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Relocation of the Pharmaceutical Industry in Europe and in the Member States.

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Abstract.

This report produced between 2020 and 2022 by OTMeds exposes the shortcomings of the current pharmaceutical system and its consequences in terms of the sustainability of health systems and access to care for people. It studies the possibilities and methods of relocating pharmaceutical production in the European Union and its Member States. The observation is made of the influence of consulting firms and lobbies on public policies, pushing for public policies that run counter to public interests. The main conclusions of the report are the absolute need to establish transparency in the medicine chain to guide industrial policy, condition public aid granted to pharmaceutical companies, and aim for price negotiations based on much more rational criteria. The report also notes that a relocation that would take place only under current market conditions, based on the principle of supply and demand, would be doomed to failure, which is why the report studies also other public production models, for essential medicines in particular, which have been the subject of stock shortages or supply tensions for the past ten years. Finally, the report highlights the importance of active pharmaceutical ingredients (API) production. Relocating part of the production without tackling the issue of API is missing the main issues. This bulk production policy must also incorporate the ethical and environmental dimension linked to the pollution inherent in this type of production. All these complex questions are addressed in this report, which is based on research work and the hearing of some fifteen experts in various fields and a review of the literature.

About of this report.

TITLE OF THE STUDY Study on the relocation of pharmaceutical production in Europe and in its Member States

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METHODOLOGY This report was conducted in several steps: research and hearing phases, in particular with a review of the literature, then additional research and analysis. The research and analysis management work was led by Pauline Londeix, and the writing and development of the final report was done under the coordination of Jérôme Martin and Pauline Londeix. OTMeds interviewed 12 people between October 2020 and June 2021 (list in appendix 4). These hearings were coordinated by Khaoula Hajarabi. A literature review was conducted by Morgane Ahmar. OTMeds would like to thank the GUEN/GL group in the European Parliament for its confidence in the production of this report, for which it funded the research, leaving full latitude to the authors concerning research and recommendations.

DISCLAIMER AND ACCESS TO INFORMATION The authors have done their best to obtain the best and most recent information and figures, but have not always been able to access all the information necessary for their research. It should be noted that the pharmaceutical sector is characterized by an opacity in the information available, as well as by a severe lack of aggregated data at the European level. Thus transparency on key information in the sector, as well as harmonization of figures, data and indicators in all the countries of the European Union could allow a better understanding of the issues and priorities to be put in place by the EU on these issues. The lack of available data raises questions about the capacity of Members of the European Parliament (MEPs) and also of the European Commission to take the appropriate decisions and to better guide public policies. This is why one of the major recommendations of this report is that the EU, through its parliamentary work and through the European Commission, implements as soon as possible the WHO 2019 resolution on transparency in pharmaceutical markets.

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Acronyms & abbreviations.

AFM-Téléthon	French Myopathies Association
AIFA	Agenzia Italiana del Farmaco
ALFOB	Association of Official Pharmaceutical Laboratories of Brazil
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé (National Agency for Medicines and Health Products Safety)
AP-HP	Assistance Publique des hôpitaux de Paris (Public Hospital System, Paris)
API	Active Pharmaceutical Ingredient
ATU	Autorisation Temporaire d'Utilisation (Temporary Authorisation for Use)
CCNE	Comité Consultatif National d'Éthique (National Consultative Ethics Committee)
CEPI	Coalition for Epidemic Preparedness Innovations
CHU	Centre Hospitalier Universitaire (University Hospital Centre)
COVAX	COVID-19 Vaccines Global Access
DNDI	Drugs for Neglected Disease Initiative
EAHP	European Association of Hospital Pharmacists
EU	European Union
FAS	France Asso Santé
FDA	Food and Drug Administration
FPLC	Fast Protein Liquid Chromatography (appareil à chromatographie)
FTA	Free Trade Agreement
GAVI	Global Alliance for Vaccines and Immunization
GUEN/GL	Gauche Unitaire Européenne/Gauche Verte Nordique (European United Left/Nordic Green Left)
HIV	Human Immunodeficiency Virus

HIC	High Income Countries
I-MAK	Initiative for Medicines Access Knowledge
LDCs	Least Developed Countries
LEEM	Les Entreprises du Médicaments (Drug Companies)
LFO	Laboratoire Officiel Brésilien (Brazilian Official Laboratory)
LMICs	Low and Middle Income Countries
MA	Marketing Authorisation
MEPs	Members of the European Parliament
Messenger RNA	Messenger RiboNucleic Acid
NHS	National Health Services
NICE	National Institute for health and Care Excellence
NPH (insulin)	Neutral Protamine Hagedorn
NGO	Non-Governmental Organisations
OTMeds	Observatory for Transparency in Drug Policies
PITCE	Politique industrielle, technologique et du commerce extérieur (Industrial, technological and foreign trade policy)
PNM	Politique Nationale du Médicament (National Drug Policy)
R&D	Research and Development
RHI	Recombinant Human Insulin
SOMO	Centre for research on multinational corporations
SUS	Sistema Único de Saúde
TAG	Treatment Action Group
TRIPS	Trade-Related aspects of Intellectual Property rights
UFC	Union Française des Consommateurs (French Consumers Union)
WTO	World Trade Organization
WHO	World Health Organization

10 emergency measures to be put in place.

The health challenges that the planet is facing — including the fight against COVID-19, the possible pandemics that are likely to emerge in the future, particularly due to climate and environmental change, the explosion of non-communicable diseases — require us to conduct drastic changes. Health must be at the center of public policies, and no longer be used for individual profit purposes, in a laissez-faire attitude on the part of the States. While we have had the demonstration that many economic activities of a country could be blocked by the emergence of a virus, access to health for populations must guide policies. Health is decisive: there are ethical imperatives, but also economic ones.

The general interest and the guarantee of a universal and effective right to health, for all, must now take precedence over the property rights of the few. While private investments in the development of health products, including medicines and vaccines, are to be recognised, their precise share must be assessed transparently and using rational criteria. Similarly, the risks and investments taken by States must be assessed, and these must be reflected in the prices set and paid by public health insurances.

This is why the establishment of transparency in the pharmaceutical chain represents a critical first step that the various Member States of the European Union and the European institutions must achieve in order to guide public policies in health and policies in industry related to the production of medicines in Europe. Transparency will allow a better understanding of the issues for political decision-makers in each country, a rebalancing in the negotiations between public regulators and the private sector, as well as a better analysis of the measures to be adopted. This transparency must also be put in place at the level of the European Commission and in all the European institutions. The information obtained must be made available to MEPs and to every citizen.

Similarly, intellectual property barriers must be removed when they represent an obstacle to access to health products, or when they constitute a danger to the financial balance of public health systems. Since patent law is a territorial law, these actions must be carried out at the European Patent Office (EPO) as well as in national patent offices. The position of the European Union in multilateral bodies (at the WTO, WHO, WIPO, etc.), through the European Commission, but also in bilateral trade agreements, must reflect this primacy of health over intellectual property.

These rational elements, stemming from the implementation of transparency at the European level and in the Member States as well as better management of intellectual property, will enable Member States to define the best industrial public production

policy for European countries, which will be guided by concrete and rational elements rather than dogmatic ones.

Finally, these public policies must be based on imperatives of health democracy. It is no longer possible for these issues to be addressed only between actors opposed to transparency who only consider the pharmaceutical sector through the prism of the private sector. This is why the question of the representativeness and training of the people involved in these policies must be raised, and it must be answered by structural reforms.

In parallel with the implementation of all these elements, the European Union and its Member States must set up an ambitious European public medicine policy, which defines public production of medicines and health products within it. This policy must begin with a mapping of production in Europe and the development of public production sites, already allowing better responsiveness in the event of a health crisis or tensions in the supply chains. Then, and given the major challenges we are facing, this production must aim to guarantee a strategic European stock for essential medicines and vaccines, but also to enable responsiveness in the event of failure in price negotiations or difficulties in producing in sufficient quantities experienced by the original producer of a therapeutic innovation.

European policy on pharmaceutical production must aim to guarantee the right to health of populations, the interests of States and protect public health systems. This policy must therefore be pragmatic and based on rational and transparent criteria.

01 Establish transparency to assess and guide industrial policy

Having accurate information is essential to rationally guide public health policies. Thus, transparency must be put in place and concern the eight themes listed in the “transparency checklist” (OTMeds, 2019. See appendix 3 of the report). They relate in particular to public and private investments in research and development, basic research, clinical research, production of finished products and raw materials, information on prices, intellectual property, business-related information regulations and conflicts of interest. The importance of this transparency was affirmed by the Member States of the WHO in a resolution adopted in May 2019. Its necessity has also been reaffirmed by numerous academic actors, elected officials, researchers and NGOs since then.

WHAT MUST BE IMPLEMENTED BY MEMBER STATES:

The Member States of the European Union must set up transparency on the various pre-listed aspects. This implementation, depending on national legislation, must be carried out directly by governments, by decree, and by legislative means, by amendments or bills. This implementation must also be requested from national research institutes, public hospitals, and the information produced must be systematically communicated to the public regulator and accessible to citizens.

WHAT NEEDS TO BE DONE AT THE EUROPEAN LEVEL:

The European Union must ask the Member States to implement this transparency, based in particular on the WHO resolution adopted in 2019. The European Union must also implement this transparency in all European agencies, and must release the details of contracts and orders for medicines or doses of vaccines (in the example of COVID-19's response), and its funding (in different forms) for research and development.

02 Mapping national and European production of pharmaceutical products in Europe and EU Member States

It is impossible to define a European pharmaceutical policy without having precise information on pharmaceutical production in Europe. Yet that is what is happening. Thus, the first step to assess the priorities and needs in terms of production is to map the private and public production sites in the Member States of the European Union. This mapping must identify the products manufactured by each site and the manufacturing phase concerned.

WHAT MUST BE IMPLEMENTED BY MEMBER STATES:

The Member States of the European Union must present to the European Parliament a mapping of the public and private production sites available in their country, specifying what is produced there.

WHAT NEEDS TO BE DONE AT THE EUROPEAN LEVEL:

The European Union must produce a mapping of the production of finished pharmaceutical products in Europe, of intermediate phases and of the production of active pharmaceutical ingredients (API) products, to best inform the strategic choices made.

03 Mapping the investments made by States, by the European Union and by the private pharmaceutical sector to assess the balance in terms of investments made for each marketed health product

Although the Member States of the EU often leave the hand to the pharmaceutical sector in medicines policies, it is essential to be able to assess the extent to which this sector is (and in what proportions it is) supported financially by the States and by the European Union. In other words, the various aids received by multinationals, in fundamental research, clinical trials, medicine reimbursements, tax evasion must be compared in order to assess the final balance. Is it in favor of the States? Do states contribute much less than firms? Or on the contrary, do the States contribute more?

WHAT NEEDS TO BE DONE AT EUROPEAN LEVEL AND IN THE MEMBER STATES:

Mapping the investments made

04 Evaluate the contribution and tax avoidance of pharmaceutical companies to better stem it

Recent reports on the subject of tax avoidance by pharmaceutical companies in the United States in particular show that it amounts to billions of dollars annually for each of the main multinationals in the sector. Thus, assessing this tax avoidance in Europe is essential.

WHAT NEEDS TO BE DONE AT EUROPEAN LEVEL:

An assessment of this tax avoidance must be carried out at European level and presented to MEPs. This is an essential step in developing an effective plan to respond to this phenomenon.

05 Define a production policy and improve inventory management

By obtaining the essential information listed above, an industrial policy serving the health of populations must be defined and implemented. This industrial policy must allow the production of national and European strategic stocks of essential medicines, to cover needs, prevent tensions, shortages and stock-outs. This policy must be carried out taking into account pandemic preparedness, but also the various definitions and existing lists of essential medicines, their interest and their limits (see the OTMeds report, part 2 section D “Which products of health are we talking about?”).

In the event of tensions over essential medicines, linked for example to a sudden explosion in demand, this policy should allow for greater responsiveness in reallocating production lines to the needs of populations. The Social Security financing bill for 2022 tabled in France by the government in September 2021 recognizes that public

production was necessary in April 2020 to compensate for curare ruptures in hospital structures.

This production should also enable EU Member States to regain power in medicines price negotiations. Thus, when a firm asks for a reimbursement price for a new medicine at a very high price, completely decorrelated from the investments made, assessed by the information resulting from the implementation of transparency, this health product will be publicly produce. This will thus allow rapid access to populations without threatening the financial sustainability of health systems. If intellectual property barriers legally prevent this, these will be lifted. Production must be designed and coordinated at European level.

WHAT NEEDS TO BE DONE AT EUROPEAN LEVEL AND IN THE MEMBER STATES:

The Member States of the European Union must set up a coordinated public production of medicines and health products, relying on existing production sites in different countries. This policy must be based on a rational assessment of needs and informed health planning. The European Union must remove the legal barriers, for example on competition law, business secrecy, which would hinder the establishment of public production.

At European level and in the Member States, regulatory issues must be adapted to allow better responsiveness in the event of a reassignment of a production line to a specific medicines to alleviate supply tensions. Stock status assessments and needs in the different countries must be better managed, based on real-time information, and the logistical aspects must also be carefully studied so these stocks «rotate» regularly, and thus prevent many medicines from expiring.

The national authorities responsible for negotiating the price of a medicinal product with an originator producer must be able, in the event of a dead-end in negotiations with the patent holder or exclusive producer, to use European public production sites to produce the product in question and thus guarantee rapid access to populations. If the medicine is under patent, compulsory license or compulsory license for governmental use must be issued and the exclusivity clauses for clinical data lifted to allow rapid marketing.

In general, the better implementation of these tools will enable the Member States of the European Union to regain power in price negotiations with manufacturers.

06 Define an ethical and ecological industrial policy

The information collected as an outcome of the implementation of transparency and the mapping of the production sites will make it possible to better understand the strategic question of the production of the raw material. The production of API is a very polluting industry, that is why it does not appear ethical for the ecological risk to be absorbed mainly by two countries in the world (China and India). Thus, a reflection must begin on the environmental consequences of the production of the API in Europe, taking into account the most ethical considerations possible in regard to ecological constraints as well as to the safety of employees and local residents. These short and long term environmental impacts should systematically be taken into account and must be balanced with the real therapeutic added value of health products for the people who need them as well.

A reflection on pharmaceutical production must also question the ethical issues of research and clinical trials. These are necessary to develop effective and safe products, but clinical trials can sometimes represent a risk for the people involved. Thus,

some trials carried out are not necessary. This is the case when a generic producer is compelled, because of the exclusivity data provision (see report, section 4D), to conduct new clinical trials, on a product that has already been validated by clinical trials, assessed and authorized, and when bioequivalence tests have already been carried out.

The model of competition in research prevents any coordination between companies. This is the reason why the research and development objectives must be thought out in a coordinated manner between the various developers. Otherwise, the risk is to develop similar products in parallel and abandon trials for profit reasons, as illustrated by Sanofi's announcement on September 28, 2021 to stop the development of its mRNA vaccine against COVID-19. Clinical trials are costly in financial terms but also in terms of mobilizing volunteers. Volunteers must be mobilized for the most relevant trials in terms of public health.

WHAT NEEDS TO BE DONE AT EUROPEAN LEVEL:

The possibility of opening new API production sites in Europe taking environmental issues into account as much as possible must be studied. An industrial policy in bulk production that respects the environment must be put in place.

A mapping of health product needs must be carried out: what are the medicines, treatments and vaccines that do not yet exist to respond to populations needs, and compare this inventory with current public and private investments in research and development. This will help identify underfunded research fields.

The clause on the exclusivity of clinical data must be removed from European law, so that a generic producer is not compelled to carry out new clinical trials to obtain a marketing authorization, when bioequivalence tests have already been successfully conducted. The EU must oblige the companies it funds to coordinate research on a product, to communication on the design of the tests, the protocols, the intermediate results so that this communication, for example of successes and errors, allows everyone to improve its own study and the safety of the people included when bioequivalence tests have already been carried out.

07 Reform patentability criteria in the European Patent Convention and implement TRIPS flexibilities in Member States

In order to address the practice of evergreening (claim of new patents on slight improvement of old medicines) and optimize the public production of the medicines and health products that we need, intellectual property barriers must be able to be lifted like the law of the World Trade Organization (WTO) allows it.

WHAT MUST BE IMPLEMENTED BY MEMBER STATES:

Member States must also amend their national law to include these flexibilities and in particular simplify the use of compulsory licenses and compulsory licenses for Governmental use. These reforms must be accompanied by the abolition of the clause of clinical data exclusivity and market exclusivity in the Member States.

WHAT NEEDS TO BE DONE AT EUROPEAN LEVEL:

The European Patent Convention must be reformed in depth, to take greater account of the flexibilities allowed under the TRIPS agreement, and only grant patents for significant therapeutic innovations (on the model of Indian, Brazilian and Argentinean laws). This reform will enable to prevent artificial maintenance of monopolies on therapeutic specialties that do not justify the granting of a twenty-year monopoly. In the event of failure of the negotiations at the level of the EPO (European Patent Office), the States which are members of it, and which differ from the Member States of the EU, must leave the EPO to regain autonomy in matters of the management of intellectual property rights, as allowed by TRIPS law.

08

Defend an ethical position in international bodies and strengthen the role of the World Health Organization (WHO)

The COVID-19 and access to vaccines crisis have shown the real position of representatives of the European Commission and some of its Member States in international bodies on intellectual property issues. During the first wave of COVID-19 that affected Western Europe, the strong need for essential medicines necessarily resulted in depriving some LMICs of some of these medicines; it is the logic of supply and demand, European countries having a greater capacity to pay than LMICs.

In multilateral agencies as well as during the negotiations of free trade agreements, the European Union has been for decades defending the interests of its industry against the effective exercise of the right to health in low and middle-income countries, hindering local production these countries. At the date of publication of this report, for example, the EC will have been opposing the demand for waiving intellectual barriers on all COVID-19 technologies filed by India and South Africa in October 2020, preventing production sites in LMICs to help increase global production and meet pandemic-related needs. Thus a minority of rich countries can block response policies to a health emergency in a majority of LMICs.

European countries must, in the name of the right to health, and in the name of global health security, allow real access to essential health products in developing countries. And they must export medicines when necessary.

WHAT NEEDS TO BE DONE AT EUROPEAN LEVEL:

The European Union must make its public production sites available to the WHO in the event of massive needs and in the event of insufficient production of these medicines by other manufacturers. The EU must support local production in LMICs, by defending in all multilateral and bilateral arenas the right to health against intellectual property. It must stop negotiating free trade or multilateral agreements that strengthen intellectual property barriers and hinder local production in LMICs.

09

Conduct an ethical training policy for political and administrative leaders, fight against conflicts of interest

Recent decisions taken on the issue of medicines in Europe and in the Member States of the European Union show a significant lack of knowledge on the functioning of the pharmaceutical sector, which forces public administrations to call on consulting firms responding to the interests of pharmaceutical companies to define public policies. In the same way, the lack of skills in the management of medicines stocks results in health authorities to rely mainly on firms and to be only in the reaction. This is why “training” is a crucial aspect to reform, as well as the limiting the impact of lobbying and consulting firms in public administrations.

WHAT NEEDS TO BE DONE AT EUROPEAN LEVEL AND IN THE MEMBER STATES:

The training of political and administrative leaders must be reviewed to take into account different skills, to put the issues of public health, ethics, general interest and health democracy at the heart of the course.

Within the EU and its Member States, conflicts of interest with pharmaceutical companies must be totally prohibited for anyone in charge of the development or application of pharmaceutical policy, and more generally health. In particular, the practice of revolving doors between public and private positions must be prohibited.

The use of private audit firms should be strictly prohibited. The contracts signed with these firms over the last twenty years must be made public. The EU must defend the ban on the use of these firms by multilateral agencies, in particular the WHO.

10 Promoting and implementing health democracy

In the Member States and within the European institutions themselves, skills and points of view are too often disregarded or ignored in the development and implementation of pharmaceutical policies: patients, health or consumer associations independent of major private companies, public researchers, doctors, trade unions, etc. This restriction of points of view prevents the implementation of appropriate and effective pharmaceutical policies, as shown by the public response in Europe to the COVID-19 crisis.

WHAT NEEDS TO BE DONE AT EUROPEAN LEVEL AND IN THE MEMBER STATES:

The EU and the Member States must include in the definition and application of its pharmaceutical policy the skills and expertise of all health actors independent of industrials.

Introduction.

The issue of health and more specifically pharmaceutical production is a major issue for populations. In Europe, the Member States of the European Union have had the opportunity, over the last ten years in particular, to see to what extent the pharmaceutical sector is strategic and can put populations and health systems in the face of complex problems.

The consequences of the COVID-19 pandemic have made these problems even more pressing. The last 2 years have been marked by shortages of essential health products for prevention, vaccination, screening, care in intensive, geriatrics and palliative cares units which have illustrated all the consequences of the outsourcing and relocation of numerous pharmaceutical production activities outside European countries. But offshoring is not the only cause of these problems. Rather, it is the salient point of a deeply flawed system that endangers the principle of universal access to health care, and which is based on logics of supply and demand.

For example, the opacity that surrounds the contracts signed by the European Commission and the firms to “pre-reserve” doses of vaccines¹, the few obligations that seem to fall to the firms in the event of failure to deliver or even the disputes with AstraZeneca² bear witness to the difficulties that have slowed down vaccination campaigns in Europe, and made them impossible in certain LMICs, and demonstrated the dependence of public authorities on private companies. However, these difficulties do not stem from the consequences of relocation, but more generally from the problematic inclusion of the pharmaceutical sector in commercial logics that is to say of supply and demand and of profits.

Therefore, the question to be debated does not seem to be: “Should pharmaceutical production be relocated?”. The reflection must rather focus on the modalities of this relocation. Should it be done by maintaining the current system which entrusts almost the entire medicine chain to private firms and largely dispossess the public authorities of their capacity for action to ensure access to pharmaceutical products?

1. Catherine Chatignoux, « La Commission européenne fait son mea culpa et promet de muscler la production de vaccins », *Les Échos*, 10 février 2021

2. « Covid-19 : l'Union européenne obtient en justice moins de doses de vaccin que réclamé à AstraZeneca », *Le Monde*, 18 juin 2021

To answer this question, the approach should be based on transparent and rational criteria whose objective is to guarantee the right to health. Health is defined by the 1946 preamble to the Constitution of the World Health Organization as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”. The right to health is understood in this same text as “the enjoyment of the best possible state of health”. The Universal Declaration of Human Rights of the United Nations of 1948 defends in its article 25 the right to health, as does article 12 of the International Covenant on Economic, Social and Cultural Rights. The latter specifies that the signatory States must take specific measures in order “to achieve the full exercise of this right”, in particular for :



- Improving all aspects of environmental and industrial hygiene;
- Prevention, treatment and control of epidemics, endemic diseases, occupational diseases and others;
- The creation of conditions that would ensure universal health care and medical care in case of illness.

The European Union upholds this right to health and its effective exercise in Article 11 of the European Social Charter, which obliges Member States to adopt measures to promote health and provide care in the event of illness. Various Member States of the European Union reaffirm in their constitutions the fundamental right to health for all.

And in order to implement this inalienable and fundamental right, recalled in all these international and national texts, pharmaceutical production is essential. Therefore, it seems logical that the production system should be evaluated according to its capacity to guarantee an effective exercise of the right to health, and not according to the criteria of industrial performance or competitiveness alone. This right comes into conflict in particular with property rights, and the latter is often privileged. This raises the question of the hierarchy of principles and should lead to a reflection on what should take precedence.

Respect for the fundamental principle of the right to health would imply that it is not the right to health that must adapt to industrial and market logic, but that the industrial system must serve the right to health. However, at Governmental levels, it seems acquired that pharmaceutical production is much more an industrial policy than a health policy.

Moreover, integrating the principle of *health democracy* into questions of pharmaceutical production in Europe or in its Member States seems also essential. The right to health being universal and inalienable, and pharmaceutical production being a key element of its exercise, it is everyone’s business. No industrial nor commercial secrecy can be imposed on it, since “trade secrecy” does not come under a fundamental right defended by international texts.

Finally, *pragmatism* dictates the last set of criteria that guided the development of this report. Because behind the will of many governments to leave the hand to the private sector in pharmaceutical production, we often hear the argument of “pragmatism”. Medicines manufacturers alone would know how to react and produce medicines in and outside of emergency situations. Patents alone would guarantee innovation and research. And reassigning production lines in case of urgent need would be impossible because it would take too much time. Or, the countries of Africa, Asia or Latin America would not have the infrastructure and the know-how to produce quality pharmaceutical products and recent technologies such as messenger RNA vaccines. These assertions are of the order of misinformation about the organization of the global pharmaceutical production system. Indeed, far from being pragmatic, these arguments are of

the order of dogmatism and the facts belie them³. The COVID-19 crisis has shown the inability of the current system to ensure a rapid and effective response to shortages of reactive kits for tests, medicines and vaccines. It also revealed the extent to which innovation depended on public funding, which massively enabled the rapid development of vaccines⁴, calling into question the legitimacy of patents supposed to reward the risk and investment inherent in research. As for adapting production lines to meet needs and emergencies, this is what pharmaceutical multinationals do constantly, not according to the needs of populations but according to market opportunities. From the start of the COVID-19 pandemic, European countries adopted emergency laws allowing them to requisition production sites to meet national needs; some have used them like Germany and Spain, others have not, like France. These are political choices, not technical capacities.

It is therefore essential to base the analysis of European pharmaceutical production on real pragmatism and to approach it holistically with a long-term vision, because the COVID-19 pandemic is not yet over at the time of the publication of this report, and the international community will have to equip itself with solid epidemic preparedness systems in the years to come, which will not be able to do without this reflection. The international community, the European Union, the Member States of the European Union will definitely have to answer various questions such as: does the system make it possible to anticipate needs and react quickly in the event of a health emergency? Are public funds used in a relevant way with regard to the objective of defending the right to health? On such a subject, many political decision-makers oppose experimenting with public production because it would be too costly and the sector would offer greater production flexibility. However, public money massively irrigates the medicines chain as it currently exists, in the greatest opacity: public aid for research and development, reappropriation of research from public institutions by the private sector, tax credits, production aid, employment aid, aid “for young innovative companies” when the development of a medicine is conducted by a start-up, reimbursement of the medicine by public health systems, reimbursement in the event of serious adverse effects by these same public systems, compensation by States for victims of health scandals, etc. Is it pragmatic to pay several times for the same product, in total opacity, without conditionalities, when public authorities, although a funder, is dispossessed of any initiative? If it means investing public money, isn't it better to fund a transparent system, governed collectively, responding to specific medium and long-term objectives and challenges defined by the requirements of the right to health and those general interest? Isn't that the real pragmatism?

In addition, recent reports in the United States in particular quantify the tax avoidance of multinational pharmaceutical companies. This amounts to several tens of billions of dollars per year for each of the firms dominating the market. These questions have guided the preparation of this report, which first presents the difficulties posed by current European pharmaceutical production and their causes, in order to take stock of the situation of this industry based on the information available, before examining the stakes of another production system and the essential elements of this one.

3. Pauline Londeix, Jérôme Martin, « Covid-19 : La levée des brevets sur les vaccins n'est pas une posture, c'est la seule voie possible » (Covid-19: The lifting of patents on vaccines is not a position, it is the only possible way), *Le Monde*, 21 May 2021

4. A team from Universities Allied for Essential Medicines (UAEM) aggregated their [data to trace sources of funding for COVID-19 vaccine research](#).

A team from the Graduate Institute in Geneva did a [similar work](#)

A study published in April 2021 in the journal *Vaccine* estimates at \$17.2 billion the public funds invested by the American NIH over twenty years, which served to develop technologies used by Moderna to perfect its vaccine: Anthony E. Kiszewski, Ekaterina Galkina Cleary, Matthew J. Jackson, Fred D. Ledley, “NIH funding for vaccine readiness before the COVID-19 pandemic”, *Vaccine*, Volume 39, Issue 17, 2021, pages 2458-2466.

Misconceptions and semantics

The battle for access to medicines, for the defense of public health systems and for pharmaceutical production aimed above all at the interests of the populations, is also played out around semantics. The words used in European directives, national texts, those used by political decision-makers very often reveal an appropriation of the discourse of the pharmaceutical industry, or a confusion that prevents thinking of a system at the service of public health. Pharmaceutical manufacturers defend private interests, which is nothing out of the ordinary in a society based on a neoliberal economic system. But we must remember that these interests do not represent public interests. This is why the semantics must be analyzed, and the words used by the representatives of the administrations and by the elected representatives must above all reflect the common interests, before the private interests. Here are some examples.

"Access market", "access to markets", vs "Access"

Access is an essential principle for the defense of the right to health. It stems from a strong ethical principle, that existing products that save lives should be made available to those who need them. The principle of access makes it possible to think of a coordinated policy to remove all the barriers that oppose it, whether they are those of price, intellectual property, lack of public health coverage, shortage of professionals / infrastructure, or even discrimination.

Through the concept of "Access market", which is increasingly widespread in institutional discussions, the pharmaceutical industry is trying to defuse the fundamental principle of the right to health. It is a semantic twist. It aims to substitute the recipients: it is no longer each citizen who is concerned by the material possibility of using medicines. It is the manufacturers who become the beneficiaries of access to economic markets for their products. In this substitution, populations are nothing more than tools of pressure on governments and States. This is a marketing strategy concept that aims to ensure that a medicine will be paid for at the price desired by the patent holder, in particular by emphasizing the need it will fill in the population. The Access Market strategy can thus recover a whole part of the activist fight for universal access to care (making emergency and care visible), but by cutting it off from any critical perspective on the functioning of the pharmaceutical industry (opacity, share of public financing, illegitimacy of prices and patents, etc.) in order to put pressure on the public authorities to accept prices that are nevertheless excessive.

"Counterfeit" vs "sub-standard" or "fake medicines"

In intellectual property law, counterfeiting is an infringement of exclusive property rights and in particular trademark law. A counterfeit is therefore in no way a pharmacological analysis of a health product, and therefore does not indicate anything about the quality of the product in question. However, for the past twenty years, pharmaceutical companies have been trying to impose this term in numerous treaties, and with leaders, including European Commission officials, researchers and journalists, as a synonym for "poor quality" medicine, a "sub-standard", a product with an under-dosed active ingredient, not having the effect it claims to have, or even being a fake medicine. Here the semantic confusion aims to create confusion between "original" medicines and quality generic medicines, using the question of quality to justify an industrial monopoly. If fake medicines and sub-standards are absolutely to be combated, in particular by guaranteeing access to quality products for all, and by removing barriers such as price barriers, the deliberate confusion between originator and generic medicines is dramatic. The challenge is then no longer to answer the question: does the medicine cure, but does it respect intellectual property rights?

Thus, the legal status of a generic medicine can vary from one country to another: authorized here, counterfeit elsewhere. However, the generic is a copy of the *originator medicine*, which, from a health point of view, has the same effect. The misuse of the term counterfeit therefore does not make it possible to fight fake medicines or sub-standards, but helps to denigrate generics. Equating generics with counterfeits therefore amounts to preventing wider access to quality care, and leaving the field open to crooks to assert their sub-standards.

"Price" vs "Cost"

The confusion between the "price" and the "cost" of a medicine prevents the legitimacy of the prices from being assessed. "Cost" generally refers to the amount needed to produce a good or service; the cost therefore represents the sum of the value of each input necessary for production, in particular raw materials, labour, capital and the company. The price, on the other hand, derives from a construction. By "price", we mean the amount of money that consumers/buyers must pay to acquire a good or service according to supply and demand, and according to a negotiation between different actors. The difference between price and cost is the profit margin. In the current system and in the majority of countries, particularly in the European Union, there is currently no correlation between cost and price. Dr. Andrew Hill's studies, presented later in this report, have shown this for a large number of health products.

In the context of medicines, the price is an exchange value fixed between the patent holder and the public authorities, in a negotiation where opacity on decisive information is the norm (information such as investments in Research and Development, the cost of production, the public aid received) and the monopoly situation give a certain advantage to the industrialist. The modalities for negotiating and fixing the prices of health products may vary from one country to another, systems based solely on the cost of production being very rare. International referencing (benchmarking) or taking into account the value in use of the medicine and its "cost-effective" nature most often form the basis of the methods for setting prices.

It is therefore essential to distinguish price and cost, to have clear ideas on the methods of setting the prices, and to have the missing information so that the public regulator can guarantee legitimate prices.

"Patent and innovation" vs. "collectivization of risks and privatization of profits"

Patents are justified by the risks and the investments that their holders would have made in the research and development of a medicine. According to this, questioning patents would slow down or even kill innovation.

However, on the one hand, the very definition of what an innovation is, and its institutional translation, are debated. On the other hand, the opacity that surrounds the economic aspects of R&D makes it impossible to assess the reality of the investments and risks taken by manufacturers. Conversely, many case studies show the preponderant share of public funding in R&D, and we will cite some in this report. Also, what is innovation? Patent offices tend to define this by the number of patents they grant. However, if the number of patents issued is constantly increasing, a precise analysis of the quality of these patents shows that they are sometimes issued for «inventions» with little therapeutic added value.

Therefore, it is essential to define collectively what an innovation is, and to be fully transparent on the economic aspects of R&D, in order to ensure that the sentence "Patents ensure innovation, which has not been questioned by European leaders, does

not in fact means: “The risk and the investment of research and production must be ensured by the public, the governance and the profits must revert to private industry.”

Context.

A. Pharmaceutical production and its challenges

A dynamic of exponential price increases

The negative impact of prices on access to health products in LMICs, or the positive impact of measures aimed at promoting the production and circulation of generics are well-documented realities¹.

But the question of price also affects High income countries, including European countries². In Greece, following the economic crisis of 2008, multinationals such as Roche and Sanofi threatened to withdraw from the national market, following non-payment by public hospitals for medicines orders. In Spain and France, in 2015, people infected with the hepatitis C virus (HCV) had to wait for the condition of their liver to deteriorate to be eligible for new treatments that could cure them. For one of the first time in France since the creation of the Health Insurance system (Assurance Maladie) after the Second World War, budgetary considerations linked to the price of a treatment had dictated the establishment of criteria for access to the medicine according to the progress of fibrosis in people's, contrary to medical recommendations. In Germany, in 2014, doctors were instructed to limit their prescriptions of this same medicine for price reasons³. In Belgium, at the end of 2019, a family appealed to the generosity of the population to help them finance the treatment of their baby suffering from a rare genetic disease, marketed by the firm Novartis for around 2 million euros (one injection). Following the scandal caused by this call for generosity, Novartis set up a draw to select a few children that could benefit from it⁴. In the United Kingdom, then still a member of the European Union, the NICE committee ("National Institute for Health and Care Excellence") contributed, in particular, to defining the list of treat-

1. German Velasquez. *Vaccins, médicaments et brevets* (Vaccines, medicines and patents), L'Harmattan, 2021.

2. Londeix P. et Vieira M. "VIH & Banque mondiale" (HIV and the World Bank), October 2018 cited in *Libération*: "Vacarme, sida et néolibéralisme" (Uproar, AIDS and neoliberalism, November 2018

3. Deutsche Aidshilfe. "Hepatitis C : keine Heilung für alle" (No cure for everyone), *HIV-Magazin*, July 2017.

4. "Novartis va offrir son médicament ultra-cher par tirage au sort à 100 bébés : 'C'est au-delà de la honte'" (Novartis to give away its ultra-expensive medicine by lottery to 100 babies: "It's beyond shame"). *La Libre Belgique*, 20 December 2019.

ments covered by the universal health system (National Health Services - NHS), ruled out the possibility of reimbursing certain medicines used against cancers and commercializing for several hundred thousand pounds (GBP £), not for therapeutic reasons, but because of a price that is too high. In the same UK, healthy people living with HIV on antiretroviral treatment (ART) that was working well were offered to switch treatment to “cheaper” triple therapies. health. In France, it had been calculated⁵ that at the price of the medicine against hepatitis C (sofosbuvir) negotiated by the French health authorities with the Gilead company, access to treatment for all people with hepatitis C would represent twice the total annual budget of the Assistance Publique des Hôpitaux de Paris (AP-HP): 14 billion euros. These examples aim to show to what extent the prices of health products in the European Union Member States weigh on health systems and are not sustainable in order to guarantee access to therapeutic innovations for populations.

Within the European Union, examples⁶ of medicines that are being “disreimbursed” are plenty. Therefore those are not available to the largest number of people because of their very high price, who weigh very heavily on the health systems. This dynamic of exponential increase in the price of treatments in the Member States of the European Union is taking place even as, in parallel, these States are multiplying the reforms of the health systems to “contain” public expenditure, by cutting certain essential expenditure (hospital systems, health human resources, prevention, etc.).

To curb this dynamic of rising prices and guide public policies, the establishment of transparency in pharmaceutical markets is absolutely essential. In May 2019, during the 72nd World Health Assembly, the Member States of the World Health Organization (WHO) committed to implement transparency in pharmaceutical markets through the resolution: “*Improve the transparency of the markets for medicines, vaccines and other health products*”⁷. Proof that the problem concerns many European countries, Italy had proposed the resolution, which had been co-sponsored by Greece, Malta, Portugal, Slovenia and Spain (among the European countries). It is difficult for States to negotiate prices with pharmaceutical companies without concrete elements allowing a rational approach in these prices. Transparency is therefore necessary throughout the chain of pharmaceutical products, for example on the origin of raw materials, essential information to ensure good responsiveness in the event of shortages, and to get out of dependence on a pharmaceutical industry whose private interests diverge from public interests.

Following the adoption of this resolution, the *Observatory of Transparency in Medicines Policies* (OTMeds) published in September 2019 a “transparency checklist” listing various information for which transparency seems essential to guide public health policies (see appendix 3).

Public investment in research and development (R&D)

If the pharmaceutical companies try to justify the prices by the investments in research and development (R&D), the investments of the public sector seem constantly concealed. However, in all the cases that researchers, NGOs or associations have been able to document, the significant share of investments and risks taken by the public seems to be underestimated. Neither the estimated production costs nor the investments in R&D therefore seem to justify this exponential dynamic of price increases. To

5. Médecins du Monde, Londeix P. avec Forette C. (march 2014), “New Treatments for HCV: Strategies for Achieving Universal Access”

6. Londeix P. and Vieira M. “VIH & Banque mondiale” (HIV and the World Bank), *Vacarme*, October 2018

7. Resolution WHA 70.12, “Improving the transparency of markets for medicines, vaccines, and other health products” (2019)

curb this dynamic, it thus seems essential to introduce rational criteria in the fixing of the price of medicines, making it possible to make the market healthier, where most of the bargaining power seems to be in the hands of the multinationals. Because multinationals refuse to communicate the figures of the amounts invested in R&D. Transparency on this aspect would also make it possible to inform public policies, particularly in these budgetary issues. This is the meaning of the resolution aimed at *“Improving the transparency of the markets for medicines, vaccines and other health products”* adopted at the World Health Assembly in May 2019. Its application is uneven in through the Member States of the European Union, but Italy has implemented part of it, through a decree published in June 2020 (see appendix 4), and in connection with investments in research and development. Indeed, for each new request for reimbursement of a pharmaceutical product, if the price deviates from that of a medicine already marketed and of the same therapeutic class, the pharmaceutical company must disclose the details of the expenses explaining such a difference.

The *Observatory of Transparency in Medicines Policies* (OTMeds) proposed in France, in October 2019 then in October 2020, a series of amendments to the social security finance bill to include elements on transparency of public contributions to research and development. One of them was adopted in December 2020 and awaits its implementation and application, after the decree was issued by the government. A report by the WHO Europe office⁸ shows that in this geographical area, the implementation of the resolution *“Improving the transparency of the markets for medicines, vaccines and other health products”* remains almost non-existent.

Shortages and other supply chain disruptions

Another major concern has been posed to European populations for ten years; sometimes pushing them to go to a neighboring country: stock-outs and medicine shortages. These stockouts and shortages are linked to structural problems of supply and demand, profitability objectives for manufacturers, just-in-time production in a globalized framework⁹; they are linked in particular to the disinterest of firms in producing certain medicines that are no longer under patent and from which they can derive a lower profit than for an originator one. These ruptures put people in danger, as highlighted by recent reports¹⁰ on this subject published in France by France Asso Santé (F.A.S) and by the U.F.C Que Choisir. Well-documented examples relate to cancer treatments, vaccines and antibiotics in particular. In 2018, a study by the European Association of Hospital Pharmacists (EAHP) attempted to assess the impact of shortages on hospital care in 38 countries¹¹. Of the 1,666 responses sent, 35% indicated that shortages affected the activity of hospital pharmacies at least once a day and 38% once a week. The professionals estimated at 5 hours per week the working time dedicated to managing ruptures.

Added to this question of structural shortages is that of cyclical shortages. The COVID-19 pandemic has shown the dependence of our States on companies in the production of essential medicines, and in particular those used in intensive care units.

8. World Health Organization (WHO), Katrina Pehudoff, Kaitlin Mara, Ellen't Hoen. : [“What is the evidence on legal measures to improve the transparency of markets for medicines, vaccines and other health products \(World Health Assembly resolution WHA72.8\)?”](#)

9. J. Delépine, 2019/11. “Pénurie de médicaments : la faute à la mondialisation”, *Alternatives économiques*, pages 36-39, N°395

10. France Asso Santé, [“Pénurie de vaccins et de médicaments : les inquiétudes de France Assos Santé confirmées par une enquête exclusive”](#), (Shortage of vaccines and medicines: the concerns of France Assos Santé confirmed by an exclusive survey), 2019 ; Que Choisir, [“Pénuries de médicaments. Devant la responsabilité criante des laboratoires, les pouvoirs publics doivent sortir de leur complaisance”](#), (Medicine shortages. Faced with the glaring responsibility of laboratories, the public authorities must awaken from their complacency), 2020

11. EAHP, [Medecine Shortages in European Hospitals](#), November 2018

If the exponential increase in demand could hardly have been completely anticipated, the unpreparedness of States and their inability to respond appropriately and quickly is very problematic. This should show the extent to which European states have delegated pharmaceutical policy and the consequences that may result from it to manufacturers. But within the European Commission, the acknowledgment of this observation took time to emerge. In a memo from early April 2020 devoted to shortages, as the main causes of shortages are mentioned the cyclical increase in demand, the ban on exports or even the constitution of national stocks, but does not analyze the organization of world supply chain and production¹².

Reinvesting in pharmaceutical issues and regaining control of production is therefore essential for European states. This must even be one of the major lessons of the health crisis.

Trade secret and transparency in medicines policies

Opacity surrounds the entire medicine chain. It is justified in particular by trade secret. Its exercise was reinforced by the European directive EU2016/943 of June 8, 2016, on the “protection of undisclosed know-how and commercial information (trade secret) against the obtaining, use and unlawful disclosure”. The directive is the subject of transcription in the national law of the member countries of the European Union: law of March 20, 2019 in Spain, of April 6, 2019 in Germany or of July 30, 2018 in France. However, trade secret opposes the exercise of the right to health since it prevents the guiding on rational basis of public health policies, which are in the general interest. In addition, real questions of legitimacy arise when the industrial sector invokes it while it receives so much public aid. Beyond the direct effects of the European directive and the national laws that have implemented it, there is an increasingly frequent use of trade secret to prevent the governance of the medicine chain from being assessed.

Opacity contributes to dispossessing public power of its ability to conduct effective health policies in terms of pharmaceutical production. The lack of visibility on the origin of bulk and raw materials, for example, prevents health actors from being reactive in the event of a shortage to turn to alternative suppliers. The opacity that surrounds all the economic aspects of the medicine (public aid received, investment made by the firm, margin of intermediaries, production cost, etc.) prevents informed negotiation on the price and leads to exorbitant price inflation that we have described. Thus, trade secret limits access to the content of the contracts concluded between the European Commission and the originator and patent holding companies relating to the pre-reservation of vaccines against COVID-19, for example in terms of the obligation of the firm to deliver in the event of failure.

Transparency is essential on a global scale. The lack of available data and the difficulties in producing them also prevent a detailed and exhaustive analysis of local production in developing countries¹³. This favors erroneous discourse minimizing production capacities in LMICs or disqualifying its quality.

Health safety and the global pandemic

In March 2020, medicines used in intensive care units in the main European hospitals experienced strong tensions, provoking a reaction from the association of the

12. European Commission, “[Guidelines for an optimal and rational supply of medicinal products in order to avoid any shortage during the COVID-19 pandemic](#)”, Communication from the European Commission, 8 April 2020.

13. W.A. Kaplan, L.S. Ritz, M. Vitello, 2011. “Local production of medical technologies and its effect on access in low and middle income countries: a systematic review of the literature”. *Southern Med Review*, Vol 4, Issue 2, pages 4-14 (doi:10.5655/smr.v4i2.1002)

major European hospitals. These tensions and disruptions were specifically linked to the slowdown in production at raw and bulk material production sites in China, then to India, which had closed its borders to exports. The French government had to recognize that the scale of the phenomenon had forced hospitals to find new producers on their own. He explains, for example, in the explanatory memorandum to article 37 of his Social Security Financing Bill for 2021: *“During the crisis, public establishments mobilized with private subcontractors to urgently produce critical medicines (cisatracurium, atracurium) in support of actions undertaken elsewhere.”*

Thus, the COVID-19 crisis has revealed to the general public the interdependence of countries in terms of pharmaceutical production, from finished products to API, no country being truly self-sufficient. The crisis has also highlighted the risks of outsourcing by European countries of the phase production chain of pharmaceuticals. In the public debate “relocating” the pharmaceutical industry thus appeared to be one of the logical steps to be taken as a result of the crisis. This proposal is put forward by representatives of the pharmaceutical industry and by many politicians across party lines. But this question must be understood in all its complexity and with its subtleties. Because in reality, many European countries continue to produce medicines, but this is private production, left in the hands of firms governed by the logic of supply and demand. However, it is these same logics that largely determine the problems already described, in particular those of prices and shortages. We cannot therefore propose relocation without talking about its terms.

One possible modality is public production. However, this is rarely considered and discussed. In April 2020, in the midst of a crisis of shortages of masks, reagents, oxygen cylinders or essential medicines for resuscitation, the European Commission was only considering increasing local production as a matter of urgency through fiscal measures and financial support to private industry¹⁴. However, during the same period, the Member States adopted exceptional laws authorizing in particular requisitions, when national law did not already authorize them. And some countries such as Germany and Spain used it. Similarly, a note from a French think tank¹⁵ describes the limits of the relocation of pharmaceutical production by highlighting the disorganization it would cause in the private sector without ever hypothesizing a collective reappropriation by a form public productive. This work is representative of the shortcomings of the public debate since it barely poses the specificities of the pharmaceutical sector and proposes to demonstrate the limits of relocation without thinking about public health, by examples taken from other industries.

Rather than considering the question of relocation in a given territory according to conditions identical to those at present, the one that could thus be posed is more: what can be done to ensure that the Member States of the European Union regain control on pharmaceutical production?

B. Typology of the pharmaceutical sector

Concentration and financialization of the market

14. European Commission, [“Guidelines for an optimal and rational supply of medicinal products in order to avoid any shortage during the COVID-19 pandemic”](#), Communication from the European Commission, 8 April 2020

15. P.-A. Hyppolite, 2020/09. [“Relocaliser la production après la pandémie ?”](#), Série “Relocaliser - Décarboner - Rapatrier”, Fondation pour l’innovation politique

In 2020, the main multinational pharmaceutical companies were Johnson & Johnson, Novartis, Pfizer, Roche, Merck & Co, GlaxoSmithKline, Abbvie, Sanofi, and Takeda. We can also add Novo Nordisk, Eli Lilly, Janssen, Bayer, Bristol Myers Squibb, and AstraZeneca. Far from popular belief, the pharmaceutical sector is rarely made up of national industries, but mainly multinational actors, whose attachment to a country is no longer really clear.

The evolution of production: mergers and acquisitions, specialisation, financialisation, outsourcing and tax avoidance

European production has followed the global evolution of the sector, marked by several phenomena¹⁶ which have affected many industrial sectors, but whose consequences are particular, given the special status of medicines. First of all, **mergers and acquisitions** have polarised production around multinationals, the “Big Pharma” The French *Rhône-Poulenc* and the German *Hoechst* merged, leading to the creation of *Aventis*, which became Sanofi. We can speak of “mega-merger¹⁷”, for which Pfizer is a model, with the acquisition of *Pharmacia Corp* in 2003 for \$ 59 billion, or *Wyeth* in 2009. These purchases reinforce the concentration of the market, in particular in sectors as decisive as active pharmaceutical ingredients (API) or the production of generics. The size of these giants also gives them additional power in negotiating with countries.

In Germany, the *Bayer* company has also made various acquisitions during its history, notably of the pharmaceutical *Schering AG* in 2006, and then, outside the pharmaceutical sector, the giant *Monsanto* in 2016.

Another key trend of the past three decades is the **specialisation** of production. The merger between *Hoechst* and *Rhône Poulenc* resulted in the creation of two entities, *Aventis*, focused on agrochemicals and pharmaceuticals, and *Rhodia* which is organised around chemistry. We have thus gone from “large vertically constituted chemical-industrial groups¹⁸” to “Big Pharma”, which have an increasing tendency to specialise in a particular pharmaceutical domain. Here again, market **concentration** is reinforced.

This market concentration is illustrated, for example, in the in-vitro diagnostics (IVD) market and in particular that of PCR (Polymerase Chain Reaction) tests. This was already the case long before the appearance of COVID-19, with in particular two major companies sharing a large part of the global market: Roche and Abbott. This market concentration has had the effect of limiting access to HIV/AIDS viral load tests, particularly in sub-Saharan Africa, or even of limiting the capacity of developing countries to carry out screening campaigns for the virus of hepatitis C (HCV)¹⁹.

Like research, pharmaceutical production is largely **financialised**. Profits are generated less by investment in production, which was the engine of capitalism until the 1990s, than by the sole circulation of assets, and speculation. The best example of this is the buyout in 2011 of *Pharmasset*, which developed the hepatitis C medicine sofosbuvir, by Gilead for \$11 billion. The single buyout announcement sent Gilead's stock market

16. The economists Philippe Abecassis and Nathalie Coutinet described them in their accessible book *L'économie du médicament* (The Medicine Economy), (La Découverte, 2018)

17. Philippe Abecassis et Nathalie Coutinet, *Économie du médicament* (The Medicine Economy), *La Découverte*, 2018, page 79

18. *Ibid.*, page 78.

19. See the reports: “[WHO, Accelerating access to hepatitis C diagnostics and treatment](#)”, January 2021 ; ALCS, Londeix P., “[Benchmark des analyses diagnostiques, d'évaluation de la fibrose et de suivi du traitement de l'hépatite virale C](#)”, May 2018

price higher, allowing the company to amortise the cost of the buyout without selling a single medicine. Similarly, in November 2020, by selling its shares the day after making announcements about the efficacy of its vaccine candidate against COVID-19, the main objective of Pfizer was to carry out an operation targeting shareholders²⁰.

The consequences for governance and the strategic choices for this development are decisive, since it is the stock price and shareholders profits, most often short term, that determine them. Thus, between 1999 and 2017, the turnover of the eleven largest pharmaceutical companies doubled, from \$197 billion to \$395 billion. In the same period, profits rose 44% (from \$34 billion to \$50 billion), as dividends more than tripled, from \$20 billion to \$71 billion. The explosion of dividends over earnings and the fact that the former overtook the latter in 2017 is a sign of a strategic orientation towards shareholder profits.

Finally, the tendency to **outsource** certain production sectors logically accompanied this financialisation, since it allows large companies to focus on marketing. Thus, in ten years, more than 30% of the total world production has been entrusted to actors specialising in production by a third party. In France, between 2009 and 2017, around fifteen sites have been taken over by actors specialising in third-party production²¹. Companies like Sanofi had stopped their research on coronaviruses before the pandemic hit. The company has also stopped its research on HIV, tuberculosis, and Alzheimer's disease, among others.

A huge tax evasion

Tax evasion and the difference in remuneration between shareholders and workers are other signs. In 2018, the American organisation *Americans for Tax Fairness* pub-

COMPANY	2018 ESTIMATED ANNUAL TAX CUT	ONE-TIME TAX CUT ON OFFSHORE PROFITS	STOCK BUYBACKS ANNOUNCED SINCE NOVEMBER 28, 2017	2018 STATED OR ESTIMATED COST OF PROMISED BONUSES	CEO-TO-WORKER PAY RATIO ***
ABBVIE*	\$ 1,316,950,210	\$ 3,881,000,000	\$ 10,000,000,000	\$ 0	144-1
AMGEN**	\$ 98,400,000	\$ 5,500,000,000	\$ 10,000,000,000	\$ 0	147-1
BIOGEN	No estimate	\$ 1,060,400,000	None announced	\$ 0	Not reported
BRISTOL-LYERS SQUIBB	No estimate	\$ 4,827,300,000	None announced	\$ 0	169-1
CELGENE	No estimate	\$ 1,953,700,000	\$ 5,000,000,000	\$ 0	Not yet available
ELI LILLY*	\$ 163,905,000	\$ 4,492,000,000	None announced	\$ 0	118-1
GILEAD SCIENCES	No estimate	\$ 7,000,000,000	None announced	\$ 0	94-1
JOHNSON & JOHNSON	No estimate	\$ 9,031,800,000	None announced	\$ 0	452-1
MERCK**	\$ 2,728,900,000	\$ 13,135,900,000	\$10,000,000,000	\$69,000,000	215-1
PFIZER*	\$ 1,070,745,480	\$ 25,503,000,000	\$10,000,000,000	\$100,000,000	313-1
TOTAL	\$ 6,267,900,690	\$ 76,385,100,000	\$ 45,000,000,000	\$ 169,000,000	N/A

Tax reduction and bonuses for the 10 largest American pharmaceutical companies
Sources : Americans for Tax Fairness

* 2018 tax cut estimated by the Senate Finance Committee

** 2018 tax cut estimated by Just Capital

*** Compiled by Bloomberg based on company reports to the SEC

20. Olivier Petitjean, "1000 milliards d'euros de profits en vingt ans : comment les labos sont devenus des monstres financiers", (€1000 billion in profits in twenty years: how the pharmaceuticals have become financial monsters), *Bastamag*, 16 January 2019.

21. PIPAME, *Enjeux et perspectives des producteurs pour tiers de principes actifs de médicaments* (Challenges and prospects for third-party producers of active medicine ingredients), DGE, Paris, 2017.

lished a study²² on these phenomena by studying public data from the ten largest medicine companies in the United States:

It specifies that the savings achieved through optimisation or tax evasion are only rarely distributed between shareholders and workers, most going to the former. These savings are not reflected in the price of the products either. Even when it concerns non-EU companies, tax evasion is also a European problem. Pfizer, for example, declares part of its income through an offshore company, which has allowed it to have a substantial tax reduction for more than ten years.

The report published in the United States by “Americans for tax fairness²³” estimated the tax avoidance in the United States of Pfizer at 25 billion dollars, for J&J at 7 billion, Gilead at 9 billion, Merck at 13 billion for a total of US\$53 billion. For the top 10 multinationals in terms of profits, “*untaxed offshore profits*” were estimated in 2017 at US\$503 billion. These data were documented in a report by the US Senate Finance Committee in 2018²⁴.

On July 13, 2021, the SOMO organization unveiled Moderna’s tax avoidance strategies. The firm, based in Massachusetts, has declared itself legally in Delaware, a tax paradise. A leaked contract with the European Commission showed that Moderna²⁵ declares its vaccine sales in Switzerland, another tax paradise. The Commission’s assent to this tax avoidance in the EU appears as another form of public support.

If we take this trend into account, combine it with public funding for research and development as well as price inflation, we conclude that the public authorities pay for medicines and health products at least four times: once through public research, once through R&D aid for private groups, a third time through medicine reimbursement, a fourth time through tolerance of tax evasion. We can add a fifth, when public authorities must compensate victims of health accidents.

The pharmaceutical industrial fabric in Europe

Opacity also reigns over the European industrial fabric, with little aggregate data available and easily accessible concerning the pharmaceutical industrial fabric on the European scale. Moreover, existing national data, such as those produced by the Banque de France and INSEE²⁶, for example, do not take into account the specificities of the pharmaceutical sector and public health objectives. Such studies consider pharmaceutical production, import and export, only in terms of competitiveness, with countries ranked on a “podium”. Such a competitive vision prevents thinking about the necessary complementarity to be implemented at European level to cover the health needs of populations.

This opacity is not specific to Europe and is also found at the global level. It prevents the constraints and consequences of local production from being assessed. It also

22. Americans For Tax Fairness, “*Bad medicine: How GOP Tax Cuts Are Enriching Medicine Companies, Leaving Workers & Patients Behind*”, 2018.

23. Americans For Tax Fairness, “*Bad medicine : How GOP Tax Cuts Are Enriching Medicine Companies, Leaving Workers & Patients Behind*”, 2018

24. US Senate Finance Committee Report, “*Trump Tax Law and the Health Care Industry: A \$100 Billion Bonanza*”, April 17, 2018

25. SOMO, “*Pocketing tax free profits from publicly funded jabs*”, 13 July 2021

26. J.-L. Cayssials & M. Ranvier, 2016. “Strategies for internationalisation in Pharma”, Quarterly selection of articles - Bulletin de la Banque de France, Banque de France, issue 42, pages 25-40, Summer.

prevents, particularly in Europe according to studies²⁷, taking into account the environmental issues associated with the production of raw materials.

According to the European Commission, the European pharmaceutical industry accounted for 800,000 direct jobs in 2019 and generated a trade surplus of €110 billion²⁸. In 2019, the pharmaceutical industries in the European Union accounted for 17.7% of global sales of new medicines, compared to 65.2% for the United States²⁹. The share of imports of pharmaceutical products in relation to production, data which may be important in measuring the issue of relocation, varies from one European country to another. The share of added value from imports of pharmaceutical products is 49% in France (vs 51% of added value produced), 42% in Germany (vs 58%) and 36% in Italy (vs 64%³⁰).

For example, the Sanofi company has finished product production sites mainly concentrated in France, Germany and Italy, and also in Spain, United Kingdom, Belgium, Hungary, Ireland, Romania, Czech Republic and Portugal. In Denmark, the industrial Novo Nordisk produces mainly insulin and hormone treatments, and it is estimated that half of the insulin marketed globally is manufactured at the Danish site of Novo Nordisk in Kalundborg³¹.

As for the production of raw material of bio-medicines, it remains largely produced by patent holders in rich countries, especially those of the European Union. The outsourcing by subcontracting thus concerns above all active ingredients (API) of generic and *originator medicines* considered to have low added value. It may also relate to APIs of medicines whose production requires production technologies that the patent holder has not deployed in its sites.

Despite the difficulties that opacity imposes on such research, we estimate today the share of these materials manufactured in countries outside the European Union, in particular Asian countries, to be from 60% to 80%, compared to 20% thirty years ago³².

The LEEM report³³ in France in 2017 indicates in particular that:

“With a turnover of more than €53 billion in 2015, the pharmaceutical industry is one of the pillars of the French economy. Its establishments employ nearly 100,000 people across France. In addition, it is very successful in exports, with €26.9 billion in sales of medicines produced internationally for a trade surplus of €7.7 billion in 2015. Within the French pharmaceutical industry, production is an essential link in terms of employment and activity, a relationship between R&D and marketing. With a historically dense industrial composition in both medicines and vaccines, production now represents more than 40% of jobs in the pharmaceutical industry, compared to 34% in 2003. [...] For a variety of reasons (pressure on medicine prices, concentration on R & D, etc.), pharmaceutical companies have gradually entrusted part of their production and related installations to specialised third parties, until they have often themselves even become third parties, using some of their own production capacities that have

27. J. Larsson, J. Fick, 2009/04. “Transparency throughout the production chain - a way to reduce pollution from the manufacturing of pharmaceuticals? : Regulatory Toxicology and Pharmacology”, Issue 53, pages 161-163

28. European Commission, *Une stratégie pharmaceutique pour l'Europe. questions et réponses* (A pharmaceutical strategy for Europe. questions and answers), November 2020.

29. IQVIA, *The Global Use of Medicines in 2019*.

30. Accenture, *Une nouvelle trajectoire pour l'industrie française* (A new trajectory for French industry), 2020

31. Eric Palmer, “Novo Nordisk investing \$117.4M in manufacturing site in Denmark”, *Fierce Pharma*, (7 february 2020).

32. Philippe Abecassis et Nathalie Coutinet, *Économie du médicament*, La Découverte, 2018, page 83.

33. LEEM, 2017 : “Enjeux et perspectives des producteurs pour tiers de principes actifs et de médicaments” (Challenges and perspectives of third-party producers of active ingredients and medicines)

not been mobilised. Most pharmaceutical companies thus use that for the manufacture of the active ingredient of the medicine and/or its formulation, like the two leading French pharmaceutical companies, Sanofi and Servier. France has the potential to position itself among the world leaders in production for third parties, with historical know-how, companies with an international dimension and dynamic and innovative SMEs."

These figures and descriptions of the French pharmaceutical and industrial sector contrast with the disarray displayed by political decision-makers in France in April 2020 when stocks of essential medicines were tight. The industrial fabric still exists in part, but seems to be controlled by multinationals, when the States seem to be helpless.

The different levels of relocation

Faced with the dramatic situations that countries faced during the first months of the COVID-19 crisis, the issue of relocating pharmaceutical production in Europe has therefore emerged in the public sphere. But around the same term "relocation", opposing ideas have sometimes been put forth. Thus, medicine companies took the opportunity to ask for more aid for pharmaceutical production, explaining that if the medicines were produced in Asia, it was because European countries in particular refused to pay higher prices. This argument is not admissible. Studies on real production costs show that Asian generic producers, producing medicines sold for €2/box in Europe, still achieve significant margins. Multinationals have therefore chosen to no longer produce these medicines, because they prefer to concentrate their production on medicines that they can charge much more for.

The problem is not that multinationals are guided by profit, that is in the very nature of the capitalist world; the problem is that the States have lost control over the production of essential medicines for their populations. This is a good illustration of the fact that healthcare products are not products like any other, and therefore they should not obey the same rules as other consumer goods. Thus, a relocation that takes place according to the same rules of supply and demand, aided by the public money granted to pharmaceutical companies, would not solve the problem.

Define the framework for relocation.

A. What stages of production are we talking about?

The different stages of the medicine production value chain must be detailed. These are the stages from the production of active pharmaceutical ingredients to the final product. The different stages represent different phases, in particular with products resulting from synthetic chemistry or biologicals for prevention, such as vaccines, and diagnostic kits. These different stages have been the subject of modeled descriptions¹.

Thus, by pharmaceutical industry, we mean different phases, which produce on an industrial scale active therapeutic substances for the purposes of treatment, prevention or diagnosis, for people or animals, as well as active ingredients intended for the production of these substances, resulting from synthetic or biological chemistry, plants, genetic products or engineering.

Pharmaceutical production on an industrial scale encompasses two broad categories, depending on whether the medicine is derived from chemistry or whether it is a bio-medicine. The first stage concerns the production of APIs and varies depending on the type of product. We thus distinguish:

- **synthetic chemistry:** production of a pharmaceutical product resulting from a chemical synthesis.
- **fermentation**, the production or separation of pharmaceutical chemicals, such as antibiotics and vitamins, from microorganisms.
- **extraction:** the production of biological or botanical products, derived from organic products from animals or plants.
- **biological production:** the use of microorganisms and genetic engineering tools to produce vaccines and monoclonal antibodies.

Then comes the **formula** step: the transformation of pharmaceutical “bulk” into different formulations, different dosages, and different forms, such as tablets, capsules, injectable solutions, creams or ointments, with the addition of excipients. To these

1. R.T. Sousa, S. Liub, L.G. Papageorgioub, N. Shaha, 2011. “Global supply chain planning for pharmaceuticals”, Journal of Chemical Engineering Research and Design, issue 89, pages 2396-2409.

steps are added production stages such as **packaging and wrapping**. This last step is sometimes delicate: in the case of certain COVID-19 vaccines, for example, it requires restrictive refrigeration conditions.

The different stages of production can be carried out by the same actors, or subcontracted under commercial agreements and voluntary licences to contractors. Very often these agreements are kept secret (protected by trade secrets) which makes transparency on the production chain very difficult and makes it almost impossible to precisely trace the production chain of a given medicine. If the medicine agencies have a certain amount of information to which the general public does not have access, in particular with regard to production sites, this information remains difficult to access, protected by trade secrets and by clauses relating to the exclusivity or usability of clinical data.

The research team at the Graduate Institute in Geneva explains, for example, how this opacity complicates the mapping it has started regarding the global production of COVID-19 vaccines: *“This dataset is based on the companies, governments and multilateral organisations that make their agreements public. There are significant gaps in the data, including the fact that not all agreements are reported in a timely manner, and reported agreements may lack one or more relevant data points, such as expected doses or expected market.”*

Today, it is difficult to map where these different steps can be achieved across the Member States of the European Union. But it seems clear that the production of raw materials and active pharmaceutical ingredients is very little done in Europe for various reasons.

B. The production of “active pharmaceutical ingredients” (API): a major issue

As the research of Carlos Correa³ and of German Velasquez⁴ at South Centre emphasises, as well as Rui T. Sousa, from the Imperial College of London⁵, one of the essential phases of pharmaceutical production is that which concerns the production of “API” (Active Pharmaceutical Ingredient), which is the active substance of a given finished product. In discussions of pharmaceutical production, the production of this raw material is often overlooked, yet it is central. While there may be many generic producers of the same medicine, there may be only one or two API producers in the world, which amounts to market concentration and control over that by these producers. In many cases, multinationals also control the API production market, either through exclusive agreements or because these producers are owned by them. The sale and purchase of these “APIs” is often carried out by stockbrokers, who do not produce themselves but who speculate on buying and selling based on supply and demand.

Thus, API production is a central issue in pharmaceutical production, often masked by the opacity of the pharmaceutical production chain. The most powerful multinational pharmaceutical companies own a large part of API production. This is the case

2. “COVID-19 Vaccine Manufacturing”, Graduate Institute, last updated on 17 June, 2021.

3. Carlos M. Correa, South Center, “Lessons from COVID-19: Pharmaceutical Production as a Strategic Goal” (July 2020)

4. German Velasquez, South Center “Re-thinking global and local manufacturing of medical products after COVID-19” (September 2020)

5. R.T. Sousa, S. Liub, L.G. Papageorgioub, N. Shaha, 2011, “Global supply chain planning for pharmaceuticals”, *Journal of Chemical Engineering Research and Design*, issue 89, pages 2396-2409.

of Pfizer, Novartis, Sanofi, Boehringer Ingelheim, and Bristol-Meyers Squibb, a production which is concentrated in Asia.

The most powerful generics producers are those who produce at least part of their API themselves, such as Teva pharmaceutical, which has more than 300 API products in its portfolio. In India, Dr. Reddy's has more than 60⁶. Cipla, Aurobindo, Ranbaxy and Sandoz are other major ones. In Egypt, the Pharco company also produces part of its API, in particular for its medicines against hepatitis C.

In the field of in-vitro diagnostics, the manufacture of the raw materials is concentrated in the hands of a handful of firms, including Roche, Abbott, and ThermoFischer Scientific. Therefore, the WHO recommended⁷ in 2011 the local production of diagnostics, especially for emerging countries, based on the examples of South Africa and Brazil.

While many pharmaceutical companies used to produce APIs themselves in high-income countries, this is no longer the case. APIs are most commonly produced in Asia, China and India. For medicines on the European market, 80% of the active ingredients are imported from China and India. Other countries, such as Bangladesh, have also developed a very large "industrial park" for API production, with the aim of developing their medicine industry. Although located in Asia, this production nonetheless remains controlled by multinationals, through voluntary licensing agreements and other forms of subcontracting, which keep the market concentrated and which limit production by third parties not validated by these multinationals (for example, producers of generics wishing to supply a country having issued a compulsory licence for the same medicine will not be able to stock up on APIs).

The regulation of the price of raw materials by the logic of supply and demand poses major ethical questions. Studies carried out by Andrew Hill (University of Liverpool) on the real costs of producing certain essential medicines demonstrate this: the concentration of API production is high, and its purchase or sale price represents a significant part of the production cost of the finished product. Thus, a producer dependent on an API production manufactured by a third party has limited freedom regarding its production.

The opacity on the medicine chain and in the production of APIs also prevents an assessment of environmental risks, an assessment that is essential to rebalance these risks on a global scale. Such an assessment is particularly incomplete in Europe⁸.

C. Market concentration: the example of midazolam

During the first wave of COVID-19 in Europe, northern countries, western Europe especially and France in particular were hit by a shortage of medicines used in intensive care, such as midazolam. After alerting the French authorities on the subject, hospital practitioners from AP-HP (France), alongside OTMeds and Prof. Andrew Hill,

6. PIPAME, « Enjeux et perspectives des producteurs pour tiers de principes actifs de médicaments » (Challenges and prospects for third-party producers of active pharmaceutical ingredients), DGE, Paris (2017)

7. Ibid.

8. J. Larsson, J. Fick, 2009/04. "Transparency throughout the production chain - a way to reduce pollution from the manufacturing of pharmaceuticals?"; *Regulatory Toxicology and Pharmacology*, Issue 53, pages 161-163

identified that there were 8 producers of midazolam raw materials in the world, most being produced in India.

This example illustrates the ultra-dependency on API production. It also shows the major danger in terms of healthcare security, leaving in the hands of a few producers, in very few countries, the global production of the same pharmaceutical substance.

Another recent example reinforces this concern. In a factory, the company Sanofi produces most of the supply of rifapentine (treatment used against tuberculosis) for the whole world. In 2020, a reported impurity at the Sanofi factory slowed global production and led to tensions in stocks and stockouts in some regions. The year before, the BCG vaccine produced by Sanofi Pasteur had run out for the same reasons.

Several actions are necessary for States:

- Constitute national strategic stocks of essential medicines. Reports published in September 2020 showed that a large part of the antivirals in the strategic medicine stock in France had expired, raising doubts about the logistical and stock turnover skills of the institutions in charge.
- Never leave to a single country or a single firm in the world the production of a medicine or raw material for the whole planet. A factory can experience impurity problems, as the Sanofi factories have recently experienced. A country can also face a conflict, or a newly elected government decides for populist reasons to block all its exports. A government can also use its medicine exports to strengthen its bargaining power of other things and thus weaken the importing country.

D. Studies on real production costs

In the early 2010s, pharmacologist Andrew Hill of the University of Liverpool initiated research⁹ to assess the real cost of producing essential medicines¹⁰. His studies, carried out for various major scientific journals, and also for the WHO, show several central elements: there is no correlation between the cost of producing a medicine and its selling price, and there is no correlation between a country's ability to pay and the price of a medicine. Prices are the result of negotiation. Thus, for the new hepatitis C treatments marketed in France for €56,000 in 2014, Andrew Hill estimated at the time that the production cost was around €120.

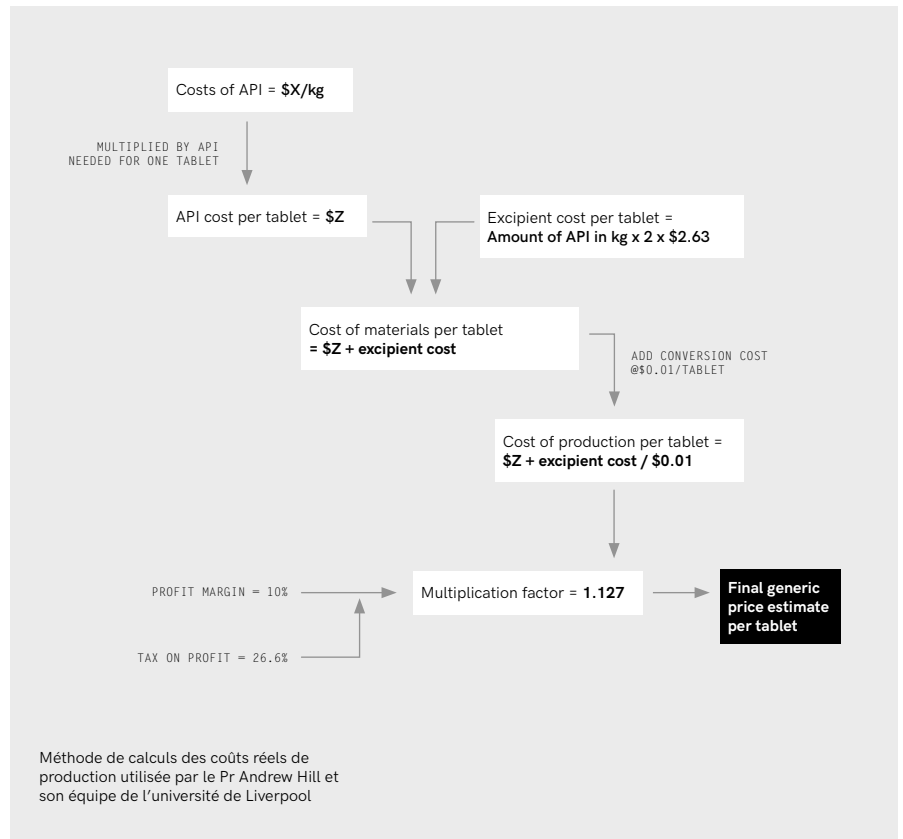
This research has shed light on the ultra-concentration of API production, and also how its selling price is often far removed from the price of the finished product. His research focused on the real cost of producing medicines used against hepatitis C, and also HIV/AIDS, insulin, cancer treatments, and candidate treatments for COVID-19 and COVID-19 vaccines.

E. What health products are we talking about?

It seems essential to us to focus on all the health products necessary for the treatment of people: medicines derived from chemistry, bio-medicines, vaccines, in-vitro

9. ["Minimum Costs for Producing Hepatitis C Direct-Acting Antivirals for Use in Large-Scale Treatment Access Programs in Developing Countries"](#) (april 2014)

10. Andrew Hill et al. ["Minimum costs to manufacture new treatments for COVID-19"](#) (april 2020)



diagnostics, reagent kits and sampling consumables, medical devices and protective equipment

(gloves, masks, condoms, etc.). However, this report focuses on the issue of medicines, bio-medicines and vaccines, and makes reference to in-vitro diagnostics.

“Essential” medicines or with “major therapeutic benefits”

Some public debates in Europe around relocation have crystallised around the example of paracetamol, the symbol of a “basic” medicine, highly prescribed, easy to produce, previously produced in Europe and now whose production has been relocated. But as we have understood, the challenge is not so much to produce this “basic” medicine again in Europe, but to have a public health policy at the European level and in its Member States able to reflect holistically and clearly on the health needs of European populations.

Thus, defining the scope of relocation or local pharmaceutical production is an essential step. Which health products should be affected by a production relocated to Europe? Different lists and different criteria can be used to define such a scope. There is of course the WHO list of essential medicines (Appendix 1), but also medicines of major therapeutic benefit, such as defined in France, for example (Appendix 2).

The WHO list of essential medicines remains a benchmark, but it must also be analysed closely, as it reflects other issues. Indeed, the WHO does not always include therapeutic innovations in its lists, insofar as it is also aimed at developing countries, which do not necessarily have the budgets to cover the arrival of new therapeutic innovations, even with major benefits for people. Thus, often, the inclusion of new medicines in this list is done when it is accompanied by access programs or funding of these medicines at the international level for developing countries. Thus, the WHO list, which to date includes 557 medicines or health products, must be supplemented by other therapeutic innovations.

Orphan and “neglected” diseases

Reflecting on access to therapeutic innovations must include the case of rare, orphan or so-called “neglected” diseases. Often developed by charities, such as AFM-Téléthon and DNDi (Drugs for neglected diseases initiative), they only interest large companies belatedly, or never, when the markets are considered too small. When they are interested, the latter compensate for the low number of beneficiaries with disproportionate prices¹¹. A local production that takes medicines out of the market logic of supply and demand must also integrate these situations where the priorities in the production criteria of a health product cannot be proven by purely quantitative approaches.

“Essential” medicines and therapeutic innovations

In France, following the arrival on the French market of new hepatitis C treatments in 2014, the National Consultative Ethics Committee (CCNE) took up the issue of access to therapeutic innovations in France. The opinion was issued in November 2020¹². The CCNE stated in particular: *“New drugs resulting from biomedical research, with construction models different from those implemented up to now in the pharmaceutical industry, now constitute therapeutic innovations with high added value. These treatments are very likely to develop and their indications to expand, for example for many cancers, and for rare diseases: they will therefore involve more and more patients. However, the exorbitant prices of these innovative therapies (up to €2 million per patient) clearly raise the question of their access for all patients who might need them. In addition, the very high prices of these treatments could compromise the financial equilibrium of the solidarity-based healthcare system, such as that which prevails in France, and lead to choices being made to restrict access to care for other patients. CCNE has taken on the ethical questions raised in this context, in particular by examining the ethical issue posed by access for all patients to innovative therapies. How can we reconcile, on the one hand, access to these very costly treatments for all those who require them and the sustainability of the health insurance system and, on the other hand, the interests of pharmaceutical companies? How can we justify such prices and how can we define fair prices?”* CCNE’s opinion recommends in particular (see box on page 43) the establishment of transparency, the reform of the resources of patent offices, and public production at the French or European level.

Choice of medicines: public authorities influenced by private audit companies

In the public debate, competing criteria are put forward to define the productions to be relocated as a priority. The public authorities and the industrialists mandate audit firms to provide the arguments justifying this selection. The joint study conducted by the *PWV Company* and the *National Purchasing Council*, made public on 9 July 2020, is representative of this discourse¹³. The analysis, which sets itself the objective of being “upstream of consideration by the public authorities”, covers all industries, beyond the pharmaceutical field, which would be interesting to relocate. The criteria are exclusively economic: current import rate of the product, French competitiveness in the sector, possible added value, etc. Applied to the pharmaceutical industry, the selection results in a prioritisation that takes no account of the specificities of the products,

11. Diana Kwon, “How Orphan Drugs Became a Highly Profitable Industry”, *The Scientist*, 1 May 2018

12. [Opinion 135 of the National Consultative Ethics Council \(CCNE\)](#) in France, November 2020

13. CNA-Pwc, [Relocalisation des achats stratégiques](#) (Relocation of strategic purchases), July 2020

health requirements or the reality of shortages. Likewise, the methodology does not indicate that healthcare actors have been consulted. The company concludes that the relocation of the production of analgesics, immunosuppressants or certain APIs is not a priority, without ever justifying it in terms of public health.

An Accenture study¹⁴ believes that “antibiotics are among the most vulnerable elements among the 2000 products analysed in the study, with a very concentrated supply in a few countries”. If we can share this observation in part, it should be noted that the practice does not include any healthcare criteria, no epidemiological data, and no perspective on antibiotic resistance. It also forgets to point out the causes of the current situation, for example the choice of Sanofi executives to abandon all work on antibiotics.

There are, however, relevant economic criteria to be taken into account to assess the impact that a relocation of production designed for collective benefit can have. For example, we must measure the weight that the pharmaceutical industry imposes on health systems by its increasingly high prices, according to known epidemiological data. Compared to the real cost of production and other data identified in our *Transparency Check List* (see Appendix 3), such an indicator would allow us to see what rapid savings such a relocation would allow, in order to shed light on debates on healthcare spending, and orient them towards the real needs of the populations.

14. Accenture, *Une nouvelle trajectoire pour l'industrie française*, 2020

PUBLIC PRODUCTION:

The Brazilian model*

In terms of public pharmaceutical production, Brazil is the pioneer country par excellence. The development of this industry took place in several stages and to meet different objectives, from the objective of building a pharmaceutical self-sufficiency, to the opening to global trade, the arrival of the AIDS pandemic, and the promulgation of a new patent law, and the development of public laboratories in particular under Luiz Inacio Lula Da Silva's presidency. With its successes and limits, many conclusions can be drawn from the Brazilian "experience".

1970s / PHARMACEUTICAL SELF-SUFFICIENCY

In the 1970s, Brazil designated as "priority" different vaccines, diagnostics and medicines, and initiated the development of its pharmaceutical self-sufficiency by launching their public production. The first initiative linking public and private production with access to these essential health products, took place in 1971, when the Centre for Medicines (CEME) was created¹. This institution, considered as important in order to guarantee national sovereignty, had as its mission to regulate the public production and distribution of medicines by these "official laboratories". During the first two decades of its existence, the CEME, in addition to centralised purchasing of a list of essential medicines, also invested in national re- search and development of medicines, including antibiotics and insulin. In 1997, the CEME was dissolved due to deviations from its main mission and allegations of corruption.

1990s / OPENING UP TO INTERNATIONAL TRADE AND THE AIDS PANDEMIC

In the early 1990s, the opening of the market to international trade, combined with nationally the crisis at the CEME had a deleterious effect on the network of public laboratories, mainly due to the absence of a medical policy to guide their actions. But, during the establishment of the universal health insurance system "Sistema Único de

* This part and analysis are based on the studies conducted by Gabriela Costa-Chaves, Jorge Bermudez, Koichi Kameda and Marcela Fogaça Vieira, outside of this report.

1. Costa Chaves & al. "Construction of health sovereignty: politics and public production of medicines in Brazil" [free translation from Portuguese]

Saúde” (SUS), when the need appeared for the healthcare system to provide the population with essential medicines, especially for the treatment of AIDS, the key role that could play the public laboratories for the health system appeared again. Thus in 1997, the Basic Pharmacy Program, made up of a list of 40 medicines produced by the network of public laboratories resumed².

1996, A NEW PATENT LAW

In 1996, two important institutional changes took place in Brazil: the approval of a law, which guarantees access to treatment for people living with HIV; and the approval of law which adapts industrial property rights to the TRIPS Agreement of the World Trade Organisation (WTO) and establishes patent protection for pharmaceutical products and processes. The immediate effect of the second law for the Sistema Único de Saúde (SUS) was an increase in expenditure due to the high prices of monopoly or patented medicines, in particular antiretroviral medicines used for AIDS, included in national guidelines since the late 1990s³.

MOBILISATION OF PUBLIC LABORATORIES

It is in this context that the public laboratories mobilised to meet the needs of the SUS, not only in the production of antiretrovirals, but also to facilitate the price negotiations that took place in the following years, by contributing to the estimates of production costs of patented medicines, as well as local production capacities of products that would be under compulsory licence, thus increasing the negotiating power of the Brazilian government. In this sense, public production has played an important role in the implementation of government strategies aimed at reducing the prices of patented medicines. It should be noted that the local production of non-patented antiretrovirals at prices lower than those charged by multinational companies, at the time, raised the awareness of governments and non-governmental organisations on the abusive prices practiced by these companies⁴.

1998: NATIONAL MEDICINE POLICY

In its 1998 Constitution, Brazil the right to healthcare for all and equality in health provision as a fundamental principle. The National Medicine Policy (PNM) was published, the result of a long negotiation process involving many actors, such as representatives of organised civil society, the pharmaceutical industry, health professionals, SUS officials and experts from the Ministry of Health and other relevant ministries. Among the eight guidelines established in the PNM is the promotion of public medicine production⁵.

NEW ERA WITH LUIZ INÁCIO LULA DA SILVA

Since the first term of former President Lula, a new era has opened for the construction of an industrial policy for the country, initially reflected in the Industrial, Technological and Foreign Trade Policy (PITCE) of the federal government in 2004. Subsequently, the Productive Development Policy was launched in 2008 and, in 2011,

2. *Ibid.*, p. 38

3. *Ibid.*, p. 38

4. *Ibid.*, p. 38

5. *Ibid.*, p. 38

under the Dilma government, the Plano Brasil Maior was launched. For a decade, with the publication of three industrial policies, the pharmaceutical sector was seen as a key element⁶.

2000s: PARTNERSHIP FOR PRODUCTIVE DEVELOPMENT (PDP) AND TECHNOLOGY TRANSFERS

The reflection on the industrial policy in the government agenda continued with the inclusion of the Economic and Industrial Health Complex as one of the planning components of the Ministry of Health, through the “PAC-Healthcare” in 2007. Among the instruments adopted is the Partnership for Productive Development (PDP) for the transfer of technology from the private sector to the public sector of products adopted by the SUS, the main incentive is the guarantee of exclusivity on the public medicine market⁷.

NETWORK OF PUBLIC LABORATORIES

An important feature of the Brazilian pharmaceutical industry is the existence of a network of public laboratories - also known as Official Laboratories (LFO) - which produce medicines and bio-medicines to support the Sistema Único de Saúde. Established LFOs have different sizes and distinct technical, administrative and financial characteristics, but their main mission is to produce the medicines listed in the National List of Essential Medicines, to meet the SUS needs.

Currently in Brazil, the network counts 25 Official Pharmaceutical Laboratories, of which 18 are active. It can be observed that the Southeast Region has all its laboratories in operation, and represents the largest proportion of the official industrial park active in Brazil. In contrast, the Northeast and South regions have half of the inactive laboratories. This result demonstrates the importance of investments in the structuring and reactivation of the official Brazilian industrial park. Most of the laboratories belong to the Association of Official Laboratories of Brazil (ALFOB), which aims to be a collective management tool for the 18 associated national public laboratories and also aims to encourage the improvement of pharmaceutical production at the governmental level. These official laboratories, structured for the most part 20 years ago within the frame of the policy implemented by the ex-CEME, urgently need modernisation of the industrial and technological park and its process of management, training, and implementation of human resources.

Despite the success of this official public laboratories in enable the medicines in Brazil, the inclusion of public production of medicines as a component of health policy also presents weaknesses and challenges.

One of them is that it is a sector that operates mainly in the production of the final product, depending on the private sector, national or international, for the acquisition of API. Thus, the evolution of public procurement rules, combined with the opening of the market, favoured the acquisition of international APIs based mainly on the cheapest item. The choices of the 1990s were reflected in the dismantling of the fine chemicals industry. In addition, experience indicates the acquisition of low-quality APIs by the public sector, with negative consequences for adherence to the delivery schedule to the healthcare system and an increase in production costs.

6. *Ibid.*, p. 38

7. *Ibid.*, p. 38

According to researchers' studies, the sector is heavily dependent on the public medicine market and is therefore vulnerable to changes in pharmaceutical policy and procurement modalities, as well as changes in government and respective guidelines regarding the role of the health policy sector.

The Sistema Único de Saúde (SUS) and the strengthening of pharmaceutical assistance face a series of challenges in the current context at the national and international levels. At the national level, the underfunding of the system seems clear. There is a process of rapid inclusion of high-priced products, many of which are under monopoly in Brazil and around the world. This not only leads to an increase in public spending, but also raises questions about the role of public medicine production in this context, whether to cope with high prices or to maintain commitment in promoting universal access to medicines⁸.

Conclusion: lessons learned from the Brazilian experience and challenges

Brazil's pharmaceutical policy is unique in the world. Its design and implementation required an extraordinary holistic vision and political will on the part of the authorities, who at the same time articulated questions of industrial production with those of intellectual property and research and development. The patent law adapting the TRIPS Agreement has made the best use of the flexibilities of the WTO Agreement on Intellectual Property, which has resulted in many patent applications not fully meeting the patentability criteria being rejected. The country has also not hesitated several times to resort to compulsory licences to give its people access to life-saving medicines. While at the same time, especially under pressure from the Global Fund to Fight AIDS, Tuberculosis and Malaria, developing countries were pressured to always buy the cheapest drug, the Brazilian government also ensured that publicly produced drugs would be available, even if they were not always the cheapest. This aspect is essential. Because while it might seem logical to systematically use the cheapest drug, this logic often prevents the development of new producers, which are sometimes more expensive when they arrive on the market. As Koichi Kameda pointed out in his work, this had a negative impact on the local public production of PCR viral load tests for HIV and hepatitis C in Brazil, with the public institute Biomanginhos investing to develop tests across the country to compete with global market leaders Roche and Abbott, and then, once the price had largely decreased for the locally produced test, there was an alignment of Abbott, followed by a proposed price even lower by Abbott, which will subsequently lead to "killing" the locally produced kit, which is more expensive than that of the brand name competitor.

The Brazilian researchers interviewed for this report also insisted on the importance of knowing the real costs of producing the originator drug for the development of Brazilian public production, so that public producers can project themselves over a few years, and not to constantly see their production called into question by lack of funding or by the arrival of cheaper drugs or products from private actors. They stressed the importance of public production lines being sustained over time and not constantly threatened with disruption due to cost issues.

8. *Ibid.*, p. 38

EXAMPLES OF:

Alternative production models.

A. The example of insulin

Although discovered a hundred years ago and sold for a symbolic dollar by its discoverers, who refused to make it a source of private profit, different forms of insulin are still under patents, as illustrated by the report of the organisation I-MAK “Overpriced, overpatented”¹, and its provision is made within an oligopoly of three pharmaceutical giants (Novo Nordisk, Sanofi and Eli Lilly) which impose very high prices. In the United States, these prices and the vagaries of the insurance companies on which the health coverage of millions of people depends limit access to insulin, and have very strong repercussions on the care of people with type 1 diabetes and leads to deaths, in particular for people who do not have access to medical coverage or cannot pay for their treatment. Studies on the real costs of insulin production and investment in research and development carried out many years ago show that nothing justifies such prices, and nothing else explains the huge price differential between a country like the United States and its Canadian neighbour. Thus, according to a study published in 2018 in the *BMJ Global Health*² “Treatments with biosimilar RHIs and NPH insulin could cost less than US \$72 per year, and insulin analogues less than US \$133 per year”, very far from the prices practiced in the United States in particular. Insulin is thus a typical case of a production and marketing model that calls into question the safety of supply of this vital product³.

THE “OPEN INSULIN” PROJECT

In the United States, a project developed by the “Open Insulin” foundation aims to produce insulin on a small scale. The Open Insulin project⁴, supported by the foundation of the same name, was born in Oakland, California in 2015 at an event organised

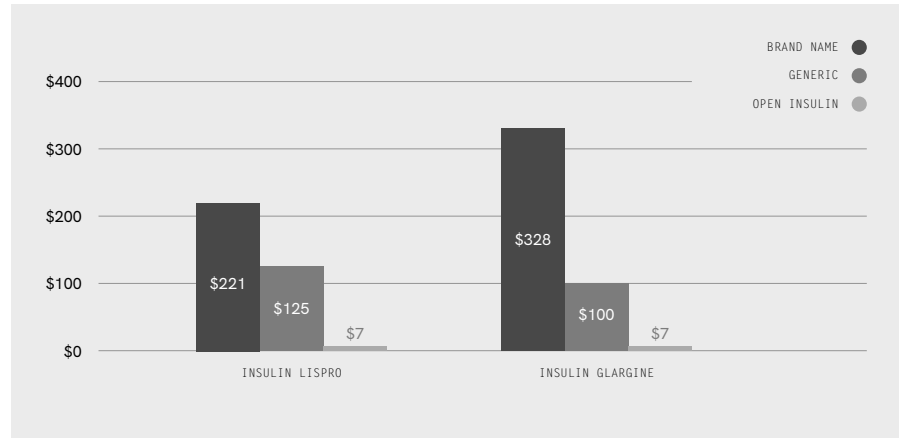
1. I-MAK, “Overpatented, overpriced, How Excessive Pharmaceutical Patenting is Extending Monopolies and Driving up Drug Prices”, 2013.

2. Dzintars Gotham, Melissa J Barber et Andrew Hill, “Production costs and potential prices for biosimilars of human insulin and insulin analogues”, *BMJ Global Health* 2018;3.

3. D. Beran, Z. Mirzab & Jicui Dongc, 2019/05/01, “Access to insulin: applying the concept of security of supply to medicines”, Bulletin of the WHO, issue 97, pages 358-364

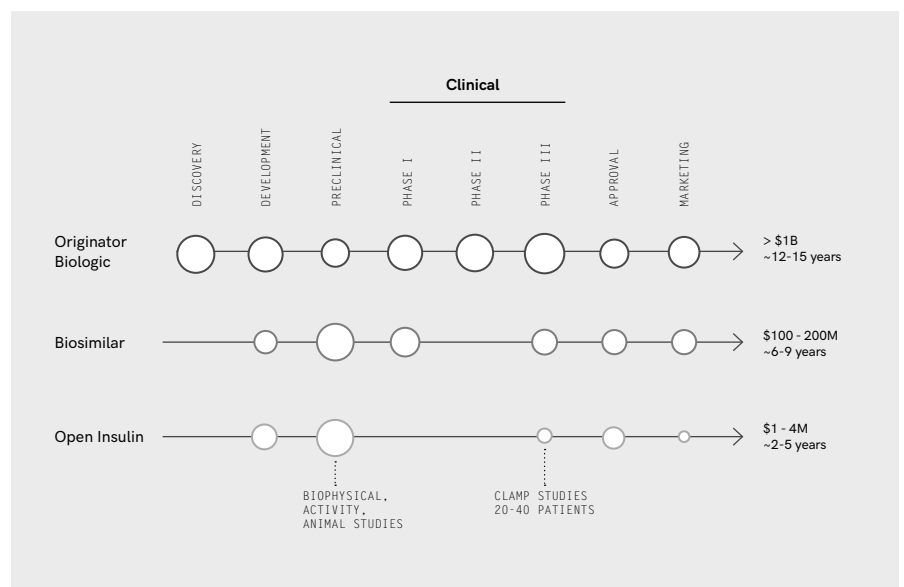
4. <https://openinsulin.org>

by the biohackers of Counter Culture Labs. Governance is provided by researchers, people with diabetes, young people (college and high school students) whose presence also testifies to the desire to democratise the debate and the thinking on healthcare products through education. The primary objective is to allow local production on a small scale, that of a city for example, of fast-acting (lispro) or slow-acting (glargine) insulin, in open source, therefore accessible and reusable without prior authorisation.



Open source involves the manufacturing process of insulin itself, and also the technologies used, such as the bioreactor or a protein purification system. Such devices, purchased on the current market, represent an initial investment incompatible with small-scale production. Open Insulin researchers are therefore also working to make these devices open source in order to lower the price. One of the objectives is, for example, to develop an open source FPLC (Fast Protein Liquid Chromatography) whose investment would not exceed \$2000, while the current price is above \$100,000. Progress in this area is slower and the work more difficult than the synthesis of insulin itself.

Likewise, Open Insulin has worked to develop best practices for insulin production to lower the cost of FDA procedures related to quality and safety assessment, without conceding anything to these two decisive requirements:



Finally, the foundation is working on an economic model of networks of small production sites, managed in particular by people with diabetes themselves, which could form partnerships with pharmacies and hospitals. It is the development of this model that seems the most problematic step. In fact, although wanting to take biopharmaceuticals out of the logic of the market and patents, the foundation finds itself confronted with that, given their importance. It must therefore develop a model while being bound by the logic of profitability and financial viability, even if it does not seek to make profits, for example in the calculation of the minimum quantity of insulin that should be produced, delivery times, and the distribution network. European institutions could promote such a model and support it financially, especially in this last stage.

If the “Open Insulin” project raises questions related to the scale of production, and about the approval of smaller-scale production units by health agencies, and thus presents limitations in a context of an ultra-concentration of this market around three large producers registered in most of the richest countries, the model deserves to be mentioned in this report and explored.

B. Cancer medicines and hospital production

In the Netherlands in 2017, hospitals decided to produce cancer medicines in public hospitals. As the Dutch health authorities failed to reach an agreement with the original producers on the price of these patented treatments, hospitals decided to take charge of the production. The intellectual property agreement allows for the lifting of intellectual property rights for research purposes or in the context of clinical research. This is the lever that was used.

Thus, in 2017, the *Erasmus medical center* in Rotterdam began production of these medicines⁵. This movement was initiated by Dutch pharmacies, and in particular the Erasmus medical center, Amsterdam’s University medical center, and the *Transvaal pharmacy* in The Hague.

To counter this initiative, pharmaceutical companies have raised the issue of the quality of the products and concerns about safety. While these issues should in no way be minimized, particularly with regard to biological medicines, and particularly those used against cancer, it must be clearly understood that the quality argument is traditionally used by multinational pharmaceutical companies to dissuade recourse by governments to medicines from other producers.

This distrust is reinforced by a legal barrier which is that of the exclusivity of clinical data, which is present in European law, for a period of 5+2+1 years. During this period, regardless of the presence or absence of a patent, a generic production will not be able to compare the results of bioequivalence studies with the clinical trials of the *originator* producer, which will oblige the generic producer to carry out new trials, which is expensive (therefore dissuasive) and unethical. Indeed, it is not ethical to multiply clinical trials, as is the case on an effective medicine already approved. Added to this are questions of the use of resources, public in particular, and the fact that it is not easy to find volunteers for the trials.

As we have seen in many recent examples, the question of quality is constantly used to discredit the production of generics and alternative initiatives. It should be remembered, and this question should not be minimized, that the production of APIs

5. Reuters, “[Dutch join backlash at expensive drugs by making their own](#)”

is concentrated in the hands of very few producers, which may be the same for producers of generics and originators. Furthermore, the recent example of the production of messenger RNA vaccines shows that it has been possible for producers with no experience of production in this field to produce these vaccines after a transfer of technology and in record times.

C. Military public production

Military pharmaceutical production must be integrated into consideration for several reasons. On one hand, some health products are the application of military research. Such is the case with the insulin injection pens, which were inspired by adrenaline injection tools for American soldiers in the 1970s. As with any product developed with public funds, the legitimacy of patents, which are supposed to reward risk-taking and investment, should be systematically questioned.

On the other hand, these institutions have developed expertise in anticipating and reacting to health, military (biological attack, for example) or civil (nuclear accident, etc.) emergencies which can be a source of inspiration for the entire medicine supply chain. Coordinating health planning with procedures for anticipation, rapid reaction and logistical organisation in the face of an emergency is an essential condition for meeting healthcare needs.

Finally, without calling into question its main objectives, military production must be coordinated with a public relocation of civilian production. The German armed forces pharmacy already produces anticancer medicines⁶ and can inspire a model. For its part, the pharmacy of the French armies produces many medicines which are destroyed⁷, and this waste can eventually be reduced by rethinking a civil orientation of products.

6. "Arzneimittelherstellung in der bundeswehr", *Wehrmedizin und Wehrpharmazie*, 6 juillet 2013.

7. Rozenn Le Saint, « Plongée dans la fabrique à antidotes de l'armée française », (Plunge into the French army's antidote factory), *Mediapart*, 26 August 2019.

Intellectual property rights.

Internationally, intellectual property rights are governed by World Trade Organisation agreements that entered into force in 1995; the TRIPS Agreement. This agreement imposes a number of obligations on the granting of pharmaceutical patents on WTO member states, including the obligation to grant patents for a minimum term of 20 years. On the other hand, the TRIPS agreement offers a certain latitude to countries to transpose into their national laws what are commonly called «flexibilities», or even «safeguards», allowing assertion of public health requirements, such as the possibility for countries to define patentable subject matter, the scope of patentability, and to exclude various elements from patentability. Very concretely, some countries have decided to allow the granting of patents for a pharmaceutical combination, others do not.

THE EXAMPLE OF RIFAPENTINE AND ISONIAZID

The textbook case study on this subject concerns treatments for tuberculosis: rifapentine and isoniazid and the Sanofi company, which, in 2013 and 2014, filed patent applications in 55 countries, including member countries of the European convention on the patent, for a combination of these two molecules, whereas Sanofi discovered neither one, and these molecules have been on the market since 1952 and 1988, respectively.

Laws such as European law allow the granting of patents on such a combination. On the other hand, countries like Brazil do not allow it. So, as was reported by the newspaper *Le Monde*, in particular following the publication of a report by the Treatment Action Group (TAG), the Sanofi company decided to withdraw its patent applications and its worldwide patents on this combination. Some countries have granted patents on this combination, notably South Africa, which has defined a very broad scope of patentability in its national law. That patents can be granted on a combination of two molecules discovered a very long time ago, and whereas the benefit of this formulation was demonstrated during tests financed by UNITAID; i.e., public money, illustrates how dysfunctional the patent system is.

* Catherine Mary, "[Tuberculosis: rifapentine-based treatment finally accessible to all?](#)", *Le Monde*, October 19 2020.

** Londeix P et Frick M., Treatment Action Group (TAG) "[Isoniazid/Rifapentine \(3HP\) Access Roadmap and Patent Landscape](#)"

The TRIPS agreement also allows countries wishing to do so, and which have already granted a patent, to have the patented object produced by a third party, through the provisions of a compulsory licence or ex officio licence. Some countries also allow the legitimacy of a granted patent to be challenged, because sometimes, due to lack of resources or by mistake, patents granted by officers in patent offices do not meet the criteria for patentability. At the European level, the exercise of this remedy is complicated by very strict criteria, in particular on deadlines which are too short. A relaxation of these criteria would allow civil society to intervene more often.

The TRIPS Agreement also allows other types of “flexibilities”, such as parallel imports, which are particularly common and current in the European common market. Parallel imports are governed by the regime of exhaustion of rights in a market. In other words, once a brand-name medicine is marketed in a given country for a given price, it can be legally imported or exported to another country at the same price, while in the country of destination, the same medicine can be marketed for a higher price.

If all these flexibilities and standards are briefly detailed here, another “flexibility” seems essential to us: the time granted to the least developed countries (LDCs) by the WTO to grant patents on pharmaceutical pro-

ducts. These countries can use a “transitional period” granted therefore by the WTO. If not all countries make full use of it, it is fundamental in its philosophy and in what it teaches us: it is based on the idea and the recognition that it is the period before the granting of patents that has enabled industrialised countries, especially European countries such as Germany and France, to develop their pharmaceutical industrial park. In other words, the WTO recognises that the development of a large industrial park is incompatible with the systematic granting of patents, and any consideration of reindustrialisation should take this into account, even in rich countries. The WTO also recognises that if the countries of Europe were able to develop their pharmaceutical industrial park in the 1970s, it was in part thanks to the absence of patents. In Switzerland, patents on pharmaceutical products were introduced in 1977 and in Germany in 1967.

The same goes for countries that have strong pharmaceutical production in developing countries, such as India, China, Bangladesh and Brazil, all of which have optimised a period without patents, or pre-TRIPS agreements, to develop their industrial park.

India replaced its “British Act of 1911” with its Patent Act of 1970, which effectively abolished all patents on medicines. From that date, and until 2005, when the country had to apply the rules of the TRIPS Agreement after a period of transition, India was able to develop a medicine and raw materials industry.

If the development of public medicine production has been so effective in Brazil in particular, it is because the country has been able to make the best use of the existing flexibilities in international law on intellectual property, World Trade Organisation (WTO) law and the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). Indeed, Brazil has been able to define in its national patent law strict conditions, criteria and exceptions to patentability, which has enabled an efficient patent office to reject patent applications that do not meet these criteria. This enabled an acceleration of the production in generic form of medicines sold as innovations and in the form of *originator medicines* in European countries. This also enabled weighing and rebalancing in part negotiating power for the health authorities, in the process of negotiating the price of these products with the laboratories.

Brazilian governments have also used other provisions of WTO law to lift patents and allow local production, especially in the case of antiretroviral medicines used for HIV/AIDS, such as efavirenz.

In Egypt, the producer Pharco has been able to juggle its factories in Egypt and Saudi Arabia for the production of active ingredients for sofosbuvir and daclatasvir, according to the patents issued in each of these countries. This production is coupled with exemplary and rigorous work on the part of the officers of the Egyptian patent office, who by their meticulous efforts have in recent years prevented the granting of patents on medicines representing only limited innovation at the molecular level, for example with sofosbuvir.

1. “Recognising also the special needs of the least developed Member countries with regard to the implementation of laws and regulations at the domestic level with maximum flexibility, so that these countries can equip themselves with a solid and viable technological base,” Preamble of the TRIPS Agreement - article 66. 1. “Given the special needs and requirements of the least-developed Member countries, their economic, financial and administrative constraints, and the fact that they need flexibility to build a viable technological base, these Members will not be required to apply the provisions of this Agreement, excluding those of Articles 3, 4 and 5, for a period of 10 years from the date of application, as defined in paragraph 1 of article 65. Upon a duly substantiated request from a least-developed Member country, the TRIPS Council will grant extensions for this period.” PART VI - TRANSITIONAL PROVISIONS - Article 66 - Least-developed Member countries (Article 3 - National treatment, Article 4 - Most-favoured-nation treatment, Article 5 - Multilateral agreements on the acquisition or maintenance of protection)

Not all countries have incorporated these flexibilities in the same way into their national law, and the European Patent Convention limits their use through different clauses. These clauses also differ from country to country in the European Union. While there is a European Patent Convention, and a European Patent Office (EPO), patent laws and the use of TRIPS flexibilities such as compulsory licences are based on national law, patent law being a territorial right.

In addition, the clause on the exclusivity of clinical data, also present in European law, also limits the use of generics and the production of patented medicines, even in the case of compulsory licence.

It is therefore impossible to grasp the issue of public pharmaceutical production in Europe or in the Member States without including in-depth reflection on intellectual property issues. European law and patent laws in the Member States must be reformed to define a more circumscribed scope of patentability, granting patents only for real therapeutic innovations, and easier recourse to opposition by third parties and to compulsory or ex officio licences.

Thus questions relating to intellectual property rights are essential elements to make production, and a relocation of pharmaceutical production in Europe, operational. Other clauses in European law, such as clinical data exclusivity and market exclusivity, should be lifted when necessary to speed up the use of generics.

TRANSPARENCY, PUBLIC PRODUCTION AND PATENT LAW REFORM ARE THE RECOMMENDATIONS OF THE FRENCH NATIONAL CONSULTATIVE ETHICS COMMITTEE (CCNE) TO GUARANTEE ACCESS TO THERAPEUTIC INNOVATIONS

The CCNE has proposed recommendations aimed at making it possible to reconcile two objectives: the optimisation of access to the best care for everyone, and the optimisation of efforts to find a lower price within the framework of the negotiations. This objective is broken down into the following triad: (1) require transparency; (2) strengthen and/or broaden the skills of public authorities; (3) develop a policy of cooperation at the European and even international level.

- 1/ The requirement for transparency is ethical and democratic before being strategic economically. This desire it is expressed through the establishment of a «Séjour du médicament», bringing together all the stakeholders in the sector, including representatives of society, to discuss the methods of developing a transparency policy based on the definition of explicit cost rules. The ceiling on authorised lobbying expenses for pharmaceutical companies, as well as the supervision of the practices of pharmaceutical representatives, must constitute measures making it possible to limit the effects of influence on marketing authorisations on European territory, as well as as on the practices of prescribers, encouraged to develop an ethical and multidisciplinary dimension in decision-making processes for the allocation of innovative medicines.
- 2/ The second part of the recommendations should make it possible to strengthen the public bodies preparing for negotiations by calling on public researchers and personalities from the world of academia to carry out medico-economic analyses, by developing real-life evaluations of the efficacy of innovative and expensive medicines. It will also be a question of consolidating the patent offices so that they have the necessary means and information (legal and regulatory provisions) to assess the effectiveness of the innovations proposed by manufacturers. Finally, one recommendation involves the criticism of the current economic model, by proposing to create a «public drug centre» (autonomous) to set up public (or mixed) entities for the production of both innovative non-profit and profitable medicines, based on the coordination of research teams.
- 3/ The third component, at the European and international level, encourages the promotion of a cooperation policy to reflect on the issues relating to the legal qualification of certain innovative medicines as «global public goods», to also reflect on the possibility of creating a European agency specialising in the economic analysis of health products, or to broaden the skills of the EMA and, more generally, to strengthen health sovereignty at the national and European level.

WHO list of essential medicines.

A

Abacavir
Abacavir + lamivudine
Abiraterone
Acetazolamide
Acetic acid
Acetylcysteine
Acetylsalicylic acid
Aciclovir
Activated charcoal
Adalimumab
Afinib
Albendazole
Alcohol based hand rub
All-trans retinoic acid
Allopurinol
Alteplase
Amidotrizoate
Amikacin
Amiloride
Amiodarone
Amitriptyline
Amlodipine
Amodiaquine
Amodiaquine + sulfadoxine + pyrimethamine
Amoxicillin
Amoxicillin + clavulanic acid
Amphotericin b
Ampicillin
Anastrozole
Anti-d immunoglobulin
Anti-rabies immunoglobulin
Anti-tetanus immunoglobulin
Antivenom immunoglobulin
Apixaban
Aprepitant
Arsenic trioxide
Artemether
Artemether + lumefantrine
Artesunate
Artesunate + amodiaquine
Artesunate + mefloquine
Artesunate + pyronaridine tetraphosphate
Ascorbic acid
Asparaginase
Atazanavir
Atazanavir + ritonavir
Atenolol
Atorvastatin
Atracurium
Atropine
Azathioprine
Azithromycin

B

Barium sulfate
Bcg vaccine
Beclometasone
Bedaquiline
Bendamustine
Benzathine benzylpenicillin
Benznidazole
Benzoyl peroxide
Benzyl benzoate
Benzylpenicillin
Betamethasone
Bevacizumab
Bicalutamide
Biperiden
Bisoprolol
Bleomycin
Bortezomib
Budesonide
Budesonide + formoterol
Bupivacaine

C

Caffeine citrate
Calamine
Calcium
Calcium folinate
Calcium gluconate
Capecitabine
Carbamazepine
Carbetocin
Carbimazole
Carboplatin
Carvedilol
Cefalexin
Cefazolin
Cefixime
Cefotaxime
Ceftazidime
Ceftazidime + avibactam
Ceftriaxone
Cefuroxime
Certolizumab pegol
Chlorambucil
Chloramphenicol
Chlorhexidine
Chlorine base compound
Chloroquine
Chloroxylenol
Chlorpromazine
Cholera vaccine
Ciclosporin

Ciprofloxacin
Cisplatin
Clarithromycin
Clindamycin
Clofazimine
Clomifene
Clomipramine
Clopidogrel
Clotrimazole
Cloxacillin
Clozapine
Coagulation factor ix complex
Coagulation factor viii
Coal tar
Codeine
Colecalciferol
Colistin
Compound sodium lactate solution
Condoms
Copper-containing intrauterine device
Cyclizine
Cyclophosphamide
Cycloserine
Cytarabine

D

Dabigatran
Dacarbazine
Daclatasvir
Dactinomycin
Dalteparin
Dapsone
Darbepoetin alfa
Darunavir
Dasabuvir
Dasatinib
Daunorubicin
Deferoxamine
Delamanid
Dengue vaccine
Desmopressin
Dexamethasone
Dextran 70
Diaphragms
Diazepam
Diazoxide
Diethylcarbamazine
Digoxin
Dihydroartemisinin + piperaquine phosphate
Diloxanide
Dimercaprol
Diphtheria antitoxin

Diphtheria vaccine
Docetaxel
Docusate sodium
Dolutegravir
Dolutegravir + lamivudine + tenofovir
Dopamine
Doxorubicin
Doxycycline

E

Edoxaban
Efavirenz
Efavirenz + emtricitabine + tenofovir
Efavirenz + lamivudine + tenofovir
Eflornithine
Emtricitabine + tenofovir
Enalapril
Enoxaparin
Entecavir
Ephedrine
Epinephrine
Epoetin alfa
Epoetin beta
Epoetin theta
Ergocalciferol
Ergometrine
Erlotinib
Erythromycin
Erythropoiesis-stimulating agents
Estradiol cypionate + medroxyprogesterone acetate
Etanercept
Ethambutol
Ethambutol + isoniazid + pyrazinamide + rifampicin
Ethambutol + isoniazid + rifampicin
Ethanol
Ethinylestradiol + levonorgestrel
Ethinylestradiol + norethisterone
Ethionamide
Ethosuximide
Etonogestrel-releasing implant
Etoposide

F

Fentanyl
Ferrous salt
Ferrous salt + folic acid
Fexinidazole
Filgrastim
Fluconazole
Flucytosine
Fludarabine
Fludrocortisone
Fluorescein
Fluorouracil
Fluoxetine
Fluphenazine
Fluvastatin
Folic acid
Fomepizole
Fosfomycin
Fresh-frozen plasma
Furosemide

G

Gefitinib
Gemcitabine
Gentamicin
Glecaprevir + pibrentasvir
Gliclazide
Glucagon
Glucose
Glucose + sodium chloride
Glutaral
Glyceryl trinitrate
Golimumab
Griseofulvin

H

Haemophilus influenzae type b vaccine
Haloperidol
Halothane
Heparin sodium
Hepatitis a vaccine
Hepatitis b vaccine
Hpv vaccine
Hydralazine
Hydrochlorothiazide
Hydrocortisone
Hydromorphone
Hydroxocobalamin
Hydroxycarbamide
Hydroxychloroquine
Hyoscine butylbromide
Hyoscine hydrobromide

I

Ibuprofen
Ifosfamide
Imatinib
Indometacin
Infliximab
Influenza vaccine (seasonal)
Insulin
Intermediate-acting insulin
Intraperitoneal dialysis solution
Iodine
Iohexol
Ipratropium bromide
Irinotecan
Isoflurane
Isoniazid
Isoniazid + pyrazinamide + rifampicin
Isoniazid + pyridoxine + sulfamethoxazole + trimethoprim
Isoniazid + rifampicin
Isosorbide dinitrate
Itraconazole
Ivermectin

J

Japanese encephalitis vaccine

K

Ketamine

L

Lactulose
Lamivudine
Lamivudine + nevirapine + zidovudine
Lamivudine + zidovudine
Lamotrigine
Latanoprost
Ledipasvir + sofosbuvir
Lenalidomide
Leuprorelin
Levamisole
Levodopa + carbidopa
Levofloxacin
Levonorgestrel
Levonorgestrel-releasing implant
Levothyroxine
Lidocaine
Lidocaine + epinephrine
Linezolid
Lisinopril + amlodipine
Lisinopril + hydrochlorothiazide
Lithium carbonate
Loperamide
Lopinavir + ritonavir
Loratadine
Lorazepam

Losartan
Lovastatin
Lugol's solution

M

Magnesium sulfate
Mannitol
Measles vaccine
Mebendazole
Medroxyprogesterone acetate
Mefloquine
Meglumine antimoniate
Meglumine iotroxate
Melarsoprol
Melphalan
Meningococcal meningitis vaccine
Mercaptopurine
Meropenem
Meropenem + vaborbactam
Mesalazine
Mesna
Metformin
Methadone
Methimazole
Methotrexate
Methoxy polyethylene glycol-epoetin beta
Methyldopa
Methylprednisolone
Methylthionium chloride
Metoclopramide
Metoprolol
Metronidazole
Miconazole
Midazolam
Mifepristone - misoprostol
Miltefosine
Misoprostol
Morphine
Moxifloxacin
Multiple micronutrient powder
Mumps vaccine
Mupirocin

N

Nadroparin
Naloxone
Natamycin
Neostigmine
Nevirapine
Niclosamide
Nicotinamide
Nicotine replacement therapy
Nifedipine
Nifurtimox
Nilotinib
Nitrofurantoin
Nitrous oxide
Nivolumab
Norethisterone
Norethisterone enantate
Normal immunoglobulin
Nystatin

O

Nystatin
Ofloxacin
Ombitasvir + paritaprevir + ritonavir
Omeprazole
Ondansetron
Oral rehydration salts
Oral rehydration salts - zinc sulfate
Osetamivir
Oxaliplatin
Oxamniquine
Oxycodone
Oxygen
Oxytocin

P

P-aminosalicylic acid
Paclitaxel
Pancreatic enzymes
Paracetamol
Paromomycin
Pegaspargase
Pegylated interferon alfa (2a)
Pegylated interferon alfa (2b)
Pembrolizumab
Penicillamine
Pentamidine
Permethrin
Pertussis vaccine
Phenobarbital
Phenoxymethylpenicillin
Phenytoin
Phytomenadione
Pilocarpine
Piperacillin + tazobactam
Platelets
Plazomicin
Pneumococcal vaccine
Podophyllotoxin
Podophyllum resin
Poliomyelitis vaccine
Polygeline
Polymyxin b
Potassium chloride
Potassium ferric hexacyanoferrate
Potassium iodide
Potassium permanganate
Povidone iodine
Pravastatin
Praziquantel
Prednisolone
Primaquine
Procaine benzylpenicillin
Procarbazine
Progesterone vaginal ring
Proguanil
Propofol
Propranolol
Propylthiouracil
Prostaglandin e1
Prostaglandin e2
Protamine sulfate
Pyrantel
Pyrazinamide
Pyridostigmine
Pyridoxine
Pyrimethamine

Q

Quinine

R

Rabies vaccine
Raltegravir
Ranitidine
Realgar-indigo naturalis formulation
Red blood cells
Retinol
Ribavirin
Riboflavin
Rifabutin
Rifampicin
Rifapentine
Risperidone
Ritonavir
Rituximab
Rivaroxaban
Rotavirus vaccine
Rubella vaccine

S

Salbutamol

Salicylic acid
Selenium sulfide
Senna
Silver sulfadiazine
Simvastatin
Sodium calcium edetate
Sodium chloride
Sodium fluoride
Sodium hydrogen carbonate
Sodium nitrite
Sodium nitroprusside
Sodium stibogluconate
Sodium thiosulfate
Sofosbuvir
Sofosbuvir + velpatasvir
Spectinomycin
Spironolactone
Streptokinase
Streptomycin
Succimer
Sulfadiazine
Sulfadoxine + pyrimethamine
Sulfamethoxazole + trimethoprim
Sulfasalazine
Suramin sodium
Surfactant
Suxamethonium

T

Tamoxifen
Telmisartan + amlodipine
Telmisartan + hydrochlorothiazide
Tenofovir disoproxil fumarate
Terbinafine
Testosterone
Tetanus vaccine
Tetracaine
Tetracycline
Thalidomide
Thiamine
Tick-borne encephalitis vaccine
Timolol
Tioguanine
Tiotropium bromide
Tranexamic acid
Trastuzumab
Triclabendazole
Tropicamide
Tuberculin, purified protein derivative
Typhoid vaccine

U

Ulipristal
Urea

V

Valaciclovir
Valganciclovir
Valproic acid
Vancomycin
Varicella vaccine
Vecuronium
Verapamil
Vinblastine
Vincristine
Vinorelbine
Voriconazole

W

Warfarin
Water for injection
Whole blood

X

Xylometazoline

Y

Yellow fever vaccine

Z

Zidovudine
Zinc sulfate
Zoledronic acid

APPENDIX 02

Medicines and diagnostic agents of major therapeutic benefit as defined by the health authorities in France.

A. Digestive pathways and metabolism

A02	Medicines for acidity disorders
A02b	Medicines for peptic ulcer and gastroesophageal reflux (ger)
A03	Medicines for gastrointestinal functional disorders
A03b	Belladonna and derivatives
A04	Antiemetics and antinausea agents
A04a	Antiémétiques et antinauséux
A05	Hepatic and biliary therapeutics
A05a	Hepatic and biliary therapeutics
A05b	Hepatic, lipotropic therapeutics
A06	Medicines for constipation
A06a	Medicines for constipation
A07	Antidiarrhoeals, intestinal anti-inflammatory and anti-infectious agents
A07a	Intestinal anti-infectious agents
A07e	Intestinal anti-inflammatory agents
A10	Medicines for diabetes
A10a	Insulins and analogues
A10b	Hypoglycemic medicines, insulins excluded

A11c	Vitamins A and D, combinations of the two included
A11d	Vitamins B1 not in combination and in combination with vitamins B6 and B12
A11h	Other non-combined vitamin preparations
A11j	Other vitamin medicines, combinations
A12	Mineral supplements
A12a	Calcium
A12b	Potassium
A12c	Other mineral supplements
A16	Other medicines of the digestive tract and metabolism
A16a	Other medicines of the digestive tract and metabolism

B. Blood and hematopoietic organs

B01	Antithrombotics
B01a	Antithrombotics
B02	Antihaemorrhagics
B02a	Antifibrinolytics
B02b	Vitamin K and other haemostatics
B03	Anti-anaemic preparations
B03a	Iron preparations
B03b	Vitamin B12 and folic acid
B03x	Other anti-anaemic preparations
B05	Blood substitutes and infusion solution
B05a	Blood and derivatives
B05b	Intravenous solutions
B05d	Solutions for peritoneal dialysis
B05x	Additives for intravenous solutions
B05z	Solution for haemodialysis and haemofiltration
B06	Other medicines used in haematology
B06a	Other medicines used in haematology

C. Cardiovascular system

C01	Cardiology medicines
C01a	Cardiotonic glycosides
C01b	Antiarrhythmics, class I and III
C01c	Cardiac stimulants, cardiotonic glycosides excluded
C01d	Vasodilators in cardiology
C01e	Other cardiology medicines
C02	Antihypertensives
C02a	Centrally acting adrenolytics
C02b	Ganglioplegic adrenolytics
C02c	Peripherally acting adrenolytics

C02d	Medicines acting on arteriolar smooth muscle
C02k	Other antihypertensives
C02l	Antihypertensives and diuretics in combination
C02n	Combinations of antihypertensives of the C02 group
C03	Diuretics
C03a	"Low-ceiling" diuretics, thiazides
C03b	"Low-ceiling" diuretics, thiazides excluded
C03c	Loop diuretics
C03d	Potassium sparing diuretics
C03e	Potassium sparing diuretics in combination
C03x	Other diuretics
C07	Beta-blockers
C07a	Beta-blockers
C07b	Beta-blockers and thiazides
C07c	Beta-blockers and other diuretics
C07d	Beta-blockers, thiazides and other diuretics
C07e	Beta-blockers and vasodilators
C07f	Beta-blockers and other antihypertensives
C08	Calcium channel blockers
C08c	Selective calcium channel blockers with vascular effects
C08d	Selective calcium channel blockers with direct cardiac effects
C08e	Non-selective calcium channel blockers
C08g	Calcium channel blockers and diuretics
C09	Medicines acting on the renin-angiotensin system
C09a	Non-combined angiotensin-converting enzyme (ace) inhibitors
C09b	Angiotensin-converting enzyme (ace) inhibitors in combination
C09c	Angiotensin ii antagonists, non-combined
C09d	Angiotensin ii antagonists, combined
C09x	Other medicines acting on the renin-angiotensin system
C010	Lipid modifiers
C010a	Non-combined lipid modifiers

D. Dermatological medicines

D01	Antifungals for dermatological use
D01a	Antifungals for topical use
D01b	Antifungals for systemic use
D03	Preparations for the treatment of wounds and ulcers
D03b	Enzymes
D05	Psoriasis medicines
D05a	Topical psoriasis medicines
D05b	Systemic psoriasis medicines
D06	Antibiotics and chemotherapy for dermatological use

D07	Corticosteroids, dermatological preparations
D07a	Non-combined corticosteroids
D08	Antiseptics and disinfectants
D08a	Antiseptics and disinfectants
D11	Other dermatological preparations
D11a	Other dermatological preparations

G. Genitourinary system and sexual hormones

G01	Anti-infectious and antiseptic agents for gynaecological use
G02	Other gynaecological medicine
G02a	Uterotonic agents
G02b	Contraceptives for topical use
G02c	Other gynaecological medicines
G03	Sexual hormones and genital function modulators
G03a	Hormonal contraceptives for systemic use
G03b	Androgens
G03c	Oestrogens
G03d	Progestins
G03g	Gonadotropins and other ovulation stimulants
G03h	Anti-androgens
G03x	Other sexual hormones and genital function modulators

H. Systemic hormones, sexual hormones excluded

H01	Hypophyseal, hypothalamic and similar hormones
H01a	Hormones of the anterior hypophysis and analogues
H01b	Hormones of the posterior hypophysis
H01c	Hypothalamic hormones
H02	Corticosteroids for systemic use
H02a	Corticosteroids for systemic use, non-combined
H02c	Adrenal hormone synthesis inhibitors
H03	Thyroid medicines
H03a	Thyroid preparations
H03b	Antithyroid agents
H03c	Iodine medicines
H04	Pancreatic hormones
H04a	Glycogenolysis hormones
H05	Calcium homeostasis medicines
H05a	Parathyroid hormones and analogues
H05b	Anti-parathyroid agents

J. Systemic general anti-infectious agents

J01	Systemic antibacterials, analgesics
J01a	Tetracyclines
J01b	Phenicolis
J01c	Beta-lactams: penicillins
J01d	Other beta-lactams
J01e	Sulfonamides and trimethoprim
J01f	Macrolides, lincosamides and streptogramins
J01g	Aminoglycoside antibacterials
J01m	Quinolone antibacterials
J01r	Antibacterial combinations
J01x	Other antibacterials
J02	Antimycotics for systemic use
J02a	Antimycotics for systemic use
J04	Antimycobacterials
J04a	Antitubercular agents
J04b	Antileprosy agents
J05	Antivirals for systemic use
J05a	Direct acting antivirals
J06	Immunoserums and immunoglobulins
J06a	Immunoserums
J06b	Immunoglobulins
J07	Vaccines
J07a	Bacterial vaccines
J07b	Viral vaccines
J07c	Combined bacterial and viral vaccines

L. Antineoplastics and immunomodulators

L01	Antineoplastics
L01a	Alkylating agents
L01b	Antimetabolites
L01c	Plant alkaloids and other medicines of natural origin
L01d	Cytotoxic and related antibiotics
L01x	Other antineoplastics
L02	Endocrine therapeutic agents
L02a	Hormones and related agents
L02b	Anti-hormones and related agents
L03	Immunostimulants
L03a	Immunostimulants
L04	Immunosuppressants
L04a	Immunosuppressants

M. Muscle and skeleton

M03	Myorelaxants
M03a	Peripherally acting myorelaxants
M03b	Centrally acting myorelaxants
M03c	Direct acting myorelaxants
M04	Antigout agents
M04a	Antigout agents
M05	Medicines for the treatment of bone disorders
M05b	Medicines acting on bone structure and mineralisation

N. Nervous system

N01	Anaesthetics
N01a	General anaesthetics
N01b	Local anaesthetics
N02	Analgesics
N02a	Opioids
N02b	Other analgesics and antipyretics
N03	Anti-epileptics
N03a	Anti-epileptics
N04	Antiparkinsonian agents
N04a	Anticholinergics
N04b	Dopaminergics
N05	Psycholeptics
N05a	Antipsychotics
N05b	Anxiolytics
N06	Psychoanaleptics
N06a	Antidepressants
N06b	Psychostimulants, agents used for adhd and nootropics
N06d	Medicines for dementia
N07	Other nervous system medicines
N07a	Parasympathomimetics
N07b	Medicines used in addiction phenomena
N07x	Other nervous system medicines

P. Antiparasitics, insecticides and repellents

P01	Antiprotozoals
P01a	Medicines for amebiasis and other protozoa
P01b	Antimalarials
P01c	Antileishmanials and trypanocidals
P02	Anthelmintics
P02b	Antitrepatodals

P02c	Antinematodals
P02d	Anticestodals
P03	External antiparasitics, including scabicides, insecticides and repellents
P03a	External antiparasitics, including scabicides

R. Respiratory system

R03	Medicines for obstructive airway syndromes
R03a	Adrenergics for inhalation
R03b	Other medicines for obstructive airway syndrome by inhalation
R03c	Adrenergics for systemic use
R03d	Other medicines for obstructive airway syndromes for systemic use
R06	Antihistaminics for systemic use
R06a	Antihistaminics for systemic use
R07	Other medicines for the respiratory system
R07a	Other medicines for the respiratory system

S. Sensory organs

S01	Ophthalmic medicines
S01a	Anti-infectives
S01b	Anti-inflammatories
S01e	Antiglaucomatics and miotics
S01f	Mydriatics and cycloplegics
S01h	Local anaesthetics
S01j	Diagnostic medicines
S01l	Medicines for ocular vascular disorders
S01x	Other ophthalmologic medicines
S02	Otologic medicines
S02a	Anti-infectives
S02b	Corticosteroids

V. Miscellaneous

V01	Allergens
V01a	Allergens
V03	All other medicines
V03a	All other medicines
V04	Diagnostic medicines
V04c	Other diagnostic medicine
V08	Contrast agents
V08a	Iodine contrast agents
V08b	Non-iodine contrast agents
V08c	Contrast agents for magnetic resonance imaging
V08d	Ultrasound agents

V09	Radiopharmaceutical agents for diagnostic use
V09a	Central nervous system
V09b	Skeleton
V09c	Renal function
V09d	Hepatic function and reticulo-endothelial system
V09e	Respiratory system
V09f	Thyroid
V09g	Cardiovascular system
V09h	Inflammation and infection detection
V09i	Tumour detection
V09x	Other radiopharmaceutical agents for diagnostic use
V10	Radiopharmaceutical agents for therapeutic use
V10a	Anti-inflammatory agents
V10b	Pain relief (agents for bone tropism)
V10x	Other radiopharmaceutical agents for therapeutic use

Transparency checklist for medicines and health products.

The “national transparency checklist for medicines and health products” was developed by the Observatory for Transparency in Medicine Policies in August 2019.

The idea behind this document is that transparency is crucial, possible and must be implemented immediately. While important tools, including databases, already exist at the international level, we believe governments have the power and responsibility to ensure that comprehensive, accessible and up-to-date tools are updated in real time and made available without further delay. The databases mentioned below must be freely accessible and their content must be systematically checked by public officials before their publication, in particular if the information comes from private entities.

Implementing the transparency checklist can help shape public health, research and development and intellectual property policies, impact medicine price negotiations, and ultimately benefit from access to the healthcare of populations, and protect and strengthen public health systems based on solidarity.

It is time to move on from a general commitment to transparency that Member States agreed to in the 72nd World Health Assembly in May 2019 to concrete actions that can be implemented without further delay by different actors at the national level.

This checklist contains detailed steps to promote transparency on 8 topics in the health products production and supply chain.

We encourage other civil society organisations to apply and adapt it to their national context and to launch observatories to monitor its concrete implementation.

Transparency databases

A database, public and freely accessible on the Internet, brings together all the information available on each medicine or each health product

For each product, the database includes:

- Registration information
- Price information
- Patent information
- Clinical trials information
- R&D spending information
- Information on medicine stock-outs and the risks of medicine shortages
- Governmental positions in international institutions and negotiations
- Conflicts of interest

01

Health product registration information

A public database provides free access on the Internet to information on medicines registered/placed on the market in the country

It is possible to access:

- all the documents presented by the company
- the full decision of the regulatory agency granting or rejecting the registration/marketing authorisation, including the analyses and/or meetings/hearings which dictated the final decision, as well as any related condition or requirement

This database includes information on:

- health products registered/placed on the market, including the characteristics of each formulation
- the name of the company that holds the registration/marketing authorisation
- the validity of the marketing authorisation
- the brand name and the name of the active ingredients
- the location where the final product was produced
- the origin of the active pharmaceutical ingredients (API)/raw materials
- the regulatory route by which the product was registered (normal, abbreviated, etc.)
- the possible portion of the data subject to data exclusivity

02 Price information

A public database provides free access on the Internet to information on the prices of health products registered/ marketed in the country

The database contains information on:

Medicines (chemical and biological)
Vaccines
Gene therapies
Diagnostic and reagent platforms
Medical devices

Price information includes:

Prices paid by the State/Health insurance
The displayed price
The transactions price
Prices for public orders
Prices in private points of sale
The margins of wholesalers, distributors and other intermediaries

The information available includes:

The supplier
The volume purchased
The date of purchase
The terms of the contract (for example: any exclusivity clause, defined duration, clause preventing the issuance of a licence, etc.)
The net price
The maximum authorised price, if a price control exists
The existence of generic versions of the product (including through imports, and prices in other countries)

03 Patent information

A public database making information on patents and other intellectual property rights in force in the country freely available on the Internet is available

If the database contains information provided by private entities, the information is verified by public officials before publication

The database is:

Regularly updated (at least once every six months)
Freely accessible

The database includes all patents and other intellectual property rights covering a particular health product in the country, including whether they are issued, rejected, have expired, and whether an application is pending decision

There is an analysis of each patent listed specifying whether or not the patent is likely to block competition by generics

The database allows searches by:

The name of the active ingredient or the international non-proprietary name (INN)

The name of the technology or brand (e.g., for diagnostic platforms)

The database includes:

Links to WIPO patent numbers/PCT information

A link to regional patent procedures, if applicable (for example: OAPI, EPO)

The title, summary and claims of the patent application are also available in the local language

The status of the request, if it is: pending, granted, rejected, expired, withdrawn, abandoned, etc.

Updated information on each step of the application review process

The complete documents of the analyses and decisions of the examiners of patent applications

Information on third parties who submitted documents related to the examination, and access to all related documents

Information on compulsory licences or ex officio licences issued for patents, and access to all related documents

Information on technology transfer agreements related to a patent/patent application, and access to all related documents

Information on any public funding related to the subject of a patent

The existence and results of legal procedures related to a patent application in the country (for example: claim of non-patentability, infringement, revocation, extension of patent claims)

Guidelines for the national or regional examination of patent applications are publicly available and easily accessible

Information is available regarding any agreement involving national patent offices and patent policies in the country, such as agreements related to the revalidation of the examination conducted in another country or any other examination route (for example: the patent processing highway)

Information is available regarding interactions between the patent office and national competition authorities in the country, including information sharing and mutual assistance (for example: investigations of anti-competitive practices related to the use of intellectual property rights)

Information is available on any event or training attended, or any technical assistance received by the patent office, its employees and collaborators, in particular on sponsors, funders and trainers.

04 Information on clinical trials

A public database makes information on clinical trials conducted in the country freely available on the Internet. It is updated according to each phase of the trial

The database includes, or allows linking with other databases which contain the following information:

- Information on trials, subject arrangements, baseline characteristics, outcomes, adverse events and other information, the protocol and subsequent modifications
- The domain/disease
- The specific intervention tested
- The objective of the trial
- The phase of the trial
- The study design and analysis plan
- The actual number of enrolled participants
- Eligibility criteria for the enrollment of participants
- The actual duration of the trial (start date and end date)
- The location(s) of the study
- The sponsor(s)/funder(s), including details of funding amounts and in-kind contributions for each
- The full budget of the trial
- Detailed information on government funding received to conduct the trials, including direct grants, tax credits and others
- All collaborators involved in the trial

05 Information on research and development (R&D)

PRE-CLINICAL DEVELOPMENT

A public database with free access on the Internet provides information on preclinical studies (data and methodology) as quickly as possible, in particular pharmacological and toxicological studies

FOR EACH HEALTH PRODUCT REGISTERED IN THE COUNTRY

A public database provides open access on the Internet to information on research and development spending for all health products registered in the country

The database includes:

Disaggregated amounts of expenditure by phase of development and over time (discovery, preclinical development broken down by type, clinical development by phase, pharmaceutical development and manufacture and packaging of clinical study materials)

A detailed list of all institutions involved in each stage/phase of development

A detailed list of all sources and amounts of funding by stage/phase of development, including private, philanthropic and public sector

Information on any public funding received by stage/phase of development, including grants, direct aid and tax credits

The start/end date of each stage/phase of development

Information on other countries or other institutions from other countries involved

FOR EACH FUNDING, DIRECT OR INDIRECT, GRANTED BY THE STATE OR BY PUBLIC INSTITUTIONS

A public database providing free access to Internet information on all public funding dedicated to research and development of health products given in the country

This database includes:

The name of the public institution that granted this funding

The recipient of public funding

The total amount of public funding

The percentage that public funding represents in the total amount of the project or of the beneficiary institution if it is core funding

The stage/phase of development covered by public funding

The start/end date of public funding

A clear description of the project, including the methodology, if applicable

The conditions attached to public funding (for example: publication of results in open access, licensing of intellectual property rights, technology transfer policies, price of the finished product, etc.)

The full results of the project

The link(s) to any publication related to the project

Information on intellectual property (e.g., patents) produced during this project, including full access to documents

Information on licensing agreements related to the project, including access to all documents

Information on technology transfer agreements related to the project, including access to all documents

FAILED PROJECTS

The information listed above is also made available for product development projects that have not reached the end of the development process (failures)

06 Shortages and stock-outs

A public database provides free access on the Internet to information on:

- Shortages and stock-outs (or risks of) of medicines or health products in the country
- The availability and stocks of health products in each region/department/city of the country, including in public and private establishments
- The production capacity of active pharmaceutical ingredients (APIs), raw materials and finished products
- The causes of these shortages
- Sanctions and publications of sanctions taken against manufacturers, distributors and wholesalers
- The legal framework of economic sanctions in force in the country

07 Position in international/multilateral institutions and in bilateral/multilateral agreements

A public database provides free access on the Internet to information on official government positions in international meetings and negotiations, in international/multilateral resolutions or in agreements

A public database provides free access on the Internet to information on all bilateral/multilateral agreements signed or under negotiation by the country

The texts of documents signed or under negotiation are available in their entirety

The official position adopted by the government in multilateral/international organisations and bilateral agreements is publicly available with regard to transparency on:

- Information on registration/entering the market
- Price information
- Patent information
- Clinical trials information

Information on R&D expenditure
Information on shortages and risks of stock-outs
Conflicts of interest

The government's position is publicly available regarding clauses that would increase opacity, such as:

The exclusivity of clinical data
Strengthening the protection of trade secrets
Documents relating to national security in the field of research

The government position on transparency is made public in real time, as well as its support for concrete initiatives, within the framework of:

Regional institutions (for example: the European Union, ARIPO, Mercosur, ASEAN)
The United Nations (including high-level meetings and special sessions)
The World Health Organisation
The World Trade Organisation
The World Intellectual Property Organisation
Other international or regional institutions

08 Conflicts of interest

A public database providing free access to Internet information on the links between policy makers and pharmaceutical companies/the private sector

This information concerns:

Heads of State
Members of the government and their cabinet
Members of parliament
Members of health regulatory administrations, particularly those in charge of negotiating the prices of medicines and health products

The database includes:

Contracts or jobs related to the industry
Contracts or salaries signed or received from industries during the mandate
Gifts or reimbursements of expenses by industries during the mandate

APPENDIX 04 (AUGUST 2, 2019)

Italian decree on transparency.

English version

[Emblem of the Italian Republic]

THE MINISTER OF HEALTH
in concert with
THE MINISTER OF ECONOMY AND FINANCE

HAVING REGARD TO Article 1, Paragraph 41, of Law no. 662 of 23 December 1996, which provides that medicines subject to the authorisation procedure laid down in Council Regulation (ECC) no. 2309/93 of 22 July 1993 shall be sold by the holder of the authorisation at a price negotiated with the Ministry of Health, with the assent of the Drugs Single Committee (Commissione unica del farmaco), in accordance with the criteria determined by the Interministerial Committee for the Economic Planning (CIPE), no later than 31 January 1997;

HAVING REGARD TO Decree-Law no. 269 of 30 September 2003, converted by Law no. 326 of 24 November 2003, and in particular to Article 48, which, as establishing the Italian Medicines Agency (Agenzia italiana del farmaco), hereinafter referred to as AIFA, under Paragraph 33 provides that, as from 1 January 2004, the prices of products reimbursed by the National Health Service shall be determined by a negotiation between the Agency and the Producers, in accordance with the procedures and criteria specified in in the CIPE Decision (Delibera CIPE) no. 3 of 1 February 2001, published in the Official Journal (Gazzetta Ufficiale) no. 73 of 28 March 2001;

HAVING REGARD TO Decree-Law no. 536 of 21 October 1996, converted by Law no. 648 of 23 December 1996;

HAVING REGARD TO Article 12 of Decree-Law no. 158 of 13 September 2012, converted by Law no. 189 of 8 November 2012;

HAVING REGARD TO Law no. 145 of 30 December 2018, bearing the State budget for the 2019 financial year and the multiannual budget for the 2019-2021 three-year period, and having particular regard to Paragraph 553 of Article 1, which refers to a decree issued by the Minister of Health, in concert with the Minister of Economy and Finance, after hearing the Standing Conference for Relations Between the State, the Regions and the Autonomous Provinces of Trento and Bolzano (Conferenza permanente per i rapporti tra lo Stato, le regioni e le province autonome di Trento e Bolzano), for the specification of the criteria and procedures which the Italian Medicines Agency (AIFA) shall respect while determining, by negotiation, the prices of medicines reimbursed by the National Health Service;

HAVING also REGARD TO Paragraph 554 of Article 1 of the above-mentioned Law no. 145 of 2018, which provides that, as from 1 January 2019, AIFA, before the expiry of the negotiation agreement with the pharmaceutical company which holds the AIC, may reopen the negotiation procedures in order to reconsider the terms of the existing agreement, in case of meanwhile changes in the market which are such as to justify the foreseeing of an increase in the use level of the medicine, or such as to amount to a cost-therapy ratio which is disadvantageous as compared with other options in the National Pharmaceutical Codex (Prontuario Farmaceutico Nazionale);

HAVING REGARD TO the above-mentioned CIPE Decision of 1 February 2001, bearing the specification of the criteria for the negotiation of the prices of medicines, published in the Official Journal no. 73 of 28 March 2001;

HAVING CONSIDERED the normative mandate laid down in the above-mentioned Paragraph 553, and having considered that medicines are means of protection of health, are supplied by the National Health Service (SSN), and, as they are included in the basic levels of welfare, have a substantial impact on the SSN;

HAVING CONSIDERED the WHA Resolution 72/2019;

HAVING DEEMED it necessary, for the negotiation between AIFA and the pharmaceutical company about the prices of medicines paid by the SSN, to provide criteria which are updated and adequate to the continuous evolution of the policy related to medicines, and which are also compliant with the necessary transparency;

HAVING HEARD the representative associations of pharmaceutical companies during the meetings held, respectively, on 1 March 2019 and on 28 and 29 May 2019;

HAVING HEARD the Standing Conference for Relations between the State, the Regions and the Autonomous Provinces in the session of (Rep. Atti n. ----/CSR);

Decrees

Article 1 (Scope)

1. The provisions of this decree shall apply during the negotiation between AIFA and the pharmaceutical companies about the reimbursement and the price of medicines paid by the National Health Service. Such provisions concern the negotiation about the reimbursement and the price of medicines authorised to be put on the market under the following procedures: centralised (centralizzata), mutual-recognition (mutuo riconoscimento), decentralised (decentralizzata) and national (nazionale) related to the

medicines which are eligible to be included in the list of medicines reimbursed by the National Health Service.

2. The provisions of this decree shall also apply for the purpose of the listing of medicines referred to in Decree-Law no. 536 of 21 October 1996, converted by Law no. 648 of 23 December 1996, and shall also apply to some specific categories of group (fascia) C and Cnn medicines purchased by the SSN bodies for public health necessities. The inclusion, in the above-mentioned listing, of medicines which are not yet on the market in Italy, or of unauthorised therapeutic indications of medicines which are already on the market in Italy for other therapeutic indications, shall be subject to the price negotiation, although by simplified and accelerated procedure (procedura semplificata e accelerata) under Article 3, Paragraph 10.

Article 2

(Procedure for the submission of the negotiation application)

1. The Company, in order to access the procedure for the negotiation of the reimbursement and prices of the medicine, must submit to AIFA the application accompanied by the documents in compliance with the indications to be set out by deliberation of the Director General of AIFA, which shall be adopted no later than 30 days from the adoption of this decree.

2. The Company must support its application with:

- a) the scientific documentation showing any added therapeutic value of the medicine, in relation with the main treatments to which the medicine is compared. Such comparison shall take into account the therapeutic alternatives used in national clinical practice, providing evaluation and information elements that indicate the main treatments to which the medicine can be compared. In order to allow a comparative evaluation of the costs of alternative treatments, the posology schemes and the duration of the treatments must be explained;
- b) the documentation that provides the economic evaluation, in accordance with the indications of the deliberation referred to in Paragraph 1;
- c) self-certified information elements, with regard to the medicine which is subject to the negotiation, concerning marketing, consumption and reimbursement in other Countries and, in this case, at what price and reimbursement terms, including any further negotiation agreement;
- d) the annual market shares expected to be acquired in the subsequent thirty-six months in the specific market segment;
- e) self-certification of the Company which certifies its capacity of production and management of possible unforeseen events that could put at risk the production standards and the activities that will be put in place in order to guarantee the adequate supply of the medicine to the SSN according to the needs of the population;
- j) the expenditure forecast and the expenditure changes for the SSN deriving from the proposed prices, with their distinct components;
- g) the self-certified quantification of any public contribution and incentive aimed at research and development programmes regarding the medicine;

- h) the quantifications of the economic and financial impact on the SSN and related consumption resulting from the potential inclusion in programmes of early access pursuant to Decree-Law no. 536 of 21 October 1996, converted by Law no. 648 of 23 December 1996, and to Article 48, Paragraph 19, Subparagraph a), of Decree-Law no. 269 of 30 September 2003, converted by Law no. 326 of 24 November 2003;
- i) the quantifications of the economic and financial impact and of the related consumption resulting from the marketing, pursuant to Article 12, Paragraph 5, of Decree-Law no. 158 of 13 September 2012;
- j) any other information that may be useful for the purposes of the negotiation, including the patent situation of the medicine.

3. If, for the medicine in question, it is not demonstrated through evidences of proven quality that there is any additional therapeutic advantage over already available products, or that the medicine is as effective and safe as other already available products, the company will have to provide further elements of interest in terms of economic advantage for the SSN, as constitutive elements of the negotiation agreement.

Art. 3

(Negotiation procedure)

1. The negotiation procedure shall be initiated by the pharmaceutical company. The procedure may also be initiated by AIFA in case it concerns medicines whose reimbursement has a significant impact in terms of SSN expenditure or of prescription inappropriateness, or that have never been subject to previous bargaining. It may also be initiated by AIFA if a previous negotiation procedure has ended with a failure to reach agreement and with the consequent placement of the medicine in group C, according to Article 8, Paragraph 10 of Law no. 537 of 24 December 1993.

2. The negotiation procedure for defining the price and reimbursement shall end within the following one hundred and eighty days, a term that may be interrupted only once, in case AIFA requests a documental integration or new evaluation elements which are necessary to institute the procedure in progress. The company that is informed of the start of the procedure may also ask for its suspension only once, and in order to provide useful elements for the negotiation.

3. The Technical-scientific Commission of AIFA (Commissione tecnico scientifica dell'AIFA- CTS), in compliance with its functions under the legislation in force, shall express itself in particular about the clinical value of the medicine and about the added therapeutic value of the medicine as compared with the medicines which are indicated as reference comparator medicines, including the drugs included in the list of drugs referred to in Decree-Law no. 536 of 21 October 1996, converted by Law no. 648 of 23 December 1996, and /or with pharmacological therapeutic strategies already consolidated. This assessment shall also be carried out on the basis of the inquiry prepared by AIFA taking into account the evaluations issued at European level, if available, as well as on the basis of a «scoping meeting», if appropriate, between the competent AIFA Offices and the reference pharmaceutical company, at the request of the parties, following the submission of the price and reimbursement dossier.

4. Where necessary, in order to ensure greater appropriateness of use or identify specific areas of use, CTS can introduce restrictions on reimbursement.

5. If the restrictions referred to in Paragraph 4 involve a significant change in the expected treatable population as compared with what was initially presented in the ne-

gotiation, the company shall transmit to AIFA the update of the documentation on the basis of the restrictions which has been introduced.

6. At the end of the evaluation, CTS shall transmit the documentation, including the update referred to in Paragraph 5, to the Price and Reimbursement Committee (Comitato Prezzi e Rimborsi- CPR), which shall initiate the procedure for the price negotiation with the concerned company. The negotiation procedure shall be considered to be unsuccessful, with prior information to the company, if the outcome of the aforementioned evaluation does not reveal the clinical superiority of the medicine which is subject to the negotiation as compared with the comparators identified by CTS, and the company does not reformulate a proposal with an equal or lower therapy cost, as compared with that of the comparators.

7. If there are no reference comparator medicines, the company shall submit economic evaluations according to the indications referred to in Paragraph 1 of this deliberation (determinazione) accompanied by adequate documentation aimed at explaining a price proposal, also based on the costs incurred for research, development, and production.

8. For the purpose of price negotiation, CPR shall examine the submitted proposals taking into account the evaluations expressed by CTS, with particular reference to the assessment about the added value of the medicine, to therapy placement, to therapy costs as compared with the already available pharmacological therapies, having also taken into account the prices charged to the institutions of the SSN, and to the number of expected treatments possibly updated with respect to the dossier initially submitted, following by reimbursement restriction terms laid down by CTS.

9. If the procedure is suspended for the request of documental integration or new evaluation elements, the said procedure shall be reactivated following the acquisition by AIFA of what has been requested. The maximum suspension period shall be 90 days. Once this period has elapsed with no result, the negotiation procedure shall come to an end with the failure to reach agreement and the placement of the medicine in group C referred to in paragraph 10 of Article 8 of Law no. 537 of 24 December 1993.

10. The negotiation of medicines referred to in Article 1, Paragraph 2, shall be initiated upon favourable opinion of CTS, on the basis of a simplified dossier (dossier semplificato), submitted for such purpose by the holder pharmaceutical company. As for the medicines which already are in the list referred to in Decree-Law no. 536 of 21 October 1996, converted by Law no. 648 of 23 December 1996, the maximum transfer price charged to the SSN shall be the price which is already charged, and shall not, in any case, exceed the maximum transfer price charged to the SSN for the other therapeutic indications which are already reimbursed for the same medicine.

11. During the price negotiation, AIFA shall also take into account, on the basis of the presumable data about consumption, the financial constraints set by the current legislation on pharmaceutical expenditure.

Art. 4 (*Negotiation agreement*)

1. The negotiation procedure shall be finalised through the agreement between AIFA and the pharmaceutical company with the laying down of the reimbursement and price conditions, in accordance with the provisions of this decree, and taking into account the following conditions:

- a) sales volumes;
- b) availability of the product for the SSN;

- e) discounts for supplies to the SSN bodies;
- d) public contributions to the medicine development and research programmes.

2. As for the finalising of the agreement, the following is provided for:

- a) the obligation to communicate annually to AIFA the sales and turnover data, the marketing costs, and the patent situation of the medicine in Italy, as well as to report any differences with respect to what previously defined;
- b) the possibility of increasing the price, in cases which are exceptional, and, anyway, exclusively for low-cost medicines for which there are objective difficulties in finding raw materials, or in which the impossibility of remaining on the market under the set conditions, as a consequence of increases in production costs, is adequately demonstrated on the basis of documented objective evidence.

3. Moreover, subject to the provisions of Article 3, AIFA shall regulate the cases in which the occurrence of deviations from the elements used as reference in the negotiation process entails the restart of the negotiation procedure already in progress, even before the term laid down in the above-mentioned Article 3. In these specific situations, the procedure shall end:

- a) with the redefinition of the price and the further negotiating elements of the medicine;
- b) with the compensation for the surplus, if expressly provided for;
- e) with the exclusion from the reimbursement.

4. AIFA may also regulate, through the regulation referred to in Paragraph 3, for the purpose of rationalising and streamlining the negotiation procedures, mechanisms of automation in favour of generic and biosimilar medicines, also as a result of requests for packaging changes, for medicines for which there are already similar drugs reimbursed by the SSN. Moreover, AIFA may indicate the conditions for automatic renewal at the expiry of the contract, providing for the cases in which shall be possible to allow progressive discounts.

5. When finalising the agreement, AIFA and the companies may agree on innovative negotiation models, in addition to conventional schemes such as, for example, price-volume, turnover ceilings and pay-back, etc .;

6. The negotiated price shall be, for the SSN bodies, the maximum purchase price for the SSN.

7. As for the market segment that passes through the channel of intermediate and final distribution, VAT and the amounts due for distribution, with respect to the provisions in force, shall be added, for the definition of the retail price, to the negotiated ex-factory price.

Art. 5
(Failure to define price)

1. If an agreement on reimbursement and price is not reached, the product shall be classified in group C, according to Paragraph 10 of Article 8 of Law no. 537 of 24 December 1993.

2. AIFA shall report the reasons for the decision through a deliberation of non-reimbursement or other appropriate means.

3. The Regions and the institutions of the SSN, when initiating purchase procedures, shall take into account the information provided by AIFA.

Art. 6

(Contract duration and renewal)

1. The price, defined at the end of the negotiation procedure as ex-factory price, shall be valid for a period of twenty-four months, without prejudice to the different contractual clauses referred to in Article 4.

2. In case of changes of the therapeutic indications and / or of the posology, which are such as to justify the foreseeing of a variation in the medicine use level, each of the parties may restart the negotiation procedure even before the expiry of the term.

3. Without prejudice to the provisions of Article 5, AIFA may also restart, before the expiry of the negotiation agreement with the pharmaceutical company that holds the AIC, the negotiation procedures in order to reconsider the conditions of the existing agreement in case of meanwhile market changes which are such as to justify the foreseeing of an excessive increase in the use level of the medicine, or such as to amount to a cost-therapy ratio which is disadvantageous as compared with other options existing in the National Pharmaceutical Codex. Furthermore, AIFA may restart the procedure, in the event that new evidence on the effectiveness and safety of the medicine emerge, such as to suggest that the therapy placement has changed, or that new evidence substantially scales down the clinical benefits as estimated at the time of the negotiation, as well as in case of overt shortage of the medicine on the Italian market.

4. The contract shall be intended to be renewed for an additional period of twenty-four months, under the conditions set for the automatic renewal, already negotiated at the time of the contract finalisation, if one of the parties does not provide, at least 60 days before the intended expiry date of the contract, a proposal for the modification of the terms, in which case the administration shall initiate the negotiation procedure according to the modalities already provided for in Article 3; and the previous agreement shall remain operational until the conclusion of the procedure.

Art. 7

(Final provisions)

1. This decree repeals the CIPE Decision (Delibera CIPE) of 1 February 2001 which is mentioned in the introduction.

The present decree will be transmitted to the control bodies for the measures within their competence and will be published in the Official Journal of the Italian Republic.

Rome,

THE MINISTER OF HEALTH
Giulia Grillo

THE MINISTER OF ECONOMY AND FINANCE
Giovanni Tria

APPENDIX 04bis (2 AGOSTO 2019)

Decreto italiano sulla trasparenza.

[Stemma della Repubblica Italiana]

IL MINISTRO DELLA SALUTE
di concerto con
IL MINISTRO DELL'ECONOMIA E DELLE FINANZE

VISTO l'art. 1, comma 41, della legge 23 dicembre 1996, n. 662 che ha disposto che medicinali sottoposti alla procedura di autorizzazione di cui al regolamento (CEE) n. 2309/93 del Consiglio, del 22 luglio 1993, sono ceduti dal titolare dell'autorizzazione ad un prezzo contrattato con il Ministero della sanità, su conforme parere della Commissione unica del farmaco, secondo criteri stabiliti dal CIPE, entro il 31 gennaio 1997;

VISTO il decreto-legge 30 settembre 2003, n. 269, convertito dalla legge 24 novembre 2003, n. 326 ed in particolare l'art. 48, che nell'istituire l'Agenzia italiana del farmaco, di seguito AIFA, con il comma 33, ha disposto che dal 1° gennaio 2004 i prezzi dei prodotti rimborsati dal Servizio sanitario nazionale sono determinati mediante contrattazione tra Agenzia e produttori secondo le modalità e i criteri indicati nella delibera CIPE 1° febbraio 2001, n. 3, pubblicata nella Gazzetta Ufficiale n. 73 del 28 marzo 2001;

VISTO il decreto-legge 21 ottobre 1996, n. 536 convertito dalla legge 23 dicembre 1996, n. 648;

VISTO l'art. 12 del decreto-legge 13 settembre 2012, n. 158, convertito dalla legge 8 novembre 2012, n. 189;

VISTA la legge 30 dicembre 2018, n. 145, recante bilancio di previsione dello Stato per l'anno finanziario 2019 e bilancio pluriennale per il triennio 2019-2021, ed in particolare il comma 553 dell'art. 1, che rinvia ad un decreto del Ministro della salute, di concerto

con il Ministro dell'economia e delle finanze, sentita la Conferenza permanente per i rapporti tra lo Stato, le regioni e le Province autonome di Trento e di Bolzano, i criteri e le modalità a cui l'AIFA si attiene nel determinare, mediante negoziazione, i prezzi dei farmaci rimborsati dal Servizio sanitario nazionale;

VISTO, altresì, il comma 554 dell'art. 1, della citata legge n. 145 del 2018, che prescrive che l'AIFA dal 1° gennaio 2019, può riavviare, prima della scadenza dell'accordo negoziale con l'azienda farmaceutica titolare di A.I.C., le procedure negoziali per riconsiderare le condizioni dell'accordo in essere, nel caso in cui intervengano medio tempore variazioni del mercato tali da far prevedere un incremento del livello di utilizzo del medicinale ovvero da configurare un rapporto costo-terapia sfavorevole rispetto alle alternative presenti nel prontuario farmaceutico nazionale;

VISTA la citata deliberazione CIPE 1° febbraio 2001, recante individuazione dei criteri per la contrattazione del prezzo dei farmaci, pubblicata nella Gazzetta Ufficiale n. 73 del 28 marzo 2001;

TENUTO CONTO del mandato normativo di cui al citato comma 553, sopra riportato, e atteso che il farmaco rappresenta uno strumento di tutela della salute e che i medicinali sono erogati dal Servizio sanitario nazionale (SSN) e, in quanto inclusi nei livelli essenziali di assistenza presentano un impatto significativo per lo stesso Servizio sanitario nazionale;

TENUTO CONTO della risoluzione WHA 72/2019;

RITENUTO di dover garantire, nella fase di negoziazione dei prezzi dei farmaci a carico del Servizio sanitario nazionale tra l'AIFA e l'azienda farmaceutica, criteri aggiornati ed adeguati alla continua evoluzione della politica del farmaco, nonché conformi alla necessaria trasparenza;

SENTITE le associazioni rappresentative delle imprese del farmaco nel corso degli incontri rispettivamente in data 1° marzo 2019 e 28 e 29 maggio 2019;

SENTITA la Conferenza permanente per i rapporti tra lo Stato, le regioni e le Province autonome nella seduta del 1° agosto 2019;

Decreta:

Art. 1

Ambito di applicazione

1. Le disposizioni di cui al presente decreto si applicano nella fase di negoziazione della rimborsabilità e del prezzo dei medicinali a carico del Servizio sanitario nazionale, tra l'AIFA e le aziende farmaceutiche. Esse riguardano la negoziazione della rimborsabilità e del prezzo dei medicinali autorizzati all'immissione in commercio secondo le procedure centralizzata, di mutuo riconoscimento, decentrata e nazionale dei medicinali idonei ad essere inseriti nella lista dei medicinali rimborsati dal Servizio sanitario nazionale.

2. Le disposizioni del presente decreto si applicano altresì ai fini dell'inserimento dei medicinali nell'elenco di cui al decreto-legge 21 ottobre 1996, n. 536, convertito dalla legge 23 dicembre 1996, n. 648, nonché ad alcune specifiche categorie di medicinali

di fascia C e Cnn acquistati dagli enti del Servizio sanitario nazionale per esigenze di salute pubblica. L'inserimento nel menzionato elenco dei medicinali non ancora in commercio in Italia, o di indicazioni terapeutiche non autorizzate di medicinali già in commercio in Italia per altre indicazioni, è subordinato alla negoziazione del prezzo, seppur con procedura semplificata e accelerata ai sensi delle disposizioni di cui all'art. 3, comma 10.

Art. 2

Modalità per l'inoltro dell'istanza di negoziazione

1. L'azienda, per accedere alla procedura per la negoziazione della rimborsabilità e del prezzo del medicinale, deve inoltrare all'AIFA l'istanza corredata dalla documentazione in conformità alle indicazioni che saranno rese con determinazione del direttore generale dell'AIFA, da adottarsi entro 30 giorni dall'adozione del presente decreto.

2. L'azienda deve supportare la propria istanza di negoziazione con:

- a) la documentazione scientifica dalla quale si evinca l'eventuale valore terapeutico aggiunto del medicinale, in rapporto ai principali trattamenti con cui il farmaco viene confrontato. Detto confronto tiene in considerazione le alternative terapeutiche utilizzate nella pratica clinica nazionale, fornendo elementi valutativi e conoscitivi che indichino i principali trattamenti con i quali il medicinale può essere confrontato. Al fine di consentire una valutazione comparativa dei costi dei trattamenti alternativi, devono essere esplicitati gli schemi posologici e la durata dei trattamenti;
- b) la documentazione che fornisca la valutazione economica, secondo le indicazioni di cui alla determinazione di cui al comma 1;
- c) elementi informativi autocertificati sul medicinale oggetto della negoziazione circa la commercializzazione, il consumo e la rimborsabilità in altri Paesi, e in tal caso a quali condizioni di prezzo e rimborsabilità, incluso ogni ulteriore accordo negoziale;
- d) le quote annue di mercato che si prevede di acquisire nei successivi trentasei mesi nello specifico segmento di mercato;
- e) autocertificazione dell'azienda che attesti la propria capacità produttiva e di gestione di possibili imprevisti che possano mettere a rischio gli standard produttivi nonché le attività che verranno poste in essere al fine di garantire l'adeguata fornitura del farmaco al Servizio sanitario nazionale in funzione dei bisogni della popolazione;
- f) la previsione e le variazioni di spesa per il Servizio sanitario nazionale derivante dai prezzi proposti, nelle distinte componenti;
- g) quantificazione autocertificata di eventuali contributi e incentivi di natura pubblica finalizzati a programmi di ricerca e sviluppo del farmaco;
- h) quantificazioni dell'impatto economico-finanziario a carico del Servizio sanitario nazionale e relativi consumi conseguenti all'eventuale inclusione in programmi di accesso precoce ai sensi del decreto-legge 21 ottobre 1996, n. 536 convertito dalla legge 23 dicembre 1996, n. 648, dell'art. 48, comma 19, lett. a) del decreto-legge 30 settembre 2003, n. 269, convertito dalla legge 24 novembre 2003, n. 326;

- i) quantificazioni dell'impatto economico-finanziario e relativi consumi conseguenti alla commercializzazione ai sensi dell'art. 12, comma 5, del decreto-legge 13 settembre 2012, n. 158;
- j) ogni altra informazione che possa risultare utile ai fini della negoziazione, ivi incluso lo status brevettuale del medicinale.

3. Qualora per il medicinale in esame non sia dimostrata, attraverso evidenze di comprovata qualità, alcun vantaggio terapeutico aggiuntivo rispetto a prodotti già disponibili, ovvero che sia efficace e sicuro nella misura pari ad altri prodotti già disponibili, l'azienda dovrà fornire ulteriori elementi di interesse, in termini di vantaggio economico per il Servizio sanitario nazionale, quali elementi costitutivi dell'accordo negoziale.

Art. 3

Procedura negoziale

1. La procedura negoziale è attivata dall'azienda farmaceutica. La procedura può, altresì, essere avviata anche dall'AIFA nel caso si tratti di medicinali la cui rimborsabilità presenti un significativo impatto in termini di spesa del Servizio sanitario nazionale o di inappropriata prescrizione, o che non siano mai stati oggetto di precedente contrattazione. Può essere, altresì, avviata dall'AIFA nel caso in cui una precedente procedura di negoziazione si sia conclusa con mancato accordo e conseguente collocazione del farmaco in fascia C, di cui al comma 10, dell'art. 8, della legge 24 dicembre 1993, n. 537.

2. La procedura negoziale di definizione del prezzo e della rimborsabilità si conclude nei successivi centottanta giorni, termine che può essere interrotto una sola volta, in caso di richiesta da parte di AIFA di integrazione documentale o di nuovi elementi valutativi necessari per l'istruttoria della procedura in corso. L'azienda che viene informata dell'avvio del procedimento può, altresì, chiederne la sospensione una sola volta e al fine di fornire elementi utili alla negoziazione.

3. La Commissione tecnico scientifica (CTS) dell'AIFA, nel rispetto delle funzioni ad essa attribuite a legislazione vigente, si esprime in particolare sul valore clinico del farmaco e sul valore terapeutico aggiunto rispetto ai medicinali indicati quali medicinali comparatori di riferimento ivi inclusi i farmaci inseriti nell'elenco dei farmaci di cui di cui al decreto-legge 21 ottobre 1996, n. 536, convertito dalla legge 23 dicembre 1996, n. 648 e/o alle strategie terapeutiche farmacologiche già consolidate. Tale valutazione è condotta anche sulla base dell'istruttoria predisposta dall'AIFA tenendo conto delle valutazioni prodotte in sede europea, quando disponibili, nonché sulla base di uno «scoping meeting», quando opportuno, tra i competenti uffici dell'AIFA e l'azienda farmaceutica di riferimento, su richiesta delle parti, successivamente alla sottomissione del dossier di prezzo e rimborso.

4. Ove ricorrano le condizioni di necessità, al fine di assicurare una maggiore appropriatezza d'uso ovvero individuare specifici ambiti di utilizzo, la CTS può introdurre limitazioni alla rimborsabilità.

5. Nel caso in cui le limitazioni di cui al comma 4 comportino una modifica significativa della popolazione trattabile attesa, rispetto a quanto prospettato inizialmente nell'istanza di negoziazione, l'azienda trasmette all'AIFA l'aggiornamento della documentazione sulla base delle limitazioni introdotte.

6. All'esito della valutazione, la CTS trasmette la documentazione al Comitato prezzi e rimborso (CPR), ivi compreso l'aggiornamento di cui al comma 5, che avvia l'iter per

la negoziazione del prezzo con l'azienda interessata. La procedura negoziale si intende conclusa negativamente, previa informativa all'azienda, nel caso in cui all'esito della predetta valutazione non emerga una superiorita' clinica del medicinale oggetto della negoziazione rispetto al/ai comparatori identificati dalla CTS e l'azienda non riformuli una proposta che configuri un costo terapia uguale o inferiore rispetto a quello dei comparatori.

7. Nel caso in cui non vi siano medicinali comparatori di riferimento, l'azienda presenta valutazioni economiche secondo le indicazioni di cui al comma 1 della presente determinazione integrate da un'adeguata documentazione volta a motivare la proposta di prezzo anche in funzione dei costi della ricerca e sviluppo e di produzione sostenuti.

8. Ai fini della negoziazione del prezzo, il CPR esamina le proposte avanzate tenendo in considerazione le valutazioni espresse dalla CTS con particolare riferimento al giudizio sul valore aggiunto del medicinale, al posizionamento in terapia, ai costi terapia confrontati con le terapie farmacologiche gia' disponibili, tenuto conto anche dei prezzi applicati agli enti del Servizio sanitario nazionale e al numero dei trattamenti attesi, eventualmente aggiornato rispetto al dossier inizialmente presentato, a seguito delle eventuali condizioni limitative della rimborsabilita' definite dalla CTS.

9. In caso di sospensione della procedura per la richiesta di integrazione documentale o di nuovi elementi valutativi, la stessa viene riattivata in seguito all'acquisizione da parte di AIFA di quanto richiesto. Il termine massimo di sospensione e' fissato in novanta giorni. Decorso tale termine senza alcun esito, la procedura negoziale si conclude con il mancato accordo e la collocazione del farmaco in fascia C di cui al comma 10, dell'art. 8, della legge 24 dicembre 1993, n. 537.

10. La negoziazione dei medicinali di cui all'art. 1, comma 2, si attiva previo parere favorevole della CTS, sulla base di un dossier semplificato, a tal fine, presentato dall'azienda farmaceutica titolare. Per i medicinali gia' presenti nell'elenco di cui al decreto-legge 21 ottobre 1996, n. 536, convertito dalla legge 23 dicembre 1996, n. 648, il prezzo massimo di cessione a carico del Servizio sanitario nazionale e' quello gia' applicato e non puo', comunque, superare il prezzo massimo di cessione al Servizio sanitario nazionale per le altre indicazioni terapeutiche gia' rimborsate relative allo stesso medicinale.

11. L'AIFA in fase di negoziazione del prezzo tiene conto, sulla base dei presumibili dati di consumo, anche dei vincoli finanziari previsti dalla vigente normativa sulla spesa farmaceutica.

Art. 4

Accordo negoziale

1. La procedura negoziale si perfeziona mediante l'accordo tra l'AIFA e l'azienda farmaceutica con la fissazione delle condizioni di rimborsabilita' e prezzo, in coerenza con le disposizioni di cui al presente decreto, nonche' tenendo conto delle condizioni di seguito indicate:

- a) volumi di vendita;
- b) disponibilita' del prodotto per il Servizio sanitario nazionale;
- c) sconti per le forniture agli enti del Servizio sanitario nazionale;
- d) contributi di natura pubblica ai programmi di sviluppo e ricerca del farmaco.

2. In sede di definizione dell'accordo e' previsto:

- a) l'obbligo di comunicare all'AIFA annualmente i dati di vendita, di fatturato, i costi di marketing e lo status brevettuale del medicinale in Italia, nonche' di segnalare eventuali difformita' rispetto a quanto precedentemente definito;

b) la possibilità di procedere ad un aumento di prezzo, per casi eccezionali, e comunque esclusivamente per farmaci a basso costo, per i quali si presentino oggettive difficoltà di reperire materie prime, o in cui sia adeguatamente dimostrata l'impossibilità a rimanere sul mercato alle condizioni stabilite per aumenti dei costi produttivi sulla base di documentate evidenze oggettive.

3. L'AIFA, inoltre, fatte salve le disposizioni di cui all'art. 3, provvede a regolamentare i casi in cui il verificarsi di scostamenti dagli elementi presi a riferimento nel processo negoziale comportino il riavvio della procedura negoziale già in corso, anche prima del termine prescritto di cui al menzionato art. 3. Per tali specifiche situazioni la procedura si conclude:

- a) con la ridefinizione del prezzo e degli ulteriori elementi negoziali del medicinale;
- b) con la compensazione dell'eccedenza qualora espressamente prevista;
- c) con l'esclusione dalla rimborsabilità.

4. L'AIFA può, altresì, ai fini della razionalizzazione e snellimento delle procedure negoziali, mediante la regolamentazione di cui al comma 3, disciplinare meccanismi di automatismo a favore di medicinali generici e biosimilari, anche in esito a richiesta di modifiche di confezioni, per farmaci per i quali sono già presenti medicinali analoghi rimborsati dal Servizio sanitario nazionale. Inoltre, l'AIFA può indicare le condizioni per procedere al rinnovo automatico alla scadenza del contratto, prevedendo i casi in cui poter riconoscere sconti progressivi.

5. In sede di definizione dell'accordo l'AIFA e le aziende possono concordare modelli negoziali innovativi, in aggiunta a schemi convenzionali quali, ad esempio, prezzo-volume, tetti di fatturato e pay-back, etc.;

6. Il prezzo contrattato rappresenta per gli enti del Servizio sanitario nazionale il prezzo massimo di acquisto al Servizio sanitario nazionale.

7. Per quanto attiene al segmento di mercato che transita attraverso il canale della distribuzione intermedia e finale, al prezzo ex-fabbrica contrattato vanno aggiunte, per la definizione del prezzo al pubblico, l'IVA e le quote di spettanza per la distribuzione, rispetto alle disposizioni vigenti.

Art. 5

Mancata definizione del prezzo

1. Nel caso in cui non si raggiunga un accordo sulla rimborsabilità e prezzo, il prodotto viene classificato nella fascia C, di cui al comma 10, dell'art. 8, della legge 24 dicembre 1993, n. 537.

2. L'AIFA attraverso determinazione di mancata rimborsabilità, o con altre idonee modalità, riporta le motivazioni della decisione assunta.

3. Le regioni e gli enti del Servizio sanitario nazionale, nell'attivare procedure di acquisto, tengono conto delle informazioni fornite da AIFA.

Art. 6

Durata del contratto e rinnovo

1. Il prezzo, definito al termine della procedura negoziale come prezzo ex fabrica, e' valido per un periodo di ventiquattro mesi, fatte salve le diverse clausole contrattuali, di cui all'art. 4.
2. Qualora sopravvengano modifiche delle indicazioni terapeutiche e/o della posologia, tali da far prevedere una variazione del livello di utilizzazione del farmaco, ciascuna delle parti puo' riavviare la procedura negoziale anche prima della scadenza del termine.
3. Fatte salve le disposizioni di cui all'art. 5, l'AIFA puo', altresì, riavviare, prima della scadenza dell'accordo negoziale con l'azienda farmaceutica titolare di AIC, le procedure negoziali per riconsiderare le condizioni dell'accordo in essere, nel caso in cui intervengano medio tempore variazioni del mercato tali da far prevedere un eccessivo incremento del livello di utilizzo del medicinale ovvero da configurare un rapporto costo-terapia sfavorevole rispetto alle alternative presenti nel Prontuario farmaceutico nazionale. Inoltre, l'AIFA puo' riavviare la procedura nel caso in cui intervengano nuove evidenze sulla efficacia e la sicurezza del farmaco, tali da far ritenere modificato il posizionamento in terapia o che ridimensionino in maniera sostanziale i benefici clinici stimati al momento della negoziazione, così come in caso di conclamata carenza del medicinale sul mercato italiano.
4. Il contratto si intende rinnovato per ulteriori ventiquattro mesi, alle condizioni previste per il rinnovo automatico, già negoziate in sede di definizione del contratto, qualora una delle parti non faccia pervenire almeno sessanta giorni prima della scadenza naturale del contratto, una proposta di modifica delle condizioni, nel qual caso l'amministrazione apre la procedura negoziale secondo le modalità già previste all'art. 3 e fino alla conclusione del procedimento resta operativo l'accordo precedente.

Art. 7
Disposizioni finali

1. Il presente decreto abroga la delibera CIPE 1° febbraio 2001, citata in premessa. Il presente decreto sara' trasmesso agli organi di controllo per i provvedimenti di competenza e sara' pubblicato nella Gazzetta Ufficiale della Repubblica italiana.

Roma, 2 agosto 2019

IL MINISTRO DELLA SALUTE
Grillo

IL MINISTRO DELL'ECONOMIA E DELLE FINANZE
Tria

Registrato alla Corte dei conti il 12 novembre 2019
Ufficio controllo atti MIUR, MIBAC, Min. salute e Min. lavoro e politiche sociali, reg. n. 3175

APPENDIX 05

List of people interviewed in the context of this report.

Jorge BERMUDEZ	Vice President of Production and Innovation, FIOCRUZ, Brazil
Gabriela COSTA-CHAVES	Pharmacologist, and expert in local public medicine production (author of a thesis on the subject), e.g. FIOCRUZ
Philippe DUNETON	Director General of UNITAID, former Director of AFSSAPS
Andrew HILL	Production Costs and Raw Material Market Specialist, University of Liverpool
Louise Lassale	Member of Open Insulin
Luca LI BASSI	Former director of the Italian medicine agency (AIFA), former Global Fund for AIDS, Tuberculosis and Malaria, and chairman of the negotiations for the “transparency” resolution (WHA72)
Fabien MALLET	CGT-Sanofi
Suerie MOON	Professor at Harvard, Global Health Specialist, Director of the Global Health Centre, Geneva
Jean-Louis PEYREN	CGT-Sanofi
Christine ROUZIUX	Virologist, diagnostic specialist, president of ARCAT, Paris
Jens SHELLEKENS	Biosimilars production specialist, University of Utrecht
Adrian VAN DEN HOVEN	Medicines for Europe (European generics producers association)

About OTMeds.

The Observatory of Transparency in Medicines Policies (OTMeds) is an organization working for better access to health, in particular through the establishment of transparency in the chain of medicines and health products. OTMeds' expertise lies at the intersections of different knowledge affecting the health and pharmaceutical sector, in particular health public policies, economics and health economics, pharmacology, industrial issues including the production, as well as intellectual property rights. The complexity of medicines policy issues requires this multidisciplinary approach. OTMeds also aims to popularize certain technical aspects and to question the political choices made.

OTMeds was founded in June 2019 by Pauline Londeix and Jérôme Martin, respectively former vice-president and former president of Act Up-Paris, to ensure the implementation in France of the "Resolution on Transparency", a resolution on transparency in pharmaceutical markets adopted at the World Health Assembly in May 2019. To date, apart from the work carried out for this report, OTMeds does not receive any funding and operates on the basis of expertise closely 20 years on these issues, and work based on a large national and international network. OTMeds has no conflict of interest with the pharmaceutical industry.

In September 2019, OTMeds published a «transparency checklist», a document that brings together many information that we believe is necessary for the public regulator to be able to assess the relevance of the price of a medicine at the time of setting its price. The "checklist" has already been used by several institutions.

In October 2019, OTMeds proposed to French parliamentarians (MPs) as well as to the French government proposals for amendments within the framework of the social security finance bill and decrees for France to begin its implementation at the national level of the resolution on transparency of the World Health Assembly. An amendment was obtained, co-signed by La France Insoumise and LREM, an unprecedented alliance which proves the interest of the approach. Censored for formal reasons by the Constitutional Council, the amendment was adopted the following year following new work by the Observatory.

Since 2019, OTMeds has been auditioned by various institutions, invited to participate in various research seminars, conferences in economics or intellectual property, to present our approach and the importance of the transparency angle to preserve the social protection systems. In France, OTMeds was heard by the National Consultative Ethics Council (CCNE) in June 2020 within the scope of its report no. 135 on access to therapeutic innovations, by the Senate in November 2020 as part of the development

a bill creating a public medicine production center, by the National Assembly as part of the medicine information mission. Various political groups in the Senate also called on our expertise at the end of 2021 and the beginning of 2022 on various legislative proposals related to medicines. In addition, we have also been interviewed by the Institutional Review Board of the Institut Pasteur. Abroad, by parliamentarians from the German Bundestag around the transparency resolution and the French amendment (February 2020) or by the Belgian National Ethics and Bioethics Council (March 2021). In May 2020, on the sidelines of the World Health Assembly, for the one year of the transparency resolution, we co-organized with the Global Health Center of the Graduate Institute of Geneva an event on the resolution and its implementation. We also took part in a session of the Fair Pricing Forum organized by the World Health Organization in April 2021. On October 21, 2021, we took part in a webinar of the Graduate Institute on the local production of essential medicines in Brazil and in Europe, and in particular to present the outline of this report.