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The Lifecycle of Pharmaceutical Innovation: The French Lag

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The Covid-19 crisis has highlighted several shortcomings in health sector for France. The unfruitful search for a vaccine, albeit originally a French invention, has shown the country's struggle to keep up the pace in this race for innovation. Moreover, the crisis has also revealed how dependent on China French supply chains are (Aghion *et al.,* 2020). This *Focus* provides a descriptive overview of France's position on the lifecycle of pharmaceutical innovation, from its genesis to its export. The stylised facts presented here converge to a central observation: France is lagging behind in the pharmaceutical innovation and production sector.

1. Introduction

The pharmaceutical industry is a model of permanent innovation; knowledge and progress in this field is continuous and all recent new medicines are based on advances in knowledge about the functioning of the immune system and genetics. For example, the identification of specific molecules within the immune system and their targeting with special antibodies has enabled a better control of certain diseases. Similarly, uncovering the function of certain genes, along with mastering gene therapy tools, greatly improved cures against rare diseases of genetic origin. Biomedicines(1) are thus becoming prominent: today 4 out of 10 new drugs are biomedicines (see LEEM, 2020b). A prime example of such innovation is the new messenger RNA vaccines developed by Pfizer-BioNtech and Moderna: rather than injecting the virus in its attenuated form, these inject only DNA or RNA molecules coding for proteins of the pathogen.

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(1) Biomedicines (or biological drugs) are the result of biotechnology and the knowledge acquired over the last few decades about the human genome. They are biotechnological products, pharmaceutically active and synthesised by a biological source (living cell) or extracted from it, and not obtained by synthetic chemistry.

These developments require increasing costs of research and development (R&D). Indeed, the average cost of developing a marketed drug was estimated at $802 million in 2003; by 2016, it was $2,558 million (DiMasi *et al.,* 2003 and 2016). It is explained by initial research whose techniques are increasingly sophisticated, and clinical trials whose costs have risen with more robust and complex methodology. In addition to being expensive, pharmaceutical research remains also highly uncertain. Among the molecules identified by academic research, only one in ten thousand will reach the clinical phase (drug candidates), and only one in ten of these drug candidates will become a marketed drug (see LEEM, 2020b). As such, the high costs and low success probability make the whole drug innovation process a very risky one. In this *Focus*, we analyse how France positions itself on the different stages of the drug lifecycle. The first part looks at the innovation stage, i.e. those of basic research, applied research, patent applications and clinical trials. The second part then looks at the production phases, as well as the export capacities of producing countries.

2. Pharmaceutical innovation: From basic research to clinical trials

As Aghion *et al.* (2020) point out, innovation is not an investment in R&D that translates with a certain probability into a result; it is a multi-organisational process that takes place in several stages. The first is basic research (the "R" of R&D). It is essentially carried out in laboratories and universities by researchers, who respond to incentives that are not purely monetary, and results likely in un-patentable discoveries. Then come the stages of applied research and development (the "D" of R&D), which given its commercial potential, is often carried out within companies. It is on these stages, and their financing, that the first part of this *Focus* focuses.

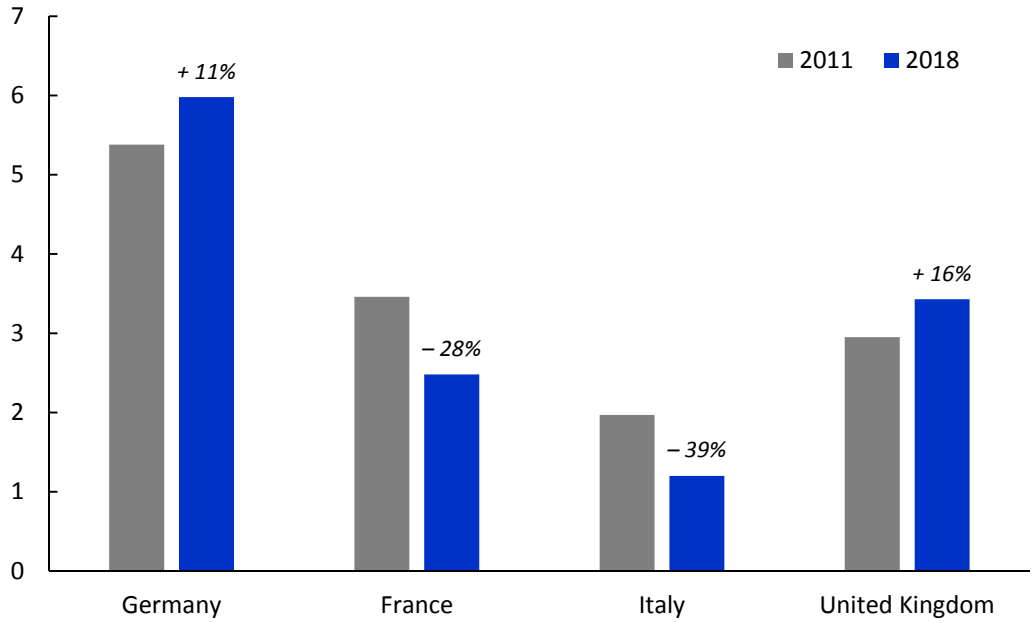
2.1. The basic research phase

Basic research is a particularly uncertain and groping process, requiring high researcher autonomy. Yet the latter must not come at the cost of sufficient means to pursue their research, especially at this stage when the commercial potential of the research is extremely uncertain. This gives a key role to public funding for research laboratories and universities. Figure 1 shows a first French weakness in this respect. Not only are public funds allocated to research less than in other similar countries, but they have fallen significantly over the last decade: the amounts have decreased by 28% in France while they increased by 11% in Germany and 16% in the United Kingdom, putting the latter ahead of France. This lack of resources also dampens the attractiveness of the research profession: the average starting salary in France is only 63% that in OECD countries (Assemblée nationale, 2020).

Beyond insufficient funding, France suffers from a weak cooperation between universities and industries. Indeed, the abovementioned distinction between basic and applied research, respectively in university's and industry's laboratories is not without overlap. Hence an encouraging factor for innovation is the ability to build and strengthen links between basic and applied research on the one hand, and universities and industry on the other. These close links facilitate the transformation of basic research into applied research and thereby the transformation of discoveries into marketable products. Figure 2 displays a ranking of university-industry collaboration[(2)]: France unsurprisingly ranks low, and the highest ranked countries are also the most innovative one (namely Switzerland and the United States). Unfortunately, this observation is no breakthrough, but had been noted before (see e.g. Aghion *et al*., 2007).

(2) The university-industry collaboration ranking is derived from the World Economic Forum's Global Competitiveness Report. This index is constructed through an opinion survey carried out at national level by the Forum's network of partner institutes such as research or university institutes, business organisations, national competitiveness councils or survey consulting firms. For this index, the following question was asked: "In your country, to what extent do companies and universities collaborate in research and development?". The score for each country is constructed by aggregating the answers of each respondent, with the proposed answers ranging from 1 to 7 [1 = do not collaborate at all; 7 = collaborate to a large extent].

Figure 1. Public R&D funding for health (in 2011 and 2018, in billions of constant 2015 dollars)

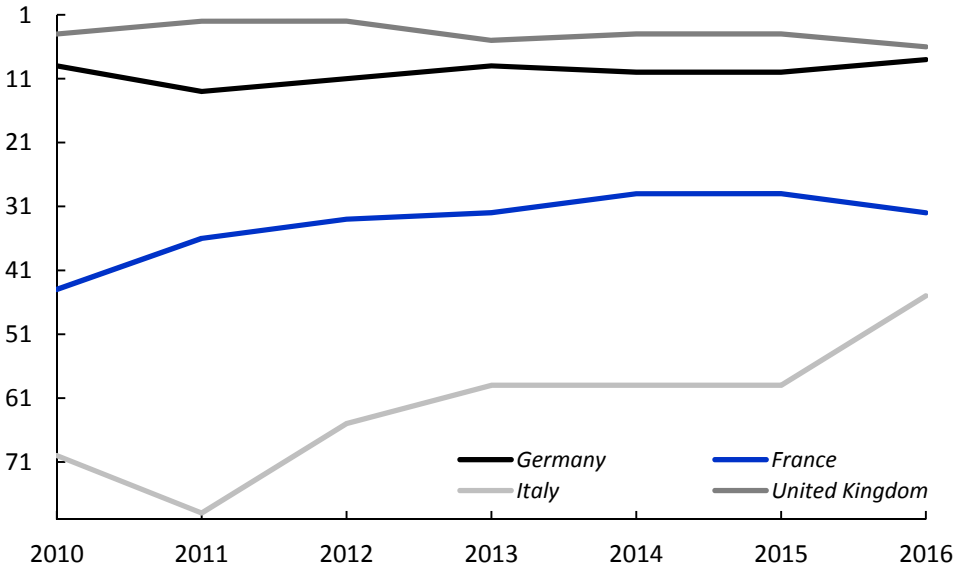


Interpretation: In 2018, public credits excluding CIR in R&D for health in France amounted to 2.5 billion dollars, compared to 3.5 in 2011; a decrease of 28%.

Particular attention must be paid to the scope of the data used. Although these data are collected *via* a questionnaire distributed and completed by each responding country, the way in which R&D credits are counted is not always homogeneous. In order to best reflect the investments of France and Germany, health R&D credits have been selected, as well as health R&D credits contributing to the "general advancement of knowledge", which are very important for these two countries. Conversely, in Italy and the United Kingdom, the funds allocated to the general advancement of knowledge are less important, and these countries have not specified how these credits are broken down between sectors (health, space, etc.). As a result, health credits contributing to the general advancement of knowledge are not taken into account for the UK and Italy because they are not reported. This underestimates the investments of the UK and Italy, but as the overall envelope indicated for "general advancement of knowledge" is higher in France and Germany, not taking this into account would further underestimate France and Germany. Therefore, these international comparisons are not perfect – no cross-country comparison is. Yet it remains that whichever indicator yields the following observation: between 2011 and 2019, France is investing less and less while our German and English neighbours are investing more and more.

Source: OECD, *Government Budget Allocations for R&D.*

Figure 2. University-Industry collaboration in R&D (2010-2016)



Interpretation: In 2010, France was ranked 44th in university-industry collaboration in R&D, then moved up the ranking to 29th place in 2015; before falling back to 32nd place in 2016.

Source: World Bank, *University-Industry Collaboration in Research and Development*.

2.2. Applied research and funding

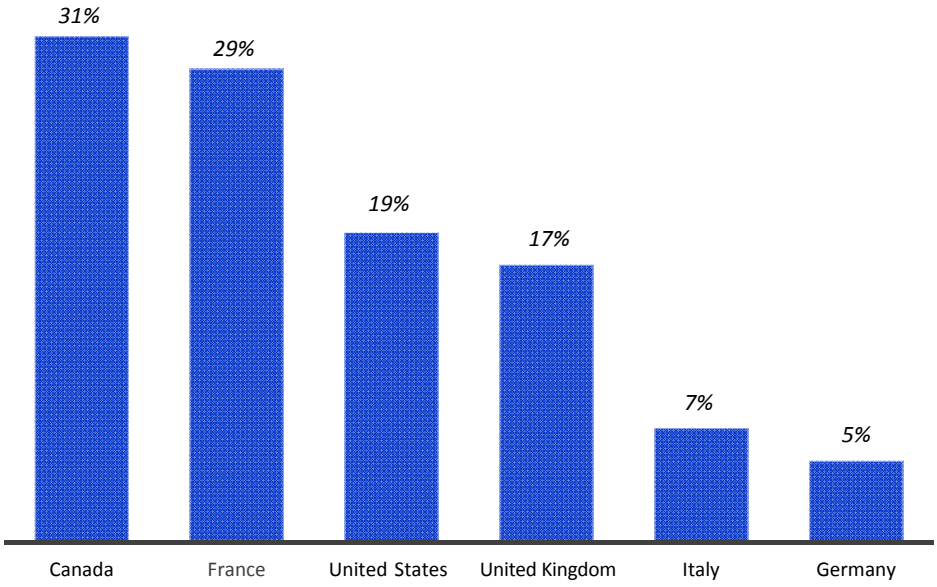
As mentioned above, the advent of biotechnology and gene therapies has profoundly changed the landscape of pharmaceutical innovation towards more expensive research and development. While large established companies have significant financing capacity, they could not have the internal capacity or skills to invest in all potentially profitable candidates. They thus need to smooth out their risks by betting on a high number of start-ups (as defined as young innovative companies without a defined business model) or by collaborating with older but still small and agile companies (like biotechs, which do have a defined business model, and may even be quoted on the stock market, e.g. BioNTech on the NYSE). Indeed these small companies and start-ups cannot diversify their risks over a large number of projects and therefore need to benefit from greater public support (for more details, see Kyle and Perrot, 2021). In this context, assessing the French position in the new pharmaceutical landscape involves an analysis of its innovation ecosystem.

One difficulty in the R&D phase of start-ups is funding. Making no profit, they rely for the most part on venture capital to finance their development, whose pace will then determine whether they can survive. Given that research requires significant funding over a long period (five to ten years), it is not always easy to guarantee sustainable funding over the whole timespan. Public seed funding is very important and effective in France (see Figure 3), coming from the State, local authorities and BpiFrance, the Public Investment Bank. In 2015, BpiFrance financed 500 biotechnology companies for 206 million euros (Abecassis and Coutinet, 2018). In addition, entities like INSERM-transfer or the French technology transfer offices (SATT) also provide support (Kyle and Perrot, 2021, *op. cit*.).

However, funding becomes chronically insufficient as start-ups grow and enter new phases. France Biotech[(3)] finds that in 2019 72% of biotechs are in search for funds and that a third of entrepreneurs' time is spent looking for funds. Taking a cross-country perspective, the French biotech sector is lagging behind its European counterparts, both in terms of the number of start-ups financed (117 against 135 in the UK, in 2019) and the amounts allocated (average ticket of 9 million euros against 12 million in the UK and 16 million in Germany, see France Biotech, 2019). Plus, the share of French biotechs in the European landscape is decreasing (see McKinsey, 2019). A comparison of the capital structure of French and American biotechs (see Figure 4) roots this in a lack of national funding.

(3) Founded in 1997, France Biotech is an independent association that brings together health innovation entrepreneurs and their expert partners. Its mission is to position itself as a leader in the health innovation ecosystem and as a privileged contact point of public authorities in France and Europe.

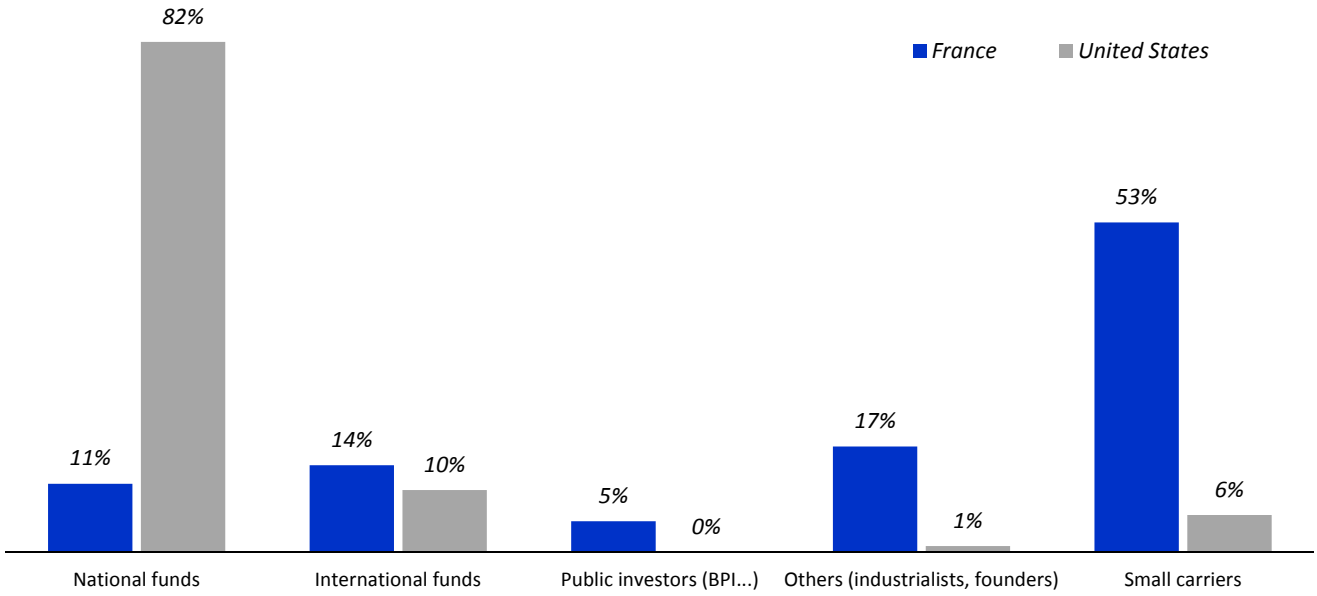
Figure 3. Public support for start-up (2016)



Interpretation: 29% of the R&D expenditure of *Health Tech start-ups in* France is supported by public funding or tax incentives such as the Research Tax Credit (CIR), funding by the Public Investment Bank (BPI) or Les *Programmes d'Investissement d'Avenir*.

Source: *Panorama France Biotech*, CIR Observatory.

Figure 4. Capital structure of biotech and medtech companies (comparison France *vs.* United States, 2016)



Source: France Biotech (2017).

2.3. Patents

A patent protects innovation. Its role is indispensable because it protects the innovator against the threat of imitation (while providing monetary rewards for its innovation). As such, the amount of patents filed provides a useful metric to measure and compare the innovative capacities of different countries.

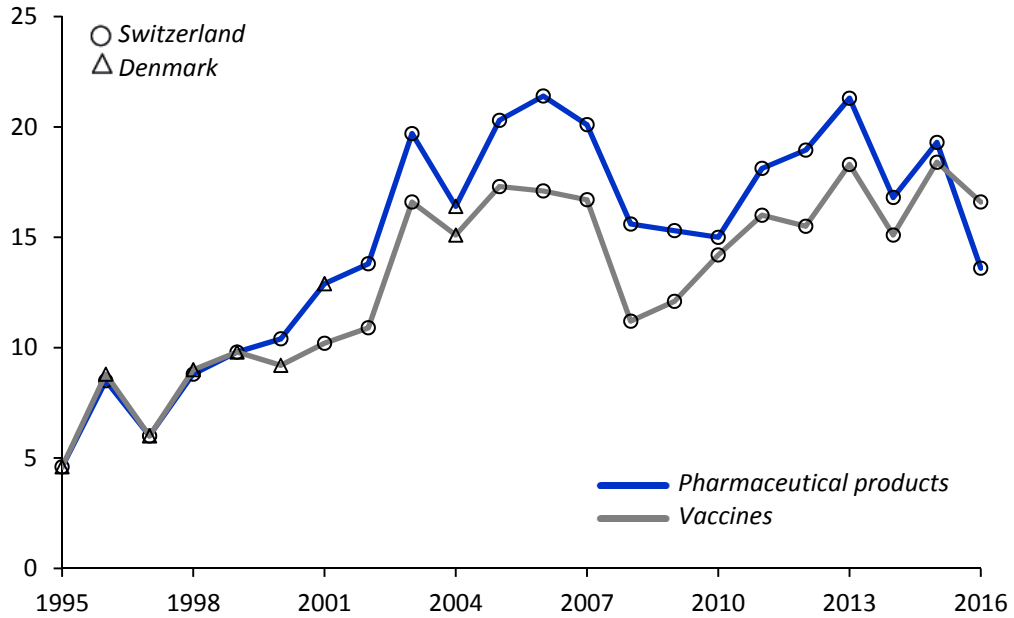
We use the OECD database "*Patents by Technology*". The location of an innovation is identified by the country of residence of its inventor. The patents selected here are the triadic patent family: a set of patents both filed to the main three global patent offices, namely the European Patent Office (EPO), the Japanese Patent Office (JPO) and the United States Patent and Trademark Office (USPTO). Selecting only triadic patents ensures that only substantial innovations are included.

Figure 5 is based on the methodology used by Aghion *et al.* (2020). We divide the number of patents filed by the population of each country, to account for various size. Then we display the difference each year between the amount of patents filed by France and that by the country filing the highest number that year. In other words, we show the distance between France and the most innovative country each year, as measured by the number of triadic patents filed. It reads as follows: in 2013, Switzerland filed 21.3 triadic pharmaceutical patents and 18.3 triadic vaccine patents per million inhabitants more than France.

Figure 6 is also expressed in patents per million inhabitants. It shows French triadic patents in the categories of pharmaceuticals, vaccines and biotechnologies and shows a decline since 2008 in France in each segment.

Finally, Figure 7 compares the number of triadic pharmaceutical patents in absolute terms, allowing France to be compared with the largest players of the sector: the United States, the EU-27, Japan and China.

Figure 5. Distance between France and the *leading* countries in innovation (1995-2016, in number of triadic(*) patents per million inhabitants)

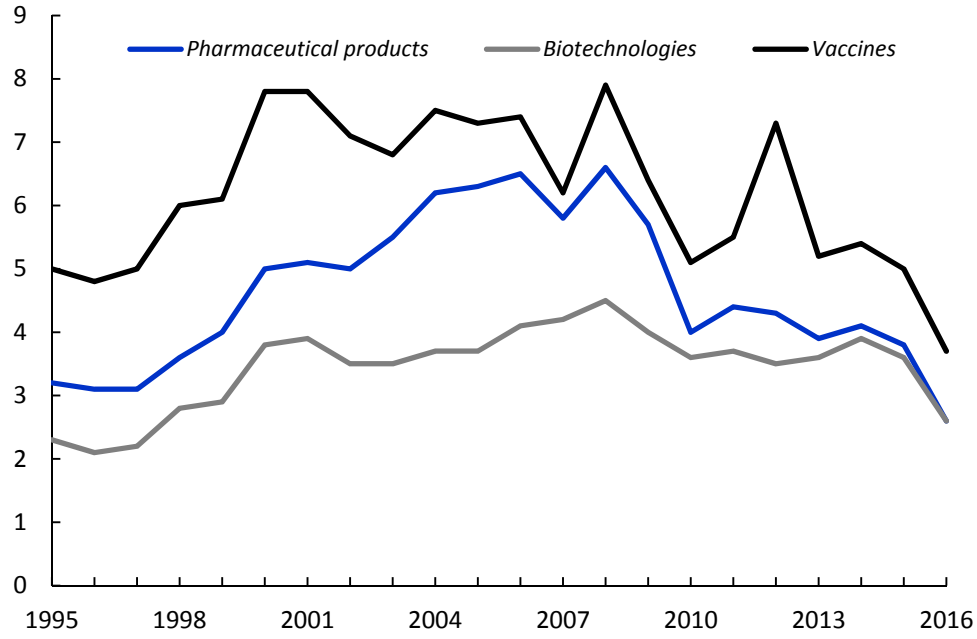


Interpretation: In 2013, Switzerland filed 21.3 triadic patents (per million inhabitants) for pharmaceuticals and 18.3 for vaccines (per million inhabitants) more than France.

Note: (*) Triadic patents are those filed with both the European Patent Office (EPO), the Japanese Patent Office (JPO) and the United States Patent *and Trademark Office* (USPTO). The location of the patented innovation is the country of residence of its inventor.

Source: OECD, *Patents by Technology*.

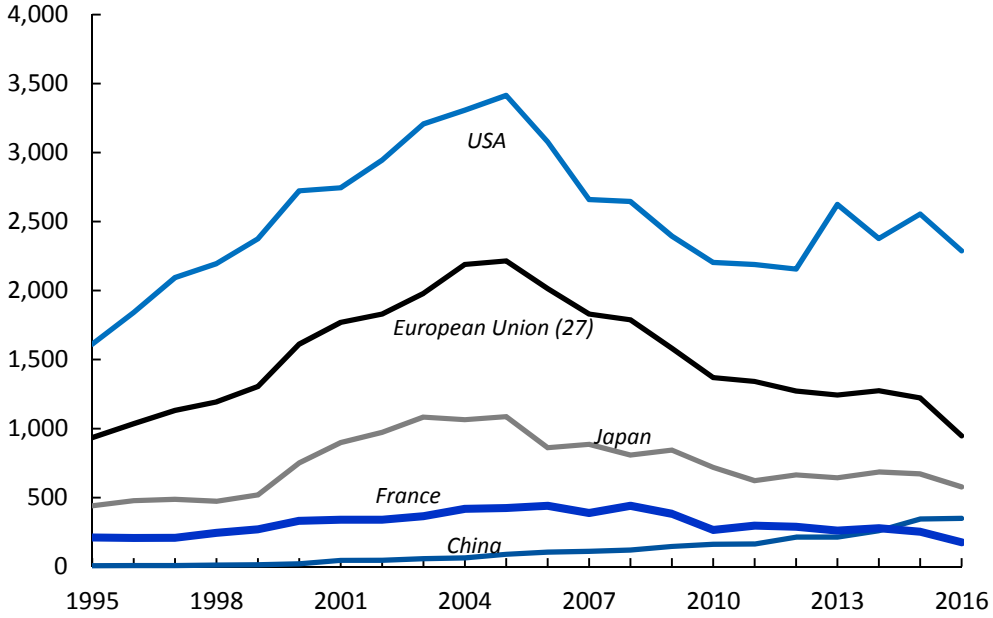
Figure 6. Number of triadic patents in France (1995-2016, per million inhabitants)



Interpretation: In 2008, France filed 8 triadic patents for vaccines, 6.6 for pharmaceuticals and 4.5 for biotechnologies per million inhabitants; compared with 3.7, 2.6 and 2.6 respectively in 2016, i.e. a decrease of 54%, 60% and 42% in each category.

Source: OECD, *Patents by Technology*.

Figure 7. Number of pharmaceutical triadics (1995-2016, in absolute terms)



Interpretation: In 2005, the EU 27 filed 2,215 triadic pharmaceutical patents in absolute terms, compared to 947 in 2016; a decrease of 57% over eleven years.

Source: OECD, *Patents by Technology*.

The most innovative country in terms of patents filed in absolute terms is undeniably the United States. Overall, there has been a decline in the number of patents filed since 2005 in all countries. This decline is due to the transition from technologies based on chemistry to new ones based on biotechnology and genomics, which lengthened and complexified the research process. Professor Bernard Meunier, in his inaugural lecture at the *Collège de France*, noted a "decline in innovation in the pharmaceutical industry in

relation to the number of molecules approved by the *Food and Drug Administration* (FDA) to the tune of one billion dollars. For this sum, we went from ten drugs to one between 1970 and the early 2000s".

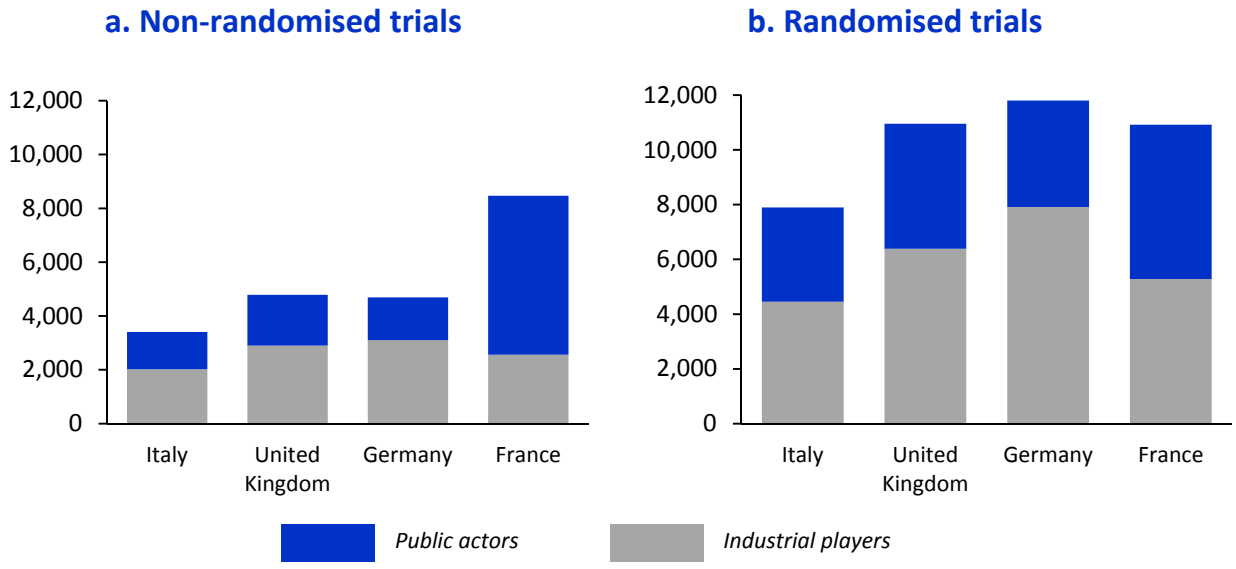
2.4. Clinical trials

In order to prove a therapeutic effect, a trial must follow a robust methodology. Otherwise it is prone to biases that prevent the inference of a causal relationship. Such a methodology involves randomisation, i.e. the random assignment of patients in the study between the treatment group, which receives the dose of the drug being tested, and the control group, which receives a placebo or *standard of care* (*a* treatment commonly used to treat the disease in question). The robustness is further improved when the experiment is said to be blind or even double-blind. This means that the participant, or even the prescriber, is not informed whether she receives the test or control drug. Indeed, the confirmation bias could lead the participant and the observer to alter the declared effects (or their absence), depending on their *ex ante* posture on the substance.

We used the database ClinicalTrials.Gov provided by the US National Library of Medicine [(4)], which lists all trials from both public and private funding, anywhere in the world. We filtered for intervention trials and grouped them by randomisation and by country. Figure 8 shows the result for four European countries.

For the reasons explained above, the European Medicine Agency (EMA) strongly encourages industry actors to conduct large and randomised trials, since these achieve a robust level of evidence to grant a marketing authorisation. As a result, a large proportion of these trials are funded by industry. However, in France, a large share of trials come from public funding. Without the marketing authorisation as an end-goal, such publicly funded interventional trials do not need to meet the EMA requirements, and hence are less prone to follow rigorous methods. This would indicate that public spending is less effective as it finances low level-of-proof research.

Figure 8. Distribution of clinical trials by type (comparison of four European countries, 2020)



Interpretation: In 2020, out of a total of 19,287 clinical trials conducted in France, 8,469 were non-randomised (of which 5,910 were publicly funded).

Source: *ClinicalTrials.gov.*

(4) *See* https://clinicaltrials.gov/ct2/resources/download#DownloadAllData

3. After innovation: Production and Export

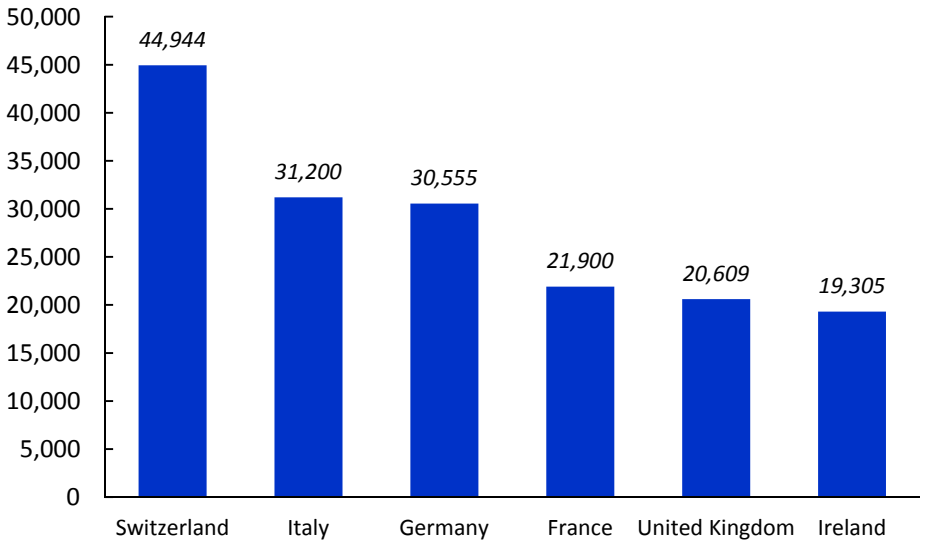
3.1. The production stage

Once the pharmaceutical company has patented the molecule, carried out the trials and obtained a Marketing Authorisation (MA), it moves on to the production stage. It has to follow the Good Manufacturing Practices (GMP) set by the World Health Organisation (WHO), which ensure that fabrication and quality-checks meet sufficient and common criteria. These standards are all the more important as value chains in the field are both global and fragmented.

The degree of global integration, hence of France's and others' exposure to these value chains, has been stark with the supply crisis in the spring of 2020. The latter sparked a debate on relocation of production. Not all forms of outsourcing are to be questioned, as one cannot find much attraction to relocating low value-added medicines like generics. However the attraction is larger on high value-added products, such as biotechnologies, and our vulnerability to these chains requires careful thinking.

In 2017, pharmaceutical production in France was worth €22 billion, compared with €45 billion in Switzerland, 31 in Italy and 21 in the United Kingdom. Figure 9 illustrates these numbers.

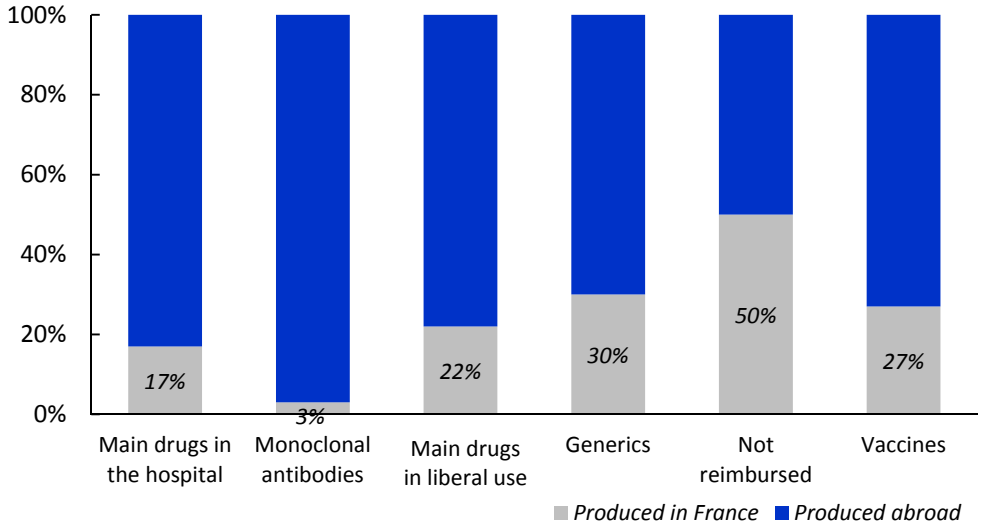
Figure 9. Drug production by European countries (2017, in millions of euros)



Source: EFPIA.

Although France remains one of the main producers of medicines in Europe, Figure 10 shows that the majority of us do not consume "Made in France" medicines. Across all medicine classes, the overwhelming majority come from abroad. The only exception is the class of non-reimbursed medicines, which are medicines with a low medical service rendered (SMR), i.e. not innovative. While this imported consumption is not really an issue as far as generics are concerned, it may be more alarming for medicines that represent strategic assets, such as monoclonal antibodies (derived from biotechnology) or vaccines.

Figure 10. Share of foreign production of medicines in French consumption (2014, as a percentage, by type of product)

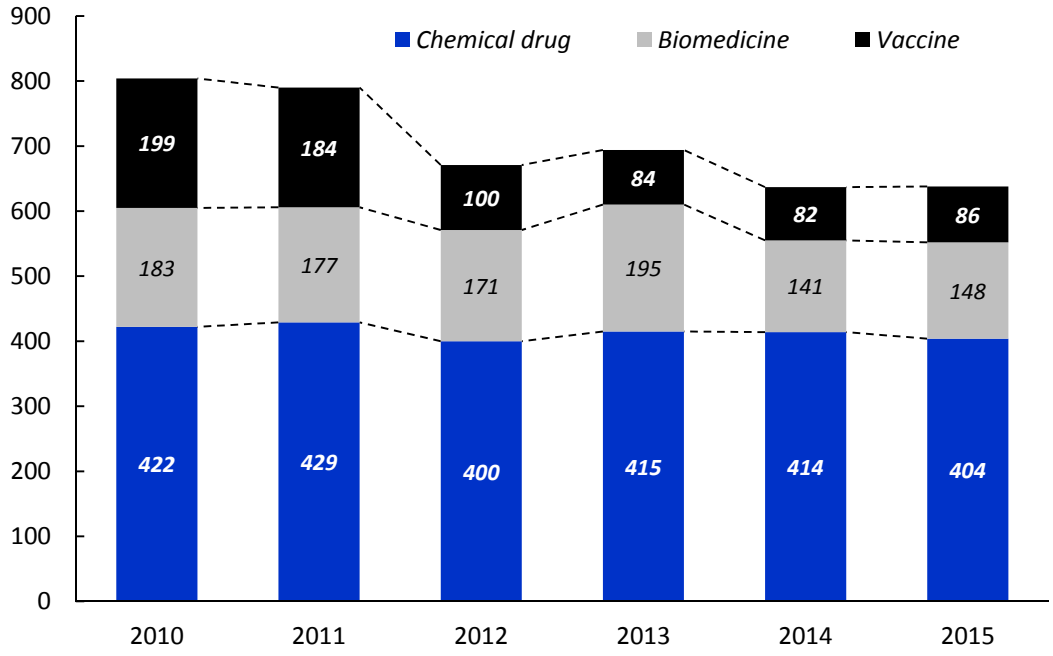


Source: Berger (2014).

While France was the leading producer from 1995 to 2008,[(5)] its position has been once again in decline since. We see two main explanations for this. First, pharmaceutical production in general has largely been subject to outsourcing. The bulk of production now takes place in low-cost producing countries such as China and India. In Europe, 60 to 80 per cent of the active ingredients of medicines are manufactured by countries outside the EU, compared with 20 per cent thirty years ago (Abecassis and Coutinet, 2018, *op. cit.*). This phenomenon of outsourcing is due to the cut in costs by shifting from production to other activities such as research and development of their originator product. Second, France has not turned its attention to the production of innovative medicines. 80 percent of French production facilities are still dedicated to medicines of chemical origin. Moreover, mature chemical drugs whose patents have expired account for 49% of production jobs in France (LEEM, 2020a). The challenge is therefore to attract the production of innovative therapies. The cause of this under-production of biomedicines lies once again in too little productive investment. Over the 2010-2015 period, there has been a decrease in investment in vaccine and biomedicine.

(5) France was the first European producer of medicines in terms of value from 1995 to 2008, see LEEM (2020a).

Figure 11. Evolution of investments in pharmaceutical production sites (2010-2015, in millions of euros, by product type)



Sources: Observatoire 2016 des investissements productifs pharmaceutiques et biotechnologiques en France, LEEM, KPMG (2017).

France is therefore experiencing a decline in drug production, itself specialised in old chemical molecules, and only few biomedicines. It has thus become dependent on and vulnerable to foreign production for most of its drug consumption.

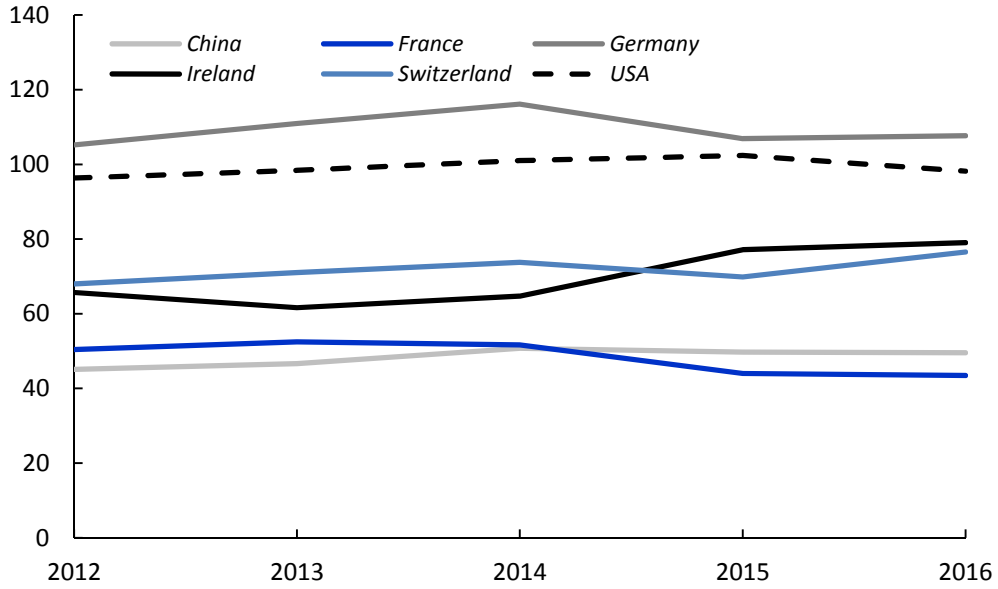
3.2. Exports of medicines

However, France remains one of the major drug exporting countries. Such exports go mainly to other European countries. Indeed the growth in exports from France to European countries amounts to 13% in 2019. Exports of medicines to Europe represent €17.8 billion in 2019 (59.4% of the total). However, it is the United States that is the leading recipient of French exports, ahead of Belgium and Germany (LEEM, 2020b).

From the BACI data provided by CEPII, we have selected the international trade flows pertaining to pharmacy. Figures 12 and 13 provide an overview of pharmaceutical exports respectively by value and volume[(6)], from 2012 to 2016. In value terms, the market is dominated by Germany and the United States. In third place comes Ireland, surprisingly. Since the country does not appear much elsewhere in pharmaceutical innovation, we suspect the country's fiscal policy creates an artificially high position in the ranking.

(6) The product codes selected here correspond to active substance-based pharmaceuticals, as well as various chemical products, medical preparations and certain plastics related to the pharmaceutical sector.

Figure 12. Exports by value (2012-2016, $ billions)

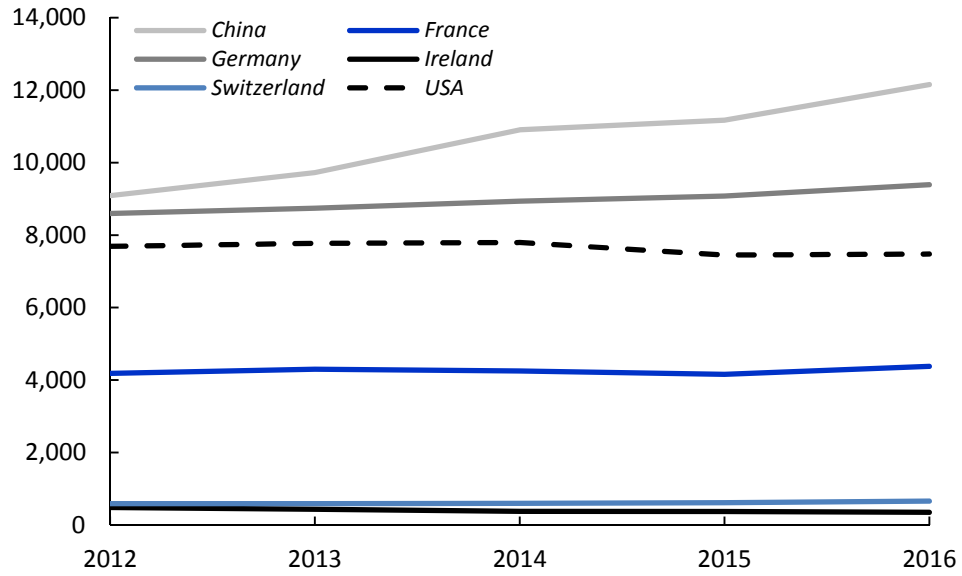


Reading: In 2013, France exported a value of 52 billion dollars worth of medicines, compared to 43 billion dollars in 2016; a decrease of 17% in three years.

Source: BACI, CEPII.

One way albeit imperfect of identifying innovative and high value-added products is to compare exports in value (Figure 12) and volume (Figure 13). The case of China is illustrative: out of 6 countries, it is 1st in terms of volume, but 5th in terms of value. Hence it exports vast amounts of medicines, but of low value-added, such as generics. Conversely, the low volume of exports from Switzerland and Ireland highlights their specialisation in the production and export of innovative products, in small quantities but of high value. Germany ranks particularly well: first on exports in value, and second on exports in volume. It exports a lot, and a variety of products (innovative and non-innovative), as does the United States. France, on the other hand, export levels have remained constant, but in value terms it has suffered a decline since 2014, which confirms that it has not turned its attention to innovative products, including biomedicines.

Figure 13. Export volumes (2012-2016, in tons)



Interpretation: In 2012, China exported 9,000 tons of medicines, compared to 12,150 tons in 2016; an increase of 35% over four years.

Source: BACI, CEPII.

As production and export are closely linked, the drop in French exports at least partly stems from the drop in production. According to an analysis carried out by LEEM, of the 315 medicines authorised by the EMA in Europe between 2016 and 2019, only 25 are produced in France, against 56 in the United Kingdom and Germany, 46 in Ireland and 28 in Italy. By overlooking its pharmaceutical production, France is foregoing exports, both current and future.

4. Conclusion

The process of pharmaceutical innovation relies heavily on R&D, which takes years before a molecule can be brought to market, if it ever does. Nevertheless, the diversification of relevant disciplines beyond chemistry in the last decade has led to a major shift and acceleration in the industry, most notably with biotechnologies. These changes are struggling to emerge in France, where upstream research is under-invested, and hence downstream production remains centred on old molecules with low added value and subject to competition from low-cost exporting countries. As a result, in almost all metrics, France is losing momentum. The recommendations of Kyle and Perrot (2021) aim at first stopping this decline, to then improve the country's position in this strategic sector.

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