy-manufacturing-process.html> [Accessed July 2022]

- For ex vivo therapies, such as autologous cell therapies, the patient is the source of raw materials.
- For in vivo therapies, such as viral vector gene therapies, raw materials are not required from patients.

For ex vivo therapies, there is therefore a need for manufacturing to occur in closer proximity or with ease of transport to where the therapy is been administered to patients. The limited stability of the material, once collected, will reduce over time post-collection, and therefore manufacturing location must be chosen in part based on availability of appropriate resources for shipping and processing starting materials.<sup>160</sup> The current concentration of ATMP manufacturing on the US East Coast can in part be attributed to the strong transport and logistics infrastructure<sup>161</sup> and the innovation centres linked to a strong landscape of universities. The critical need for effective transportation routes was highlighted during the COVID-19 pandemic when two thirds of cell therapy companies reported supply chain disruptions caused by transport and travel restrictions of regulators to approve these products.<sup>162</sup>

To ensure an efficient manufacturing process, there is also a greater need versus traditional therapies for high flexibility and to be ready to start manufacturing when a patient enrolls onto the therapy: personnel, cold rooms (needed to guarantee stability) and innovative equipment must be ready at any time, meaning clean rooms will run below capacity for a significant proportion of time.<sup>163</sup> Hospital or bedside manufacturing might be anticipated in the future; this is currently in a pilot phase.

The manufacturing of both ex vivo and in vivo ATMPs relies on access to highly qualified staff, given the complexity of the manufacturing processes. With the increasing number of ATMPs being developed globally, demand for talent is high and can limit the expansion of manufacturing capacity. Companies so far have launched most of the world's ATMPs out of the US and have focused on building manufacturing capacity in the US first before expanding to Europe. Indeed, estimates suggest that two of the largest ATMP manufacturing plants in the US will soon match Europe's total manufacturing capacity.<sup>164</sup> European scientists are therefore being drawn to the US for job opportunities, creating a talent gap in Europe.<sup>164</sup> The US is also investing heavily in the skill of its workforce: for

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160 Cell & Gene Therapy Insights (2019) Managing starting material stability to maximize manufacturing flexibility and downstream efficiency. Available at: <https://insights.bio/immuno-oncology-insights/journal/article/209/managing-starting-material-stability-to-maximize-manufacturing-flexibility-and-downstream-efficiency> [Accessed July 2022]

161 AreaDevelopment (2021) Location Factors for Cell and Gene Therapy Companies. Available at: <https://www.areadevelopment.com/Biotech/Q4-2021/location-factors-for-cell-and-gene-therapy-companies.shtml> [Accessed July 2022]

162 McKinsey & Company (2020) COVID-19 and cell and gene therapy: How to keep innovation on track. Available at: <https://www.mckinsey.com/industries/life-sciences/our-insights/covid-19-and-cell-and-gene-therapy-how-to-keep-innovation-on-track> [Accessed July 2022]

163 Clarke, D. & Smith, D. (2019) Managing starting material stability to maximize manufacturing flexibility and downstream efficiency. *Cell & Gene Therapy Insights*, 5(2): 303–314. Available at: doi.org/10.18609/cgti.2019.033

164 McKinsey & Company (2021) A call to action: Opportunities and challenges for CGTs in Europe. Available at: <https://www.mckinsey.com/industries/life-sciences/our-insights/a-call-to-action-opportunities-and-challenges-for-cgts-in-europe> [Accessed July 2022]

example, the New Jersey Institute of Technology and the New Jersey Innovation Institute have recently launched the US's first master's degree programme and professional graduate certificate in cell and gene therapies, and an apprenticeship programme for biomanufacturing.<sup>165</sup> Similar programs are observed in Ireland with the expansion of cell and gene therapy manufacturing training at Ireland's National Institute for Bioprocessing Research and Training (NIBRT).<sup>166</sup> Countries with a large existing footprint of pharmaceutical activity are also often more attractive to manufacturers, as the existing talent pool can be used and upskilled to meet the needs of new technologies.<sup>167</sup> For example, UCB's new gene therapy process development and clinical manufacturing facility is under construction on the site of their existing campus in Braine-l'Alleud, Belgium. The campus is already home to a community of engineers and manufacturing personnel skilled in biologic manufacturing,<sup>168</sup> which has overlaps with the processes needed for viral vector gene therapies.<sup>169</sup>

IMP manufacturing for ATMPs is also more likely to be co-located with commercial manufacturing and/or R&D for knowledge transfer and scalability reasons (e.g. Box 7). There are efficiencies to be gained in doing so for many types of therapy, but particularly for new therapeutic solutions for which accelerating internal competencies and shortening time-to-market is a key driver and affects where and how investment happens.<sup>170</sup>

#### **Box 7: Case studies | Co-location of the value chain for new therapeutic solutions**

In February 2022, Eli Lilly and Company announced an investment of \$700 million in a new facility in Boston which, once complete, will house the Lilly Institute for Genetic Medicine.<sup>171</sup> The aim of the Institute is research and development of innovative RNA- and DNA-based therapies to treat and prevent diseases. For Lilly, this is the first instance in which research, IMP manufacturing and commercial manufacturing will occur in one facility.<sup>172</sup> Depending on where a drug candidate or product is in its life cycle, it will be able to be transferred around to the relevant section of the facility rather than being moved to a separate site. In May 2022, Lilly also invested \$2.1 billion in two new

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- 165 The New Jersey Institute of Technology, NJIT to start programs in cell and gene therapy. Available at: <https://www.choosenj.com/news/njit-to-start-programs-in-cell-and-gene-therapy/> [Accessed July 2022]
- 166 National Institute for Bioprocessing Research & Training. Available at: <https://www.nibr.ie/>
- 167 AreaDevelopment (2021) Location Factors for Cell and Gene Therapy Companies. Available at: <https://www.areadevelopment.com/Biotech/Q4-2021/location-factors-for-cell-and-gene-therapy-companies.shtml> [Accessed July 2022]
- 168 UCB (2022) UCB expands innovation footprint with new state-of-the-art gene therapy facility. Available at: <https://www.ucb.com/stories-media/Press-Releases/article/UCB-expands-innovation-footprint-with-new-state-of-the-art-gene-therapy-facility> [Accessed July 2022]
- 169 Information from interview programme with pharmaceutical company representatives, June–July 2022.
- 170 Information from interview programme with pharmaceutical company representatives, June–July 2022.
- 171 Lilly (2022) Lilly Announces the Institute for Genetic Medicine and \$700 Million investment in Boston Seaport Site. Available at: <https://investor.lilly.com/news-releases/news-release-details/lilly-announces-institute-genetic-medicine-and-700-million> [Accessed July 2022]
- 172 Information from interview with pharmaceutical company representative, June 2022.

manufacturing sites in Indiana, which will expand the company's manufacturing network for active ingredients and new therapeutic modalities, such as genetic medicines.<sup>173</sup>

In 2021, Sanofi announced that a €400 million annual investment would be made in an mRNA vaccine centre of excellence in Cambridge, Massachusetts (US) and Lyon, France.<sup>174</sup> The sites will bring together R&D, digital, and chemistry, manufacturing and controls (CMC) teams, allowing end-to-end development and accelerating the mRNA vaccines pipeline. In Lyon, Sanofi already has both an R&D and a manufacturing presence, so the existing internal capabilities and infrastructure can be utilised.

### 3.4. Summary

As described in Chapter 2, Europe's relative global performance in attracting research, clinical trials and IMP and commercial manufacturing investments differs substantially for each activity. Understanding the drivers impacting the location of these activities (summarised in Figure 15) helps us to explain this trend and identify Europe's areas of strength and weakness.

- *Research hubs:* Companies are primarily driven to locate their research activities in places with access to world-leading research staff. Given Europe's and the US's strength in producing highly qualified researchers, this explains their historical dominance in attracting R&D investment; and China's recent heavy investments in higher education and scientific infrastructure have seen corresponding increases in private investment. Where the US leads and China is catching up, is in the strength of the overall innovation ecosystem, meaning access to research funding, public-private partnerships and other collaboration opportunities. Europe has historically lagged in this domain. However, it is also seen as important to have a research hub in leading pharmaceutical markets, and the opening of hubs in China needs to be seen in this light (rather than as a movement away from Europe).
- *Clinical trials:* Europe continues to perform strongly in attracting clinical trial investments. However, we observed in Chapter 2 that this is not the case for some new therapeutic solutions, such as ATMPs. The reasons for China's dominance in ATMP clinical research appear multifaceted and may include the strong government support for ATMP clinical trials, the focus on improving regulatory pathways, and the existence of leading specialist centres. The US's attractiveness as a location for ATMP clinical trials appears driven by many of the world's leading academic centres, the overall strength of the innovation ecosystem, and the commercial attractiveness of the US ATMP market.
- *IMP manufacturing:* IMP manufacturing location should be considered mostly separately to commercial-scale manufacturing, as the drivers of investment location more closely mirror those of research hubs. They are related to a smaller

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173 Lilly (2022) Lilly plans to invest \$2.1 billion in new manufacturing sites in Indiana. Available at: <https://investor.lilly.com/news-releases/news-release-details/lilly-plans-invest-21-billion-new-manufacturing-sites-indiana> [Accessed July 2022]

174 Sanofi (2021) Sanofi launches dedicated vaccines mRNA Center of Excellence. Available at: <https://www.sanofi.com/en/media-room/press-releases/2021/2021-06-29-08-00-40-2254458> [Accessed July 2022]

scale and better demand planning: companies look for areas where they can conduct high-quality manufacturing and innovation in manufacturing facilities and techniques to support the clinical development process, supported by access to knowledgeable staff and quality infrastructure. For many new therapeutic solutions, decisions may also involve more co-location with late-stage R&D to ensure knowledge transfer. We find this is a critical decision factor for ATMPs.

- *Commercial manufacturing:* Commercial manufacturing is driven largely by the financial viability of investment in a given location, which can explain – particularly for generic medicines – the increasing outsourcing of API to lower-cost jurisdictions such as Asia. More recently, accelerated by the COVID-19 pandemic, there have been calls in the US, China and some European Member States for localisation of commercial manufacturing of products and components to improve security of pharmaceutical supply chains, and this may disrupt the trend towards outsourcing in the future. We expect trends to differ slightly for some new therapeutic solutions, specifically for ATMPs as lower shelf life drives more local manufacturing. This is seen to be occurring in markets with higher affordability and ability to reimburse innovative products. This is also driven by the quality of the manufacturing processes as it is imperative to their success, so companies look for the areas in which they have greatest confidence in being able to access the right workforce in order to deliver the product.

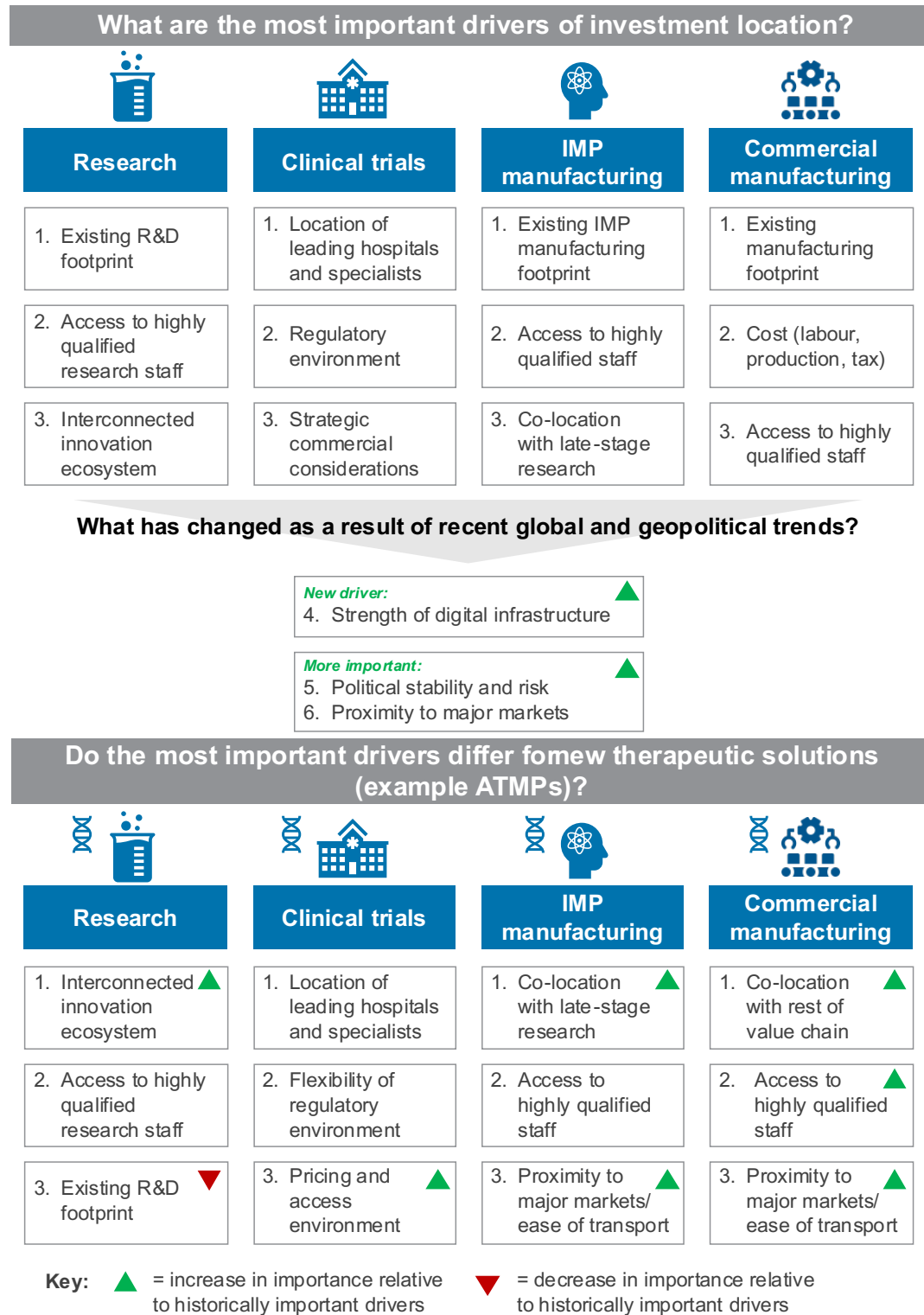
In Chapter 4, we use this assessment to identify potential areas for improvement in the European industrial policy environment that would serve to attract greater pharmaceutical investments in the future.

#### **Box 8: Summary of key findings**

- The factors driving Europe's relative global performance in attracting research, clinical trials and IMP and commercial manufacturing investments differ substantially for each activity.
- The location of talent and the strength of clusters is important for R&D. Europe's and the US's strength in producing highly qualified researchers helps explain their historical dominance in attracting R&D investment. However, China's large investments in higher education and scientific infrastructure have seen corresponding increases in private investment.
- Europe continues to attract clinical trial investments; this is primarily due to long-term competitive advantages regarding the national healthcare systems, with hospitals, competences and knowledge for conducting clinical trials. However, this appears to be changing, with the commercial environment attracting an increasing number of clinical trials outside of Europe.
- The drivers of IMP manufacturing location more closely mirror those of research hubs. IMP manufacturing is often co-located with late-stage R&D to ensure knowledge transfer.
- Commercial manufacturing is driven by financial viability of investment in a given location. However, for new therapeutic solutions, such as ATMPs, companies look for the areas in which they have greatest confidence in quality but also in

being able to access the right workforce and patients in order to deliver the product.

**Figure 15: Summary of factors driving the location of biopharmaceutical investments**





## 4. Attracting greater biopharmaceutical inward investment in Europe

The European Commission has noted the pharmaceutical industry as one of the most important industries in Europe.<sup>175</sup> This was repeated in the Pharmaceutical Strategy for Europe, where the industry is recognised as being “of key importance for the EU’s economy in terms of creation of highly skilled jobs and investment in innovation”. Previous analysis estimates the pharmaceutical industry contributed over €200 billion in Gross Value Added (GVA) and 2.5 million jobs in Europe. Per employee, this equates to a higher GVA than other major European industries such as automotive manufacturing, aerospace manufacturing and computer programming.<sup>176</sup> Looking at the EU R&D Scoreboard, the pharmaceutical industry also emerges as the industry with the highest R&D intensity in the EU.<sup>175</sup>

The previous chapters have shown how Europe is falling behind other regions, and even maintaining Europe’s share of current investments will likely become increasingly challenging over time, given the factors drawing companies towards locating their activities in the US and China, as outlined in Chapter 3. If investments into Europe are to return to a stronger growth pattern, there is a need to critically assess policy factors in Europe relative to those on offer from other competitive regions. However, there are relatively few policies highlighted in the Pharmaceutical Strategy that aim to improve the attractiveness of Europe.

The purpose of this paper is not to repeat the many existing reports calling for strong venture capital or better investment in STEM education. Instead, drawing from the review of statistics, the literature review and the interviews, we have developed seven new areas where policymaking should focus. We evaluate the extent to which current EU policy priorities are in line with these focus areas, and also consider lessons for the UK and Switzerland. The seven recommendations below are not set out in order of relative importance; instead, they are categorised into three strategic themes:

- 1. Addressing Europe’s relative decline in attractiveness as a centre for biopharmaceutical investment**
- 2. Responding to the impact of new therapeutic solutions on dynamics and location of investment (examples used: ATMPs and digital technology)**
- 3. Learning from COVID-19 and managing risk and the external environment**

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175 European Commission (2018) R&D and innovation activities in companies across Global Value Chains. Available at: <https://iri.jrc.ec.europa.eu/sites/default/files/contenttype//publication//reports//1568800267//R%26D%20and%20innovation%20activities%20in%20companies%20across%20Global%20Value%20Chains.pdf> [Accessed October 2022]

176 PwC (2019) The economic and societal footprint of the pharmaceutical industry in Europe. Available at: <https://www.efpia.eu/media/412941/efpia-economic-societal-footprint-industry-technical-report-250619.pdf> [Accessed July 2022]

#### 4.1. Addressing Europe's relative decline in attractiveness as a centre for biopharmaceutical investment

##### *Recommendation 1: Incentivise the development of truly world-class innovation hubs*

There is a general consensus on where the world's leading research hubs are located, e.g. Cambridge (Massachusetts) and San Francisco (California) in the US.<sup>177</sup> As set out in the previous chapters, these benefit from world-class universities and a cluster of the world's leading companies. These are also recognised as the leading hubs in the US, and this is a policy dimension that contributes to their development.<sup>178</sup> There are the well-recognised differences in the venture capital funding (including by state institutions, e.g. National Institutes of Health) and the strength of the specialist healthcare institutions, but an area that gets less attention is whether this is a result of innovation policy in the US. In 2017, it was reported that "California and Massachusetts rank first and second in terms of total NIH funding to its institutions. And Massachusetts ranks a far-and-away first with regards to NIH funding per capita, nearly 3x higher than most other strong states (like CA, NY, PA, NJ, etc.). Five of the top six NIH-funded independent research hospitals are in the Boston area. Fund flows like these further contribute to the consolidation of biomedical activity into the key clusters."<sup>179</sup>

To investigate this, we consider the distribution of NIH spending per capita across US states in 2021 (Figure 16). We see that Massachusetts continues to lead in terms of receipt of NIH funding per capita, followed by other bioclusters in Maryland, Washington DC and North Carolina. As in Europe, this only reflects part of the total funding; indeed, state-based funding has multiplied the impact of the NIH.<sup>180</sup>

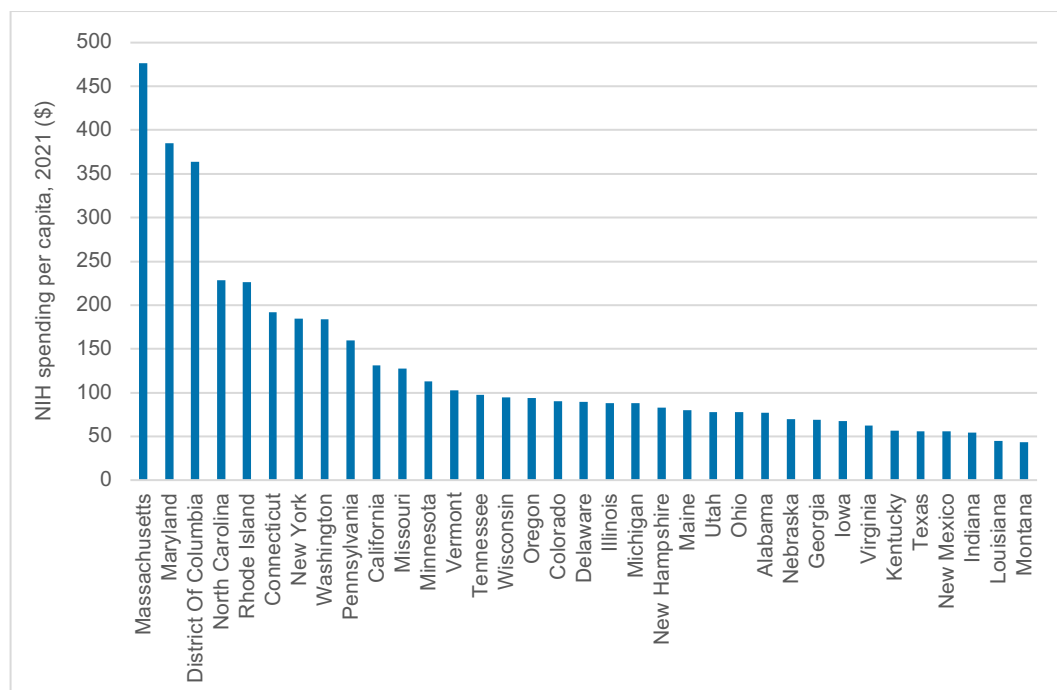
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177 <https://lifescivc.com/2017/03/inescapable-gravity-biotechs-key-clusters-great-consolidation-talent-capital-returns/> [Accessed July 2022]

178 <https://www.fiercebitech.com/special-reports/top-biotech-hubs> [Accessed July 2022]

179 <https://lifescivc.com/2017/03/inescapable-gravity-biotechs-key-clusters-great-consolidation-talent-capital-returns/> [Accessed July 2022]

180 <https://cognite.co/where-is-the-most-innovative-square-mile-on-the-planet/> [Accessed July 2022]

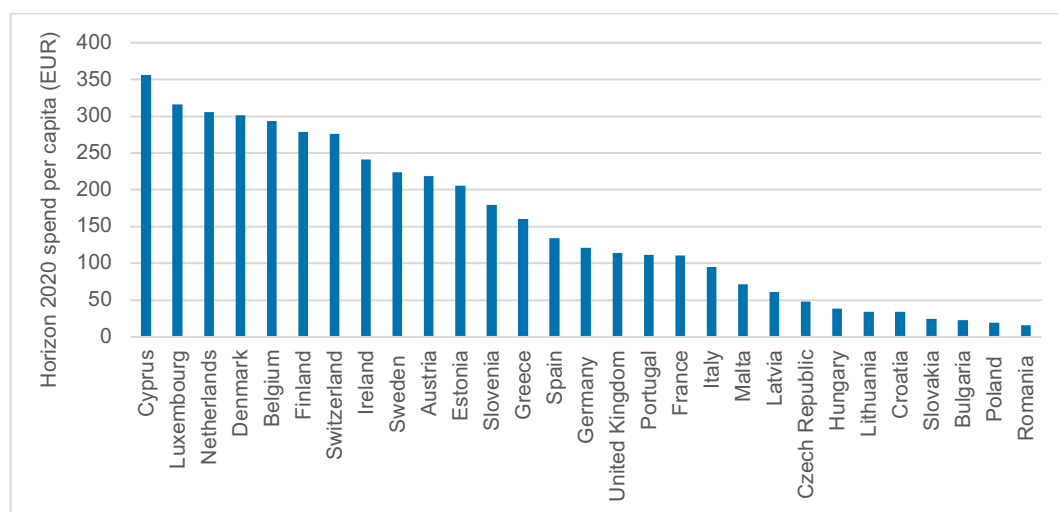
**Figure 16: NIH spending per capita is greater in the strongest US bioclusters**

Source: CRA analysis of data retrieved from <https://report.nih.gov/award/index.cfm#tab1> (NIH funding) and <https://data.ers.usda.gov/reports.aspx?ID=17827> (state population size) [Accessed September 2022]

Given Europe's long history in pharmaceutical innovation, it is inevitable, and a strength, that biopharmaceutical companies are spread across Member States. However, although many countries attract investment because of the legacy of company structure, in terms of world-class centres, our interviewees generally reported the Basel and Zurich areas in Switzerland, followed by the UK,<sup>181</sup> as having world-class science and a hub for innovation that would be considered for a greenfield site. When considering European policymaking, it is notable that both countries are outside of the European Union. The distribution of EU research spending is significantly more uniform than that of the US, and the countries with the highest EU spending (focusing on Horizon 2020) relative to their Gross Domestic Product (GDP) are not the centres of innovation (Figure 17).

181 <https://www.pmlive.com/pharma-intelligence/Building-European-biotech-firms-to-rival-those-of-the-US-1301494> [Accessed July 2022]

**Figure 17: Horizon 2020 research spending in Europe is not concentrated in Member States with high R&D activity**



Source: Horizon 2020 dashboard (<https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/horizon-dashboard>) and Eurostat ([https://ec.europa.eu/eurostat/databrowser/view/NAMA\\_10\\_GDP/default/table?lang=en](https://ec.europa.eu/eurostat/databrowser/view/NAMA_10_GDP/default/table?lang=en)) [Accessed September 2022]







Unlike the US, spending by the European Commission appears negatively correlated with high levels of spending by Member States.<sup>182</sup> Instead, the concern seems to be about how to even out the spending on European research.<sup>183</sup> This appears a weak strategy for supporting European innovation, particularly given the evidence indicating that international R&D investments generate knowledge and investment flows across borders, and therefore suggests that the economic benefits of policy-induced investments in one Member State are likely to spread to others<sup>184</sup> (in addition to the European-wide societal benefits of new innovations reaching patients).

<sup>182</sup> <https://www.researchprofessionalnews.com/rr-news-europe-views-of-europe-2021-3-take-this-chance-to-reboot-europe-s-r-d-spending/> [Accessed July 2022]

<sup>183</sup> Horizon 2020: Geographical balance of beneficiaries: Performance gap between EU13 and EU15 Member States “The reasons for lower participation of the EU13 Member States in Horizon 2020 are related mainly to the size and performance of the national research and innovation systems, quality of research, and weaker connections to European research collaboration networks.”

<sup>184</sup> <https://blogs.lse.ac.uk/businessreview/2018/05/05/when-multinationals-offshore-production-where-do-they-locate-innovation/> [Accessed July 2022]

**Figure 18: Individual European clusters are outcompeted by those in the US based on presence of major biopharmaceutical companies**

<b>Boston<sup>65</sup></b>  Market position: Globally leading cluster Approximate # of employees: 74'000 Main players: Novartis, Merck, Takeda, Pfizer, Bayer, Roche, Johnson & Johnson, Sanofi, Boston Scientific Cluster focus: Mainly innovative medicines, but also generic drugs. Additionally, massive biotech cluster.	<b>Basel<sup>28</sup></b>  Market position: European leading cluster Approximate # of employees: 25'000 Main players: Novartis, Roche, Actelion, Bayer, Boehringer Ingelheim, Basilea, Vifor Pharma, Johnson & Johnson Cluster focus: Mainly innovative medicines, but also generic drugs. No general product focus due to size of cluster	<b>Øresund<sup>31,66</sup></b>  Market position: European leading cluster Approximate # of employees: 22'000 Main players: Novo Nordisk, LEO Pharma, Baxter Gambro, Lundbeck, AstraZeneca Cluster focus: Focus on oncology, nervous system and immunology for drug compound development
<b>SF Bay Area<sup>67</sup></b>  Market position: Globally leading cluster Approximate # of employees: 52'000 Main players: Pfizer, Novartis, Roche, Boehringer Ingelheim, Bayer, Merck, Actelion, Boston Scientific, Google Cluster focus: Mainly innovative medicines, but also generic drugs. Additionally, massive biotech cluster.	<b>Flanders<sup>68</sup></b>  Market position: European leading cluster Approximate # of employees: 11'000 Main players: Johnson & Johnson, Bayer, Pfizer, Novartis, Omega Pharma Cluster focus: Mainly innovative medicines, but also generic drugs. More specialized on biopharma.	<b>Cambridge<sup>69</sup></b>  Market position: Smaller European cluster Approximate # of employees: 5'000 Main players: AstraZeneca, Pfizer Cluster focus: Numerous local SME'S (93% of cluster participants have less than 250 employees. Additionally, boasts Europe's largest hospital network.

Source: Pharmaceutical Industry in Basel, Switzerland – Cluster Analysis

### Recommendation

A policy that focuses on developing a truly world-class innovation hub would serve Europe well. For example, the European Commission should consider more strategic allocation of resources to foster growth of world-leading research centres. The EU should consider sponsoring a review of existing life science industrial policies across Member States to identify success factors and opportunities for replication. The same applies to the UK and Switzerland, where a continued focus on key hubs is clearly a policy priority.

### Current policy priorities

The Pharmaceutical Strategy for Europe emphasises the need for a resource-efficient EU pharmaceutical industry in the context of industry's investment into different therapeutic areas, but not in the context of geographic areas. Building on the success of public-private research partnerships remains a priority for the EU, but no specific mention is made of the geographic distribution of such funding sources.<sup>185</sup> In non-EU industrial policy, the UK government's 10-year Life Sciences Vision supports the growth of specific clusters across the country, highlighting where there is potential for growth of world-leading research centres of excellence, and separately the formation of manufacturing clusters.<sup>186</sup> There is potential in the implementation of the Pharmaceutical Strategy and in the revision of the EU's pharmaceutical legislation to adopt a more strategic approach to allocation of EU funding for innovation.

### *Recommendation 2: Enhance end-to-end capabilities and funding of disruptive pharma innovation*

The pharmaceutical industry is made up of very large and very small companies. In Europe there are approximately 1,400 biotech companies involved in the innovative pharmaceutical

185 European Commission (2020) Pharmaceutical Strategy for Europe. Available at: [https://health.ec.europa.eu/system/files/2021-02/pharma-strategy\\_report\\_en\\_0.pdf](https://health.ec.europa.eu/system/files/2021-02/pharma-strategy_report_en_0.pdf) [Accessed September 2022]

186 HM Government (2021) Life Sciences Vision. Available at: <https://www.gov.uk/government/publications/life-sciences-vision> [Accessed September 2022]

industry.<sup>187</sup> Early-stage, emerging companies play an important role in innovation. Latest figures show that emerging biopharma companies (defined as those with less than \$500 million in annual sales and less than \$200 million in annual R&D spend) currently represent 65% of the total global drug development pipeline.<sup>188</sup> The share of European-headquartered emerging biopharma companies has been declining over the last 10 years, with the US dominating in terms of number of companies and their contribution to the global pipeline, and China growing rapidly at a rate of 456% between 2016 and 2021.<sup>188</sup> We see this reflected in the EU R&D Scoreboard, which noted China overtaking the EU in terms of number of world-ranking companies in 2018, and the gap has widened every year since. In 2021 the number of world-ranking companies in China had grown by 61 compared to 2020, whereas in Europe the number had declined by 20.<sup>189</sup>

The traditional argument is that we should not be concerned by the source of companies but rather the activities they undertake. However, Europe's comparative weakness in attracting and growing emerging biopharma companies is a cause for concern if the goal is to boost Europe's attractiveness as a place to invest for biopharma companies of all sizes, from within and beyond Europe. Unanimous feedback from interviews with large biopharma company decision makers suggests that an important driver of most new investments is the location and performance of their existing R&D or manufacturing footprint.<sup>190</sup> This is because it is often more cost-efficient and time-efficient, and less risky, to continue to invest in a location where human capital, company culture, expertise and infrastructure have already been established. This is particularly true for research sites, where it is important to have a critical mass of expertise in one location to sustain the research efforts there over time, whereas innovation can be hindered by having the workforce spread thinly over too many locations.<sup>190</sup> Once a company is well established, investing in a brand new region where they have no existing presence would require a substantial financial- or talent-related pull factor to overcome the efficiency lost by not building up existing sites.<sup>191</sup> Our findings are consistent with the literature, where consensus is that geographic distance is negatively associated with the location of company investment activities. When greenfield R&D investments occur, evidence indicates that a company's previous R&D and manufacturing activities in a given global city increase the probability of that city being chosen as the location for the new R&D investment.<sup>192</sup> The strength of the US and China in growing emerging companies may in part explain their increasing global R&D footprint relative to Europe over the last two decades, explained in Chapter 2 of this report.

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187 <https://www.mckinsey.com/industries/life-sciences/our-insights/infographic-biotech-hot-spots-in-a-fragmented-european-landscape> [Accessed July 2022]

188 IQVIA Institute for Human Data Science (2022) Available at: <https://www.iqvia.com/insights/the-iqvia-institute/reports/emerging-biopharma-contribution-to-innovation> [Accessed July 2022]

189 European Commission et al. (2022) The 2021 EU industrial R&D investment scoreboard, Publications Office of the European Union. Available at: <https://data.europa.eu/doi/10.2760/559391> [Accessed July 2022]

190 Information from interview programme with pharmaceutical company representatives, June–July 2022.

191 Information from interview programme with pharmaceutical company representatives, June–July 2022.

192 Castellani, D., Latoratori, K. (2019). Location of R&D Abroad – An Analysis on Global Cities. In: Capik, P., Dej, M. (eds) Relocation of Economic Activity. Springer, Cham. [https://doi.org/10.1007/978-3-319-92282-9\\_9](https://doi.org/10.1007/978-3-319-92282-9_9)

Therefore, where a company is growing as it becomes established is critical. The declining share of emerging biopharma companies originating in Europe can be read as a warning signal that as emerging US- and China-headquartered companies continue to grow into small-, medium- and large-sized enterprises, their investments will be more heavily directed towards the US and China over Europe (i.e. close to their home base). We can observe the consequences of headquarter location by looking at the history of today's top biopharma companies. All of the top 20 global pharmaceutical companies have an active R&D centre in their home country (Table 2). Roche, for example, was founded in 1896 in Basel, Switzerland, and today invests almost €12 million per working day in R&D in Switzerland, employs over 5,000 scientists, and conducts over 100 clinical studies in the country each year.<sup>193</sup> In 2020, work began on a new €1.2 billion upgrade of the Basel R&D site.<sup>194</sup> Companies also do not tend to change the location of their headquarters, even in the face of changes to the external environment. Despite the EU–UK Trade and Cooperation Agreement introducing new trading barriers versus membership of the EU, no UK-headquartered pharmaceutical companies, such as GSK and AstraZeneca for example, relocated their headquarters from the UK following Brexit. Major companies in other industries have since relocated.<sup>195</sup>

**Table 2: Global pharmaceutical companies typically conduct R&D across a range of major markets, including their headquarter location**

Company	Headquarter location	Proximity of R&D locations to headquarter
<b>US-headquartered companies</b>		
<b>Johnson &amp; Johnson</b>	New Brunswick, NJ, US	Same country
<b>Pfizer</b>	New York, NY, US	Same country
<b>AbbVie</b>	Chicago, IL, US	Same country
<b>MSD</b>	Kenilworth, NJ, US	Same city
<b>BMS</b>	New York, NY, US	Same country
<b>Eli Lilly</b>	Indianapolis, IN, US	Same city
<b>Gilead</b>	Foster City, CA, US	Same city
<b>Amgen</b>	Thousand Oaks, CA, US	Same country
<b>Moderna</b>	Cambridge, MA, US	Same city
<b>Viartis</b>	Canonsburg, PA, US	Same city
<b>Europe-headquartered companies</b>		
<b>Roche</b>	Basel, Switzerland	Same city

193 <https://www.roche.ch/dam/jcr:82edb623-2dcc-4fe9-b406-b140cf3ef99f/en/roche-in-switzerland-2021.pdf> [Accessed July 2022]

194 <https://www.pharmaceutical-technology.com/projects/roches-basel-expansion-basel/> [Accessed July 2022]

195 <https://readyforbrexit.co.uk/the-list-of-companies-leaving-the-uk-because-of-brexit-grows/> [Accessed July 2022]

Company	Headquarter location	Proximity of R&D locations to headquarter
<b>Novartis</b>	Basel, Switzerland	Same city
<b>GlaxoSmithKline</b>	Brentford, UK	Same country
<b>Sanofi</b>	Paris, France	Same city
<b>AstraZeneca</b>	Cambridge, UK	Same city
<b>Bayer</b>	Leverkusen, Germany	Same city
<b>Boehringer Ingelheim</b>	Rhein, Germany	Same country
<b>Novo Nordisk</b>	Bagsværd, Denmark	Same city
<b>BioNTech</b>	Mainz, Germany	Same city
<b>Asia-headquartered companies</b>		
<b>Takeda</b>	Tokyo, Japan	Same country

Source: Top 20 pharmaceutical companies and headquarter information taken from <https://www.fiercepharma.com/special-reports/top-20-pharma-companies-2021-revenue>. Research hub locations from company websites.

We do also observe companies moving research activities or parts of it away from headquarter locations. Arguments in the literature suggest that due to companies' ability to transfer external and internal knowledge across geographies, geographical distance may play less of a role in R&D location decisions. The drive to access external knowledge or infrastructure, for example in a specialised cluster, may therefore overrule the desire to invest in more familiar locations.<sup>196</sup> Amgen, for example, moved 100 R&D jobs from its headquarters in Thousand Oaks, California, into the Cambridge, Massachusetts, and San Francisco, California, bioclusters in 2017.<sup>197</sup> However, this does not demonstrate a departure from Amgen's home country, and this pattern is not the norm (as indicated in Table 2). Departures from headquarter location are also more likely to apply to large-sized companies, where there are greater capabilities to coordinate firm operations across geographically dispersed sites.<sup>198</sup>

### Recommendation

Through the Innovative Medicines Initiative (IMI), built upon by the Innovative Health Initiative and other EU programmes, the EU and EFPIA are already supporting several of these initiatives through provision of research funding, but there could be benefit from adopting a more proactive coordination role. It could be useful to develop an audit of these largely national initiatives, identifying which business models stand out, and suggest pan-

<sup>196</sup> Castellani, D., Lavoratori, K. (2019). Location of R&D Abroad – An Analysis on Global Cities. In: Capik, P., Dej, M. (eds) Relocation of Economic Activity. Springer, Cham. [https://doi.org/10.1007/978-3-319-92282-9\\_9](https://doi.org/10.1007/978-3-319-92282-9_9)

<sup>197</sup> <https://www.fiercebiotech.com/biotech/amgen-moves-r-d-jobs-from-hq-to-cambridge-and-san-francisco-as-rolling-reorganization> [Accessed July 2022]

<sup>198</sup> Castellani, D., Lavoratori, K. (2019). Location of R&D Abroad – An Analysis on Global Cities. In: Capik, P., Dej, M. (eds) Relocation of Economic Activity. Springer, Cham. [https://doi.org/10.1007/978-3-319-92282-9\\_9](https://doi.org/10.1007/978-3-319-92282-9_9)



European strategies to fund and accelerate the adoption of similar models in other EU countries or to explore closer cross-country collaborations (e.g. the original setup of the Horizon research initiative including UK and Switzerland). There could also be a role for EU-led benchmarking of emerging European biopharma companies against the emerging companies from the US clusters to establish a long-term view of Europe's performance and global competitiveness.

### **Current policy priorities**

The Pharmaceutical Strategy for Europe acknowledges the importance of EU-level funding and national schemes to enable R&D for small- and medium-sized companies (SME). Initiatives such as the EU SME Strategy for a sustainable and digital Europe, Startup Europe, the European Innovation Council, and the European Institute of Innovation and Technology are listed as tools for creating an environment conducive to the growth of emerging companies.<sup>199</sup> As these initiatives are already in place, and at the same time we observe the declining competitiveness of Europe in growing biopharma companies, a more critical look at the design and effectiveness of these programmes in the context of the pharmaceutical industry may be warranted.

Within EU Member States, some positive trends can be observed in supporting the growth of small- and medium-sized companies. In Denmark, efforts have been channelled into growing new successful companies; approximately 200 new life sciences companies were founded in the eastern Denmark cluster between 2017 and 2022. The success of Danish-headquartered companies has also been supported via the government-led 'Innovation Centre Denmark' in Boston, which aims to accelerate cooperation between the clusters and to support entry of Danish companies into the Boston area.<sup>200,201</sup>

## **4.2. Responding to the impact of new therapeutic solutions on dynamics and location of investment, using ATMPs and digital technologies as examples**

### ***Recommendation 3: Rethink policies along the supply chain to attract ATMP investment in Europe***

The importance of new therapeutic solutions in the industry pipeline has clearly been growing for some time and will continue to do so. In this report, we focus on ATMPs as a case study, given the wealth of recent data that are available for evaluation. These data are serving as example for the entire landscape on biopharmaceutical innovation. In 2021, there were 804 next-generation biotherapeutics (defined as cell therapies, gene therapies, gene editing, nucleotide and RNA interference or mRNA therapies) in development from

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199 European Commission (2020) Pharmaceutical Strategy for Europe. Available at: [https://health.ec.europa.eu/system/files/2021-02/pharma-strategy\\_report\\_en\\_0.pdf](https://health.ec.europa.eu/system/files/2021-02/pharma-strategy_report_en_0.pdf) [Accessed September 2022]

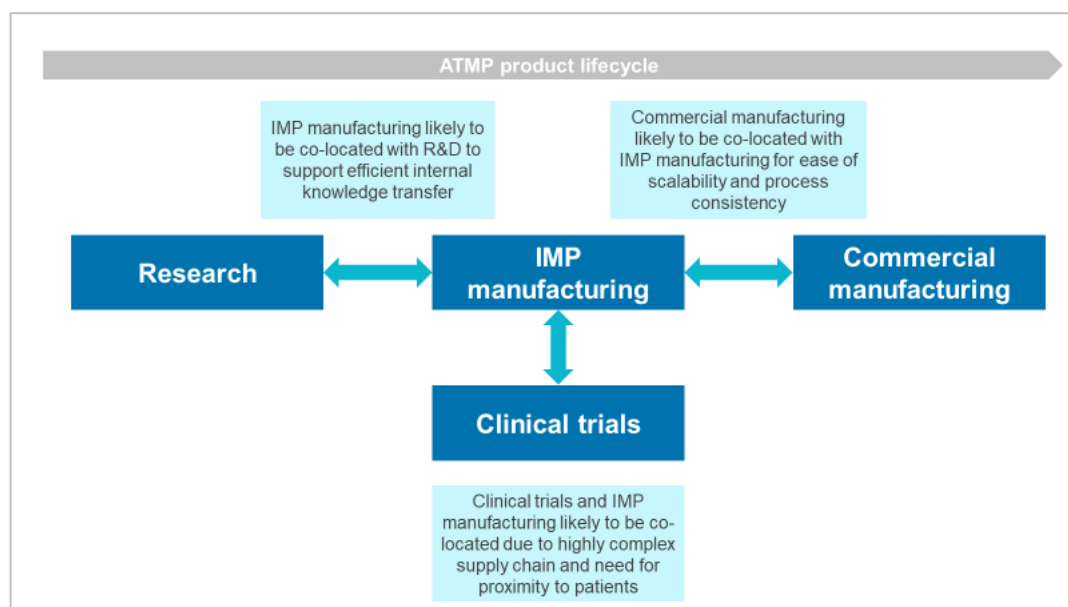
200 Øresundsinstittutet on behalf of the Interreg-project Greater Copenhagen Life Science Analysis Initiative 2022, available at: [https://mva.org/wp-content/uploads/2022/05/20220518\\_Life\\_science\\_easter\\_denmark.pdf](https://mva.org/wp-content/uploads/2022/05/20220518_Life_science_easter_denmark.pdf) [Accessed July 2022]

201 <https://usa.um.dk/en/about-us/danish-missions/innovation-centre-denmark-boston> [Accessed July 2022]

Phase 1 through filing with a regulatory agency.<sup>202</sup> This represents a 27% compound annual growth rate (CAGR) since 2016. As reviewed in Chapter 2 of this report, we see that Asia has been the most competitive region in attracting ATMP clinical trials for the last seven years, and that the number of trials conducted in Europe has fallen (Figure 5). In manufacturing, the US leads, with approximately 50% of the world's ATMP manufacturing facilities. There is, therefore, clearly a high level of global competition for attracting investment from companies leading the next phase of biopharmaceutical R&D and production.

There appears to be a view in the European policy debate that Europe can focus on elements of the value chain, such as manufacturing. However, for Europe to start competing more effectively for ATMP investment, it needs to recognise the increased complexity of these new technologies, and the scientific and logistical precision required to ensure effective development, quality production and timely delivery to patients. This means the value chain is likely to be more interconnected (Figure 19). When referring to interconnectivity, it is also important to distinguish between the implications for ex vivo and in vivo technologies (as described in Chapter 3). Close proximity and connection to the patient population, for clinical trials and commercial launch, is critical for ex vivo technologies as these rely on tissues extracted from patients. For both ex vivo and in vivo technologies, proximity with the patient population is not a deciding factor for the location of investment, but interconnectedness with the right labour pool and knowledge-sharing across the value chain (e.g. between early research, process development and manufacturing) bring substantial benefits.

**Figure 19: There is a degree of interconnectivity in the value chain for ATMPs, between research, clinical development and manufacturing**



Source: Interviews with companies locating activities associated to ATMPs

202 IQVIA (2022) Global Trends in R&D 2022. Available at: <https://www.iqvia.com/insights/the-iqvia-institute/reports/global-trends-in-r-and-d-2022> [Accessed July 2022]

Competing globally for investment starts with attracting research. Private investment into ATMP research is primarily drawn to where the academic expertise exists and is supported by a well-developed, innovation-oriented ecosystem. Europe performs strongly in academic research for ATMPs, with European institutions authoring 48,000 more publications than the US between 2017 and 2019, and 20,000 more than China.<sup>203</sup> This provides a highly educated, highly trained workforce for biopharma companies. Where Europe lags behind the US is in the supportiveness of the broader ecosystem. The success of supportive ecosystems in attracting investment is evident in the emergence and growth of a few key ATMP clusters, for example in Boston and North Carolina, where investing companies can establish partnerships with leading universities, medical schools and hospitals, and access the facilities of incubators, accelerators and research parks.<sup>204</sup>

IMP manufacturing for ATMPs, which occurs at a lower production scale and relies on specific, innovative techniques, is likely to be co-located with research activities. Even more than biologics, for ATMPs “the process is the product” and ability to transfer and share knowledge iteratively with research staff during the development of production processes is critical.<sup>205</sup> This is consistent with broader literature that finds that “the complexity of products and processes, the increasing rate of industry change and new product introduction, low maturity of production process and low degree of modularity are factors that may increase the need of proximity” of R&D and production.<sup>206</sup> We also see co-location evidenced in the US:

- In 2021, the Center for Advanced Biological Innovation and Manufacturing (CABIM), a public-private partnership led by Harvard and the Massachusetts Institute of Technology (MIT), announced the acquisition of a site in Massachusetts that will contain both *research and manufacturing facilities* to provide a bridge between academic research and private investment.<sup>207</sup>
- In 2022, Vertex opened a new ATMP *research and clinical manufacturing site* in the Boston cluster and at the same time announced an additional facility in Boston for *research and clinical manufacturing activities*.<sup>208</sup>
- ATMP clusters are, in general, hybrids of both R&D and manufacturing activity. In North Carolina, for example, there is a density of academic and corporate research,

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203 Loche, A. et al. (2021) A call to action: Opportunities and challenges for CGTs in Europe. Available at: <https://www.mckinsey.com/industries/life-sciences/our-insights/a-call-to-action-opportunities-and-challenges-for-cgts-in-Europe> [Accessed July 2022]

204 <https://www.areadevelopment.com/Biotech/Q4-2021/location-factors-for-cell-and-gene-therapy-companies.shtml> [Accessed July 2022]

205 Information from interview programme with pharmaceutical company representatives, June–July 2022.

206 Ketokivi, M. and Ali-Yrkkö, J. (2009) Unbundling R&D and Manufacturing: Postindustrial Myth or Economic Reality? *Review of Policy Research*, 26 (1–2): 35–54.

207 <https://news.harvard.edu/gazette/story/2021/01/center-for-cell-and-gene-therapy-to-open-next-year/> [Accessed July 2022]

208 <https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-further-expansion-boston-seaport-dedication> [Accessed July 2022]

CROs, CMOs, and IMP and commercial-scale manufacturing capabilities.<sup>209</sup> This differs from the pattern observed in other biopharma clusters, where R&D (e.g. Basel in Switzerland, Cambridge-Oxford-London in the UK) and manufacturing (e.g. Ireland, Singapore) activities tend to cluster in separate locations.

Improving Europe's competitiveness in attracting early- and late-stage research is therefore likely to lead to spillover benefits in attracting greater investments in early manufacturing. Europe has an opportunity to catch up by innovating future new modalities. Commercial manufacturing is similarly likely to follow suit because of complexities involved in moving activities away from the site of IMP production while ensuring absolute consistency in the manufacturing process and resulting product. This again diverges from the traditional biopharma business model, under which typically commercial manufacturing will be drawn towards locations in which scaling-up production can be done in a cost-efficient way (for example, due to lower labour costs or favourable tax rates).

### **Recommendation**

There are positive examples in Europe of ATMP investment clusters. Stevenage in the UK, for example, is home to 13 ATMP companies, benefitting from proximity to the government-supported Stevenage Bioscience Catalyst (SBC) and the Cell and Gene Therapy Catapult manufacturing centre, who work with companies to help progress therapies through development and production.<sup>210</sup> The Belgian region of Wallonia has become a "global powerhouse of cell therapy research and development"<sup>211</sup> over the past 20 years and continues to attract investment for other advanced therapies. In 2022, UCB announced their decision to locate their new gene therapy facility in Belgium in order to tap into the existing community of scientists, technicians, engineers and manufacturing personnel.<sup>212</sup>

The EU could benefit from taking a more proactive role in coordinating and fostering the growth of these emerging ATMP clusters and by seeing R&D, IMP and commercial manufacturing as interdependent. This could involve directing funding and supporting talent development to meet the needs of the interconnected activities concentrated at these locations. Learnings can also be taken from the Commission's reaction to the COVID-19 pandemic, during which the genetically modified organism (GMO) approval requirement for clinical trials was suspended for COVID-19 vaccines and therapeutics. Extending this more broadly could increase manufacturers' interest in performing ATMP clinical trials in Europe,

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209 <https://www.ncbiotech.org/transforming-life-sciences/sectors-attention/gene-and-cell-therapy> [Accessed July 2022]

210 SQW (2021) Life sciences in Hertfordshire and the emergence of a global and gene therapy cluster. Available at: <https://www.hertfordshirelep.com/media/e3dhe4jc/hertfordshire-s-cell-and-gene-therapy-cluster-july-2021.pdf> [Accessed July 2022]

211 <https://www.nature.com/articles/d43747-020-00721-0> [Accessed July 2022]

212 <https://www.thepharmaletter.com/article/ucb-expanding-gene-therapy-facilities-with-200-million-euro-investment> [Accessed July 2022]

which, given the interconnectedness of value chains, particularly for ex vivo therapies, could also positively affect IMP manufacturing investments.<sup>213</sup>

The learnings from the ATMP example should be used in preparing Europe to create ideas and support future innovation more broadly.

#### **Current policy priorities**

The Pharmaceutical Strategy for Europe emphasises the complexity of pharmaceutical manufacturing and supply chains but not their interconnectedness with research activity and clinical trials, nor the specific challenges presented by new life sciences technologies.<sup>214</sup>

#### ***Recommendation 4: Support innovation by implementing early access mechanisms, including generation and use of real-world evidence***

The traditional life cycle of medicine development is changing. Given the focus on rare diseases and precision medicines, it is more common for products to gain marketing approval with Phase II trials. For example, of 19 ATMP approvals in Europe as of September 2021, fewer than half included a pivotal Phase III trial.<sup>215</sup> Given the challenges in evidence development, it is more common for products to be given conditional approval and for RWE to be collected. The regulatory, value assessment and price and reimbursement systems need to reflect this to ensure patient access. However, this is also important for innovation.

Speed to market can be supported in part through internal factors, such as co-locating R&D with existing company footprints of expertise and infrastructure (see Recommendation 2) and with the location of innovative, high-quality academic research (see Recommendation 3). Biopharma companies are also continually exploring new CMC approaches to reduce development time of ATMPs.<sup>216</sup>

However, time and efficiency of the development process is also influenced by the external environment in which companies choose to locate their activities. For example, this can be supported by regulatory agencies through use of adaptive regulatory frameworks to keep up with the fast pace of pharmaceutical innovation and expedite development and approval of new therapies.<sup>217</sup> Companies may also be drawn to conducting clinical trials in locations where there is support and infrastructure for conducting long-term registry-based trials, given that regulators are increasingly looking at RWE of potentially curative therapies when

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213 ARM, EFPIA, EuropaBio, and Beattie, S. (2021) Call for More Effective Regulation of Clinical Trials with Advanced Therapy Medicinal Products Consisting of or Containing Genetically Modified Organisms in the European Union. *Hum Gene Ther.* 32(19–20): 997–1003.

214 European Commission (2020) Pharmaceutical Strategy for Europe. Available at: [https://health.ec.europa.eu/system/files/2021-02/pharma-strategy\\_report\\_en\\_0.pdf](https://health.ec.europa.eu/system/files/2021-02/pharma-strategy_report_en_0.pdf) [Accessed September 2022]

215 Iglesias-Lopez, C. et al. (2021) Current landscape of clinical development and approval of advanced therapies. *Molecular Therapy Methods & Clinical Development.* 23: 606–618.

216 <https://bioprocessintl.com/sponsored-content/reducing-cell-and-gene-therapy-development-time-and-cost-with-new-purification-strategies/> [Accessed July 2022]

217 <https://www.ema.europa.eu/en/human-regulatory/research-development/adaptive-pathways> [Accessed July 2022]

assessing effectiveness.<sup>218</sup> Even if long-term RWE is not required for initial marketing authorisation, companies will approach the decision on where to locate ATMP pivotal studies with this long-term view, given that these patients may be required to roll on to an extension study to generate the required RWE. It is also practical for companies to co-locate clinical trials with target patient populations for ATMPs:

- China's leadership in attracting ATMP clinical trials may be attributed to a range of factors, but at least in part to the large demand for access to these therapies. A high prevalence of rare diseases (76 cases per 100,000 population)<sup>219</sup> and an overall large population size generates high demand and eases patient recruitment for studies. However, the eventual commercial success is less certain: although the National Reimbursement Drug List (NRDL) is increasingly funding more new therapeutic solutions, reimbursement of ATMPs remains highly uncertain and large price cuts are expected.<sup>220</sup>
- The US is the second most frequently chosen location for ATMP clinical trials, which may be because it is the largest global market for pharmaceuticals. Data show that 64.4% of sales of new medicines launched between 2016 and 2021 were in the US market (compared with 16.8% in European markets).<sup>221</sup> Companies with a higher proportion of their business in the US vs Europe tend to display higher R&D investments.<sup>222</sup> ATMP developers may therefore be favouring the US for clinical trial investments given the advantages associated with familiarising clinical key opinion leaders with a new product pre-launch to support its rapid uptake post-marketing authorisation.

There has been recognition of the importance of the regulatory process for ATMPs, and despite their different procedures, the regulatory pathways in the US and Europe are seen to lead to broadly similar results.<sup>223</sup> However, there has been less focus across geographies on the role of the price and reimbursement system. New drugs typically reach the public more quickly in the US than in Europe.<sup>224</sup> Systems that delay patient access

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218 <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/long-term-follow-after-administration-human-gene-therapy-products> [Accessed July 2022]

219 Wakap, S. W. et al. (2019) Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *European Journal of Human Genetics*, 28:165–173.

220 Deloitte (2020) Winning in the cell and gene therapies market in China. Available at: [https://www2.deloitte.com/content/dam/insights/us/articles/APAC\\_63550\\_Winning-in-the-cell-and-gene-therapies/DI\\_China\\_CGT\\_white\\_paper.pdf](https://www2.deloitte.com/content/dam/insights/us/articles/APAC_63550_Winning-in-the-cell-and-gene-therapies/DI_China_CGT_white_paper.pdf) [Accessed July 2022]

221 EFPIA (2022) The pharmaceutical industry in figures 2022. Available at: <https://www.efpia.eu/media/637143/the-pharmaceutical-industry-in-figures-2022.pdf> [Accessed July 2022]

222 Eger, S. and Mahlich, J. C. (2014) Pharmaceutical regulation in Europe and its impact on corporate R&D. *Health Econ Rev.* 4: 23.

223 Iglesias-Lopez, C. et al. (2021) Comparison of regulatory pathways for the approval of advanced therapies in the European Union and the United States. *Cytotherapy*. 23(3): 261–274.

224 Van Norman, G. A. (2016) Drugs and Devices: Comparison of European and U.S. Approval Processes. *JACC Basic Transl Sci.* 1(5):399-412.

obviously have a direct impact on patients but also affect the attractiveness of undertaking innovative activities in Europe.

### Recommendation

Early access and strong reimbursement needs to be supported through a streamlined regulatory process and early access mechanisms, preventing the HTA system or reimbursement from being a barrier for early access, and ensuring RWE is used as a mechanism for encouraging faster patient access. In the EU, ensuring the success of ongoing initiatives to improve RWE and data operability – for example, as DARWIN (Data Analysis and Real-World Interrogation Network) and the European Health Data Space (EHDS) evolve – should take into account their ability to support and attract clinical trials for ATMPs.

### Current policy priorities

The Commission's Pharmaceutical Strategy for Europe shares some of these objectives. Supporting innovative trial designs and new methods of evidence generation and assessment, including use of RWE, are priorities.<sup>225</sup> This is similarly reflected in the inception impact assessment for the upcoming revision of the EU's general pharmaceutical legislation, which discusses future-proofing the legislation to account for the new ways in which innovative medicines are developed and evidence is generated.<sup>226</sup>

What the Strategy and the impact assessment do not cover is the link between access mechanisms and the attractiveness of Europe as a destination for companies to locate their research, clinical trials and manufacturing, particularly for new technologies.

### ***Recommendation 5: Boost EU digital transformation and support development of digital capabilities***

There is strong consensus, in our interviews with biopharma companies, that digital transformation in life sciences is increasingly impacting all business functions and all aspects of the value chain, including research, development and different types of manufacturing. This affects the needs of different types of biopharma companies and thus their choice of where to locate R&D and manufacturing activities:

- *Large pharmaceutical companies* are currently working through the transition of their activities from traditional on-site and lab-based science to hybrid models that leverage digital technologies and related innovation. With decades of heritage in traditional science-led research, this transformation is complex. When considering which countries to locate their activities in, large companies are therefore now also considering the level of support each country can offer, including support with digitalisation.<sup>227</sup> For example, this may require existence of local organisations to support internal digital transformation, establish data infrastructure in life sciences

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225 European Commission (2020) Pharmaceutical Strategy for Europe. Available at: [https://health.ec.europa.eu/system/files/2021-02/pharma-strategy\\_report\\_en\\_0.pdf](https://health.ec.europa.eu/system/files/2021-02/pharma-strategy_report_en_0.pdf) [Accessed September 2022]

226 European Commission (2021) Evaluation and revision of the general pharmaceutical legislation: Inception Impact Assessment. Available at: [https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation\\_en](https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation_en) [Accessed September 2022]

227 Information from interview programme with pharmaceutical company representatives, June–July 2022.

and support firms who can advise and aid in internal digitalisation and automation of value chains.

- *Newer small- and medium-sized companies* are being established from the start with a large focus on leveraging digital technologies throughout their organisation, granting them such internal capabilities. Moderna, for example, founded only twelve years ago in Massachusetts, relies on artificial intelligence (AI) and robotic automation in R&D and production processes. These were used to help them move from manually producing around 30 mRNA molecules per month to around 1,000 per month to accelerate development of their COVID-19 vaccine.<sup>228</sup> Externally, what newer companies look for when choosing where to invest is the existence of a highly qualified workforce, well versed in digital technology and data management, that they can add to their existing teams.<sup>229</sup>

Looking at the digital competitiveness of countries (ranked by the International Institute for Management Development (IMD) based on 52 digital criteria), we see as expected that the US is among the leading countries, but notably there are also five European countries in the global top 10 countries for digitalisation (Figure 20). China, somewhat surprisingly, is ranked 17<sup>th</sup>. This is attributed to the state-based model of digitalisation it has adopted, potentially leading to concerns about data access and ownership.<sup>230</sup> From an EU perspective, there may nevertheless be concern that major hubs of biopharma R&D and manufacturing investment are lagging behind, such as Germany (19<sup>th</sup>), Belgium (23<sup>rd</sup>) and Ireland (24<sup>th</sup>).

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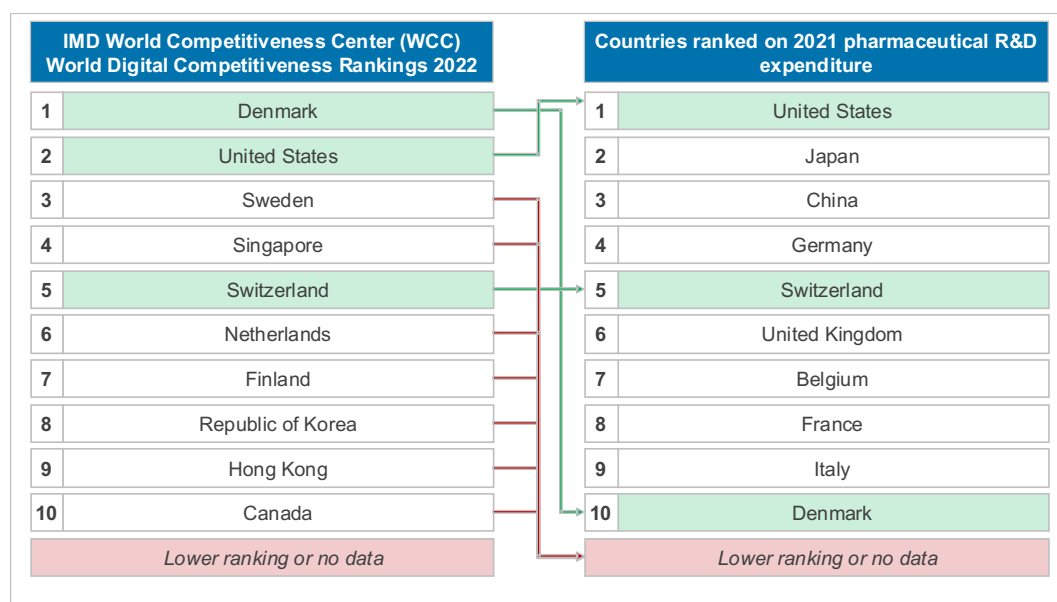
228 <https://theprint.in/tech/ai-helped-moderna-speed-up-covid-vaccine-development-now-it-can-help-climate-too/955061/> [Accessed July 2022]

229 Information from interview programme with pharmaceutical company representatives, June–July 2022.

230 <https://www.imd.org/news/updates/China-US-pursuing-markedly-different-but-equally-competitive-digital-transformations-WCC/> [Accessed July 2022]



**Figure 20: Europe's strongest biopharma R&D centres do not rank highly on digital competitiveness**



Source: <https://www.imd.org/centers/world-competitiveness-center/rankings/world-digital-competitiveness/> [Accessed October 2022]. Pharmaceutical R&D expenditure from Pharmaceutical Research and Manufacturers of America, PhRMA Annual Survey; China source: Chinese Statistical Yearbook; Japan source: Japan Pharmaceutical Manufacturers Association, R&D Expenditures of the Pharmaceutical Industry; Europe source: European Federation of Pharmaceutical Industries and Associations, the Pharmaceutical Industry in Figures.

### **Recommendation**

More effort is needed to increase the interconnectedness of these hubs or to upskill these nations to help ensure that they continue to remain attractive locations for pharmaceutical investment in the future.

Specifically, one action emphasised by pharmaceutical companies during our interview programme was the need to future-proof the skills of the European workforce to match the new hybrid science-digital approach required for modern R&D and manufacturing. The skill set required to support pharmaceutical innovation and production is changing; whereas traditionally Europe has performed well in producing a workforce of world-leading biologists, chemists and bioengineers, modern processes require the workforce to be literate in both pure science and digital skills. Lessons could be learnt from the success in Ireland in developing a flexible pharmaceutical workforce that can adapt to changing industry needs. There are continuing education programmes that, for example, enable the retraining of parts of the workforce involved in small molecule manufacturing to support new biologic manufacturing processes.<sup>231</sup> We now observe pharmaceutical companies investing in upskilling their own workforce to meet new digital needs, such as Moderna's 'AI Academy' launched for all 2,400 of Moderna's employees at all levels to help them

231 Information from interview programme with pharmaceutical company representative, June 2022.

integrate artificial intelligence into their work.<sup>232</sup> If Europe can proactively create a digital-ready talent pool, this could offer a competitive advantage in attracting future investments.

A more fundamental shift of mindset towards proactivity may also be to Europe's advantage. With digitalisation, and with innovation and production of novel therapies such as ATMPs, this analysis has focused on identifying opportunities for Europe to catch up to the standard being set largely by the US, China, and individual Member States within Europe. While Europe is now adopting a more digital mindset, as evidenced in the Pharmaceutical Strategy for Europe and with recent creation of the European Health Data Space, this is occurring later than in markets such as the US, where proactive policy in the late 2000s resulted in rapid early adoption of digital technologies in the health sector, with 96% of hospitals now using electronic health records (EHRs) versus 9% in 2008.<sup>233</sup>

Following the paths set by other major economies is a risky strategy to adopt; as we described in Recommendation 2, a compounding effect can set in, with pharmaceutical companies now being drawn towards US clusters for ATMP development activities, as an example, because the workforce and ecosystem is already there. With each new technology, there is a new opportunity for a shift in investment activity. The pharmaceutical industry is more likely to invest in areas where they have a footprint of activity and expertise; when a new technology comes along, in which they do not yet have a footprint, companies show greater flexibility in relocating where the investment goes. This creates an opportunity for Europe to have a competitive edge. Europe could benefit from horizon scanning and proactively preparing the life sciences ecosystem for new upcoming transformational technologies, beyond digital and ATMPs.

#### **Current policy priorities**

The EU's Pharmaceutical Strategy shares a focus on preparing for the digital transformation. Specifically, the Commission sets out an aim to ensure Europe's pharmaceutical policy evolves in line with the digital transition. This includes, for example, the creation of the European Health Data Space, which is now under establishment and aims to optimise data sharing and use in Europe. However, there is a lack of strong emphasis in the Strategy on broadly supporting Member States in modernising their digital infrastructure to support development and production of, and access to, innovative medicines.

### **4.3. Learning from COVID-19 and managing risk and the external environment**

#### ***Recommendation 6: Foster adoption of sustainable procurement and pricing policies for innovation***

The importance of creating an ecosystem in Europe that supports early access, leans into the digital transformation and supports the use of RWE as well as protecting IP, is clear for new therapeutic solutions such as ATMPs. At the same time, as a result of the global disruption caused by the COVID-19 pandemic, we see the EU prioritising initiatives to

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232 <https://www.modernatx.com/en-US/media-center/all-media/blogs/moderna-launches-ai-academy-all-employees> [Accessed July 2022]

233 <https://healthcare-in-europe.com/en/news/the-usa-s-digital-healthcare-revolution.html> [Accessed July 2022]

strengthen supply and production of these medicines. The EU Pharmaceutical Strategy, for example, focuses on boosting the EU's "strategic autonomy" in medicine supply, noting that there may be a need for production of certain critical medicines within the EU.<sup>234</sup> There is a danger that industrial policy focuses on the most innovative medicines while the relocation of manufacturing focuses on off-patent medicines, leaving a gap in the middle. Interviews with pharmaceutical companies called out a lack of such support for established conventional medicines.

### **Recommendation**

The solution to ensuring sustainability of these medicines is likely to be multifaceted.

- Investment in R&D for traditional technologies continues to play a critical role; even in rapidly evolving therapy areas and vaccines, traditional technologies continue to account for a large proportion of innovation. In neurology, for example, for which there are many promising transformative therapies in development, 77% of the pipeline consists of small molecule products.<sup>235</sup> Continuing to attract these types of investments is therefore important to Europe's overall competitiveness in the biopharmaceutical industry. While there are successful examples of EU-led initiatives to support innovative medicines and technologies, such as Horizon 2020, these need to support innovation in the round and maximise involvement of other like-minded science-strong countries in the region, including the UK and Switzerland.
- Approaches need to reflect the development of medicines and improve the manufacturing process post-launch. Medicines continue to be developed after they are initially approved in the EU, in terms of targeted patient population, forms of administration and new indications, as well as in optimising the manufacturing process. Many of these improvements are perceived as being more valued outside of Europe. This has implications for where companies will invest in upgrading and improving manufacturing capabilities.
- Support is needed for flexible approaches to procurement that do not focus on the lowest prices. Some individual Member States are already piloting novel models to promote sustainability, from which there may be lessons for the EU more broadly: for example, the French government has guaranteed no further price cuts to paracetamol between 2022 and 2025 in response to Seqens agreeing to invest €100 million in the creation of a new factory to manufacture the API to promote supply resilience.<sup>236</sup> For this model to be effective in promoting sustainability, such investments at the EU level would need to be respected in the reimbursement

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234 European Commission (2020) Pharmaceutical Strategy for Europe. Available at: [https://health.ec.europa.eu/system/files/2021-02/pharma-strategy\\_report\\_en\\_0.pdf](https://health.ec.europa.eu/system/files/2021-02/pharma-strategy_report_en_0.pdf) [Accessed July 2022]

235 IQVIA (2022) Global Trends in R&D 2022. Available at: <https://www.iqvia.com/insights/the-iqvia-institute/reports/global-trends-in-r-and-d-2022> [Accessed July 2022]

236 <https://www.apmhealthurope.com/story.php?objet=80563> [Accessed July 2022]

process in all Member States, as companies cannot sustainably manufacture all medicines in every Member State.<sup>237</sup>

- There is a need to support continued investment in manufacturing. Cost-containment policies targeting older, established medicines push prices downward and reduce profit margins, which limits resources available for manufacturing capacity and quality investments in innovation and improvements. Furthermore, medicine production cost increases are anticipated by the industry, particularly in light of the increasing energy crisis. Markets need to be sustainable in supporting ongoing investment in manufacturing capacity.

### **Current policy priorities**

The Pharmaceutical Strategy for Europe adopts a narrower definition of sustainability than described above, focusing on medicine production and promoting supply chain sustainability, environmental sustainability and financial sustainability of health systems. Sustaining the health of the innovative industry is not a primary objective of the strategy, nor is it highlighted as a potential tool to restore economic growth in Member States post-COVID and in the face of the Russia–Ukraine war and subsequent energy crisis. Further, the ongoing revision of intellectual property rights in the EU risks sending a negative signal to companies considering future investments.

### ***Recommendation 7: Develop a longer-term, collaborative method for encouraging growth in Europe’s attractiveness for biopharmaceutical investments***

Decisions regarding investment in research hubs, IMP manufacturing and commercial manufacturing are long-term decisions. Even clinical trials programmes are conducted over a number of years and require consideration of what might change in the environment. However, over the last few years, we have seen considerable global challenges: crises like the COVID-19 pandemic, the war in Ukraine, tensions over global trade and the materialisation of the climate emergency have all come into focus, most recently with the spiralling energy crisis. This has led to significant policy debate regarding the localisation of the industry, the implications of sanctions and import and export bans, the role of joint purchasing and the introduction of environmental, social and governance (ESG) standards.

Perhaps surprisingly, this was not a topic that weighed heavily on decisions regarding actual investment with decision makers (although many of these were made pre-COVID, and all were investments made before the Russia–Ukraine war and subsequent energy crisis). There are a number of reasons for this: (1) the industry has long been a global industry and is used to managing business risks across regions and countries; (2) unlike other industries, there is a responsibility to continue to supply medicines in many markets, meaning that some continued investment in infrastructure is inevitable; (3) some global risks, such as the environment, are longstanding and the industry has already worked extensively on it;<sup>238</sup> and (4) the existence of a global regulatory system – inspections by FDA and EMA and by Pharmaceutical Inspection Co-operation Scheme (PIC/S)

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237 <https://www.apmhealthurope.com/story.php?objet=80563> [Accessed July 2022]

238 López-Toro et al. (2021) Influence of ESGC Indicators on Financial Performance of Listed Pharmaceutical Companies. *Int J Environ Res Public Health*. 18(9): 4556

participating authorities – means that the industry faces the same rules independent of location.<sup>239</sup>

However, there are clearly potential risks that can have large impacts on investment decisions. For example, international trade was noted in some interviews. The US has proposed legislation to better regulate outbound investments in countries such as China and Russia, seeking to move more of the supply chain for critical sectors like technology to countries that are seen to comply with international best practices.<sup>240</sup> This could affect funding for new facilities like factories, joint ventures that involve technological transfers to China and capital investments in Chinese start-ups and technology firms.

The increase or perceived increase in risk in the global environment will have some implications:

- Managing risk of disruption and reducing carbon footprints is likely to lead to a shorter supply chain and greater requirements in terms of monitoring.<sup>241,242</sup> This can be considered specially for high-volume products. On the face of it, this would be seen to benefit Europe – where production has commonly been undertaken in India and China – but in reality this will also focus location on markets with the highest growth: the US and Asia.
- The location of clinical trials will adapt. This will mean avoiding some locations that are seen as highly risky from a geopolitical perspective. However, it will also mean adapting to address diversity within clinical trials. This will be affected by policy and regulatory decisions; for example, the acceptance of trials conducted in a single region or country is still evolving, with recent decisions by the EMA and the FDA.

### **Recommendation**

Given the long-term focus on investment decisions, regions that offer long-term stable environments coupled with growing markets will benefit from decreased perceived risk. This necessitates ongoing dialogue between policymakers and other stakeholders, including the industry, on how the environment needs to adapt and be renewed. For the EU, Europe needs to establish an effective process for implementing the Pharmaceutical Strategy (its first in over 50 years since the first pharmaceutical legislation was implemented

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239 <https://www.accessmedicineindex.org/amr-benchmark/research-areas/responsible-manufacturing#> [Accessed July 2022]

240 Leonard, J. (2022) New Rules for U.S. Investments in China Face Fresh Hurdle: Biden's Team. Available at: <https://www.bloomberg.com/news/articles/2022-04-29/biden-team-splits-on-new-rules-for-u-s-investments-in-china> [Accessed July 2022]

241 Bottomley, K. (2022) The growing impact of Environmental, Social, and Governance ("ESG") on pharmaceutical supply chains. Available at: <https://resultsiq.com/the-growing-impact-of-environmental-social-and-governance-esg-on-pharmaceutical-supply-chains/> [Accessed July 2022]

242 Black, M. (2022) ESG and supply chains: assessing the growing risks. Available at: <https://global.lockton.com/gb/en/news-insights/addressing-growing-supply-chain-risks-from-an-esg-perspective> [Accessed July 2022]

in the EU<sup>243</sup>) with ongoing dialogue regarding how the environment will change over 5-, 10- and 20-year time periods, the expected and actual impact of policy changes, and ensuring a focus on innovation and production.

#### **Current policy priorities**

There is an acknowledgement in the Pharmaceutical Strategy of the need for “future-proofing” legislation, particularly as the current pharmaceutical legislation was developed at a time when certain technologies that exist today were either absent or in their infancy. There is an opportunity with the implementation of the Strategy and with the revision of the pharmaceutical legislation to adopt a long-term outlook. Specifically, this should involve an evaluation of the likely long-term effects of policy decisions being undertaken and consideration of whether these will support the objective of increasing Europe’s attractiveness as a location to invest in the long-term. Ongoing dialogue with industry will be important to establish a forward-looking partnership. Tangible and relevant key performance indicators can be co-created to ensure revised legislation is having its intended impact, and to enable benchmarking of Europe’s long-term competitiveness for attracting investment relative to countries such as the US and China.

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243 European Commission Legal framework governing medicinal products for human use in the EU. Available at: [https://health.ec.europa.eu/medicinal-products/legal-framework-governing-medicinal-products-human-use-eu\\_en#](https://health.ec.europa.eu/medicinal-products/legal-framework-governing-medicinal-products-human-use-eu_en#). [Accessed July 2022]

## Appendix

### *Kearney Foreign Direct Investment (FDI) Confidence Index*

**Table 3: Kearney FDI Confidence Index rankings show investors remain most confident in the US market**

Country	2010	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
US	2	4	1	1	1	1	1	1	1	1	1	1
Germany	5	5	7	6	5	4	2	3	2	3	3	2
Canada	9	20	4	3	4	3	5	2	3	2	2	3
Japan	-	21	13	19	7	6	6	6	6	4	5	4
UK	10	8	8	4	3	5	4	4	4	6	4	5
France	13	17	12	10	8	8	7	7	5	5	6	6
Italy	-	-	-	20	12	16	13	10	8	9	8	7
Spain	-	24	16	18	17	13	11	15	11	11	9	8
Switzerland	-	22	18	14	14	11	12	9	13	10	10	9
China + HK	1	1	2	2	2	2	3	5	7	8	12	10
Australia	7	6	6	8	10	7	9	8	9	7	7	11
New Zealand	-	-	-	-	-	-	23	16	19	13	13	12
Sweden	-	-	-	16	18	22	15	14	15	15	14	13
UAE	11	15	14	-	-	-	21	-	-	19	15	14
Netherlands	-	-	-	22	13	14	14	13	12	14	11	15
South Korea	-	19	21	-	16	17	18	18	17	17	21	16
Belgium	-	-	-	21	19	19	22	21	18	16	17	17
Singapore	-	7	10	9	15	10	10	12	10	12	16	18
Portugal	-	-	-	-	-	-	-	22	-	21	20	19
Austria				-	21	24	24	-	-	-	19	20

Source: Kearney FDI Confidence Indices 2010–2020<sup>244</sup>

**Investment case studies and additional contributions**

The interview programme was structured around a series of case-study based interviews with senior executives at pharmaceutical companies, listed below in Table 4.

Additional non-case-study based discussions were held with a number of individual companies and trade associations, which also fed into the development of the report, including:

- Johnson & Johnson (J&J)
- The Association of the British Pharmaceutical Industry (ABPI)
- Pharmaceutical Research and Manufacturers of America (PhRMA)

**Table 4: Sixteen biopharmaceutical investment case studies were reviewed during the interview programme**

1. Research investment case studies		
European companies investing in Europe		
Company	Case study	Source
Roche	CHF 1.2 billion expansion of existing Basel R&D site announced in 2020	245
Roche	Global IT Centre in Poland with R&D support capabilities, established 2004 and headcount expanded in 2018	246
Merck KGaA	R&D and Investigational Medicinal Product (IMP) biologic manufacturing site in Switzerland	247
US companies investing in Europe		
MSD	New central London R&D site with investment of \$1.3 billion; expected completion in 2025	248
Moderna	Global mRNA research centre planned in the UK; deal reached with UK government also on manufacturing	249
US and European companies investing in US		
Eli Lilly	\$200 million gene therapy R&D site (Lilly Institute for Genetic Medicine) established in Boston in 2022	250
Sanofi	Combined €400 million annual investment in mRNA vaccine research in US and France sites	251

245 Available at: <https://www.biopharmadive.com/news/roche-to-spend-32b-on-massive-rd-cluster-in-basel/326244/> [Accessed June 2022]

246 Available at: <https://impactcee.com/2018/05/09/roche-sees-the-potential-in-it/> [Accessed June 2022]

247 Available at: <https://www.fiercepharma.com/manufacturing/merck-kgaa-antes-up-eu250m-to-bridge-r-d-manufacturing> [Accessed June 2022]

248 Available at: <https://www.msd.com/stories/our-new-london-discovery-research-center-site/> [Accessed June 2022]

249 Available at: <https://www.gov.uk/government/news/moderna-to-open-vaccine-research-and-manufacturing-centre-in-uk> [Accessed July 2022]

250 Available at: <https://investor.lilly.com/news-releases/news-release-details/lilly-announces-institute-genetic-medicine-and-700-million> [Accessed June 2022]

251 Available at: <https://investor.lilly.com/news-releases/news-release-details/lilly-announces-institute-genetic-medicine-and-700-million> [Accessed June 2022]



European companies investing in China		
Sanofi	Establishment of Sanofi's first global research institute in China	252
2. Manufacturing investment case studies		
European companies investing in Europe		
Menarini	€150 million investment in new Florence commercial manufacturing site	253
UCB	New €200 million gene therapy Investigational Medicinal Product (IMP) manufacturing site in Belgium	254
Bayer	Bayer's public-private partnership in Germany for a cell and gene therapy translation centre	255
US, Chinese and Japanese companies investing in Europe		
Pfizer	Recent €50 million investment into high-tech continuous manufacturing site in Freiburg, Germany	256
WuXi	€500 million investment in biologic and vaccine manufacturing in Ireland in 2018/2019	257
Takeda	Cell therapy commercial manufacturing sites in Europe, US, and Japan	258
US and European companies investing in the US and Puerto Rico		
Biogen	Investigational Medicinal Product (IMP) manufacturing of gene therapies in US	259
3. Clinical trial case studies		
European companies investing in Asia		
PTC Therapeutics	Taiwan-based pivotal clinical trial studies for Upstaza	260

- 252 Available at: <https://www.yicai.com/news/sanofi-unveils-first-global-research-institute-in-china-to-develop-innovative-drugs> [Accessed June 2022]
- 253 Available at: <https://www.menarini.com/en-us/news/news-detail/menarini-invests-150-million-euros-in-a-new-pharmaceutical-plant-in-italy> [Accessed June 2022]
- 254 Available at: <https://www.ucb.com/stories-media/Press-Releases/article/UCB-expands-innovation-footprint-with-new-state-of-the-art-gene-therapy-facility> [Accessed June 2022]
- 255 Available at: <https://www.bayer.com/media/bayers-bluerock-therapeutics-establishes-european-site-for-cell-therapy-innovation/> [Accessed June 2022]
- 256 Available at: <https://www.gesundheitsindustrie-bw.de/en/article/news/industry-40-pfizer-opens-continuous-manufacturing-plant-in-freiburg> [Accessed June 2022]
- 257 Available at: <https://www.irishtimes.com/business/health-pharma/wuxi-biologics-ireland-in-679-6m-gain-after-restructuring-1.4699274> [Accessed June 2022]
- 258 Available at: <https://www.takeda.com/newsroom/featured-topics/takeda-breaks-ground-on-commercial-cell-therapy-manufacturing-facility-in-lexington-massachusetts/> [Accessed June 2022]
- 259 Available at: <https://investors.biogen.com/news-releases/news-release-details/biogen-announces-plans-build-new-state-art-gene-therapy> [Accessed June 2022]
- 260 Available at: <https://ir.ptcbio.com/news-releases/news-release-details/ptc-therapeutics-receives-positive-chmp-opinion-upstazatm> [Accessed June 2022]