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Pharmaceutical Innovation: How Can France Catch Up?

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The pharmaceutical industry has experienced major changes in recent years. The shift from chemistry to biotechnology and genomics made the innovation process more complex and costly. Firm structure and financing have also evolved. Collaboration between large established companies and smaller, younger firms is now widespread, and academic research and university spin-offs are often the origins of biopharmaceutical innovation. In this new landscape, France is lagging far behind, particularly due to the lack of public funding allocated to research and the innovation ecosystem. We recommend an increase in public funds allocated to basic research and the continuation of efforts to strengthen collaboration between universities and start-ups. We also recommend earmarking public funding for clinical trials with high standards of scientific evidence.

A catch up is also necessary in research policy and in innovation governance. First, however essential the patent system is, it may prove too rigid in some cases. At the European level, we recommend designing rewarding innovative treatments with market exclusivity that varies according to the degree of innovation or importance of the drug. Moreover, for priority diseases, international innovation prizes could be established, assuming a credible ex-ante commitment to finance the amount. Second, the French pricing policy needs rethinking. We recommend making its pricing rules more consistent and adaptive as real-life data becomes available. Experimentation with performance-based pay contracts and other new pricing approaches should be encouraged. The process of commercializing a drug in France should be simplified, with regulations applied consistently. We recommend creating a single point of contact for innovators, who could then help shepherd a new drug through each step by articulating the various requirements of each institution involved.

Data exploitation is a major source of potential benefits in public health. And France possesses high quality data bases. We therefore support the consolidation and opening of data nationally (within the Health Data Hub) and at the European level (within the European Health Data Space initiative), to facilitate both the development of new medicines and their evaluation by health agencies. Finally, there is the question of the low use of generics in France and the best use that could be made of spending on medicines. In this respect, we recommend evaluating the effectiveness of the latest measures to encourage substitution towards generics (LFSS 2019), to ensure competition plays its role, thereby freeing some budget to finance more innovative drugs.

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Pharmaceutical innovation is the process by which scientific discoveries capable of addressing a health need are brought from the experimental setting to clinical implementation. For both medicines and vaccines, pharmaceutical innovation[1] management faces challenges on health, economic and budgetary fronts. Health issues are obviously at the forefront as the aim is to preserve or improve the health of citizens. Second, the economic stakes relate to innovation incentive mechanisms, which must both reward innovators and generate competition, in a sector where along with large multinationals, small companies (particularly university spin-offs)[2] play an increasing role. Finally, the stakes are also budgetary in that health insurance covers the price of medical innovations used by patients. And although an innovation may be very costly in the immediate term, its benefits may produce systemic effects in the medium- and long-term, thereby raising the problem of the time horizon for assessing the benefits. Ideally, innovations improve the cure and prevention for patients, all the while remaining at costs under control for public authorities.

The new landscape of pharmaceutical innovation

From chemistry to biology and genomics

The pharmaceutical industry has experienced major changes in recent years, moving from technologies rooted primarily in chemistry to new technologies based on biotechnology and genomics. Drug discovery has thus evolved from random screening of chemicals to a more "rational" design of drugs, based on the understanding of biological processes. Traditional "small molecule" treatments are relatively easy to make by chemical synthesis. Biotechnology-based drugs (including most vaccines) are extracted, semi-synthesised or manufactured in living organisms, and are much more difficult to make. This trend is illustrated in particular by the number of biological molecules approved per year by the US Food and Drug Administration (FDA): between 2004 and 2008, this figure averaged 2.6 per year, rising to 13 between 2015 and 2019. In 2018 and 2019, the FDA approved 17 new biologic products each year. An example of an advance in genomics is the CRISPR[3] technology, currently used to create treatments for lung cancer, blindness, Huntington's disease and other diseases. A major consequence of such a change is the shift from blockbuster drugs to complex, technologically advanced drugs for smaller markets (*niche-busters*). For example, the number of annual authorisations by the European Medicines Agency (EMA) for drugs treating orphan diseases, by definition intended for small population of patients, has risen from 2 in 2000 to a record 185 in 2016, and 113 in 2019.[4] In addition, some innovations are creating a paradigm shift by promising a full cure of the disease in a single dose, as opposed to a treatment that a patient would consume for his entire life.[5] The promises of these new treatments then require "real-life" monitoring to ensure their effectiveness, especially as their initial cost is exorbitant for the usual public budgets.

A simultaneous evolution of market structure

The organisation and financing of pharmaceutical innovation have co-evolved with this technological shift. Pharmaceutical innovation is now largely based on university research, and often initially developed in university spin-offs. Biotechnology has led to a growing need for new and evolving knowledge, most often developed in academic laboratories. In fact, many recent advances are the result of start-ups created close to basic research centres. For example, BioNTech (one of the companies responsible for a Covid-19 vaccine) was founded by three researchers in Germany in 2008, and has grown by conducting cutting-edge developments in immunotherapy. It continues to develop close to research centres and university hospitals in Germany (Mainz, Munich, etc.) and the United States (Cambridge, San Diego). Similarly, another Covid-19 vaccine producer, Moderna, was founded by a Harvard biologist to commercialise his stem cell research. These small organisations specialise in drug research and discovery, and generally rely on large multinationals to manage development and marketing. Indeed, licensing agreements, partnerships or venture capital investments by large pharmaceutical companies provide essential funding. Research funding needs to be tailored to the risk involved, and unlike large pharmaceutical companies (*big pharma)*, small companies (biotechs and SMEs or mid-sized companies) cannot diversify the risk over a large number of projects. Despite this, they

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[1] This *Note* does not address the issue of innovation in medical technologies such as devices or surgical techniques, but focuses on pharmaceutical innovation. For stylised facts on the entire cycle of pharmaceutical products (innovation, production, export), see the associated Focus: Alla A., J. Beuve and B. Savatier (2021): "The Lifecycle of Pharmaceutical Innovation: France is Lagging Behind", *Focus du CAE*, no 053-2021, January.

[2] A university spin-off is a new company created from a university for the purpose of exploiting knowledge developed there through commercial activities involving teachers, researchers or students of the university.

[3] Awarded the Nobel Prize for Chemistry 2020 to French researcher Emmanuelle Charpentier.

[4] EMA Directory of Orphan Diseases (2020).

[5] This is the case of sofosbuvir (trade name Sovaldi) which treats patients with hepatitis C.

do not necessarily benefit from greater public support. In France, direct public support as a percentage of total R&D was 11.2 for SMEs compared to 9.8 for large companies (in 2017).[6] Thus, although large companies in the sector maintain parallel research activities, the bulk of research is being developed in a collaborative manner. While large company funding remains crucial, the role of biotechs SMEs is becoming predominant.

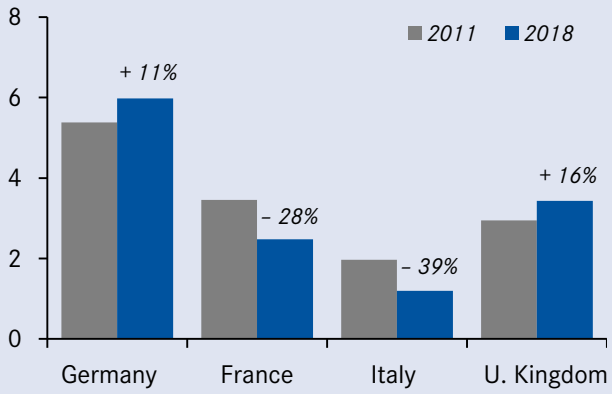
The innovation process in France

Basic research: insufficient means and low attractiveness

Typically, the innovation process begins with a fundamental discovery, such as a new molecule or target (basic research stage). On the basis of this discovery, further research takes place to develop a new commercial product, drug or vaccine (applied research stage). The results of basic research are not immediately marketable and not usually patentable. Public financing of this stage is usually essential. Applied research can generate private gains through patenting and commercialization, and is usually financed by the private sector.

Basic research is critical to the innovation process. Several studies highlight the positive impact of wider access to basic research on innovation, illustrating the complementarity between basic research and its commercial exploitation.[7] Basic research is most often carried out by university researchers. Their discoveries are shared at international symposia and disseminated in publications in specialised scientific journals, after peer review by other experts in the field, a *sine qua non* condition for their validation by the scientific community. Academic research has many appealing features: an academic researcher is free to organise her research agenda and to exchange ideas with other researchers.[8] This freedom is essential for the diversity and dissemination of new ideas and, ultimately, for innovation. However, while basic research historically accounts for a smaller share of total spending than applied research, it nevertheless needs resources. The greater the resources available for basic research, the larger the positive effect on innovation. However, the French public envelope dedicated to research in biology and health is shrinking, while the total budget allocated to research is stagnating (or even slowing down slightly) at low levels compared to our European neighbours. While Germany devotes 3% of its GDP to research, France barely exceeds 2% (far from the 3% set as an objective by the "Lisbon Strategy" and taken up by "Europe 2020"), of which only 18% is dedicated to biology-health.[9] Moreover, public R&D funding for health is almost half of Germany's and has decreased by 28% between 2011 and 2018, whereas it increased by 11% in Germany and 16% in the United Kingdom over the same period (see Figure 1).

1. Public R&D funding for health (in billions of dollars)



Reading: In 2018, public R&D credits (excluding CIR) for health in France amounted to 2.5 billion dollars against 3.5 in 2011, a decrease of 28%. For more details, see Alla A., J. Beuve and B. Savatier (2021): "The Lifecycle of Pharmaceutical Innovation: France is Lagging Behind", *Focus du CAE*, no 053bis-2021, January.

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

We can at best only draw a mixed picture of the evolution of the attractiveness and international impact of French universities in the field of health. Despite efforts to consolidate French universities into strategic consortia, the Shanghai international ranking of universities included no French institution in the top 50 in Public Health, only two in Pharmaceutical Sciences, and just one in Biological Sciences.[10] While the number of French scientific publications is increasing, France's share of international publications is shrinking as the contribution of emerging countries to science has grown. It should be noted that the quality of French publications seems to have improved: they are more frequently cited and have had a greater impact in recent years. Finally, several reports warn of the loss of attractiveness of the job of a researcher: the average salary at the beginning of a French researcher's career is only 63% of the OECD average.[11]

[6] Ministère de l'Enseignement supérieur, de la recherche et de l'innovation (2020): *État de l'enseignement supérieur, de la recherche et de l'innovation en France*, no 13.

[7] See, for example, Aghion P. and X. Jaravel (2015): "Knowledge Spillovers, Innovation and Growth", *The Economic Journal*, vol. 125, no 583, pp. 533-573.

[8] Aghion P., M. Dewatripont and J.C. Stein (2008): "Academic Freedom, Private-Sector Focus and the Process of Innovation", *RAND Journal of Economics*, vol. 39, no 3, pp. 617-635.

[9] www.academie-medecine.fr/communique-de-lacademie-pandemie-de-covid-19-une-lecon-pour-la-recherche-en-biologie-sante/

[10] Sorbonne University at the 48th position, see shanghairanking.com.

[11] www.assemblee-nationale.fr/dyn/15/textes/l15b3234_projet-loi

Applied research and development: An insufficient ecosystem for innovation

The second stage, applied research and development, faces two major challenges. The first is to promote the transition from basic to applied research, or in other words, to facilitate interaction between universities and companies. The second challenge is to organise funding in a context where the initial costs, duration and risks of failure in the development of new drugs are very high.

After a basic research scientific discovery, molecules are developed into drugs in pharmaceutical laboratories or, increasingly for innovative medicines, in biotechnology spin-offs. The gap between University research and commercialization in the private sector, coined the "valley of death," must be bridged. In 1980, the Bayh-Dole Act in the United States allowed universities to patent and license the inventions of their faculties through technology transfer offices. While there is some debate about who should hold the patent between the university or the researcher, it appears that this Act closed the "valley of death" to a greater degree than in France, where there is little collaboration between universities and companies. For example, France ranks 32nd in the World Bank's R&D University-Industry Collaboration ranking in 2016, with Switzerland, the United States, the United Kingdom and Germany occupying 1st, 4th, 6th and 8th positions respectively.[12] However, efforts have recently been made in France. Today, a scientist with results that can be developed into a product must submit an declaration of invention to the valorisation services of his university and then be accompanied by a technology transfer office (for example, a *Société d'accélération de transfert de technologie*, SATT: Technology Transfer Acceleration Company). Then, if the inventor wishes to participate in the creation of the start-up, he must go before the *Commission nationale de déontologie* (CND: National Ethics Commission). A 2018 report by the *Cour des Comptes* (Court of Auditors) indicates that the income earned by SATTs from their maturation action has grown very rapidly, from €221,000 in 2012 to €13.2 million in 2017. Over the same period, the number of licences has risen from 3 to 174, and the SATTs had enabled the creation of 231 start-ups by 2018.[13] This type of public policy is essential to enable the emergence of start-ups and innovations, and its reinforcement is desirable to improve pharmaceutical innovation in France.

As mentioned, the growing complexity of medical innovation makes R&D increasingly difficult to finance. Indeed, the average cost of developing a marketed drug was estimated at $802 million in 2003; by 2016, it was $2,558 million, with capitalized costs increasing by 8.5% per year.[14] In 2017, the pharmaceutical sector spent $97.2 billion and leads all sectors in terms of R&D intensity. While large companies have significant financing capabilities, they do not have sufficient internal capacity or expertise to invest in all potentially profitable drug candidates. Therefore, they often hedge risk by investing in start-ups (defined as young innovative companies without a defined business model) or by collaborating with smaller, more agile companies like BioNTech (which have a defined business model, and which may be publicly traded). Smaller companies are often financed by venture capital funds, which invest in them in the hope of a subsequent profit on resale. Well-functioning capital markets, and more specifically venture capital (VC) markets, are essential to the existence and potential success of start-ups. The bio-pharmaceutical sector in particular exhibits a need for very high initial capital, a long period of development (10-15 years) and a lower chance of success. This leads to a structural financing gap in the sector, which persists despite the expansion of VC and of efforts to develop a start-up ecosystem, including in biotechnology.[15] In France, the biotech sector is still lagging behind its European counterparts. Fewer start-ups are financed (117 in 2019 against 135 in the United Kingdom); lower amounts are allocated (average ticket of 9 million euros in France against 12 million in the United Kingdom and 16 million in Germany);[16] and the share of French biotechs in the European landscape is decreasing.[17] To improve France's position in this landscape, it is essential to first provide greater support for basic research, at the origin of innovation, and second, encourage exchanges between basic research in academia and applied research in the private sector. In this respect, the measures announced under the Recovery Plan and the *Programme d'investissements d'avenir* (PIA: Future Investment Programme) go in the right direction, but more needs to be done to reach the level of our most successful European partners.

Recommendation 1. Increase public funding for basic research and continue efforts to strengthen collaborations between universities and start-ups.

[12] World Bank (2016): *University-Industry Collaboration in R&D*.

[13] See Cour des Comptes (2019): *Les outils du PIA consacrés à la valorisation de la recherche publique*, Thematic Public Report and LEEM (2020): *Bilan économique*, 2020 edition.

[14] DiMasi J.A., R.W. Hansen and H.G. Grabowski (2003): "The Price of Innovation: New Estimates of Drug Development Costs", *Journal of Health Economics*, vol. 22, no 2, pp. 151-185 and DiMasi J.A., H.G. Grabowski and R.W. Hansen (2016): "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs", *Journal of Health Economics*, no 47, pp. 20-33.

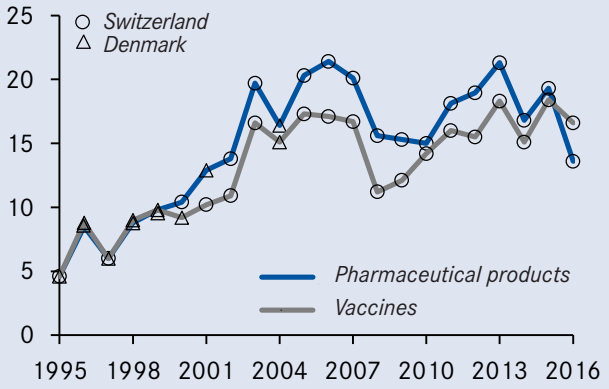
[15] Report prepared for DG Enterprise of the European Commission (2010): *The Financing of Biopharmaceutical Product Development in Europe*.

[16] France Biotech (2019): *Panorama France Healthtech 2019*, 17th edition.

[17] McKinsey (2019): *Biotech in Europe: A Strong Foundation for Growth and Innovation*, McKinsey & Compagny.

Added to this is the difficulty for SMEs to grow in size and market once a product has been developed.[18] The need for cash factors favours large companies, to the detriment of SMEs, whether young or established. Yet the latter are often the source of innovation. Moreover, the pharmaceutical industry is characterized by capital-intensive and long R&D processes, with meagre chances of success. Particularly for orphan diseases, the potential market is limited. As a result, the sector suffers from a structural lack of financing to enable companies to reach a profitable scale. Recent contributions[19] have proposed the creation of "mega funds" to finance a large number of "drug candidates" in order to diversify risks. Faced with this challenge of scale, it is at the European level that action must be taken, in particular with the European Investment Bank (EIB). Some initiatives already exist, such as the EU Health Programme, which aims to strengthen European health systems and promote innovation in health. The European recovery plan also aims to strengthen innovation in health, notably through the "Horizon Europe" Program (budget of €80.9 billion) which includes a specific health cluster; or the "InvestEU" fund which will mobilise public and private investment with an EU budget guarantee of €38 billion and whose aim is to support the EIB's investment projects.

2. Distance between France and the leading countries in innovation
(in number of triadic patents[a] per million inhabitants)



Reading: 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: [a] 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. For more details, see Alla A., J. Beuve and B. Savatier (2021): "The Lifecycle of Pharmaceutical Innovation: France is Lagging Behind", *Focus du CAE*, no 053bis-2021, January.

Source: OECD, *Patents by Technology*.

Patents: the long French decline

As soon as a promising drug candidate is identified, patent applications are filed. After a pre-clinical stage in animals, the drug candidates are tested in three phases of clinical trials in humans, the costs of which increase with each phase. Failures are frequent: the probability of reaching the market for a project at the preclinical stage is less than 5%. Thus, on average, out of 10,000 targeted molecules, only 100 are tested and then give rise to only ten drug candidates, of which only one will finally reach the market. The development of vaccines differs from that of other pharmaceutical products in several respects. Because vaccines are used in healthy patients to prevent disease, rather than to treat a patient, adverse events are potentially more costly. In addition, to demonstrate the effectiveness of a vaccine in preventing a disease, a large population must be exposed to the disease and the results must be observed over a long period of time, requiring more and more expensive clinical trials than for most pharmaceuticals.

While France was long at the forefront of innovation in certain sectors, it has not managed to find a place for itself in this rapidly changing system. Figure 2 illustrates the distance between France and the leading countries in terms of innovation, which is measured by the number of patents filed divided by the number of inhabitants. For both pharmaceutical and vaccines patents, the observation is the same: France has lost ground between the mid-1990s and the 2000s, and today remains far from the technological frontier. Recent developments, however, give some reason for optimism. In 2019, the *Institut national de la santé et de la recherche médicale* (INSERM: National Institute of Health and Medical Research) was the top patent applicant in pharmaceuticals and the third highest in biotechnology at the European Patent Office. The number of French biotechnology patent applicants increased by 12% between 2018 and 2019.[20] It remains to be seen whether these efforts will translate into innovative products through clinical development. One way of understanding why France is struggling to position itself effectively in this new landscape and looking for ways to make up for any shortcomings is to break down the innovation process and analyse the incentive mechanisms.

Clinical trials: weaknesses in the environment

Clinical trials are crucial to the innovation process as they offer a number of advantages for the countries in which they are carried out. First, they allow certain patients to have rapid access to new therapies. Second, they enable doctors to gain

[18] European Investment Bank (EIB) (2018) : *Financing the Next Wave of Medical Breakthroughs. What Works and what Needs Fixing?*, Report.

[19] Fagnan D.E., N. Yang, J.C. McKew and A.W. Lo (2015): "Financing Translation: Analysis of the NCATS Rare-Diseases Portfolio", *Science Translational Medicine*, vol. 7, no 276.

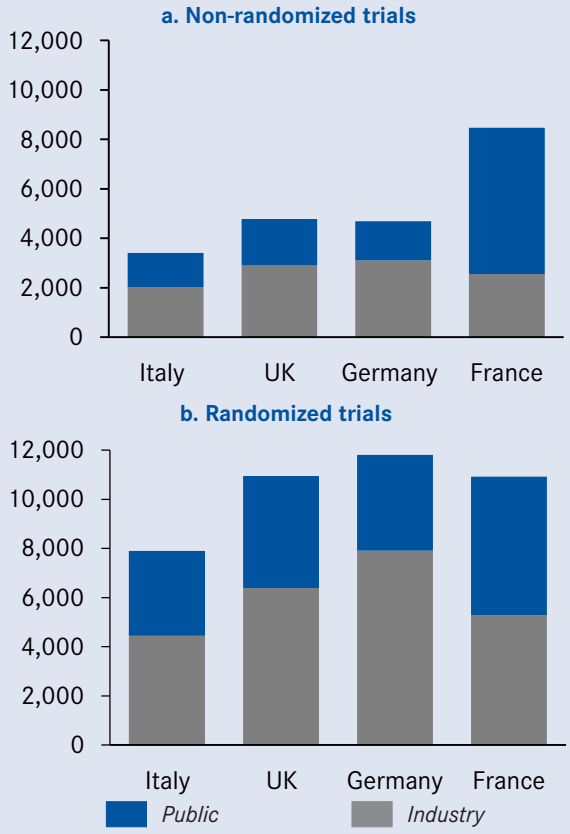
[20] www.epo.org/about-us/annual-reports-statistics/statistics/2019/statistics/patent-applications.html#pharmaceuticals

experience in administering these therapies. In addition, they generate knowledge spillovers, which allow further progress to be made. Finally, the data generated by clinical trials on local patients is particularly valuable in understanding the benefits of new therapies for the local population.

However, a review of clinical trial registries highlights certain weaknesses in the French environment. Although France hosts a large number of trials (notably on Covid-19, partly due to the high prevalence of the virus in the country) of sometimes excellent quality (as in the case of oncology research),[21] too many of these trials have low scientific standards, in that they are non-randomised, in much higher proportion than in neighbouring countries (see Figure 3). This type of trial cannot prove a causal link between taking the drug and the subsequent state of health. A recent example is Didier Raoult's clinical trial of hydroxychloroquine for the treatment of Covid-19.[22] Furthermore, these low-evidence trials are for the most part financed by public funds. In contrast, industry-funded trials must provide a high level of proof for the EMA to approve their products. As a result, the vast majority of the trials they fund meet high standards of scientific evidence. These trends suggest that beyond its level, public funding for research suffers from a problem of misallocation. Moreover, the existence of these trials can make it more difficult to recruit patients into more rigorous studies. Nevertheless, France also conducts a significant number of good quality trials (see Figure 3). It could position itself as the European leader in clinical trials if it were to allocate public funding more rigorously.

Recommendation 2. Earmark public funding for clinical trials with high standards of scientific evidence.

3. Clinical trials, financing and methodologies
(2020)



Reading: In 2020, out of a total of 19,287 clinical trials conducted in France, 8,469 were non-randomised (including publicly funded 5,910). For more details, see Alla A., J. Beuve and B. Savatier (2021): "The Lifecycle of Pharmaceutical Innovation: France is Lagging Behind", *Focus du CAE*, no 053-2021, January.

Source: ClinicalTrials.gov

Research policy and governance of the innovation process

The posture of the state: *push or pull*?

Innovation policies "pull" investments by increasing an innovator's expected revenues, or "push" investments by reducing an innovator's R&D costs. Examples of pull policies are patents, prizes, or advance market commitments. Conversely, push policies include government grants, tax credits, and subsidies. In both cases, the aim is to align an innovator's private benefits with the social value of the product. However, this social value is difficult to establish: unlike typical markets in which information is aggregated to assess it, market failures and the resulting regulation do not lead to a competitive industry in the case of pharmaceuticals. One of these market failures stems from information asymmetry: who holds the information advantage? Who bears the risk? In *pull* policies, investors bear most of the risk, since they only recoup their investments if the innovation is successful; they must therefore be able to identify promising research and be located in environments with well-developed capital markets. Conversely, governments bear most of the risk in *push* policies: they pay for grants and subsidies (or reduce their tax revenues in the case of tax credits) *ex ante,* even if the research does not lead to a commercialized innovation. This also requires the government to identify the most promising developments and technologies. Finally, in encouraging innovation, the international factor also plays

[21] In oncology, France participates in nearly one trial out of five initiated in the world. Oncology accounts for 45% of the industrial trials in which France participates (compared with 25% in Europe). Twelve French hospitals are among the top 100 oncology hospitals in the world, *cf.* LEEM (2018): *Attractivité de la France pour la recherche clinique*.

[22] Gautret P., J-C. Lagier, P. Parola, Van Thuan Hoang, L. Meddeb, M. Mailhe, B. Doudier, J. Courjon, V. Giordanengo, V. Esteves Vieira, H. Tissot Dupont, S. Honoré, P. Colson, E. Chabrière, B. La Scola, J-M. Rolain, P. Brouqui and D. Raoult (2020): "Hydroxychloroquine and Azithromycin as a Treatment of COVID-19: Results of an Open-Label Non-Randomized Clinical Trial", *International Journal of Antimicrobial Agents*, vol. 56, no 1, July.

a major role. A single country is often too small for its innovation policy to have an impact on overall incentives to innovate. Indeed, a small country has the possibility of free-riding on the innovation incentives created in other countries.

Patents: an essential part of the innovation ecosystem but not always ideal

Pharmaceutical products are characterised by very high fixed development costs –mainly the provision of clinical evidence of a product's safety and efficacy– but relatively low imitation costs, once the innovation is on the market. If imitators (i.e. generics) were able to enter the market immediately, the investor would not be able to recover development costs. The main mechanism for protecting innovation is the patent, which allows the developer to market his product without competition for a fixed period of time and provides the possible recovery of R&D costs. Patents also facilitate financing and licensing, which is essential in today's innovation ecosystem involving collaboration between different parties. They can be used to securitise loans, and are an asset that venture capitalists can leverage. Patents also allow companies to exchange and spread knowledge contained in a drug candidate by contracting with other parties. Thus, patents are an essential element of innovation policy. First, there are few alternatives: the use of trade secrets is limited by drug regulations requiring transparency. Second, the use of patents is also promoted by the trade agreements on intellectual property (the Trade-Related Aspects of Intellectual Property Rights: TRIPS agreement at the WTO: World Trade Organization) to which all members and candidates to the European Union (EU) are signatories. These agreements reduce the risk of free-riding on the incentives for innovation that a third country could create and have the effect of generalising the use of patents by most players. However, even with patent protection, many diseases –especially those disproportionately affecting developing countries or those with very small patient populations– are not profitable enough to attract private sector interest.

From the perspective of preserving so-called Schumpeterian innovation, patent policy requires finding a balance between a sufficiently long period of protection to encourage developers to invest in new products by amortising their development costs, and a sufficiently short period so that once the product is marketed, competitors (here generics) can enter the market, drive down prices, and thus encourage developers to turn to the research and development of a new product.

Currently, patents provide the innovator with a 20-year right to exclude others from production. However, these 20 years do not correspond to the commercial exploitation period of the product: they include the period of tests and clinical trials and, when successful, the administrative process of placing the product on the market. This period sometimes reduces the duration of marketing under patent from 5 to 10 years, distorting incentives for innovation: products with a longer development time have a shorter residual patent life. Researchers have highlighted, in the context of cancer research, an under-investment in long-term projects, since the period of profitability of exploitation under patent would be reduced.[23] In order to preserve incentives, the European Union allows a pharmaceutical patent to be extended for up to five years by a supplementary protection certificate, as well as a ten-year period of data and market exclusivity from the date of first marketing authorisation in an EU country. During this period, no generics may be marketed. The conditions of patent protection and data exclusivity are applied uniformly to all new chemical or biological entities, regardless of their therapeutic value.

Market exclusivity is part of a policy to encourage the development of orphan drugs. However, these extensions also have unintended consequences that distort innovation incentives. Although the number of treatments for orphan diseases has increased considerably, some treatments are "converted" drugs, originally developed to treat other conditions. In other cases, the developer uses a very narrow definition of the disease in order to qualify its product as an orphan treatment and to benefit from the extended protection reserved for this type of drug, but then extends its use to other non-orphan diseases. These windfall effects of the patent system can be counterproductive for innovation. Other possible negative effects include the reluctance to license patents to other researchers, or the fact that patent-holding trolls may overly attack any use of the patent in question (through legal or intimidation tactics). In a recent lawsuit, a patent troll (i.e. a company with no manufacturing activity, created to generate revenues through licensing and lawsuits) attacked a manufacturer of Covid-19 tests for infringing patents that had originally been granted to Theranos, a company that went bankrupt in 2018. Without going as far as trolling, companies can protect a single molecule with numerous patents covering manufacturing methods or new uses, a practice sometimes called evergreening, and thus earn more royalties. While these "secondary" patents create legal uncertainty and are the subject of much litigation, periods of regulatory exclusivity provide greater clarity.

Finally, an important flaw in this mechanism is that the patent system treats major breakthroughs and marginal innovations indiscriminately; all patented inventions benefit from the same term of protection, while some of them contribute far more than others to medical innovation. All these limitations (insufficient incentives for some diseases, deadweight losses...), lead to the conclusion that alternative mechanisms for encouraging innovation are preferable in certain circumstances. On the one hand, an alternative mechanism could better account for the degree of innovation of

[23] Budish E., B.N. Roin and H. Williams (2015): "Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials", *American Economic Review*, vol. 105, no 7.

medicines and, on the other hand, setting up *ex ante* actions to encourage investment in the treatment of pathologies with a high social value via calls for tenders with advance market commitments.

Recommendation 3. At the European level, allow the duration of market exclusivity to vary according to the degree of innovation of the medicine.

Recommendation 4. For certain priority diseases, launch prizes or innovation competitions for pharmaceutical innovations and make a credible commitment to finance the amount. These tenders should be coordinated between Member States (and even beyond) to be effective and attractive to companies as well as to avoid free-riding between countries.

Price: An element of regulation that needs rethinking

Typically, the price of a product is determined by the law of supply and demand. For medicines, several factors make it impossible to achieve this balance: in addition to the positive externalities that would distort this price for vaccines and some other treatments, the collective choice has been made for universal access to health care. Insurance coverage makes consumers less sensitive to price, since the State pays the bulk of the cost. Therefore, the producer of a patented drug has theoretically the possibility of charging high prices without reducing demand from patients who do not face the true cost, which puts a strain on the budget of public payers. In response, France –like most developed countries– regulates pharmaceutical prices. It should also be noted that although marketing authorisations (MAs) are increasingly issued at the European level, price setting is a strictly national competence, which even puts some countries in indirect conflict. Many states refer to other countries' prices when setting their domestic prices. This policy discourages or delays the launch of new products in countries where prices are lower, particularly in Southern and Eastern Europe.[24] These unforeseen effects have led to the use of secret discounts. Discounts granted by laboratories on the basis of the list price (or manufacturer's price) can be of different kinds: price-volume agreements, "first-box" discounts, clauses on the daily treatment cost, etc. The importance of the discount policy is twofold: first, discounts make it possible to contain reimbursement expenditure by lowering the real price of reimbursable medicines. Second, for the laboratories, these discounts, which are often secret, make it possible to maintain a high list price, which is crucial since drug price negotiations often use external referencing (i.e. reference to other nearby markets). But as a result, the lack of knowledge of real prices makes it difficult to assess their impact on many outcomes, including the location choices of firms.

In France, the *Comité économique des produits de santé* (CEPS: Economic Committee for Health Products) is responsible for setting the price of medicines arriving on the market, in negotiation with the manufacturer. Many procedures depend on the sector (retail pharmacy or hospital) and whether or not the drug is reimbursed. For sale through retail pharmacies, price negotiations for reimbursable medicines that have already obtained their MA take place after two successive decisions by the *Haute autorité de santé* (HAS: High Authority for Health). One of them assesses the *Service médical rendu* (SMR: medical service rendered), i.e. the improvement in life that the drug should be able to provide. The other, the *Amélioration du service médical rendu* (ASMR: improvement in the medical service rendered), is in principle decisive in setting the price because it takes into account drugs already on the market. Hence it only assesses the improvement compared to an existing comparable drug (typically the cheapest) in terms of mortality, morbidity, desirable effects and risks. The Social Security Code thus states that "the setting of this price takes into account mainly the improvement in the medical service provided by the medicine, the prices of medicines with the same therapeutic purpose, the expected or actual sales volumes and the foreseeable and actual conditions of use of the medicine".

However, in the current situation, the price difference between a non-innovative drug (ASMR IV-V) and an innovative drug (ASMR I-III) is due to the fact that in the first case the price is limited by the price of drugs already on the market, while in the second case it is influenced by the German, Spanish, Italian and British prices, through external referencing. Thus, the incentive to innovate provided by the French price depends on prices in neighbouring countries, rather than only on a medical, socio-economic or health technology assessment in France. These imperfections are compounded by major changes underpinning the pharmaceutical sector. First, newly available drugs treat orphan diseases in small markets. To be profitable, the prices of these treatments must be high. Second, some drugs offer a single cure, which limits the duration of treatment. As the producer does not expect any market in the future, she demands a high price today. On the other hand, some treatments, particularly for cancers, may be used over long periods of time and/or in combination with other treatments, making their lifetime cost difficult to assess. Finally, it is possible to discover new applications and/or new markets for certain existing drugs. For example, remdesivir was initially developed to treat the Ebola virus and was granted orphan drug status in the EU in 2016. More recently, it received conditional marketing authorisation for the treatment of Covid-19. The latter is clearly not a small

[24] Kyle M. (2007): "Price Controls and Entry Strategies", *The Review of Economics and Statistics*, vol. 89, no 1, pp. 88-99.

market, for which the price of orphan drugs can be justified. Moreover, the effectiveness of remdesivir against Covid-19 remains uncertain. The current system does not allow for new information and/or new contextual elements that may arise during the life of the drug to be taken into account. The health system, set up at a time of acute diseases (especially infectious diseases), must now adapt to the challenges of an ageing population living with chronic diseases that require long-term care. Overall, estimating the social or therapeutic value of a drug is difficult because clinical data is limited at the time of market introduction, but it can be improved over time with data collected in real life.

Recommendation 5. Improve the alignment of pricing rules in France with innovation incentives and allow them to evolve on the basis of real life data. Encourage experimentation with performance-based remuneration contracts and other new pricing methods.

Data sharing far from its exploitation potential

Data on patients and their treatments enables evaluation and comparison of various therapies in real time and in real practice. It makes it possible to better estimate treatment effects and adjust pricing. Rich data can also aid in the creation of rigorous control groups during the development of new molecules, which ultimately leads to better innovation. Health databases in France are very large and cover the entire population because of public health insurance.

Recently, France has understood the public health and innovation challenges associated with the use of these databases and has modified its policy in this area. Since Cédric Villani's Report "Research Funding" in 2019, which focused on the importance of investing in artificial intelligence, a new project has been launched in France: the Health Data Hub (HDH). The aim of this platform is to centralise all health data in France and make it available to researchers: health insurance data, hospitalisation data, causes of death, disability data, etc. The HDH will be the first of its kind in France. It offers to both centralise existing data with a powerful artificial intelligence system, and to bring new data such as from biological examination results into the field of exploitation. Launched in 2020, this technological platform is very promising. Following a selection process made of a call for projects and authorisation by the *Commission nationale de l'informatique et des libertés* (CNIL: National Commission for Digital Liberties), the first projects are starting now, and, during this peculiar time of the Covid-19 pandemic, the HDH was indeed the recipient of all the data and hosted all the dedicated research projects. To have access to these data, researchers in the public or private sectors must demonstrate the public interest of their project before an ethical and scientific committee, and then receive the approval of the CNIL.

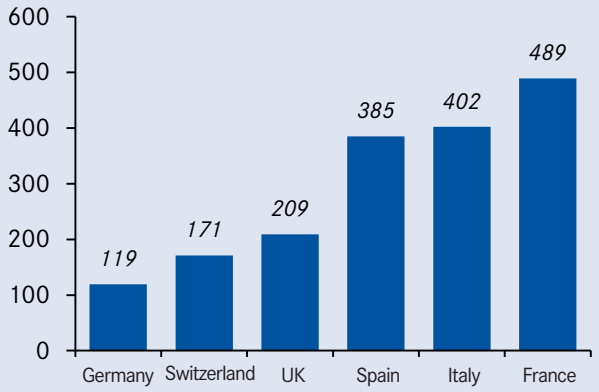
At the European level, there is also interest in the collection and processing of such databases, through the creation of a European Health Data Space as one of the European Commission's priorities for the period 2019-2025. The primary objective of this database would be to support health care provision, with a secondary objective to support health research and policy development. However, health databases are currently neither open, harmonised nor standardised at the European level. A European coordination of secure availability of patient data requires political negotiations which, if successful, will see implementation after several years. In this time frame, nothing prevents France from acting as a leader and enabling the secure use and protection of patients' digital privacy to enable rapid real-life assessments and provide reliable controls for medicines in development.

Recommendation 6. Support the European Health Data Space initiative for data sharing at European level to develop research and evaluation of new medicines by health agencies. Continue the work on opening up data within the Health Data Hub at national level.

Drug commercialization in France: A complex process

The drug circuit in France is made up of a multitude of institutions. When a company develops a medicinal product, it must wait to receive a marketing authorisation (MA) issued by the EMA or the *Agence nationale de sécurité du médicament et des produits de santé* (ANSM: National Agency for the Safety of Medicines). Following the MA, the HAS via the Transparency Commission must issue an opinion that will determine the medical service rendered (SMR and ASMR, measuring the medicine improvement for a patient) of the medicinal product, and the *Commission* évaluation économique *et de santé publique* (CEESP: Economic Evaluation and Public Health Commission) issues an opinion on the product's efficacy. On this basis, the *Union nationale des caisses d'assurance maladie* (UNCAM: National Union of Health Insurance Funds) defines a reimbursement rate and the *Comité* économique *des produits de santé* (CEPS: Economic Committee for Health Products) sets the price of the medicine. Finally, the French Minister of Health makes the reimbursement decision and a reimbursable medicine is placed on the market. Non-reimbursable medicines are placed on the market at a price chosen by its manufacturer after the MA. This multiplicity of institutional players in France makes procedures more complex and lengthens the timeframes, particularly those for launching reimbursable innovations (see Figure 4). This can ultimately have negative consequences on research and innovation.

4. Market access timeframes (in days, 2015-2017)



Reading: In the United Kingdom, it takes an average of 209 days between obtaining marketing authorisation for a drug and its launch on the market.

Source: *EFPIA's Patients WAIT Indicator, 2015-2017.*

It should nevertheless be noted that the authorities are aware of these inefficiencies and are trying to improve the process. Since the beginning of the health crisis, all procedures have been accelerated. ANSM is thus reducing its regulatory obstacles to innovation (which can delay the decision to invest or the manufacture of a drug) by opening fast-track processes (reduction of waiting times from 45 days on average to 20-25 days in the fast track procedure) and an innovation-orientation point of contact in order to simplify procedures and quickly put project leaders in touch with the right ANSM contacts. Likewise, the ANSM can issue TAU (temporary authorisation for use) and TRU (temporary recommendation for use), which allow a drug that does not yet have an MA to be prescribed while being closely monitored to assess its effects as quickly as possible. Similarly, the CEPS can sign conditional financing contracts for innovative medicines, allowing them to be placed on the market at a price higher than that defined by the ASMR level, provided that the laboratory provides proof of real-life efficacy greater than that defined by its ASMR level. For the time being, the first conditional finance contracts have not proved their worth: real-life revaluations have not led to justification of higher prices than those set by the ASMR.[25]

Recommendation 7. Establish a single point of contact for innovators, so as to improve the coherence of and articulate the requirements set by the various institutions involved in the development and launch of a new medicine.

Pharmaceutical innovation and competition

The relationship between innovation and competition is complex. Much work is devoted to the question of which degree of competition best promotes the development of innovations.[26] On the one hand, very intense competition may prevent firms from generating sufficient profits and re-investing in R&D; on the other hand, insufficient competitive intensity leads to concentrated market structures in which the incentives for innovation may be weak and firms may exploit market power. The theoretical relationship between competition and innovation is generally agreed to have an inverted "U" shape. The public authorities must then try to achieve the optimum, by playing on the duration of patent protection (see above) but also by guaranteeing respect for healthy competition.

Big pharma and anti-competitive practices

Looking at the pharmaceutical market as a whole, the market shares do not correspond to dominant positions and are far from the scrutiny thresholds by the competition authorities. However, as one drug is sometimes difficult to substitute for another, it is at the level of the therapeutic class that market concentration is relevant. At this level, large pharmaceutical groups may have significant market power and may be tempted to implement anti-competitive strategies that may have negative effects on innovation. Two of these practices have attracted considerable attention from competition authorities: "killer acquisitions" and so-called "pay-for-delay" strategies, which involve paying generic companies to refrain from entering the market and competing with the originator (i.e. the reference molecules discovered after a success in the R&D process).

Changes in the pharmaceutical sector have led to research being outsourced from large firms to a multitude of smaller start-ups, between which competition is strong. Large companies monitor scientific and technological advances and select innovative start-ups to partner with. However, recent work has highlighted the possible incentives for large companies to acquire a start-up with the aim of nipping in the bud an innovation that would threaten their position, hence the name "killer acquisition." In particular, the study by Cunningham *et al.* (2020) shows that the development rate decreases by 23.4% when acquisitions involve projects associated with similar product classes, that these results are mostly observed in market segments where competition is weak, and that 5-7% of all acquisitions of start-ups by large pharmaceutical firms

[25] Jacquet L.R., L. Toulemon, V. Raimond, A. Degrassat-Théas, L. Rochaix and P. Paubel (2018): « Le prix des médicaments en France : présentation synthétique des évolutions récentes du système français de fixation des prix », *Revue Française des Affaires Sociales*, no 3, pp. 47-67.

[26] Aghion P., N. Bloom, R. Blundell, R. Griffith and P. Howitt (2005) : "Competition and Innovation: An Inverted-U Relationship", *The Quarterly Journal of Economics*, vol. 120, no 2, May, pp. 701-728.

can be considered as killer acquisitions.[27] However, Letina *et al.* (2020) suggest that the prohibition of all potentially lethal acquisitions could have a chilling effect on innovation.[28] Two previous *CAE Notes*[29] recommend that the Competition Authority should be allowed to take *ex post* control of mergers that would appear questionable even if they did not require prior approvals, thereby treating such acquisitions as abuses of dominance. At the same time, it is necessary to guard against the danger of making it more difficult for large firms to buy out start-ups, since such acquisitions are often the very objective of the start-ups, which see themselves "reimbursed" for the R&D efforts made in the absence of turnover, without having to go through the development phase themselves. This also allows an innovation to be made available on a much larger scale, with *big pharma* having much greater financial and commercial clout.

Since the early 2000s, competition authorities have devoted considerable resources to challenging and monitoring patent and late payment settlements, including pay-for-delay practices, which account for 31% of the total number of cases handled by the European Commission between 2009 and 2017.[30] As a result of these efforts, all such settlements are reported to DG Competition and today more than 90% of these settlements do not require further examination by competition authorities. A major obstacle to generic competition has thus been reduced.

The importance of generics

Unlike an originator company, a generic producer does not need to engage in the discovery of new medicines. Rather, it focuses on imitating an existing drug and producing it at the lowest possible cost. The cost of market entry for a generic imitation of an already approved drug is low compared to the cost of developing a new molecule: the risk is much lower, since the safety and efficacy of the original molecule has already been established. Generic market entry is one of the mechanisms by which competition comes into play and the price declines. For molecules with many generic competitors, competition can be expected reduce price to marginal cost, and it is not uncommon for generic prices to be 25% lower than the brand name version (and even greater price reductions in the US market). While generics are essential to control expenditure and expand access to care, they have ambiguous effects on the incentive to innovate. On the one hand, long-term protection from generic entry is favourable to innovation because it offers the prospect of higher profits. And the higher these potential profits, the stronger the incentive for companies to invest large sums (of research and development) in uncertain processes. On the other hand, insufficient recourse to generics would only exert a weak competitive pressure on companies and would not encourage them to maintain their innovation efforts. In line with such an argument, it may be thought that France's low adoption of generics (generics only represent in volume terms 30% of the market in France, whereas they represent 81% of the German market and 85% of the British market)[31] could also be an explanatory factor for less innovation. However, further academic research is needed to better understand and explain the links between competition, health spending efficiency and innovation. For example, recent studies find that an increase in the period of market exclusivity for the first entrant into a therapeutic class is associated with an increase in the entry of other innovative products into the same class[32] and that a reduction in expected exclusivity decreases the likelihood of bringing a potential innovative treatment to market.[33] In any case, the absence of generic competition implies expenditure on older medicines that could be more usefully directed towards newer and better treatments. The savings made could also be channelled into public funds supporting basic and applied research.

Recommendation 8. Assess the effectiveness of the latest measures to promote generic substitution (LFSS 2019) in order to bring competition to bear and free up the budget for spending on innovative medicines.

At European level, the pharmaceutical sector is characterised by a high rate of innovation as well as practices scrutinized by competition authorities. This illustrates the importance of having competition authorities with sufficient technical and human resources and the need to reflect on possible developments in competition law, which has already been dealt with in previous *CAE Notes*.[34]

[27] Cunningham C., F. Ederer and M. Song (2020): "Killer Acquisitions", *Journal of Political Economy*, forthcoming.

[28] Letina I., A. Schmutzler and R. Sejbel (2020): "Killer Acquisitions and Beyond: Policy Effects on Innovation Strategies", *University of Zurich Working Paper*, no 358.

[29] Jean S., A. Perrot and T. Philippon (2019): "Competition and Trade: Which Policies for Europe?", *Note du CAE*, no 51, May and Bourreau M. and A. Perrot (2020): "Digital Platforms: Regulate Before it's Too Late", *Note du CAE*, no 60, October.

[30] European Commission (2019): *Report on Competition Enforcement in the Pharmaceutical Sector (2009-2017)*, available at https://ec.europa.eu/competition/sectors/pharmaceuticals/report2019/index.html.

[31] OECD (2019): *Health at a Glance 2019*.

[32] Gilchrist D.S. (2016): "Patents as a Spur to Subsequent Innovation? Evidence from Pharmaceuticals", *American Economic Journal: Applied Economics*, vol. 8, no 4, pp. 189-221.

[33] Gaessler F. and S. Wagner (2019): *Patents, Data Exclusivity, and the Development of New Drugs*, Mimeo.

[34] Jean, Perrot and Philippon (2019), *op. cit*. and Bourreau and Perrot (2020), *op. cit*.

All in all, France suffers from a series of malfunctions in the pharmaceutical field, which have caused it to lose places in the international race for innovation. Recent initiatives such as the Research Act and the 4th part of the Future Investment Program (PIA) respond to the need to invest more in research. However, more has to be done: reducing the complexity of the administrative maze, bringing the world of basic and applied research closer together, and making better use of data for a treatment economic assessment would define a base of measures conducive to innovation in this important sector.

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Focus

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The Lifecycle of Pharmaceutical Innovation: France is Lagging Behind

Ariane Alla, Jean Beuve and Baptiste Savatier(*)

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.

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