European Commission

# Top EU R&D investors in the global economy
# Benchmarking technological capabilities in the health industry

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# Contents

# Foreword

This study is linked to the 'EU Industrial R&D Investment Scoreboard', an EU flagship publication produced by the JRC Directorate B (Growth & Innovation, Unit B7) in collaboration with DG-RTD Directorate E (Prosperity, Unit E1).

The EU Industrial R&D Investment Scoreboard provides economic and financial information based on the most recent balance sheets of the world's top 2,500 corporate R&D investors and a subsample of 1,000 companies based in the EU. The 2021 report was presented past 17 December by Mariya Gabriel, Commissioner for Innovation, Research, Education, Culture and Youth, and the full report with company data here: https://iri.jrc.ec.europa.eu/rd_monitoring.

Regarding the health industry, the Scoreboards show a major EU-US gap in R&D investment of the pharmaceuticals and biotechnology subsectors, with more marked differences in the latter. In pharmaceuticals, EU companies increased 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. In biotechnology, the R&D growth of US-based companies was remarkably higher: in 2020 they outperformed their EU counterparts in terms of R&D investment (11 times larger) and number of companies (166 vs 20) and, to a lesser extent, recorded a higher R&D intensity (30.6% vs 26.5%).

The Scoreboard raises important policy questions, such as the need to increase the number of innovative companies in key sectors, increase scaling-up and commercialisation of research and innovation results, and fostering growth opportunities for innovative companies and breakthrough innovations.

The present study has deepened the Scoreboard's recurrent findings on the R&D and patent gaps in pharmaceuticals & biotechnology. It adds evidence on the EU positioning in healthcare equipment & services as well as COVID-19/immunology-related capabilities, using the last 10 editions of the Scoreboard (2012-2021).

## Executive Summary

The health industry has experienced a great transformation in recent decades and accounts for a substantial chunk of worldwide research and development investments, which may lead to important breakthroughs. This has become even more emphasised during the COVID-19 pandemic when there was an urgent need to obtain possible vaccine candidates and treatments.

The objective of the report is to analyse innovation dynamics of the health industry using data from the EU Industrial R&D Investment Scoreboard (SB) for 2012-2021. For each year, the SB includes the top 2,500 companies worldwide in terms of research and development (R&D) investment. These companies represent 87.3% of global R&D. The analysis is completed by combining the SB dataset with data on patents filed by companies operating in the health industry at the European Patent Office and the US Patent and Trademark Office from 2016 to 2018.

Some of the main findings of this work are the following:

- There is an increasing number of health companies among the top corporate R&D investors which has been driven by the rise of the number of biotech and pharmaceutical companies.
- The profitability of the sector has declined until recent years to then stabilize; with the COVID-19 pandemic the profitability of most companies has risen.
- EU-27 based companies have substantially increased their R&D investments over the last 10 years. EU-27 is the second economic area in terms of R&D investment but it still lags considerably behind the US.
- Even though biotech and pharma are often considered as two different health sectors, biotech and pharmaceutical companies present a similar technological specialization.
- Scoreboard companies file 44% of the worldwide patent families related to health technologies, a much lower share compared to information and communication technologies. Public institutions, research centres and small firms play an important role in the development of health technologies.
- According to the patent to R&D ratio, EU companies are performing well; their capacity to transform R&D into innovation is in line with the US and other main economic areas.
- The location of the inventors of a patented invention can be used to proxy for the location of R&D activities. The flows of R&D from the EU to the US are much higher than those from the US to the EU, while the EU records positive R&D net inflows from the rest of Europe (particularly from Switzerland-based companies).
- Research and development of different types of immunotherapies (including vaccines and mRNA techniques) and the use of pathogens are changing the way in which the research community approaches several diseases. A focus on patents related to this set of technologies (Immuno+) by Scoreboard companies in the health industry reveals that:
    - Approximately 23% of patents are related to Immuno+ technologies.
    - Immuno+ related patents are, on average, more complex than other patents (i.e., combine a broader set of technical knowledge).
    - The US, other European countries and the rest of the world appear to be specialized in the production of Immuno+ technologies; China, Japan and the EU not. However, there is a marked heterogeneity across EU countries with Belgium, Spain, France, the Netherlands and Denmark resulting as specialized in Immuno+.

The analysis provided allows us to have a better understanding about how the health industry is performing, helps identifying areas of future research and informs policymaking. Moreover, it also proposes an analysis of Immuno+ technologies, which are changing the way in which the research community approaches several diseases and seem to be very promising for future health advances.

## Abstract

This report analyses the health industry through the lens of the top 2,500 corporate R&D investors worldwide, coupling R&D and patent analysis to provide new evidence on the EU specificities with respect to other main economic areas.

During the last 10 years R&D investments in the biotech sector have increased by a factor of 3.6, increasing its prominence in the health industry. However, biotech and pharma companies present similar technological portfolios, whit pharma companies owning more biotechnology patents. Focusing too much on the lack of EU biotech companies among top corporate R&D investors might overemphasize a potential gap with the US in the development of biotechnologies.

In this work we identify a set of technologies related to immunology, immunotherapy, bioinformatics and combinatorial chemistry – *Immuno+* technologies – and show that these are complex and increasingly pervasive. The gap with the US is large and a sense of urgency would help the EU jump into this new technological wave.

The key question for EU policy makers is how to foster the overall development of the health and biotech innovation system in the EU.

Understanding where, how and what type of research is performed in the EU compared to other economic areas is of great importance. This report provides insights that can support the ongoing revision of the general pharmaceutical legislation on medicines for human use. However, more evidence is needed to evaluate and implement the new healthcare industrial and innovation policies in the years to come. Disentangling the role played by large R&D investors in the EU innovation system and the interactions between private and public research activities seems to be particularly relevant as concerns the health industry.

# 1 Introduction

The health industry has experienced a great transformation in the last decades, marked by the transition from the development of traditional compounds that characterized the pharmaceutical sector in the 20th century, to the raise of biotechnological technologies, personalised medicines and the increasing development of medical devices favoured by improvements in digital technologies (Deloitte, 2018; Pardi et al., 2018). The health industry accounts for a substantial chunk of worldwide research and development investments, which may lead to important breakthroughs, associated to pressures to adopt controls on pharmaceutical prices (Lakdawalla, 2018) or to face upcoming threats.

It is therefore crucial to look at the technological development in the health industry from the perspective of the EU Industrial R&D Investment Scoreboard, a database collected by the Joint Research Centre (JRC) to monitor the activities of the top corporate R&D investors worldwide. This will allow us to better understand the dynamics of a sector where new drug development has become particularly expensive, with yearly increases of total capitalised costs per drug development in the order of 8.5% (DiMasi et al., 2016; DiMasi & Grabowski, 2007). The development of new pharmaceutical compounds not only requires high R&D investments, but also important investments related to their testing to guarantee safety and effectiveness, necessary to get approval for public authorities like the European Medicines Agency (EMA) in the EU or the Federal Drug Administration (FDA) in the USA.

Indeed, while research and development in pre-clinical phases can be performed by research institutes or specialized small and medium enterprises, the financial resources required for later stages are massive. For this reason, in the last few decades the health industry has been through a major consolidation, resulting in a handful of large life-sciences firms active on the market (Veugelers & Zachmann, 2020). Only large companies have the financial resources to afford the most expensive stages of development, testing (i.e., clinical trials) and regulatory approval procedures, and the commercialisation capabilities to operate on a global scale (manufacturing, distribution and marketing).

A recent example of collaboration between a (relatively) small, specialised company and a main sector player is provided by the Pfizer and BioNTech partnership to development and commercialise the Comirnaty vaccine for COVID-19. This collaboration is also a clear example that blockbuster drugs guarantee very high profits and the race to the COVID-19 vaccine favoured companies performing R&D activities exploring new technological solutions that have a great transformative potential (e.g., mRNA-based drugs). New and emerging approaches in the medical field are associated with strong market opportunities, thus somehow balancing the increasing risks and costs associated with drug development. In recent years, many research-based pharmaceutical companies have reported an uptick in revenue and profits (Deloitte, 2018).

In the biotechnology and pharmaceuticals sectors, patents and new drugs development may guarantee particularly high returns (Dosi et al., 2021), thus making it cumbersome to evaluate the returns to R&D in an industry where companies rely on very large R&D budgets linked to the commercialisation of products (main players) and/or on the development of brand-new classes of medical solutions that require time and investments to reach the market (specialised companies). Indeed, in the biotechnology and pharmaceuticals sectors the success of companies relies particularly on the right balancing of the innovation strategies pursued by firms, and the linkages to basic science and novel approaches that can help firms achieving a higher technological impact (Ke, 2020).

This report analyses the health industry through the lens of the top 2500 corporate R&D investors worldwide, what we will call the 'Scoreboard companies'.

First, it looks at the evolution of the health industry companies over the last decade to assess their relevance among the Scoreboard companies, the rise of biotechnology companies, the evolution of profitability in the industry and some aggregate evidence to compare the performance of the EU with respect to other main economic areas.

Second, it analyses the patent portfolios of Scoreboard companies to assess their relevance in the global development of health-related technologies and to explore the extent to which the patent-R&D relationship is sector- or country-specific and how the relative sectoral specialisation of economic areas has evolved along time.

Third, it analyses the R&D flows of health companies across economic areas and for the three sectors composing the industry: pharmaceuticals, biotechnology, and health equipment & Services. The approach allows us to follow R&D investment across areas and to assess the capacity to attract investments in specific sectors, which in turn can be seen both as a measure of attractiveness of the various innovation systems and a proxy for evaluating where new knowledge and skills are created and accumulated.

Finally, it focuses on a set of new technological solutions related to immunology, immunotherapy, bioinformatics and combinatorial chemistry, a burgeoning field of research and development with a high transformative potential. This set of technologies will be labelled as 'Immuno+'.

A summary of the main findings, and a set of implications and further questions raised by the report both for policy and research, concludes the report.

## 2 Evolution of the health sector over the last 10 years

*The analysis presented in this section is based on the last 10 editions of the EU Industrial R&D Investment Scoreboard (2012–2021), considering the top 2,500 ranking companies in each edition and analysing the dynamics of the health industry and the three sectors composing it: pharmaceuticals, biotechnology, and health equipment & services.*

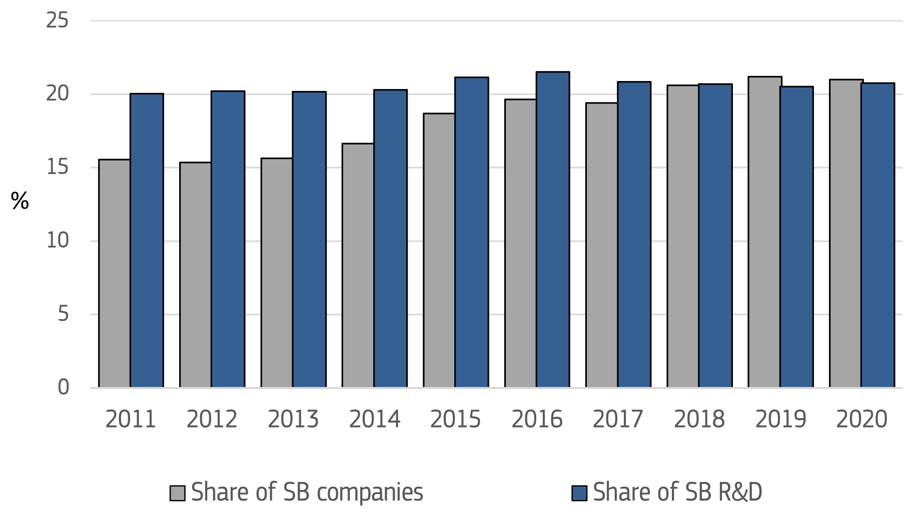
*Main findings:*

- The number of health companies in the Scoreboard has steadily increased over the last 10 years.
- This growth has been largely driven by biotech companies, which have increased their R&D investment (x3.6 in 10 years) more than companies in the other two sectors of the health industry.
- The profitability of the health industry declined until recent years, to a point where it then stabilised (at an average of 12%), which can be at least partially due to the structural transformation taking place in the industry.
- Due to the COVID-19 pandemic, the profitability of the industry has risen when considering an indicator not influenced by the figures provided by the largest companies.
- Overall, EU based companies have substantially increased their R&D investments during the period considered (almost doubled), keeping pace with the growth registered by US ones.

The number of companies operating in the health industry who ranked among the top corporate R&D investors worldwide has increased substantially over the last 10 years. In 2011,[1] about 15.6% of the top 2,500 R&D investors were companies operating in the health industry. This share has continuously risen until 2018, to then remain constant; in 2021 about 21% of scoreboard companies were in the health industry.

Interestingly, the increasing share of health companies in the Scoreboard has not been mirrored by a concomitant increase in their share of overall R&D investment in the sample. Indeed, R&D performed by companies in the health industry represents about one fifth of the total R&D investment of scoreboard companies, a figure that has remained quite stable in the last 10-years (see Figure 1).

**Figure 1.** Share of healthcare companies and of their R&D among top R&D investors




*Source: 10 editions of the EU Industrial R&D Investment Scoreboard (SB), top 2500 companies.*

[1] There is a lag of 1 year between an edition of the EU Industrial R&D Investment Scoreboard and the time reference of most updated data: e.g. the 2012 edition of the Scoreboard corresponds to the 2011 fiscal year. In the following, unless specifically stated, we will refer to the fiscal year.

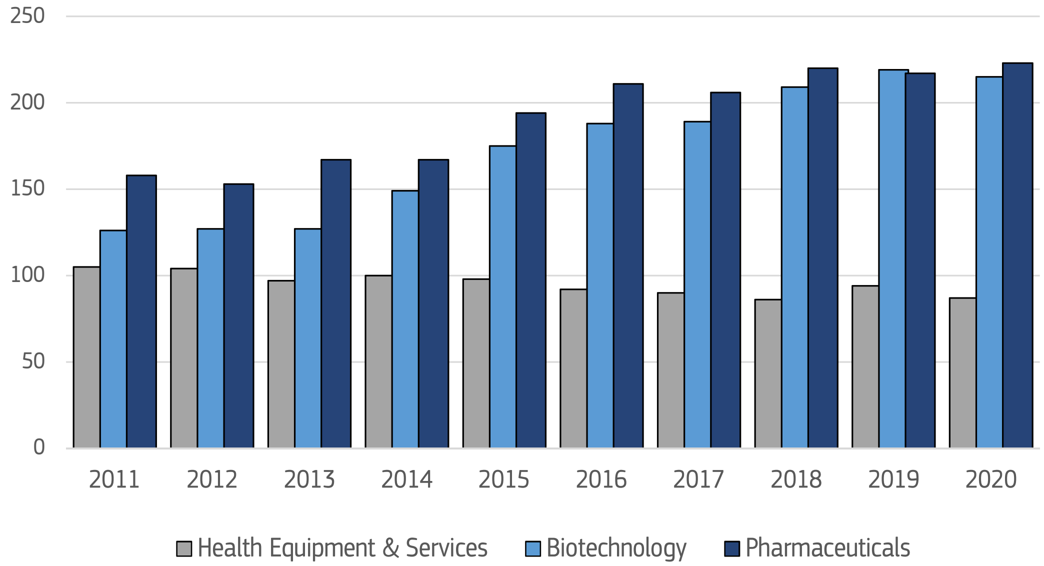
Taken together, these two trends suggest that (on average) health companies among the top 2,500 corporate R&D investors worldwide have become relatively smaller than their counterparts operating in other sectors.

This is partly due to the spectacular growth of R&D investments in the ICT (Information and communication technology) sector, coupled with the rise of large multinational companies toward the top of the ranking. In 2020, the 6 larger R&D investors (Alphabet, Huawei, Microsoft, Samsung, Apple and Facebook) were providing ICT products and services investing about €100 billion in R&D, which in turn tends to move the sample average upward (JRC, 2021). However, the rising share of companies also suggests a substantial entry of health companies among the top R&D investors with respect to other sectors and high number of companies (often specialised) at the bottom of the ranking.

In the following we disentangle this latter dynamic looking at the evolution of the three sectors composing the health industry: health equipment & services, biotechnology and pharmaceuticals. This will allow us to look at sub-sectoral dynamics and assess quantitatively the transformation occurring in health industry as discussed in the introduction.

Figure 2 shows the number of companies in the health equipment & services, biotechnology and pharmaceuticals over the last 10-years. As shown in the figure, the increasing presence of health companies among the top corporate R&D investors has been driven by the rise of the biotechnology and pharmaceuticals sectors, with a concomitant decrease of companies operating in health equipment & services.

**Figure 2.** Number of healthcare companies in the Scoreboard, by health sector



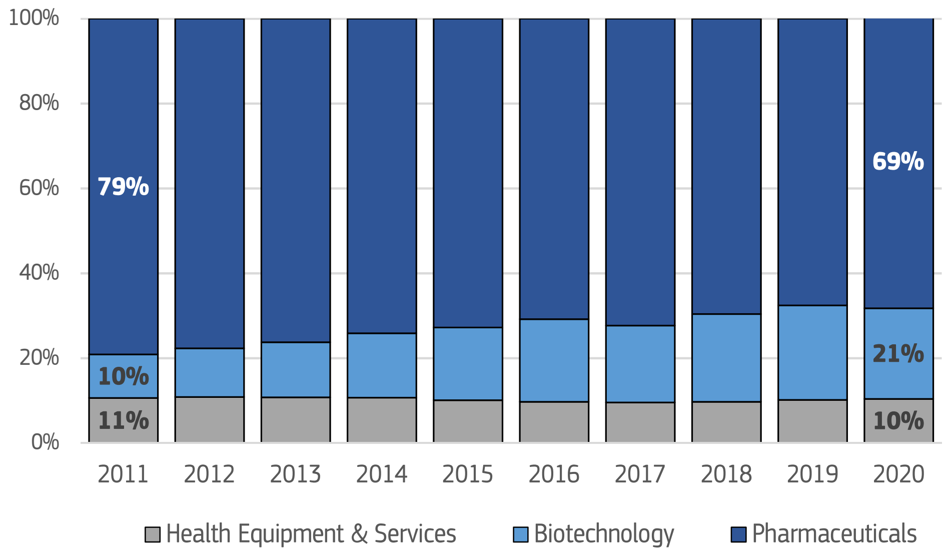

*Source: 10 editions of the EU Industrial R&D Investment Scoreboard, top 2500 companies.*

Particularly relevant is the rise of biotechnology companies among the top R&D investors (+71%), which has been accompanied by an increased relevance also in terms of R&D expenditures. Figure 3 shows the percentage of the overall R&D investment of health companies performed in each sector. Consistent with their increasing presence among the top R&D investors, biotechnology companies have also improved their relevance in terms of R&D investment.

Indeed, their share of R&D has more than doubled, passing from 10% to about 21%. Interestingly, the increasing share of biotechnology companies has been almost completely matched by a contextual decrease of the pharmaceuticals sector (which is, however, still performing a much larger share of investment), which is experiencing a structural transformation from more traditional (chemical) medicine to the development of biotechnologies and molecular medicine.

At the same time, the share of R&D investment performed by health equipment & services companies has remained substantially stable; coupled with a decreasing number of companies, this trend suggests that companies in this sub-sector have grown in size, at least in terms of average R&D investment.

**Figure 3.** Share of R&D across healthcare sub-sectors




*Source: 10 editions of the EU Industrial R&D Investment Scoreboard, top 2500 companies.*

The shift toward an increasing share of R&D expenditures by the biotechnological sector is particularly interesting, especially considering two aspects:

(1) most of the top biotechnological companies present in the earliest versions of the Scoreboard have been acquired by pharmaceuticals companies (Hernández et al., 2013);

(2) the rise of R&D investment by biotech companies may have brought changes in the overall R&D-patent relationship of the health industry, due to the possibly different costs involved in the pre-clinical and clinical phase in the pharma and biotech sectors (DiMasi & Grabowski, 2007) and by the fact that many biotech companies at the bottom of the Scoreboard ranking show a very high R&D intensity (largely due to low or almost non-existent sales).[2]

The second point will be further explored later in the report by means of patent analysis.

To complete the overview of the dynamics of the last decade, we list in Table 1 the top 25 R&D investing companies in 2011 together with those of 2020 (Scoreboard, 2021). For each year the table displays the name of companies, the country of their headquarters, the sector in which they operate and their ranking position among the whole Scoreboard sample (i.e., considering also other industries). At the bottom of the table is also reported the share of the top 25 companies with respect to the R&D of the whole health industry.

Different aspects are worth noticing in Table 1:

- The world ranking of the very top companies in 2020 is in general lower than their respective positions in 2011, which is partly due to rise of ICT companies among the top R&D investors. Noticeable exceptions are Johnson & Johnson (entering the top 10), the raise of some biotech companies (Gilead Science +98 and Biogen +58 positions), and of Medtronic Public Limited, a world leader in medical devices.

[2] R&D intensity is the ratio between R&D investment and net sales of a given company or group of companies.

- Most of the companies are present in both rankings, suggesting a substantial stability among the largest R&D investors in the health industry.
- The share of R&D of the top 25 companies with respect to the overall industry R&D investment has decreased substantially (-12 percentage points), pointing to a decreased concentration of R&D expenditures among industry leaders.

**Table 1.** Top 25 healthcare companies in terms of R&D, 2011 and 2020

| 2011 (SB 2012) | | | | | 2020 (SB 2021) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Company | Country | Sub-sector | World rank | R&D (€ mil) | Company | Country | Sub-sector | World rank | R&D (€ mil) |
| Novartis | CH | Pharmaceuticals | 4 | 7,001 | Roche | CH | Pharmaceuticals | 8 | 11,247 |
| Pfizer | US | Pharmaceuticals | 6 | 6,806 | Johnson & Johnson | US | Pharmaceuticals | 10 | 9,909 |
| Roche | CH | Pharmaceuticals | 7 | 6,631 | Bristol-Myers Squibb | US | Pharmaceuticals | 13 | 8,409 |
| Merck Us | US | Pharmaceuticals | 10 | 6,090 | Merck Us | US | Pharmaceuticals | 14 | 8,331 |
| Johnson & Johnson | US | Pharmaceuticals | 11 | 5,834 | Pfizer | US | Pharmaceuticals | 15 | 7,837 |
| Sanofi-Aventis | FR | Pharmaceuticals | 16 | 4,795 | Bayer | DE | Pharmaceuticals | 16 | 7,704 |
| Glaxosmithkline | GB | Pharmaceuticals | 17 | 4,377 | Novartis | CH | Pharmaceuticals | 18 | 7,114 |
| Eli Lilly | US | Pharmaceuticals | 27 | 3,880 | Sanofi | FR | Pharmaceuticals | 24 | 5,527 |
| Astrazeneca | GB | Pharmaceuticals | 28 | 3,668 | Abbvie | US | Pharmaceuticals | 28 | 5,037 |
| Abbott Laboratories | US | Pharmaceuticals | 35 | 3,191 | Glaxosmithkline | GB | Pharmaceuticals | 29 | 5,034 |
| Bayer | DE | Pharmaceuticals | 38 | 3,045 | Astrazeneca | GB | Pharmaceuticals | 31 | 4,896 |
| Bristol-Myers Squibb | US | Pharmaceuticals | 39 | 2,967 | Gilead Sciences | US | Biotechnology | 38 | 4,106 |
| Takeda Pharmaceutical | JP | Pharmaceuticals | 41 | 2,803 | Boehringer Sohn | DE | Pharmaceuticals | 45 | 3,696 |
| Boehringer Ingelheim | DE | Pharmaceuticals | 46 | 2,516 | Takeda Pharmaceutical | JP | Pharmaceuticals | 49 | 3,584 |
| Amgen | US | Biotechnology | 51 | 2,177 | Eli Lilly | US | Pharmaceuticals | 51 | 3,456 |
| Astellas Pharma | JP | Pharmaceuticals | 58 | 1,888 | Amgen | US | Biotechnology | 52 | 3,428 |
| Daiichi Sankyo | JP | Pharmaceuticals | 60 | 1,840 | Biogen | US | Biotechnology | 53 | 3,252 |
| Otsuka | JP | Pharmaceuticals | 72 | 1,583 | Merck De | DE | Pharmaceuticals | 68 | 2,263 |
| Merck De | DE | Pharmaceuticals | 77 | 1,517 | Medtronic Public Limited | IE | Health Equip. & Serv. | 77 | 2,032 |
| Eisai | JP | Pharmaceuticals | 88 | 1,244 | Abbott Laboratories | US | Pharmaceuticals | 81 | 1,913 |
| Novo Nordisk | DK | Pharmaceuticals | 90 | 1,210 | Novo Nordisk | DK | Pharmaceuticals | 85 | 1,845 |
| Medtronic | US | Health Equip. & Serv. | 96 | 1,165 | Daiichi Sankyo | JP | Pharmaceuticals | 89 | 1,788 |
| Celgene | US | Biotechnology | 98 | 1,131 | Incyte | US | Biotechnology | 90 | 1,785 |
| Biogen Idec | US | Biotechnology | 111 | 943 | Astellas Pharma | JP | Pharmaceuticals | 92 | 1,765 |
| Gilead Sciences | US | Biotechnology | 113 | 929 | Otsuka | JP | Pharmaceuticals | 95 | 1,705 |
| Share of these 25 companies over total health industry | | | 74% | | Share of these 25 companies over total health industry | | | 62% | |

*Source: 2012 and 2021 editions of the EU Industrial R&D Investment Scoreboard.*

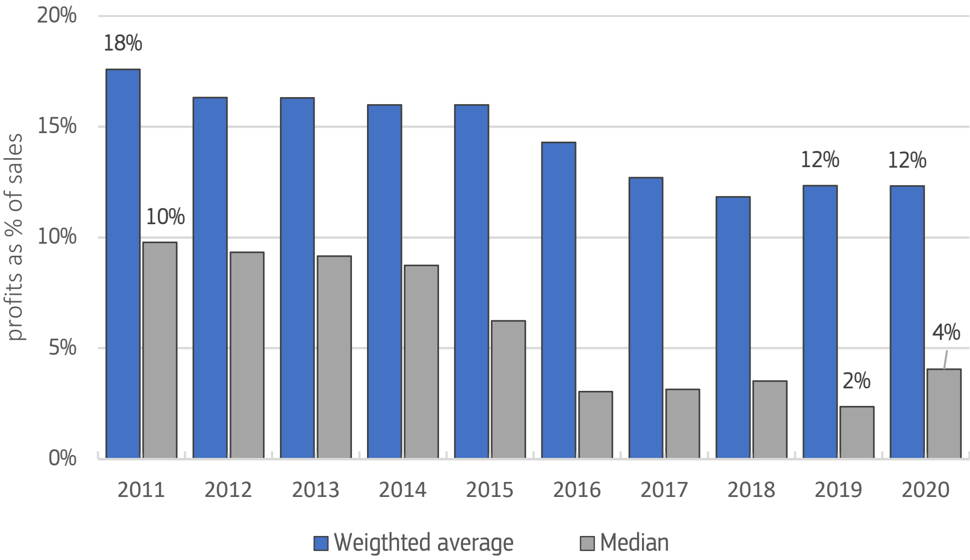
The changes that occurred in the health industry – in terms of distribution of companies across sectors, decreasing R&D concentration and decreasing average size – have implications on the overall industry performance indicators. Indeed, as we said, several biotechnology companies at the bottom of the ranking combine high R&D expenditures with basically no sales. Many of these companies are developing new bio-medical drugs that are still in the clinical or pre-approval phase, therefore representing huge growth potential and capacity to attract investors and sustain their R&D activities.

The possible decline in technological opportunities and the relative increase of the costs associated with research and development has been a recently discussed topic in specialised literature on innovation in the medical sector.

Figure 4 displays the average (weighted by the size of net sales) and median profitability in the health industry. The weighted average gives more weight to large companies, while the median provides a figure that is robust from deviations and independent of firm size (50% of companies have a profitability greater or equal to the median and 50% equal or lower).

Both indicators present a decreasing pattern that has flattened in recent years. Interestingly, in 2020 the median value of profitability increased with respect to that of 2019 (from 2% to 4%), suggesting that the median company doubled its profitability (profits as % of sales) during the first phases of the COVID-19 pandemic.

**Figure 4.** Profitability of healthcare companies, using different Scoreboards



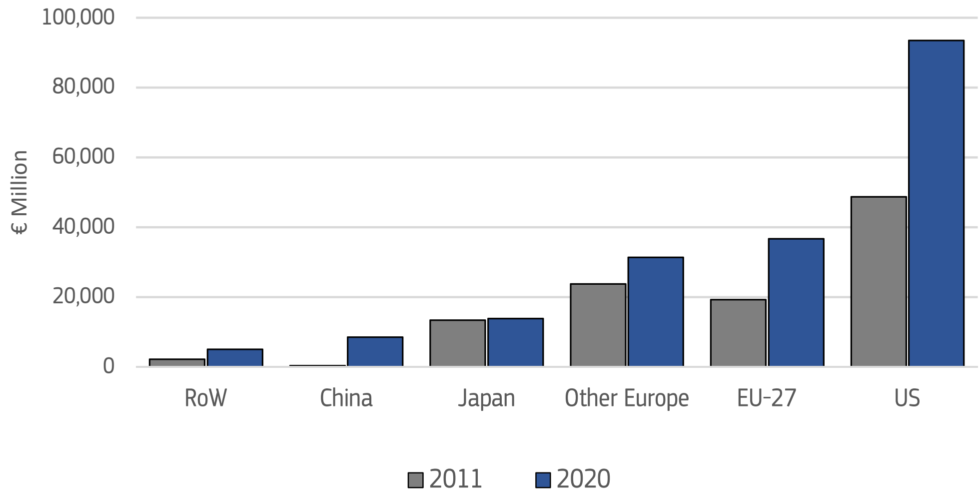

*Source: 10 editions of the EU Industrial R&D Investment Scoreboard.*

The shock represented by the pandemic signified a major change in the industry regarding the efforts and R&D investments, made to develop vaccines: both from the private and the public sectors. Moreover, the development of mRNA-based vaccines and their success in beating the market has raised public awareness (and sometimes resistance) about new technological developments in the health industry.

In section 5, we will focus on the COVID vaccines and on a series of patented technologies characterizing the evolution of technological development related to immunology, bioinformatics and combinatorial chemistry; a broad set of technologies that is revolutionizing the industry.

Finally, we conclude this section on the long-term dynamics in the health industry by comparing the overall levels of R&D investment among main economic areas. Figure 5 shows the total R&D investment by economic area for 2011 and 2020. The US is the country with the highest investment in R&D, representing about 50% of the whole R&D investment performed by the Scoreboard companies operating in the health industry.

**Figure 5.** R&D expenditures of healthcare companies by economic area, 2011 and 2020

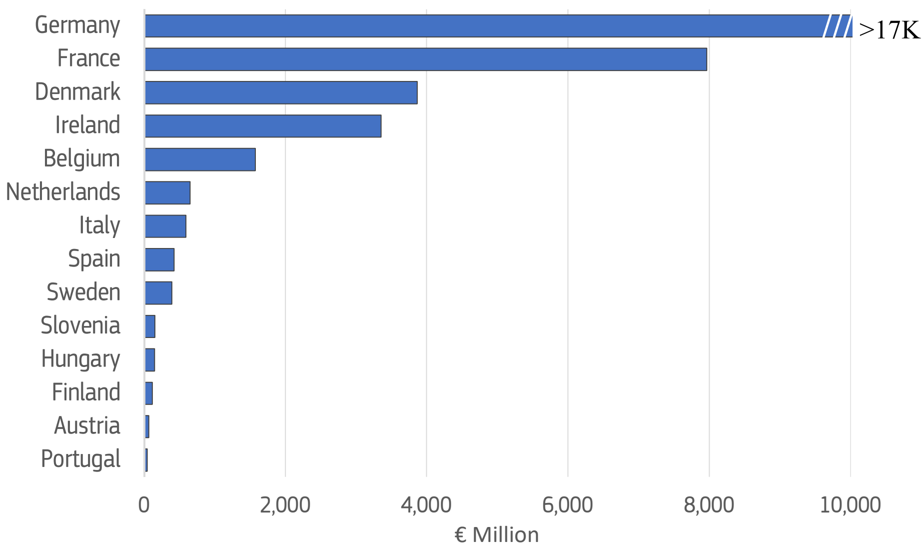



*Source: 2012 and 2021 editions of the EU Industrial R&D Investment Scoreboard.*

The EU ranks second with an overall share of R&D of about 19%, slightly higher than the 18% recorded in 2011. Thanks to a more sustained growth, companies located in the EU have outpaced the investment made by companies located in other European countries (mostly Switzerland and UK) but have not been able to close the gap with the US. A look at the main Asian economies returns a relatively static profile for Japanese companies and a sustained increase in R&D investment by China headquartered companies. These have moved in 10 years from a negligible share of overall R&D investment (about 0.3%) to a remarkable 4%, a tenfold increase in their relative worldwide weight.

Figure 6 focuses on the R&D investment by UE-27 based companies in 2020. German-based companies account for a very high share of EU R&D investment in the health industry (about 47%), followed by companies based in France (21.7%) and companies based in Denmark (10.5%).

**Figure 6.** R&D expenditures of EU based healthcare companies in 2020




*Note: for presentation purposes the bar for Germany has been cut, R&D investments are well above 10K millions.*
Source: the *EU Industrial R&D Investment Scoreboard (2021 edition).*

The R&D of companies located in these three countries combined, represents about 80% of overall EU R&D in the health industry. Ireland ranks fourth but, as we will show below, this reflects the fact that some large US companies have moved the headquarter (but not their actual research activities) in Ireland for tax related reasons.

In the following section we will explore more in-depth differences across main areas and across sectors, by adding to the analysis insights for the companies in the 2019 Scoreboard edition and looking at their patent portfolios.

# 3 Relevance of Scoreboard companies in developing health technologies

*The analysis of patent portfolios is based on the JRC/OECD COR&DIP© database, v.3. 2021, a database recently built by the JRC in collaboration with the OECD matching the 2019 edition of the Scoreboard with Pastat (Amoroso et al., 2021). Patent portfolios are built using (inpadoc) patent families filed at USPTO or EPO.*[3]

*Main findings:*

- Compared with the whole patented technologies, Scoreboard companies own a lower share of world patents in health technologies. Public institutions and small firms play a major role in the development of health technologies.
- Despite a different sector classification, biotech and pharma companies present a similar technological specialisation (in both sectors the bulk of patents is related to pharmaceuticals).
- Pharma companies file the highest number of biotech patents: looking at technological development provides a more precise picture than just comparing R&D by sector.
- Most patents in the health industry are related to medical technology (devices), which involves a much lower cost of development than drugs.
- Differences in the patent-R&D relationship are mainly due to specific features of the sector or technology in question. Firms in the health equipment & services tend to have a much higher propensity to patent than their counterparts in pharma & biotech.
- The EU does not present a patent propensity gap with respect to the other world areas.
- Over the last decade, the EU has increased its world share in pharmaceutical and health equipment & services, while losing ground in biotech. However, a large part of the EU R&D in health equipment & services is due to US companies with headquarters but no real research activities in Ireland.

A first look at the patent portfolios of Scoreboard companies reveals the relevance of these firms in the worldwide development of new technologies (Figure 7, left).

**Figure 7.** Share of EPO-UPSTO patents families by 2019 world's top R&D investors, 2016-18

*All technologies* *Health technologies*


*Source: JRC/OECD COR&DIP© database, v.3. 2021 and Patstat 2021a.*

[3] An inpadoc patent family is defined as comprising all the patent documents sharing directly or indirectly (e.g., via a third document) at least one priority. The use of inpadoc patent families instead of simple patent counting allows us to avoid double counting patent documents filed by a company that contain very similar technical content (e.g., the same invention protected at the EPO and at the USPTO). EPO stands for European Patent Office, while USPTO stands for United States Patent and Trademark Office.

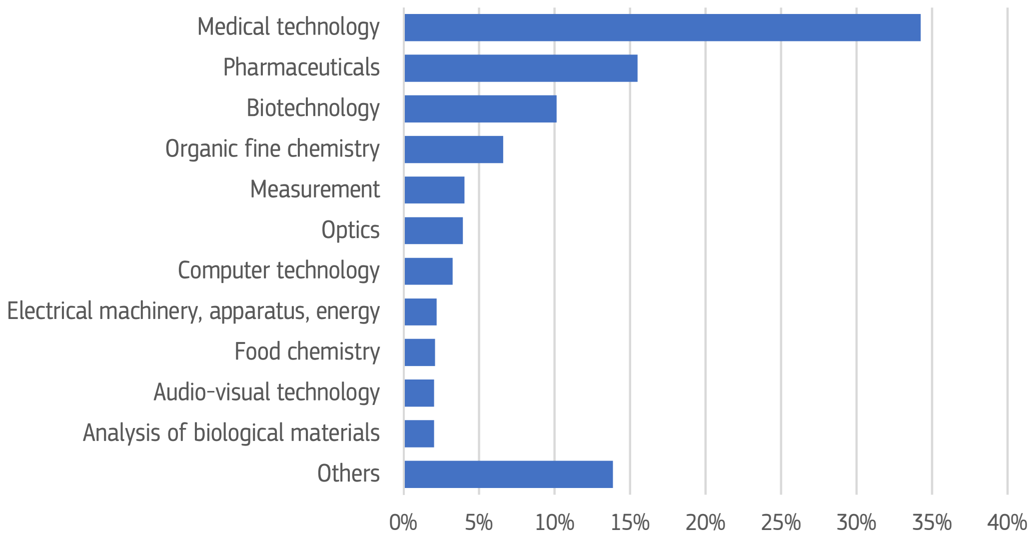
During the 2016-2018 period, Scoreboard companies filed about 668,000 of inpadoc families at USPTO or EPO, which correspond to about 58% of the overall inpadoc families during the same period; a share much in line with that obtained taking into account IP5 patent families (Dernis et al., 2019). Overall, Scoreboard companies tend to present a specialisation in the development and patenting of Information and Communication Technologies (Dernis et al., 2019), with the highest shares of patents in 'Computer technology', 'Electrical machinery, apparatus, energy' and 'Digital communications' (Gkotsis & Vezzani, 2022).

When considering *health technologies*,[4] Scoreboard companies file slightly less than half of the overall patent families (44%, corresponding to about 69k patents), hinting at the relatively higher importance of other actors than Scoreboard companies in contributing to the technological development of medical-related solutions. Of course, patents related to *health technologies* can be developed by companies not classified in the health industry (e.g. related to cosmetics, veterinary, smart devices); at the same time, health companies can file patents not directly related to health technologies.

In the following we will therefore focus on the patents filed by companies operating in the health industry.

Figure 8 shows that about 35% of patents families filed by companies in the health industry are related to 'Medical technologies', followed by 'Pharmaceuticals' and 'Biotechnologies' (about 14% of patent families are related to fields not included in the chart). The figure also illustrates the non-marginal shares of patents related to instruments and computer technologies, reflecting the importance of ICT-related technologies for the development of health solutions.

**Figure 8.** Distribution of patents of healthcare companies by technology, 2016-18




*Note: only technological fields representing at least 2% of the patent portfolio are reported.*
*Source: JRC/OECD COR&DIP© database, v.3. 2021.*

When focusing only on the 5 technological fields usually considered as directly related to health, medical technologies represent about 50% of patent families. The share of 'Pharmaceuticals' patents is much lower than the share of R&D from Pharmaceuticals companies: comparisons based on technological development provide complementary information to those considering the sectoral classification of firms.

[4] To assess the relevance of Scoreboard companies in technological development, we consider among health technologies those patent families including IPCs classified by the WIPO as "Analysis of biological material", "Medical technology", "Organic fine chemistry", "Biotechnology", and "Pharmaceuticals".

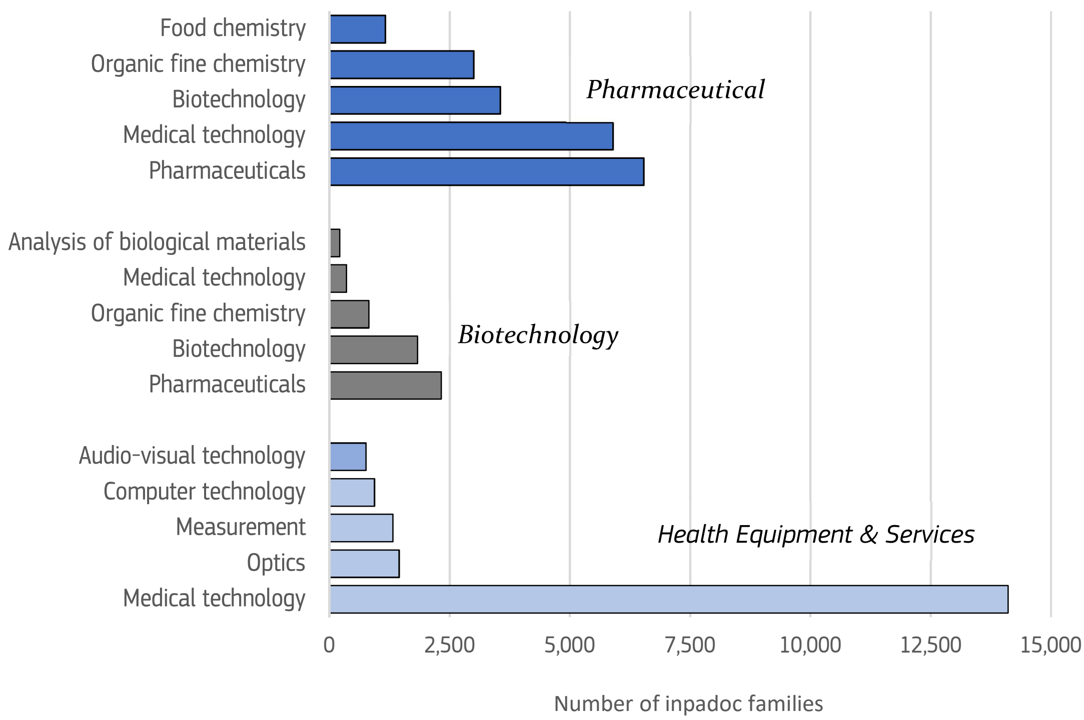
Figure 9 shows the top 5 technology classes in terms of patent families for each health sub-sector.

Pharmaceutical companies file the highest number of biotechnology-related patents, which is not completely surprising considering that they are much bigger than biotech companies and that they have acquired successful biotech companies over the years, probably to diversify or enter the biotech business via controlled investments.

The figure also illustrates another interesting point: the distribution of patents across the technologies presented above, and in particular the relevance of medical technologies, is mostly driven by the health equipment & services companies. The different shares of patents compared to R&D distribution across sectors can be due to a different patent propensity or a different cost of developing technologies. Putting it differently, patents related to ICT technologies can be so numerous both because they reflect a shift in the technological development in the health industry and because they involve much lower R&D investments → i.e. the development of new 'Medical technologies' and 'Computer technologies' is less expensive than that of 'Pharmaceuticals' and 'Biotechnology' (Gkotsis & Vezzani, 2022).

The difference in patenting activity across sectors suggest that differences across economic areas can derive from a different composition (specialisation) of their health companies and therefore reflecting structural features rather than intrinsic firms' factors (Moncada-Paternò-Castello and Grassano, 2021). Before moving forward in presenting patent statistics, we illustrate this point in the following table.

**Figure 10.** Top 5 technology classes by health sub-sector, 2016-18




*Source: JRC/OECD COR&DIP© database, v.3. 2021.*

Table 2 shows the share of R&D across economic areas by health sub-sector. The table highlights the increasing relevance of China based companies relative to overall R&D investment in all the health sub-sectors; moving from a negligible share, their R&D share has increased particularly in biotechnology and pharmaceutical. At the same time, the share of R&D performed by Japan-based companies has decreased across the board.

**Table 2.** Share of R&D across economic areas by sub-sector, 2011 and 2019

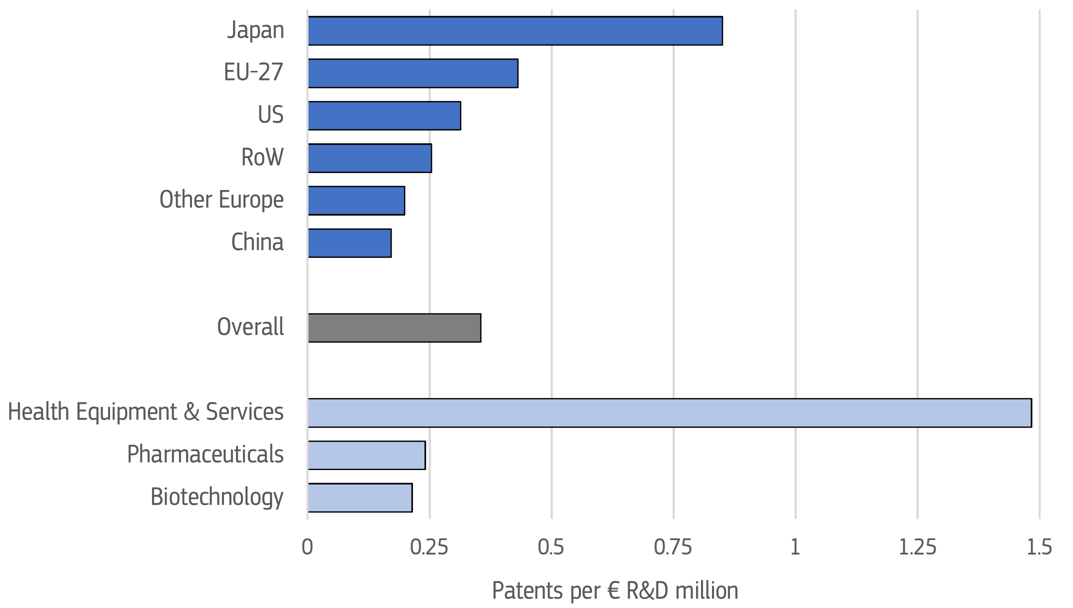
| | Health Equipment & Services | | | Biotechnology | | | Pharmaceuticals | | |
|---|---|---|---|---|---|---|---|---|---|
| | 2011 | 2019 | Difference | 2011 | 2019 | Difference | 2011 | 2019 | Difference |
| China | 0.8% | 2.9% | ↗ 2.1% | 0.0% | 3.6% | ↑ **3.6%** | 0.3% | 3.6% | ↑ **3.3%** |
| EU-27 | **20.4%** | **30.7%** | ↑ **10.3%** | **8.3%** | **6.4%** | ↓ **-1.9%** | **18.8%** | **22.2%** | ↑ **3.4%** |
| Japan | 11.3% | 8.3% | ↘ -3.0% | 0.4% | 0.1% | -0.3% | 14.1% | 10.2% | ↓ **-4.0%** |
| Other Europe | 2.9% | 3.5% | 0.7% | 3.2% | 3.6% | 0.4% | 27.0% | 23.3% | ↓ **-3.7%** |
| RoW | 1.5% | 1.3% | -0.2% | 3.3% | 3.3% | 0.0% | 2.0% | 2.8% | 0.9% |
| US | **63.2%** | **53.3%** | ↓ **-9.9%** | **84.8%** | **83.0%** | ↓ **-1.8%** | 37.7% | 37.9% | 0.2% |
| Total | 100.0% | 100.0% | | 100.0% | 100.0% | | 100.0% | 100.0% | |

*Source: 10 editions of the EU Industrial R&D Investment Scoreboard.*

The EU and the US present opposite patterns in the health equipment & services sub-sector where changes are quite strong (in the order of 10%), with EU based companies strongly increasing their share with respect to the global R&D investment in this sub-sector, but USA based companies still performing more than half of the global R&D investment. Both the EU and the US have seen their share in biotech fall (but US still has a share above 80%). While the EU has somewhat improved its position in pharmaceuticals, the US does not show appreciable changes in terms of its share of worldwide R&D investment in this sector.

In Figure 11 we report the patent-to-R&D ratio, or the number of patents per R&D investment, both by economic area and health sector. The patent propensity of Japanese companies, traditionally strong in the development of instruments, is the highest among the different areas plotted, while that of Chinese companies is the lowest. EU based companies show a good patent-to-R&D ratio, slightly above the other areas considered.

**Figure 11.** Patents per million R&D by economic area and sector, 2016-18




*Source: JRC/OECD COR&DIP© database, v.3. 2021.*

To conclude this section on the patent propensity of Scoreboard companies, we try to disentangle the relationship between patents and R&D –considering both the technological specificities of the three health sub-sectors and economic area-specific factors –to evaluate their performance in the health industry.

Table 3 shows the results of a linear regression using the 386 Scoreboard companies with inpadoc families filed in 2016-2018, where the logarithm of patents (2016-2018) is regressed against the logarithm of R&D expenditure (2016-2018), and then fixed effects are added for sector and economic area.

The coefficient attached to R&D is positive but statistically lower than one, suggesting that an increase of 10% in a firm R&D expenditure is associated with an increase of about 8.6% in patents (see the last column). This implies that patents respond less than proportionally to increases in companies' R&D budgets. Consistent with the descriptive statistics presented above, when accounting for R&D investment the firms operating in the biotechnology and pharmaceuticals sectors file less patents than their counterparts in the health equipment & services. Interestingly, in general we do not find differences between firms headquartered in different economic areas, with only China based firms showing a lower patenting activity with respect to EU based ones (the baseline).

All in all these results can be read as evidence that if a technology gap exists, this is due to the intrinsic characteristics of the health sub-sectors rather than to differences across economic areas. Of course, this evidence is not suggesting that there are no differences in the technological development of health technologies across economic areas, but that differences are mostly due to diversities in the sectoral specialisation and in the level of R&D investment (with the increase of firm size patents increase less than proportionally).

**Table 3.** Patent and R&D, linear regression results

| | Patents (log) | Patents (log) | Patents (log) | Patents (log) |
|---|---|---|---|---|
| R&D (log) | 0.875*** | 0.878*** | 0.850*** | 0.856*** |
| | *(0.048)* | *(0.042)* | *(0.048)* | *(0.042)* |
| *Sector (baseline -> health equipment & services)* | | | | |
| Biotechnology | | -1.410*** | | -1.377*** |
| | | *(0.147)* | | *(0.148)* |
| Pharmaceuticals | | -1.622*** | | -1.626*** |
| | | *(0.143)* | | *(0.145)* |
| *Area (baseline -> EU)* | | | | |
| China | | | -0.730*** | -0.569** |
| | | | *(0.272)* | *(0.236)* |
| Japan | | | 0.252 | 0.312 |
| | | | *(0.254)* | *(0.220)* |
| Other Europe | | | -0.144 | -0.063 |
| | | | *(0.252)* | *(0.217)* |
| RoW | | | -0.371 | -0.126 |
| | | | *(0.274)* | *(0.237)* |
| US | | | -0.130 | -0.175 |
| | | | *(0.169)* | *(0.149)* |
| Constant | -0.646*** | 0.566** | -0.393 | 0.776*** |
| | *(0.230)* | *(0.231)* | *(0.284)* | *(0.267)* |
| Observations | 386 | 386 | 386 | 386 |
| Adj. R-squared | 0.464 | 0.603 | 0.474 | 0.611 |
| RMSE | 1.193 | 1.026 | 1.182 | 1.017 |

*Note: Standard errors in parentheses. *** p<0.01, ** p<0.05, * p<0.1.*

In section 5 we will focus on the patenting activity of Scoreboard companies in a set of technologies that have a high transformative potential for the health industry, in order to evaluate the performance of the EU based companies with respect to their main world competitors. The aim is to assess whether the EU is lagging behind in a new wave of technological change that will potentially determine the competitiveness of its health industry in the years to come.

# 4 Mapping knowledge flows in the health industry

*In this section, we present R&D flows across main economic areas thorough the use of patents. For each company R&D is equally distributed across patents and then international R&D flows are proxied according to those patents that have been developed by inventors located in countries different from the head-quarter of the Scoreboard company.*

*Main findings:*

- ❖ The flows of corporate R&D investments from the EU to the rest of the world are higher than the R&D the EU receives from other areas.
- ❖ The imbalance is mainly due to the EU's strong negative balance with respect to the US. In contrast, the EU records a positive balance with respect to the rest of Europe (mainly due to investment from Switzerland-based companies).
- ❖ Some differences arise across sectors in R&D flows, but a closer look at the dynamics reveals that this seems to be driven by large R&D investment by few companies.
- ❖ Bayer (DE) and Sanofi (FR) appear to be the two companies with the largest outflows toward the US. The other largest outflows of R&D are associated with Medtronic Public Limited and Allergan (IE), for both of which all the R&D is actually performed in the US: these companies are headquartered in Ireland for fiscal reasons but innovate (and produce) in US.
- ❖ The non-EU companies investing more in the EU are Roche and Novartis (Switzerland) and Abbvie (US). Our proxy for R&D flows suggests that each of these companies invests more than €1 billion per year in the EU.

In the previous section we considered the patenting activities of Scoreboard companies from a headquarters viewpoint, by allocating patents according to the company as the applicant to the USPTO or EPO. Localising patents according to their ownership provides the perspective of the subject (company) that is capturing the returns from innovation. Patent documents also contain information about the residence of the inventor(s) and allocating patents according to the location of the inventors is a more suitable proxy for where corporate R&D is performed, and knowledge produced (Alstadsæter et al., 2018; Picci, 2010).

## 4.1 R&D flows across main economic areas

In this section, we proxy the location of R&D activities based on the location of the inventors of a patented invention. From this information we compute R&D flows across different areas by allocating the R&D reported by Scoreboard companies to different economic areas according to the spatial distribution of inventors.

In other words, we build the R&D flows comparing (a) the distribution of R&D when assigning patents according to the Scoreboard companies owning them (i.e., where returns to knowledge are appropriated), with (b) that obtained allocating R&D according to the patent inventors' location (i.e., where knowledge is produced). Table 4 shows the outward and inward flows of R&D investment from and to the EU. The difference between inflows and outflows gives the net R&D balance for the EU.

Overall, the EU health industry shows a negative balance of R&D flows with respect to the US of around 6.6€ billion (€12.2 billion of outflows to the US and €5.5 billion of inflows). The EU also shows a negative balance with respect to the Rest of the World (RoW). In contrast, the inflows of R&D from the 'Other Europe' (mainly Switzerland) to EU are higher than the R&D flows in the opposite direction, giving the EU a positive balance of the EU of about €4.4 billion. Similarly, the EU shows a positive balance, albeit small, with respect to Japan and China.

**Table 4.** R&D flows from and to the EU in the health industry (€ million)

*HQ versus inventors' location*

| | China | Japan | Other Europe | RoW | US |
|---|---|---|---|---|---|
| **Outflows** *(from EU companies to other areas)* | 130 | 241 | 2,445 | 1,362 | 12,190 |
| **Inflows** *(from other areas to EU)* | 227 | 686 | 6,805 | 627 | 5,556 |
| **EU net balance** *(inflows - outflows)* | 97 | 445 | 4,360 | -735 | -6,634 |

*Source: JRC/OECD COR&DIP© database, v.3. 2021.*

These figures can be taken as a sort of warning message when compared with the analysis of the R&D flows presented in the 2016 edition of the EU Industrial R&D Investment Scoreboard (Guevara et al., 2017). Indeed, at that time, the negative R&D balance of the EU was marginal and since then it has grown a lot, especially due to a significant increase of R&D investments from the EU to the US.

To better characterize the R&D flows the aggregate balance figures will be disaggregated in two ways. First, we report the detailed R&D flows for the sub-sectors of the health industry. Second, we report the Scoreboard companies headquartered in the EU generating the highest flows of R&D to other economic areas, and the companies headquartered outside the EU that generate the highest flows of R&D toward the EU.

The figures below show the R&D flows for the pharmaceutical, biotechnology and health equipment & services sub-sectors.

The outflows from one economic area to the others can be read by row (→), while the inflows can be read by column (↓). In the upper part of the chart absolute flows are reported and cells are coloured according to the row's relative volume, from low (red) to high (green). In the bottom part of the chart share are reported and only cells containing values greater than 20% are coloured.

All in all, the US tend to attract significant shares and volumes of R&D in all three sub-sectors. In particular, it has a very strong capability to attract R&D investments in the pharmaceuticals sector, which is also the sector with the highest volumes of R&D (see Figure 12).

The R&D flows of companies based in Other Europe hide two difference profiles: Switzerland-based companies balance their R&D flows toward the EU and the US, while the R&D flows from UK based-companies to the US are much larger than those to the EU. Switzerland-based Scoreboard companies seem to be much more integrated in the EU research and development area than their UK counterparts.

**Figure 12.** R&D flows across main economic areas: pharmaceuticals

*HQ R&D versus performed R&D, allocated according to inventors*

Values of R&D flows should be read by row (from --> to)

| R&D FROM | R&D TO | | | | | |
|---|---|---|---|---|---|---|
| | China | EU-27 | Japan | Other EU | RoW | US |
| China | 2643 | 158 | 6 | 97 | 105 | 217 |
| EU-27 | 87 | 14221 | 209 | 2277 | 1110 | 9128 |
| Japan | 43 | 653 | 5266 | 281 | 1322 | 3998 |
| Other Europe | 543 | 6619 | 590 | 6861 | 583 | 12837 |
| RoW | 11 | 353 | 13 | 198 | 2169 | 845 |
| US | 1359 | 3137 | 60 | 1413 | 2657 | 36534 |

Shares (coloured cells contain values above 20%)

| R&D FROM | R&D TO | | | | | |
|---|---|---|---|---|---|---|
| | China | EU-27 | Japan | Other EU | RoW | US |
| China | 82% | 5% | 0% | 3% | 3% | 7% |
| EU-27 | 0% | 53% | 1% | 8% | 4% | 34% |
| Japan | 0% | 6% | 46% | 2% | 11% | 35% |
| Other Europe | 2% | 24% | 2% | 24% | 2% | 46% |
| RoW | 0% | 10% | 0% | 6% | 60% | 24% |
| US | 3% | 7% | 0% | 3% | 6% | 81% |

*Source: JRC/OECD COR&DIP© database, v.3. 2021.*

The biotechnology sector is the one with the highest shares of R&D performed "at home" (on the diagonal), which can be partly due to the relatively small size and high specialization degree of companies operating in this sector (Figure 13).However, in this sector the R&D flows from US companies to the EU are almost double with respect to the EU R&D to the US (€1,215 million vs. €677).

**Figure 13.** R&D flows across main economic areas: biotechnology companies

*HQ R&D versus performed R&D, allocated according to inventors*

Values of R&D flows should be read by row (from --> to)

| R&D FROM | R&D TO | | | | | |
|---|---|---|---|---|---|---|
| | China | EU-27 | Japan | Other EU | RoW | US |
| China | 905 | 0 | 0 | 0 | 6 | 86 |
| EU-27 | 17 | 1600 | 7 | 30 | 18 | 677 |
| Japan | 0 | 0 | 34 | 42 | 0 | 0 |
| Other Europe | 1 | 128 | 0 | 797 | 15 | 258 |
| RoW | 0 | 236 | 0 | 74 | 608 | 243 |
| US | 67 | 1215 | 58 | 616 | 1369 | 26107 |

Shares (coloured cells contain values above 20%)

| R&D FROM | R&D TO | | | | | |
|---|---|---|---|---|---|---|
| | China | EU-27 | Japan | Other EU | RoW | US |
| China | 91% | 0% | 0% | 0% | 1% | 9% |
| EU-27 | 1% | 68% | 0% | 1% | 1% | 29% |
| Japan | 0% | 0% | 44% | 55% | 0% | 0% |
| Other Europe | 0% | 11% | 0% | 66% | 1% | 22% |
| RoW | 0% | 20% | 0% | 6% | 52% | 21% |
| US | 0% | 4% | 0% | 2% | 5% | 89% |

*Source: JRC/OECD COR&DIP© database, v.3. 2021.*

The R&D flows in the health equipment & service sector tend to be concentrated toward the US (Figure 14). Indeed, both EU-based companies and companies based in the Other Europe concentrate the highest share of their R&D activities in the US; higher than those performed at home. As shown before, this sector strongly relies on technologies related to medical instruments, optics, measurement and computer technologies. The US superiority in the development of ICT technologies can be a factor determining its attractiveness for R&D investments in this sector.

**Figure 14.** R&D flows across main economic areas: health equipment & services companies

*HQ R&D versus performed R&D, allocated according to inventors*

**Values of R&D flows should be read by row (from --> to)**

| R&D FROM | R&D TO | | | | | |
|---|---|---|---|---|---|---|
| | China | EU-27 | Japan | Other EU | RoW | US |
| China | 310 | 69 | 0 | 1 | 0 | 59 |
| EU-27 | 26 | 2067 | 25 | 138 | 234 | 2385 |
| Japan | 0 | 33 | 1371 | 20 | 8 | 140 |
| Other Europe | 0 | 57 | 1 | 231 | 6 | 338 |
| RoW | 0 | 37 | 0 | 1 | 122 | 9 |
| US | 13 | 1203 | 61 | 335 | 500 | 6762 |

**Shares (coloured cells contain values above 20%)**

| R&D FROM | R&D TO | | | | | |
|---|---|---|---|---|---|---|
| | China | EU-27 | Japan | Other EU | RoW | US |
| China | 71% | 16% | 0% | 0% | 0% | 13% |
| EU-27 | 1% | 42% | 1% | 3% | 5% | 49% |
| Japan | 0% | 2% | 87% | 1% | 1% | 9% |
| Other Europe | 0% | 9% | 0% | 37% | 1% | 53% |
| RoW | 0% | 22% | 0% | 1% | 72% | 5% |
| US | 0% | 14% | 1% | 4% | 6% | 76% |

*Source: JRC/OECD COR&DIP© database, v.3. 2021.*

## 4.2 The Scoreboard companies generating R&D from and to the EU

To further disentangle the R&D flows and assess whether these are generated by the investment patterns of a few large companies or by a more distributed tendency across companies, it is possible to look at those companies generating the highest international flows of R&D.

Table 5 shows the 15 EU-based companies with the largest outflows of R&D versus other areas. In the table we report the total amount of outflows and the first two areas of destination, with the respective amounts of R&D and their share of the company's overall R&D investment.

According to our proxy Bayer appears as the company with the largest outward R&D flow, coupled with a high share of R&D performed in US (62%), which can be due to the recent acquisition of the large multinational Monsanto.[5] Other significant R&D outflows to the US are associated to Sanofi (24%) and to Medtronic Public Limited and Allergan, two companies headquartered in Ireland that perform most of their R&D activities in the US (88% and 92%, respectively).

It is worth noticing that 6 out of the 15 of the companies generating the highest R&D flows toward the US are based in Ireland. Moreover, in line with the strong concentration characterizing many dimensions of the Scoreboard sample, the international R&D flows also appear to be highly concentrated: the 15 companies reported in table 5 generate about 92% of the R&D flows from the EU to the US. The only company not targeting the US as the first destination of R&D investment among those listed in the table is UCB, which

[5] A snapshot at the merge and acquisition activities of Bayern can be found at: https://mergr.com/bayer-ag-acquisitions.

registers a high flow of R&D toward Other European countries. Finally, while many EU based companies register significant R&D flows to other countries, none of those reported in the table have Japan or China among the top 2 destination locations.

**Table 5.** Top 15 EU companies in terms of R&D outflows

| | | | First location of R&D flows | | | Second location of R&D flows | | |
|---|---|---|---|---|---|---|---|---|
| **Company** | **HQ country** | **R&D outflows (mil.)** | **Area** | **R&D (mil.)** | **% of R&D** | **Area** | **R&D (mil.)** | **% of R&D** |
| BAYER | DE | 3,486 | US | 3,188 | 62.4% | RoW | 234 | 4.6% |
| SANOFI | FR | 2,327 | US | 1,383 | 23.5% | Oth. EU | 850 | 14.4% |
| MEDTRONIC PUBLIC LIMITED | IE | 1,944 | US | 1,797 | 88.3% | RoW | 102 | 5.0% |
| ALLERGAN | IE | 1,895 | US | 1,813 | 91.7% | RoW | 42 | 2.1% |
| BOEHRINGER SOHN | DE | 989 | US | 746 | 23.6% | Oth. EU | 104 | 3.3% |
| MERCK DE | DE | 916 | US | 405 | 18.2% | Oth. EU | 251 | 11.3% |
| UCB | BE | 818 | Oth. EU | 653 | 58.0% | US | 156 | 13.9% |
| MYLAN | NL | 534 | US | 289 | 47.0% | RoW | 235 | 38.2% |
| FRESENIUS | DE | 361 | US | 323 | 45.9% | RoW | 30 | 4.3% |
| MALLINCKRODT | IE | 306 | US | 280 | 88.8% | RoW | 16 | 5.0% |
| ALKERMES | IE | 277 | US | 277 | 92.0% | | | |
| IPSEN | FR | 238 | US | 116 | 38.5% | Oth. EU | 116 | 38.4% |
| FERRING PHARMACEUTICALS | DK | 165 | US | 165 | 100.0% | | | |
| ENDO INTERNATIONAL | IE | 150 | US | 127 | 78.4% | RoW | 21 | 12.7% |
| JAZZ PHARMACEUTICALS | IE | 145 | US | 105 | 56.0% | RoW | 37 | 19.8% |

*Source: JRC/OECD COR&DIP© database, v.3. 2021.*

Table 6 reports the companies with the highest R&D flows toward the EU. Roche is by far the company with the largest R&D flows (€3 billion), followed by Novartis (about €1.7 billion). Both companies are headquartered in Switzerland.

**Table 6.** The 15 companies with the largest R&D flows toward the EU

| **Company** | **HQ country** | **R&D (mil.)** | **R&D to EU (mil.)** | **% of R&D** |
|---|---|---|---|---|
| ROCHE | CH | 9,798 | 2,988 | 30.5% |
| NOVARTIS | CH | 7,998 | 1,651 | 20.6% |
| ABBVIE | US | 4,567 | 1,035 | 22.7% |
| GLAXOSMITHKLINE | GB | 4,141 | 987 | 23.8% |
| JOHNSON & JOHNSON | US | 9,410 | 677 | 7.2% |
| MERCK US | US | 8,456 | 670 | 7.9% |
| ASTRAZENECA | GB | 4,631 | 653 | 14.1% |
| ASTELLAS PHARMA | JP | 1,644 | 431 | 26.2% |
| AMGEN | US | 3,264 | 315 | 9.7% |
| TEVA PHARMACEUTICAL INDUSTRIES | IL | 1,059 | 275 | 26.0% |
| BAXTER INTERNATIONAL | US | 549 | 273 | 49.6% |
| IDORSIA | CH | 259 | 232 | 89.4% |
| CSL | AU | 726 | 231 | 31.9% |
| PFIZER | US | 6817 | 214 | 3.1% |
| THERMO FISHER SCIENTIFIC | US | 845 | 155 | 18.4% |

*Source: JRC/OECD COR&DIP© database, v.3. 2021.*

The table lists companies headquartered in a wide range of countries. Among them there are also Biotechnology companies (e.g. Amgen) and companies involved in the development and commercialization of the COVID-19 vaccines: Pfizer, which collaborated with BioNTech for the clinical trials, logistics, and manufacturing of the mRNA (messenger ribonucleic acid) vaccine first developed by the German company, and Johnson & Johnson, which "old style vaccine" (encoding a stabilized variant of the SARS-CoV-2 Spike protein) was first developed by Jensen Pharmaceutica Nv, a Belgian subsidiary particularly active in health projects funded by the H2020 program (Vezzani et al., 2021).

# 5 Focus on immunology, bioinformatics and related technologies

*The analysis presented in this section is based on a set of technical codes reported in the patent documents analysed in this report, which relate to immunology, immunotherapy, bioinformatics and combinatorial chemistry (Immuno+).*

*Main results:*

- ❖ Immuno+ technologies are, on average, more complex and associated with a higher number of patents than other health technologies.
- ❖ Overall, the EU lacks specialization in the development of Immuno+ technologies and the gap in terms of patents closely reflects the R&D gap: EU patents in Immuno+ are half the US ones.
- ❖ Many countries show a specialization in Immuno+ technologies, Belgium appears as the most specialized country among those included in the Scoreboard.
- ❖ The development and commercialization of COVID-19 vaccines has some Scoreboard companies as main players, these are among the most active in Immuno+ technologies.
- ❖ The economic and financial performances of companies developing mRNA vaccines have been spectacular; this can have profound effects on technological development of the health industry.

## 5.1 Immuno+ technologies in the Scoreboard

The immune system is a microcosm of interconnected cells, tissues and factors. Current research is trying to put the pieces of this complex puzzle together to obtain the most complete possible picture of the immune system. The research carried out in this field, the development of different types of immunotherapies (including vaccines) and the use of pathogens or cellular immunotherapies are changing the way in which the research community approaches several diseases (Varadé et al., 2021).

In recent years mRNA vaccines have been raised as a promising alternative to conventional vaccines because of their high potency, capacity for rapid development and potential for low-cost manufacture and safe administration (Pardi et al., 2018). Indeed, while mRNA techniques have been popularised among the general public during the COVID-19 crisis (along with the daily news about the development of vaccines based on different competing technologies to stop the pandemic) mRNA techniques have already been studied and tested for many years for applications related to cancer, HIV or the Zika, influenza and Ebola (for more information on leading developers of mRNA vaccines and examples of clinical trials before 2018, see Table 14 and Table 15 in the appendix).

Due to its transformative potential, in this section we focus on patents that are related to a broad set of technologies associated with this burgeoning field of research (and development). To identify patents pertaining to immunology and other related technical solutions, we performed a keyword search on the over than 75,000 IPC 8-digit level codes used to classify patent documents according to their technical contents.[6] Our searching strategy identified 723 IPC codes, of which 626 are contained in the patent documents filed between 2016 and 2018 by Scoreboard companies operating in the health industry. We label these technologies Immuno+.

Before looking at country performances and the main players in this new wave of health technologies, we assess their quantitative relevance with respect to the overall patent portfolio of Scoreboard companies and investigate whether this set of technologies is more complex or potentially more valuable than other health technologies.

There are basically two ways of assessing the relevance of a technology:

(1) counting the number of patents related to a given IPC code with a fractional approach (fractionally dividing a patent across the technological codes reported in the patent document);

(2) counting the number of patents with at least one IPC code related to a specific technology (in this case the set of Immuno+ codes).

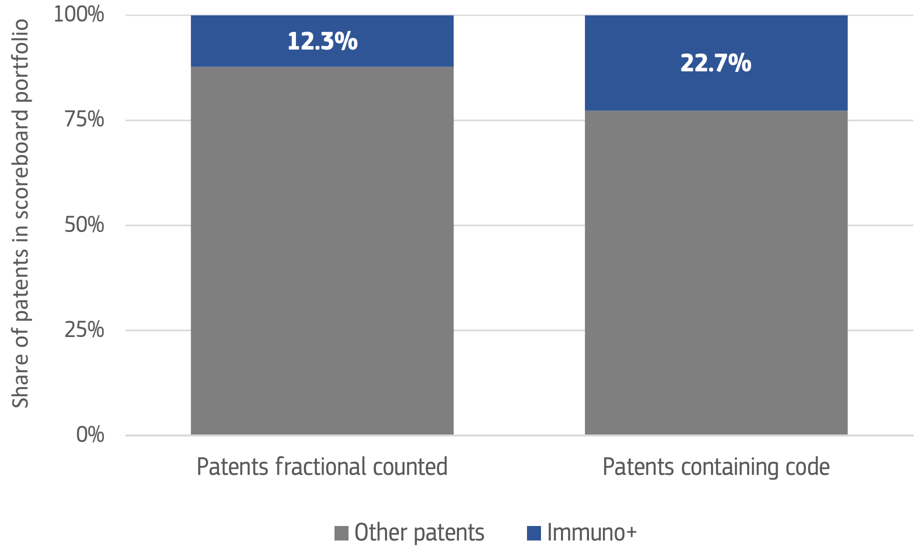
[6] See Appendix A for a description of the methodology and the list of IPC codes used.

The first approach is widely used because it allows us to avoid issues with double counting patents (if a patent contains 2 IPC codes, each of the codes receives a fraction - ½ - of the patent). However, the second may provide complementary insights because it allows us to better appreciate the role of pervasive and complex technologies.

Indeed, the more pervasive a technology is, the more it will be combined with other codes in patent documents, and the more a technology contributes to the development of complex products, the higher the number of codes that will be attached to a patent related to that technology. As a result, the fractional counting approach may penalise technological fields that are more pervasive and complex. Therefore, we combine both approaches to analyse the characteristics of Immuno+ related patents developed by the Scoreboard companies.

Figure 15 displays the share of Immuno+ related patent families with respect to the overall patent portfolio of the Scoreboard companies operating in the health industry. On the left, the figure reports the share of fractionally counted patents, while on the right the share of patents containing at least one Immuno+ code is displayed. The share of Immuno+ patents is relevant in both cases and particularly important when considering the second approach: almost one patent in four contains at least one Immuno+ code. Few IPC codes represent a significant share of the Scoreboard patent portfolios.

**Figure 15.** The relevance of Immuno+ patents in the portfolio of healthcare Scoreboard companies




*Source: derived from the JRC/OECD COR&DIP© database, v.3. 2021*.

The figure suggests that Immuno+ technologies might particularly pervasive. To further assess this possibility, we perform two tests. First, we test whether more (fractionally counted) patents are associated to IPC codes related to Immuno+ technologies compared to other technologies; this would indicate the relative relevance of Immuno+ for Scoreboard companies. Second, we test whether patents related to Immuno+ technologies contain a higher number of IPC codes (i.e., they have a higher scope[7]), which would indicate that they have a higher complexity with respect to the rest of health patents.

[7] Patents' scope is one of the patent quality indicators proposed by Squicciarini et al. (2013) and has been shown to affect the valuation of firms (Lerner, 1994).

Table 7 shows the results of mean comparison tests to assess whether Immuno+ technologies are statistically different from other health technologies. The results confirm that Immuno+ technologies are on average related to more complex patents (higher scope) and associated with a higher number of patents.

**Table 7.** Comparing Immuno+ technologies with other technologies

| | Immuno+ | | Other technologies | T-test (p-val) | Results |
|---|---|---|---|---|---|
| Mean patent scope | 6.58 | > | 5.20 | 0.000*** | Scope statistically larger |
| Mean IPC numerosity | 11.63 | > | 2.61 | 0.000*** | Numerosity statistically higher |
| Mean IPC numerosity (a) | 17.33 | > | 9.31 | 0.000*** | Numerosity statistically higher |

*Note: (a) to check robustness to IPC codes with very low frequency this test restricts the sample to codes with a least a full fractionally counted patent; the test in this case compares 415 8-digit Immuno+ codes against 5104 other 8-digit IPC codes.*

*Source: derived from the JRC/OECD COR&DIP© database, v.3. 2021.*

Before moving to the analysis of specific features of companies and economic areas, we list in Table 8 the most frequent 8-digit IPC codes composing the Immuno+ technology patent group. The table shows codes with at least 100 inpadoc patent families in the sample and shows that these are related mainly to organic chemistry (C07), biochemistry (C12), medical science and hygiene (A61), and measuring and testing (G01).

**Table 8.** Immuno+ patents, most frequent IPC codes

| IPC class symbol | Description of the technical content | Fractional count |
|---|---|---|
| C07K 16/28 | Immunoglobulins against receptors, cell surface antigens or cell surface determinants | 479 |
| C12Q 1/68 | Measuring or testing processes involving enzymes, nucleic acids or microorganisms; Compositions therefor; Processes of preparing such compositions | 414 |
| A61K 39/00 | Medicinal preparations containing antigens or antibodies | 387 |
| A61K 39/395 | Antibodies; Immunoglobulins; Immune serum (e.g. antilymphocytic serum) | 333 |
| C12N 15/113 | Non-coding nucleic acids modulating the expression of genes [Mutation or genetic engineering; DNA or RNA concerning genetic engineering, vectors or their isolation, preparation or purification; Use of hosts therefor] | 206 |
| G01N 33/574 | Use of compounds or compositions for colorimetric, spectrophotometric or fluorometric investigation for cancer | 145 |
| C12N 15/10 | Processes for the isolation, preparation or purification of DNA or RNA (genetic engineering) | 133 |
| G01N 33/50 | Chemical analysis of biological material, Testing involving biospecific ligand binding methods; Immunological testing [Investigating or analysing materials] | 125 |
| C07K 16/18 | Immunoglobulins against material from animals or humans | 120 |
| C07K 16/00 | Immunoglobulins (monoclonal or polyclonal antibodies) | 114 |
| C07K 16/30 | Immunoglobulins against receptors, cell surface antigens or cell surface determinants from tumour cells | 114 |
| A61K 38/00 | Medicinal preparations containing peptides | 109 |
| A61K 47/68 | Medicinal preparations characterised by non-active ingredients being chemically bound to the active ingredient (e.g. polymer-drug conjugates) and the modifying agent being an antibody, an immunoglobulin or a fragment thereof (e.g. an Fc-fragment) | 107 |
| C07K 16/24 | Immunoglobulins against cytokines, lymphokines or interferons | 107 |

*Note: IPC 8-digit codes related to Immuno+ technologies with the highest number of patent applications by Scoreboard companies during 2016-2018.*

*Source: derived from the JRC/OECD COR&DIP© database, v.3. 2021.*

More specifically, they include a series of techniques related to antibodies (e.g., Immunoglobulins), antigens, genetic engineering and testing: the set of technologies that are revolutionizing health-related research. Finally, the table also suggests a quite focused research activity, with about 40% of Immuno+ patents related to the few codes reported in the table.

## 5.2 Immuno+ technologies: countries and main players

Which are the economic areas that are more specialised in developing Immuno+ technologies? How does the EU perform compared with the other main economic areas? Which Scoreboard companies are more active in the development of Immuno+ technologies? What are those companies doing?

We try to reply to these questions below.

To assess the relative specialisation of different economic areas we use the 'revealed technological advantages' (RTA), which are computed by dividing each area's share of Immuno+ patents by the sample mean. Values above 1 correspond to economic areas (and countries) that are relatively specialised in developing Immuno+ technologies.

Figure 16 displays the RTA by economic area on the left and the total number of patents on the right. The figure highlights the high specialization in Immuno+ technologies of Other European countries, followed by the Rest of the World and the US. Together with China and Japan, the EU registers an RTA value below 1, indicating its lack of specialisation in the developing this set of promising health technologies. Companies based in the US filed the largest amount of Immuno+ related patents, more than twice those filed by companies based in the EU and in the Other Europe.

**Figure 16.** Immuno+ by economic area, specialization (left) and total number of patents (right)

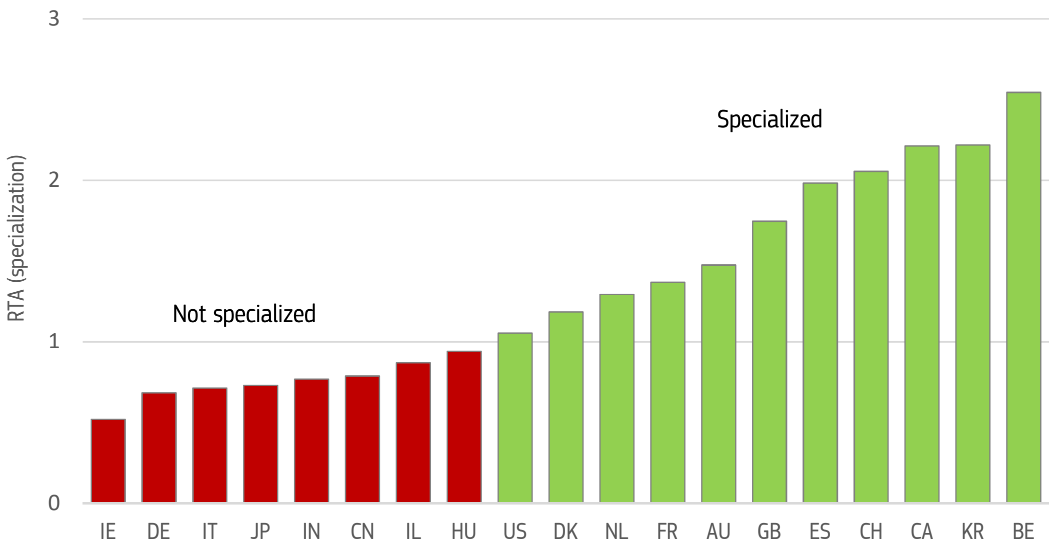

*Source: derived from the JRC/OECD COR&DIP© database, v.3. 2021.*

Grouping countries by economic areas (EU, RoW and Other Europe) may possibly hide a high degree of heterogeneity among them. In figure 17 we report the RTA of a selected group of countries to evaluate the extent at which they deviate from the overall picture above; the group is selected to show figures only for countries with at least 10 Immuno+ patent families filed between 2016 and 2018.

Figure 17 reveals the marked heterogeneity of the countries' specialisation in Immuno+ technologies, both within EU and across economic areas. The relatively low level of specialisation of the EU is mainly driven by German-based companies, together with companies headquartered in Ireland and Italy. At the other end of the spectrum, companies based in Belgium appear as the most specialised ones.

Other countries highly specialised in Immuno+ technologies are Korea, Canada and Switzerland, all showing an RTA value above two (i.e., their share of patents in these technologies is twice the sample average). Interestingly, the RTA of US-based companies is just above one, indicating that they are not strongly specialised in this set of technologies. However, this value should be read together with the much higher R&D investments (and number of patents) of the American health industry. The strength of this country resides in a very strong sectoral innovation system that allows for experimentation, provides financial capital, and favours the development (and commercialization) of new emerging technologies.

**Figure 17.** Revealed technological advantages in Immuno+ by country




*Note: shows countries with at least 10 Immuno+ patent families between 2016 and 2018.*
*Source: derived from the JRC/OECD COR&DIP© database, v.3. 2021.*

The strength of the US system in supporting the creation and growth of new technology companies is evident in Table 9. The table shows the 25 most specialized companies in developing Immuno+ technologies; 16 out of 25 are based in the US.

**Table 9.** The 25 most specialized companies in Immuno+ technologies

| Company | SB rank | Sector | Country | Patent families | Share of Immuno+ |
|---|---|---|---|---|---|
| Translate Bio | 1806 | Pharmaceuticals | US | 47 | 100% |
| Crispr Therapeutics | 1082 | Biotechnology | CH | 31 | 100% |
| Macrogenics | 946 | Pharmaceuticals | US | 30 | 100% |
| Morphosys | 1212 | Biotechnology | DE | 29 | 100% |
| Adaptimmune Therapeutics | 1036 | Biotechnology | GB | 28 | 100% |
| Prothena | 1168 | Biotechnology | IE | 27 | 100% |
| Immunocore | 1434 | Biotechnology | GB | 27 | 100% |
| Agenus | 1128 | Pharmaceuticals | US | 27 | 100% |
| Cytomx Therapeutics | 1148 | Biotechnology | US | 25 | 100% |
| Xencor | 1418 | Biotechnology | US | 23 | 100% |
| Five Prime Therapeutics | 1114 | Biotechnology | US | 22 | 100% |
| Kymab Group | 1785 | Biotechnology | GB | 21 | 100% |
| Acceleron Pharma | 1271 | Biotechnology | US | 49 | 98% |
| CSL | 205 | Biotechnology | AU | 83 | 97% |
| Merrimack Pharmaceuticals | 1993 | Biotechnology | US | 40 | 96% |
| Ionis Pharmaceuticals | 1543 | Biotechnology | US | 105 | 96% |
| **Moderna** | 447 | Biotechnology | US | 103 | 94% |
| Momenta Pharmaceuticals | 1295 | Biotechnology | US | 32 | 94% |
| Seattle Genetics | 286 | Biotechnology | US | 62 | 93% |
| Alexion Pharmaceuticals | 231 | Biotechnology | US | 70 | 93% |
| Arbutus Biopharma | 1924 | Biotechnology | CA | 37 | 92% |
| **Biontech** | 1130 | Biotechnology | DE | 46 | 91% |
| Sarepta Therapeutics | 370 | Biotechnology | US | 42 | 90% |
| Immunogen | 752 | Biotechnology | US | 51 | 90% |
| Exact Sciences | 1558 | Biotechnology | US | 36 | 89% |

*Note: the table shows companies who filed at least 20 patent families filed between 2016 and 2018.*
*Source: derived from the JRC/OECD COR&DIP© database, v.3. 2021.*

Although some companies are classified as pharmaceutical, the vast majority are in the Biotechnology sector, indicating that having a high number of specialised R&D developers may be seen as a sign of the health industry dynamism and suggesting that several Immuno+ solutions might be in the pipeline.

However, as we have seen before (Section 3), pharmaceuticals companies are also active in the development of biotechnological solutions and can in turn be developing Immuno+ technologies. Therefore, to complete the picture of the companies developing such technologies we show the 25 companies with the highest number of Immuno+ patents.

Table 10 shows the name, world R&D rank, sector and country where the headquarters are located for the 25 companies with the highest number of Immuno+ related patents. On the top of the list are ranked large pharmaceuticals conglomerates but the list includes also smaller biotechnology companies.

The first company in terms of patent filings is Roche, with about half of its patent portfolio related to Immuno+ technologies. With 407 Immuno+ patents Medtronic is the leading company from the health equipment & services. Medtronic is based in Ireland, but its operational offices are in Minnesota (US) and is a world leader in medical devices; in 2020 it shared its portable ventilator design specifications during the outbreak of COVID-19 pandemic in order to accelerate global ventilator production. The leading biotechnology company in terms of number of patents is Biogen Idec, a company based in Cambridge (Massachusetts), which specialises in therapies for treating neurological diseases.

**Table 10.** The 25 most specialized companies with the highest number of Immuno+ related patents

| Company | Scoreboard rank | Sector | Country | Patent families | Share of Immuno+ |
|---|---|---|---|---|---|
| Roche | 8 | Pharmaceuticals | CH | 1,255 | 54% |
| Takeda Pharmaceutical | 54 | Pharmaceuticals | JP | 1,179 | 40% |
| Bayer | 26 | Pharmaceuticals | DE | 544 | 20% |
| Merck US | 12 | Pharmaceuticals | US | 423 | 47% |
| Medtronic Public Limited | 70 | Health equipment & services | IE | 407 | 9% |
| Novartis | 14 | Pharmaceuticals | CH | 367 | 33% |
| Glaxosmithkline | 34 | Pharmaceuticals | GB | 326 | 57% |
| Thermo Fisher Scientific | 186 | Health equipment & services | US | 316 | 35% |
| **Johnson & Johnson** | 9 | Pharmaceuticals | US | 312 | 9% |
| Sanofi | 22 | Pharmaceuticals | FR | 312 | 38% |
| Bristol-Myers Squibb* | 24 | Pharmaceuticals | US | 271 | 41% |
| **Pfizer** | 17 | Pharmaceuticals | US | 236 | 41% |
| **Astrazeneca** | 29 | Pharmaceuticals | GB | 218 | 59% |
| Biogen Idec | 62 | Biotechnology | US | 197 | 43% |
| Gilead Sciences | 41 | Biotechnology | US | 197 | 45% |
| Celgene* | 37 | Biotechnology | US | 185 | 54% |
| Abbott Laboratories | 74 | Pharmaceuticals | US | 177 | 12% |
| Amgen | 50 | Biotechnology | US | 174 | 60% |
| Boehringer Sohn | 52 | Pharmaceuticals | DE | 174 | 43% |
| Abbvie | 30 | Pharmaceuticals | US | 164 | 47% |
| Regenxbio | 1343 | Biotechnology | US | 159 | 34% |
| Illumina | 262 | Biotechnology | US | 159 | 60% |
| Becton Dickinson | 179 | Health equipment & services | US | 155 | 14% |
| Sysmex | 737 | Health equipment & services | JP | 152 | 60% |
| Novozymes | 539 | Biotechnology | DK | 149 | 35% |

*Note: * on November 2019 Bristol-Myers Squibb completed the acquisition of Celgene, which is reported in the table because still independent in 2018 (the year to which the Scoreboard 2019 refers to).*
*Source: derived from the JRC/OECD COR&DIP© database, v.3. 2021.*

It is worth noting that the companies listed in the 2 tables include most of the companies that have been involved in developing and commercializing COVID-19 vaccines.[8] We therefore look closely at the performances of these companies, using secondary data, on their technological trajectories.

## 5.3 Scoreboard companies and the COVID-19 vaccines

In 2020 several companies were developing potentially good candidates for the COVID-19 vaccine, which triggered a race among wealthy countries to guarantee a vaccination coverage with pre-orders that reached more than 2 billion doses (Callaway, 2020). This rush was criticised from multiple sources, with many public-health experts urging that vaccines should be equitably distributed across the world. At the end of 2021 few companies were providing vaccine at a global level.

Table 11 reports the stock price performances of the six Scoreboard companies that have developed and commercialised a vaccine to fight the diffusion of the COVID-19, and of Novavax. The table reports the opening stock price on 5 January 2020 (before the pandemic), the stock price at the end of November 2021 (almost two years after), the percentage change among the two values and the highest price during the period considered.

In mid-2021 BioNTech announced that, in partnership with Pfizer, they had supplied more than 1 billion doses of the BNT162b vaccine (Tozinameran) and signed agreements for about other 2.2 billion doses; their total revenues were estimated to be around €5 billion for the trimester April-June 2021, more than 100 times the € 41.7 million registered for the trimester April-June 2020.[9] BioNTech is also developing several cancer vaccines and immunotherapies and its stock values increased by 767% during the period considered.

The growth of BioNTech has been so spectacular that, as reported by Reuters, it could have boosted economic growth in Germany by up to 0.5% in 2021.[10] During the same period, the stock price of Pfizer, which is a much larger and established company, increased by +45%.

**Table 11.** Market performances of the companies that developed a COVID related vaccine

| Company | Stock price (USD) | | Stock price growth | Stock price peak (USD) |
|---|---|---|---|---|
| | 5-Jan-2020 | 28-nov-21 | | |
| BioNtech (DE) | 39.68 | 344.06 | 767% | 389.01 |
| Moderna (US) | 19.14 | 306.72 | 1503% | 449.38 |
| Johnson & Johnson (US) | 145.06 | 159.38 | 10% | 179.44 |
| Novavax (US) | 3.93 | 160.48 | 3983% | 220.94 |
| Pfizer (US) | 37.41 | 54.27 | 45% | 52.27 |
| Astrazeneca (GB) | 49.85 | 54.23 | 9% | 63.09 |

*Note: data from https://www.marketwatch.com, retrieved on 3 December 2021. The stock price peak is the maximum share price during between 5 January 2020 and 28 November 2021.*

Moderna also developed a market-beating vaccine and registered an increase in its stock prices of more than 1500%. Novavax, which officially applied to EMA for conditional marketing authorisation in November 2021, recorded a stock price growth in the order of 4000% due to the high expectations for the performance of its vaccine.[11,12]

8 Basically, only Novavax is not included in the two tables.

9 From the BioNTech announcement for the Second Quarter 2021 Financial Results and Corporate Update: https://investors.biontech.de/node/10446/pdf.

10 https://www.reuters.com/article/us-germany-economy-biontech-idUSKBN2FB15A

11 https://www.ema.europa.eu/en/news/ema-receives-application-conditional-marketing-authorisation-novavaxs-covid-19-vaccine-nuvaxovid.

12 Novavax vaccine takes a different approach with respect to other mRNA vaccines; it contains the spike protein of the coronavirus itself but formulated as a nanoparticle that cannot cause disease instead of creating parts of the virus that can trigger the immune system.

Johnson & Johnson (+10%) and AstraZeneca (+9%) are the two companies with the smaller increases in stock prices among those reported in Table 11. Both developed an “old style” vaccine made up of another virus of the adenovirus family modified to contain the gene for making a protein from SARS-CoV-2; however, partly due to their slightly lower efficacy these vaccines are less used than the mRNA-based ones. Use of the AstraZeneca vaccine, in particular, was limited by side effects (classified by EMA as “very rare”) and related widespread public concerns.

All in all, COVID-19 has acted as a booster for the health industry in terms of R&D investments and governments support, and as a trigger for advancing the development and commercialization of new drugs based on frontier technology. Successful vaccines are blockbuster drugs (extremely popular drugs generating annual sales of at least USD 1 billion), which have boosted the economic and financial performances of the developing companies and may have wider spillover effects in the technological development of the industry.

It is too early to say, but healthcare companies may have found the kind of general purpose technology (equivalent to the microprocessor for ICT) that was envisaged as a game changer, unleashing the industry’s revolutionary and promising potential (Archibugi, 2017).

# 6 Conclusions

The health industry has experienced a decade of profound transformations with the increasing prominence of biotech companies among the top corporate R&D investors worldwide. During the last 10 years R&D investment in the biotech sector has increased by a factor of 3.6 with a concomitant increase in the sector share of overall health industry R&D investment (from 10% to 21%). At the same time the profitability of the health industry declined until recent years, stabilising at an average of 12% around 2017. The profitability of the median firm – an indicator not influenced by the performances of larger companies – appears much lower than the industry average (4%), suggesting that larger companies are able to leverage their size when testing and commercialising innovative medical solutions (and possibly re-invest profits in R&D or in the acquisition of promising companies). With the COVID-19 pandemic the profitability of the industry has raised by 2 percentage points when considering the median firm.

Over the last 10 years, EU-based companies in the health industry have increased their R&D investments in line with the growth shown by US-based companies. However, this should not be taken as a too positive signal because it implies that the EU has not been able to close the R&D gap with respect to the US: EU companies invest less than half the R&D of their US counterparts. Moreover, only 6 of the top 25 R&D investors in the health industry are EU-based companies.

This evidence suggests that two questions for long-term policy are particularly compelling in a key sector for EU citizens' wellbeing:

- How to create an environment conducive to increasing private R&D investment in the EU health industry?
- How to favour the growth of new innovative EU companies?

Industrial classifications do not perfectly reflect what companies are actually doing from a technological and product point of view, so we have relied on patent information to dig into the technological capabilities of firms. Companies in the biotech and pharmaceutical sectors present similar specialisation; in both sectors most patents are related to pharmaceutical technologies and, given their larger size, pharmaceutical companies file more patents related to biotechnology.

Moreover, EU based companies do not file less patent per R&D spent compared to other areas; differences among firms are mainly driven by specific sectoral features (e.g., medical devices involve lower research and development costs compared to drugs) and size (smaller companies tend to file more patents per R&D spent). In other words, the EU gap in overall development of health technologies with respect to the US reflects the gap observed in R&D investment.

Patent analysis suggests that focusing on the lack of EU biotech companies among the top R&D investors might overemphasize a potential gap with the US in the development of biotechnologies. In this work we have identified a set of technologies related to immunology, immunotherapy, bioinformatics and combinatorial chemistry – Immuno+ technologies – and showed that these are complex and increasingly pervasive. The gap with the US is large and a sense of urgency would help the EU to jump into this new technological wave.

The key question for EU policy makers should not be how to increase the number of companies active in the biotech sector, or how to increase the rate of innovation per R&D spent (in search of some kind of efficiency), but rather how to foster the overall development of the health and biotech innovation system in the EU. Following the launch of the Pharmaceutical Strategy for Europe the EU is on the way of profoundly revising the existing general pharmaceutical legislation on medicines for human use (Directive 2001/20/EC) to ensure an affordable, competitive and future-proof medicines regulatory system.

Understanding where, how and what type of research is performed in the EU compared to other economic areas is of great importance to provide evidence that can better support health and innovation policies. Micro-level information (e.g., on researchers, inventors, labs or cooperation networks) can and must complement that derived from financial accounts, often used to compare countries and region performances. Disentangling the role played by large R&D investors in the EU innovation system and the interactions between private and public research activities is particularly relevant as concerning the health industry. This evidence will contribute to the evaluation and implementation of healthcare industrial and innovation policies in the years to come.

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## Annex. The methodology to identify Immuno+ patents and the relative IPC codes

The IPC classification was designed to provide an internationally uniform classification of patent documents. Its primary aim is to establish an effective search tool for retrieving of patent documents by intellectual property offices and other users to evaluate the technical disclosures in patent applications.

The IPC is a hierarchical classification system where contents of lower levels are subdivisions of the contents of the higher hierarchical levels to which the lower levels are subordinated. Graphically it can be imagined as a pyramid with 8 entries at the top and more than 61,397 entries at the bottom (the 8-digit level). A more detailed description of the IPC classification can be found here:

https://www.wipo.int/edocs/pubdocs/en/wipo_guide_ipc_2019.pdf

The identification of Immuno+ related patents was based on a text search for a list of keywords on the 8-digit IPC codes attached to patent documents; IPC codes contain detailed descriptions of the technical contents of the patented invention.

The original list of keywords is shown in Table 12 and was used to retrieve all the IPC codes containing the keywords. The text search was performed using "IPC-help", an online tool developed by the World Intellectual Property Organization to support both examiners and practitioners; variations of the keywords and meaningful truncations are included in the text search.

The resulting IPC codes, as well as codes in the same nest of the hierarchical structure, were all checked. This procedure allowed us to supplement the initial list of IPC codes with some relevant codes that were in the neighbour of the retrieved ones.

**Table 12.** List of keywords for code search

| | | |
|---|---|---|
| Angiotensin | DNA | Immunotherapy |
| Antibodies | Epitope | Lymphocytes |
| Antigens | Genetic | MHC |
| Bioinformatics | Immune response | Nanomedicine |
| Biological material analysis | Immune phenotype | Phenotype |
| Biomarkers | Immuniz(s)ation | RNA |
| Biomaterial | Immunoassay | Vaccine |
| Combinatorial Chemistry | Immunoglobulin | |
| Cytokine | Immunology | |

*Note: MCH stands for major histocompatibility complex*

Both the list of keywords and the resulting (or the excluded) IPC codes have been validated by Claudia Matteucci; Associate Professor in Microbiology and Clinical Microbiology at the Department of Experimental Medicine of the University of Rome Tor Vergata, expert in Microbiology and Immunology.

The search of IPC codes on the overall corpus of patent documents in Patstat found 723 entries at the IPC-8 level. When considering the sample of inpadoc families filed by the Scoreboard companies between 2016 and 2018 the resulting IPC codes are 626.

Table 13 displays the list of codes relative to Immuno+ technologies. When a code in the table has less than 8-digits it means that all the lower codes in the hierarchical structure have been included.

**Table 13.** List of IPC codes included in the technology focus analysis

| IPC code | IPC label |
|---|---|
| **A61B 10/00** | Other methods or instruments for diagnosis, e.g. for vaccination diagnosis; Sex determination; Ovulation-period determination; Throat striking implements |
| **A61B 17/20** | [surgical instruments] for vaccinating or cleaning the skin previous to the vaccination |
| **A61D 1/02** | [surgical instruments, veterinary] Trocars or cannulas for teats; Vaccination appliances |
| **A61K 31/50** | [medicinal preparation containing...] Pyridazines; Hydrogenated pyridazines |
| **A61K 35/12** | [medicinal preparation containing...] Materials from mammals; Compositions comprising non-specified tissues or cells; Compositions comprising non-embryonic stem cells; Genetically modified cells |
| **A61K 35/13** | [medicinal preparation containing...] Tumour cells, irrespective of tissue of origin |
| **A61K 35/14** | [medicinal preparation containing...] Blood; Artificial blood |
| **A61K 35/15** | [medicinal preparation containing...] Cells of the myeloid line, e.g. granulocytes, basophils, eosinophils, neutrophils, leucocytes, monocytes, macrophages or mast cells; Myeloid precursor cells; Antigen-presenting cells, e.g. dendritic cells |
| **A61K 35/16** | [medicinal preparation containing...] Cells of the myeloid line, e.g. granulocytes, basophils, eosinophils, neutrophils, leucocytes, monocytes, macrophages or mast cells; Myeloid precursor cells; Antigen-presenting cells, e.g. dendritic cells |
| **A61K 35/17** | [medicinal preparation containing...] Lymphocytes; B-cells; T-cells; Natural killer cells; Interferon-activated or cytokine-activated lymphocytes |
| **A61K 35/18** | [medicinal preparation containing...] Erythrocytes |
| **A61K 35/74** | [medicinal preparation containing...] Bacteria |
| **A61K 35/76** | [medicinal preparation containing...] Viruses; Subviral particles; Bacteriophages (adenovirus is among examples) |
| **A61K 35/19** | [medicinal preparation containing...] Platelets; Megacaryocytes |
| **A61K 38/00** | Medicinal preparations containing peptides (peptides containing beta-lactam rings A61K 31/00; cyclic dipeptides not having in their molecule any other peptide link than those which form their ring, e.g. piperazine-2,5-diones, A61K 31/00; ergoline-based peptides A61K 31/48; containing macromolecular compounds having statistically distributed amino acid units A61K 31/74) |
| **A61K 39/00** | Medicinal preparations containing antigens or antibodies |
| **A61K 47/48** | [Medicinal preparations...] the non-active ingredient being chemically bound to the active ingredient, e.g. polymer drug conjugates |
| **A61K 47/62** | [Medicinal preparations...] the modifying agent being a protein, peptide or polyamino acid |
| **A61K 47/64** | [Medicinal preparations...] Drug-peptide, drug-protein or drug-polyamino acid conjugates, i.e. the modifying agent being a peptide, protein or polyamino acid which is covalently bonded or complexed to a therapeutically active agent |
| **A61K 47/65** | [Medicinal preparations...] Peptidic linkers, binders or spacers, e.g. peptidic enzyme-labile linkers |
| **A61K 47/66** | [Medicinal preparations...] the modifying agent being a pre-targeting system involving a peptide or protein for targeting specific cells |
| **A61K 47/68** | [Medicinal preparations...] the modifying agent being an antibody, an immunoglobulin or a fragment thereof, e.g. an Fc-fragment |
| **A61K 48/00** | Medicinal preparations containing genetic material which is inserted into cells of the living body to treat genetic diseases; Gene therapy |
| **A61K 49/14** | [Preparations for testing in vivo...] Peptides, e.g. proteins |
| **A61K 49/16** | [Preparations for testing in vivo...] Antibodies; Immunoglobulins; Fragments thereof |
| **A61K 51/08** | [Preparations containing radioactive substances for use in therapy or testing in vivo...] Peptides, e.g. proteins |
| **A61K 51/10** | [Preparations containing radioactive substances for use in therapy or testing in vivo...] Antibodies or immunoglobulins; Fragments thereof |
| **A61K 51/12** | [Preparations containing radioactive substances for use in therapy or testing in vivo...] characterised by a special physical form, e.g. emulsion, microcapsules, liposomes |
| **A61K 9/127** | Liposomes |
| **A61P 31/00** | Antiinfectives, i.e. antibiotics, antiseptics, chemotherapeutics |
| **A61P 37/00** | Drugs for immunological or allergic disorders |
| **B82Y 5/00** | Nanobiotechnology or nanomedicine, e.g. protein engineering or drug delivery |
| **C07K 1** | General processes for the preparation of peptides |
| **C07K 2** | Peptides of undefined number of amino acids; Derivatives thereof |
| **C07K 4** | Peptides having up to 20 amino acids in an undefined or only partially defined sequence; Derivatives thereof |
| **C07K 5** | Peptides having up to four amino acids in a fully defined sequence; Derivatives thereof |

| | |
|---|---|
| **C07K 7** | Peptides having 5 to 20 amino acids in a fully defined sequence; Derivatives thereof |
| **C07K 9** | Peptides having up to 20 amino acids, containing saccharide radicals and having a fully defined sequence; Derivatives thereof |
| **C07K 11** | Depsipeptides having up to 20 amino acids in a fully defined sequence; Derivatives thereof |
| **C07K 14** | Peptides having more than 20 amino acids; Gastrins; Somatostatins; Melanotropins; Derivatives thereof |
| **C07K 16** | Immunoglobulins, e.g. monoclonal or polyclonal antibodies |
| **C07K 17** | Carrier-bound or immobilised peptides; Preparation thereof |
| **C07K 19** | Hybrid peptides |
| **C12N 15/00** | Mutation or genetic engineering; DNA or RNA concerning genetic engineering, vectors, e.g. plasmids, or their isolation, preparation or purification; Use of hosts therefor |
| **C12N 5/00** | Undifferentiated human, animal or plant cells, e.g. cell lines; Tissues; Cultivation or maintenance thereof; Culture media therefor |
| **C12N 7** | Viruses, e.g. bacteriophages; Compositions thereof; Preparation or purification thereof (medicinal preparations containing viruses A61K 35/76; preparing medicinal viral antigen or antibody compositions, e.g. virus vaccines, A61K 39/00) |
| **C12P 21/08** | Monoclonal antibodies |
| **C12Q 1/68** | [measuring or testing processes...] involving nucleic acids |
| **C40B** | Combinatorial Chemistry; Libraries, e.g. chemical libraries |
| **G16B** | Bioinformatics, i.e. Information And Communication Technology [ICT] Specially Adapted For Genetic Or Protein-Related Data Processing In Computational Molecular Biology |
| **G01N 33/48** | [investigatig or analyzing ...] Biological material, e.g. blood, urine; Haemocytometers |
| **G01N 33/50** | [investigatig or analyzing ...] Chemical analysis of biological material, e.g. blood, urine; Testing involving biospecific ligand binding methods; Immunological testing |
| **G01N 33/53** | [investigatig or analyzing ...] Immunoassay; Biospecific binding assay; Materials therefor |
| **G01N 33/536** | [investigatig or analyzing ...] with immune complex formed in liquid phase |
| **G01N 33/537** | [investigatig or analyzing ...] with separation of immune complex from unbound antigen or antibody |
| **G01N 33/541** | [investigatig or analyzing ...] Double or second antibody |
| **G01N 33/547** | [investigatig or analyzing ...] with antigen or antibody attached to the carrier via a bridging agent |
| **G01N 33/549** | [investigatig or analyzing ...] with antigen or antibody entrapped within the carrier |
| **G01N 33/557** | [investigatig or analyzing ...] using kinetic measurement, i.e. time rate of progress of an antigen-antibody interaction |
| **G01N 33/558** | [investigatig or analyzing ...] using diffusion or migration of antigen or antibody |
| **G01N 33/561** | [investigatig or analyzing ...] Immunoelectrophoresis |
| **G01N 33/563** | [investigatig or analyzing ...] involving antibody fragments |
| **G01N 33/564** | [investigatig or analyzing ...] for pre-existing immune complex or autoimmune disease |
| **G01N 33/577** | [investigatig or analyzing ...] involving monoclonal antibodies |

***Note**: the labels of the IPC codes have been adapted for presentation purposes. The table includes codes from different versions of the IPC classification to capture both patents classified (or reclassified) to reflect the 2021 version of the IPC classification and other previous versions.*

**Table 14.** Leading mRNA vaccine developers: research focus, partners and therapeutic platforms

| Institution | mRNA technology | Partners | Indication (disease target) |
|---|---|---|---|
| Argos Biotechnology | mRNA neoantigens (Arcelis platform) | NA | Individualized cancer vaccines, HIV-1 |
| BioNTech RNA Pharmaceuticals GmbH | Nucleoside-modified mRNA (IVAC Mutanome, FixVAC) | Genentech/Roche | Individualized cancer vaccines |
| | | Bayer AG | Veterinary vaccines |
| CureVac AG | Sequence-optimized, purified mRNA (RNActive, RNArt, RNAdjuvant) | Boehringer Ingelheim GmbH | Cancer vaccines (lung cancer) |
| | | Johnson & Johnson | Viral vaccines |
| | | Sanofi Pasteur | Infectious disease vaccines |
| | | BMGF | Infectious disease vaccines |
| | | IAVI | HIV vaccines |
| eTheRNA Immunotherapies | Purified mRNA (TriMix) | NA | Cancer (melanoma, breast), viral vaccines (HBV and/or HPV) |
| GlaxoSmithKline/ Novartis | Self-amplifying mRNA (SAM) (alphavirus replicon) | NA | Infectious disease vaccines |
| Moderna Therapeutics | Nucleoside-modified mRNA | Merck & Co. | Individualized cancer vaccines, viral vaccines |
| | | BMGF, DARPA, BARDA | Viral vaccines (influenza virus, CMV, HMPV, PIV, chikungunya virus, Zika virus) |
| University of Pennsylvania | Nucleoside-modified, purified mRNA | NA | Infectious disease vaccines |

*Note: Reproduced from (Pardi et al., 2018)*

**Table 15.** Clinical trials with mRNA vaccines against infectious diseases

| Sponsoring institution | Vaccine type (route of administration) | Targets | Trial numbers (phase) | Status |
|---|---|---|---|---|
| Argos Therapeutics | DC EP with autologous viral Ag and CD40L mRNAs (i.d.) | HIV-1 | • NCT00672191 (II)<br>• NCT01069809 (II)<br>• NCT02042248 (I) | • Completed[105]<br>• Completed; results NA<br>• Completed; results NA |
| CureVac AG | RNActive viral Ag mRNA (i.m., i.d.) | Rabies virus | NCT02241135 (I) | Active[56,91] |
| Erasmus Medical Center | DC loaded with viral Ag mRNA with TriMix (i.nod.) | HIV-1 | NCT02888756 (II) | Recruiting |
| Fundació Clínic per la Recerca Biomèdica | Viral Ag mRNA with TriMix (NA) | HIV-1 | NCT02413645 (I) | Active |
| Massachusetts General Hospital | DC loaded with viral Ag mRNA (i.d.) | HIV-1 | NCT00833781 (II) | Completed[104] |
| McGill University Health Centre | DC EP with autologous viral Ag and CD40L mRNAs (i.d.) | HIV-1 | NCT00381212 (I/II) | Completed[102] |
| Moderna Therapeutics | Nucleoside-modified viral Ag mRNA (i.m.) | Zika virus | NCT03014089 (I/II) | Recruiting[85] |
| | | Influenza virus | NCT03076385 (I) | Ongoing[22] |

*Note: Reproduced from (Pardi et al., 2018), it summarizes the clinical trials registered at ClinicalTrials.gov as of 5 May 2017.*

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