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For a secure supply of pharmaceutical products

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Introduction

Long viewed as the "pharmacy of the world", Europe still boasts a powerful, innovative and multifaceted industry that contributes to economic growth and employs hundreds of thousands of people in companies of varying sizes and positions. However, in recent years it has been suffering from major supply shortages for medicines, further exacerbated by the health crisis and the war in Ukraine.

This problem, caused by a combination of many internal and external factors, has many ramifications for patients, doctors and healthcare systems. EU Member States and institutions must therefore find ambitious initiatives as a matter of priority.

The European Commission is gearing towards presenting a major overhaul of the pharmaceutical framework with this objective. Its goal is twofold: to guarantee access to affordable quality healthcare for all citizens and to help the continent to strengthen its health independence, undermined by the outsourcing of a rising share of the production of certain active pharmaceutical ingredients (API)[1].

1 The active pharmaceutical ingredient (API) is a substance of chemical or natural origin responsible for the therapeutic or preventive properties of a pharmaceutical product or medicine.

I . A globalised and fragmented pharmaceutical industry

I A RISING SHARE OF EUROPEAN PRODUCTION OUTSOURCED

Europe's medicine supply should actually be more secure, particularly as it still has a "strong and competitive" pharmaceutical industry[2]. While the North American market remains by far the largest (47.2% of global sales), the European market ranks second (24.5% market share), ahead of China (9.7%) and other countries in the Asia-Pacific region (13.2%). Within the EU, the main medicine-producing countries are Italy, Germany and France, followed by Belgium, Ireland, Spain, Denmark and Sweden. Out of 488 medicines authorised in Europe between 2016 and 2021, 112 were authorised in Germany, 87 in Ireland, 48 in Spain, 42 in France and 38 in Italy[3]. The industry provides 800,000 direct jobs in all Member States and records a trade surplus of almost €110 billion, making the EU the biggest exporter of pharmaceutical products in the world. The industry made the largest contribution in Europe to research and development investments in 2019, to the tune of €37 billion[4], against the backdrop of a booming market: development of gene and cell therapies, development of personalised medicine and targeted therapies, tightened international intellectual property regulations, etc.

Launched in a major movement of mergers and acquisitions in the 1990s and 2000s, the pharmaceutical industry remains relatively atypical in its organisation. A very wide range of stakeholders of extremely differing sizes, organisations and functions meet production needs: patent-holding multinationals (Big Pharma) and highly innovative small structures (often start-ups), pharmaceutical firms and biotechnology companies, producers of originator medicines and generic medicines, manufacturers of active ingredients and third-party manufacturers[5]. The international fragmentation of production lines has limited production cost growth upstream, while **Europe, retaining significant advantages in top-of-the-range basic products, has a leading position in "pharmaceutical preparations"** and has benefitted extensively from the price dynamic downstream[6]. Around 40% of medicines marketed in the EU nevertheless originate in third countries, and Asia has made a remarkable breakthrough on low added value basic pharmaceutical products.

"The major pharmaceutical players have a very strong presence in the production phases or value chain components that guarantee the highest return on investment, but they are increasingly turning to sub-contractors for whom they are bringing costs down. This outsourcing does not bring about lower prices for patients or social

2 Pharmaceutical strategy for Europe, Communication of the Commission, 25 November 2020

3 In 2021, the global market for medicinal products reached €1,211 billion ($1,291 billion) in sales, up more than 6.8% year-on-year. The five leading global groups have a 22% share in this market. For comprehensive data on the pharmaceutical industry, see the latest report of leem (professional organisation of pharmaceutical companies operating in France) (in French).

4 Emerging biopharmaceutical companies alone account for more than 70% of the reserve for research projects worldwide (compared to 60% in 2009).

5 The WHO and the European Union define a "medicinal product" as "a substance or combination of substances that is intended to treat, prevent or diagnose a human disease". Originator medicine is an original chemical or biotechnological medicinal product that is protected by a patent. It is used as a reference for generic and biosimilar products and for me-too drugs. A generic product is a medicine that has the same properties (same active ingredient) and the same pharmaceutical form as the reference product. A biosimilar product is similar to a reference biological product. A biotechnological product is manufactured or derived from a biological source. A me-too drug is a similar medicinal product that may be protected by new patents.

6 Pharmaceutical preparations are medicines, therapeutic serums, vaccines and other preparations. Industrie pharmaceutique européenne: quand rentabilité rime avec vulnérabilité. La lettre du CEPII, January 2022.

security bodies, but instead for Big Pharma. If pension and investment funds are as involved as they are in these companies' share capital, it is because they are highly profitable. If the sector is as lucrative and financialised as it is, this is due to patents and the fact that the market in the major Western countries is viable thanks to social security bodies", states health economist Nathalie Coutinet[7].

THE EUROPEAN ECONOMIC MODEL DISRUPTED BY THE ARRIVAL OF BIOTECHNOLOGIES

With the arrival of medicines produced using biotechnologies, which need greater financial resources and expertise than those manufactured using chemical syntheses, the industry underwent a genuine revolution in the early 1990s, with far-reaching implications for its production and supply conditions. This shift "disrupted the methods for discovering and developing new molecules and occurred alongside a restructuring of Big Pharma and the emergence of innovative start-ups. These small firms were often founded in cooperation with public and private research centres"[8]. Flexible but financially vulnerable, these young companies look after some of the discovery phases and preclinical testing on behalf of multinationals. The multinationals then finance the subsequent phases, develop clinical trials or co-fund companies specialised in conducting these tests. The molecules under development are then incorporated into their own production processes, often by acquiring the companies with a strong potential for innovation. A prime example is the partnership between Pfizer and BioNTech for the development of a Covid-19 vaccine.

The process is not without risk: out of the many available avenues, only a few will result in clinical development, and fewer still in pharmaceutical use. On average, the development of a new treatment takes thirteen years and costs more than €2 billion. The major pharmaceutical companies therefore innovate less than before, while remaining key players in the mass production process due to their industrial capacity and financial resources. Given both the complex nature and the cost of new techniques, they also tend to be specialised in the most profitable therapeutic areas such as oncology, the leading global market for the pharmaceutical industry ahead of auto-immune diseases and anti-diabetic medication. One such booming area is biotechnologies, for which production originates in living organisms or their cellular components. This comes at the expense of mature, less profitable medicines, vaccines and treatments for certain conditions such as paediatric cancers and rare diseases.

Public authorities bear some of the responsibility for this situation. Back in the 2000s, when there were fewer discoveries, some countries such as France signed agreements with industrial players under which the prices of older therapies (excluding patents and generics) would be reduced, while the price of new treatments would be significantly higher. The objective was twofold: to control healthcare spending while making savings, and to encourage innovation, even in some cases by issuing marketing authorisations in advance. The original idea was that the same companies would work in both areas, but Big Pharma preferred to pull out of the least lucrative productions, which distorted competition. The upshot is that generic medicines now account for 70% of the medication sold in Europe, but less than 30% of the related expenses. "For the last twenty years, the focus has been on the price of new products but this ultimately becomes untenable for older products, which

7 Interview with the author, February 2023. Nathalie Coutinet is a professor-researcher at Paris Nord University. She is a member of the Economistes Atterrés collective.

8 *L'Économie du médicament*, Philippe Abecassis and Nathalie Coutinet. Editions La Découverte, 2018 (in French). Distribution in electronic format by Cairn for La Découverte.

are still essential for treating certain conditions", deplores Bruno Bonnemain, Vice-Chair of the French National Academy of Pharmacy[9]. Mature or generic medicines make up the bulk of shortages.

We can therefore see the emergence of two parallel economies: on one side, very high added-value products and on the other, mature and less profitable medicines. It is therefore impossible to use the profits of one side to offset the higher production costs on the other, which would have a stabilising effect on resilience and self-sufficiency by discouraging the manufacturers concerned from outsourcing part of their production and lengthening manufacturing lines (see below).

The EU is facing a twofold challenge: to maintain its ability to be at the cutting edge of technology while producing sufficient quantities of mature medicines. This challenge is even more acute as the EU is losing ground in terms of innovation, while fifteen years ago research and development spending in the pharmaceutical sector was more or less the same on both sides of the Atlantic. While overall clinical research was maintained due to the pandemic, "the dynamic in the major global regions has shifted", states the economic report of the professional organisation for pharmaceutical companies operating in France (Leem). North America still ranks first but Europe has fallen from second to third place below Asia and suffers from significant discrepancies between Member States[10].

I MULTIFACETED PUBLIC INTERVENTION

In addition to manufacturers, many stakeholders play a key role in the pharmaceutical industry, including buyers, patients/consumers, health insurance systems and of course regulatory authorities. The legal framework for the European Union covers the entire cycle, from clinical trials to marketing authorisations, pharmacovigilance to potential withdrawals. A medicine can only be marketed if it has received a marketing authorisation from health authorities, at the end of a process geared towards demonstrating its quality, safety and efficacy. Twenty years after having imposed such a procedure on all Member States for pharmaceutical products, the EU founded its own Agency in 1995, which became the European Medicines Agency (EMA) in 2004. Once marketed, medicines are monitored throughout their life cycle under the pharmacovigilance system intended to identify any adverse effects. Any stakeholder involved in the process requires an authorisation and may be subject to sanitary inspections[11].

Marketing authorisation is granted either on a European level by the Commission on the basis of a positive opinion from the European Medicines Agency, or on a national level by the competent body, according to the procedures specific to each country. In the first instance, the procedure is centralised, mandatory for most innovative products including treatments for rare diseases, and results in a single authorisa-

9 Interview with the author, February 2023. Bruno Bonnemain is Vice-Chair of the National Academy of Pharmacy (France). See also the White Paper of the National Academy of Pharmacy on medicine shortages (in French).

10 Figures of the European Federation of Pharmaceutical Industries and Associations (Efpia) quoted by MSD pharmaceutical company in its Pharmaceutical Policy Passport.

11 The production of a molecule entails three phases: the production of the active pharmaceutical ingredient, a substance of chemical or natural origin responsible for the therapeutic or preventive properties of a medicine; the formulation of the medicine (combination of the active ingredient with the excipients, which are generally products that are also used in the agri-food and cosmetic industries such as flavourings and sugars and which give the medicine a form that is easy to administer – tablet, capsule, syrup, injectable solution etc.; and packaging. The active ingredients of originator medicines are generally manufactured by the pharmaceutical companies holding the patent (most often in developed nations for biomedicines). The active ingredients of generic medicines are chiefly produced by sub-contractors located in India and China.

tion that is valid across the EU[12]. In the second, more common instance, there are two ways of obtaining an authorisation in several Member States: the decentralised procedure, in which companies can apply for authorisations in several countries simultaneously for a medicine that has not yet been authorised, or the mutual recognition procedure, whereby a marketing authorisation granted in one Member State can be recognised in other EU countries. For both of these procedures, the rules and requirements applicable to pharmaceutical products are identical across the EU[13].

Decisions relating to price and reimbursement levels are then negotiated and taken within each Member State. While non-reimbursable products can be marketed directly and freely, other medicines must wait for the outcome of a long assessment period based on different criteria, specific to each country: the concerns take into consideration therapeutic, medico-economic, security-related, ethical, equality and compassionate factors. A medicine must wait for a year and a half on average before being made available in the EU, much longer than the 180 days stipulated in the 2001 European Directive[14]. Despite a downward trend, timeframes for the period from 2017 to 2020 ranged from 133 days in Germany to 899 days in Romania (497 days in France). They can be six times longer in Southern and Eastern Europe compared to the rest of the continent. Different factors underpin these figures, such as administrative complications specific to each Member State, the often very high cost of new products and pricing and coverage issues for national healthcare systems, which vary according to financial resources and the objectives to be achieved[15].

II • Supply shortages, a health and strategic risk

I SHORTAGES EXACERBATED BY THE GEOPOLITICAL SITUATION

Citizens' access to innovative and affordable medication is a European priority and a central thrust of the Commission's pharmaceutical strategy. This ambition, however, faces a dual barrier: firstly, the difficulties experienced by the least wealthy countries to obtain the most innovative products which are too expensive, and secondly, the growing supply shortages in the last ten years against a backdrop of strong annual growth in global demand, particularly in emerging countries. This is detrimental to healthcare systems, which must manage major disruption. Doctors are forced to propose alternative treatments where possible, which may be less effective or not as tolerated. Patients suffer from major psychological stress and have a reduced chance of recovery. They may even see a worsening of their condition.

Shortages have increased by a factor of 20 between 2000 and 2018 (a twelvefold increase since 2008). They affect in particular chemical products that are inexpensive and easy to manufacture or older products such as **antibiotics, analge-**

12 Information on the authorisation procedures can be found on the European Medicines Agency website.

13 An emergency authorisation is possible for Member States but not on an EU level. However, fast-track procedures exist for innovative molecules. A conditional marketing authorisation approves a medicine that addresses unmet medical needs before long-term data on efficacy and safety is available. It is granted for one year and may be renewed. The 2004 Directive authorises MA applications for generic medicines before patent expiry (Bolar exception). In 1992, France introduced the ATU (temporary authorisation for use) to provide early access to medicines for patients with a severe disease prior to market authorisation. The system was replaced in 2021 by the "early access" system which allows patients who have reached a therapeutic impasse to benefit, on an exceptional and temporary basis, from certain medicinal products that are not authorised in a specific therapeutic indication.

14 The Wait (Waiting to Access Innovative Therapies) study published by the European Federation of Pharmaceutical Industries and Associations (Efpia), 12 May 2022.

15 Report of the Belgian Health Care Knowledge Centre (KCE), 2021.

sics, corticoids, anaesthetics, cancer drugs and vaccines. Therapies to treat cancer, infections and disorders of the nervous system alone account for over half of medicines in short supply, according to the European Parliament[16]. The situation is so acute that certain people in hospitals or pharmacies spend hours searching for missing products or discussing appropriate alternatives with prescribers. **The shortages affect injectable formulations more than tablets and capsules.** The former are mainly used in hospitals and involve a highly complex production system. Many batches are rejected for failing to meet standards, a fact which deters manufacturers from investing in these production lines. It should be noted, however, that countries are seldom all affected at the same time[17].

Identified as a "major public health issue" by the European Parliament and the EU Council, these shortages have given rise to various resolutions, conclusions and initiatives[18]. There are multiple causes and each crisis may be due to a different one. At the start of the Covid-19 pandemic, manufacturers were unable to meet the upsurge in demand for paracetamol (viewed at the time as one of the only means of treating the disease) and curare (used in anaesthesia and resuscitation), which suddenly underscored the weaknesses of the value chain and the EU's reliance on third countries. At the end of 2022, the rare conjunction of three epidemics (influenza, Covid and bronchiolitis) resulted in a shortage of Amoxicillin, a broad-spectrum antibiotic frequently prescribed for children. This was particularly due to manufacturers poorly predicting their sales, based on very low demand the previous winter.

This is compounded by the geopolitical situation. After suddenly lifting the health restrictions of its zero-Covid strategy, in force for the last three years, in December 2022 China briefly blocked exports of certain medicines, as it had already done to a much greater extent at the start of the pandemic. The war in Ukraine also resulted in a restricted supply of various raw materials used for packaging, such as cardboard, aluminium (used in blister packs) and glass (used for bottles). Above all, the risk of the conflict escalating and the prospect of an economic war brought on by the technological rivalry between China and the US raise concerns regarding a risk of restricted exports and supply shortages as a coercive measure[19].

INDEPENDENCE UNDERMINED BY INTERNATIONAL SUB-CONTRACTING

In addition to these cyclical factors, supply shortages are also due to a series of structural factors, the first of which is the outsourcing of a growing share of production.

The EU still has a strong manufacturing footprint for high added-value molecules. Indeed, for all the active pharmaceutical ingredients required to manufacture medicines, **production in the EU-27 accounts for around half of these needs**[20]. However, more than two thirds of generic API production (against 20% thirty years

16 Resolution of the European Parliament of 17 September 2020 on the shortage of medicines – how to address an emerging problem.

17 See the study published in November 2021 on shortages, conducted under the aegis of the European Commission's Directorate-General for Health and Food Safety. Future-proofing pharmaceutical legislation – study on medicine shortages: final report.

18 In December 2016, the European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMA) created a Task Force which led a pilot programme to introduce a network of single points of contact for medicine shortages with a view to improving the sharing of information among Member States, the EMA and the Commission and to coordinate actions. On this basis, the EMA created the Medicines Shortages Single Point of Contact (SPOC) Working Party in May 2020.

19 Europe's response to the Sino-American rivalry. Elvire Fabry, Policy Paper, Jacques Delors Institute, February 2023.

20 International EU27 pharmaceutical production, trade, dependencies and vulnerabilities: a factual analysis. European Centre for International Political Economy (ECIPE), 2021.

ago) is now concentrated in Asia, mainly in China and India, compared to barely more than 20% in the EU[21]. This high level of dependence is even more problematic as **the sector is experiencing a concentration in production and it is very difficult for the EU to diversify its supply for certain products**: China and India alone produce 60% of the world's paracetamol, 90% of its penicillin and 50% of its ibuprofen, according to the European Parliament[22], while India itself is highly dependent on active ingredients originating in China. Approximately 80% of the total volume of APIs imported in the EU come from five countries: China (45%), the USA, the UK, Indonesia and India, sometimes with a limited number of suppliers.

Any failing by a manufacturer is therefore likely to result in supply shortages. "For the last ten years or so, the production and distribution chain has grown more complex. Some raw materials are primarily manufactured in China and India and therefore if there is the slightest issue, they don't arrive in Europe or arrive at a later date", notes Bruno Bonnemain[23]. This major relocation movement can be explained by a number of factors. Firstly, the very low price of non-patented medicines, which incited industrial players either to completely withdraw from production (which resulted in a lower supply of certain molecules) or to transfer part of their production to low-cost countries. Secondly, the tightening of European labour and environmental regulations, which motivate the same players to move to countries where the requirements are less stringent and the costs less high.
This outsourcing has a detrimental environmental effect as the carbon footprint is not reduced but exported. It also places Europe in a situation of dependence on third countries which can suddenly suspend deliveries for health, political or other reasons, or decide unilaterally to hike up their prices. "International sub-contracting, which further fragments production phases and increases the specialisation of production sites, increases the risk of inventory shortages and compounds the difficulties related to product quality control. Together with just-in-time production methods, when there is a shortage of a compound, the entire production chain is stalled"[24]. The relocation of the production of some APIs to Europe is currently still not enough to reverse the process, while the technologies required to manufacture some raw materials are no longer available in the EU.

A STRAINED SINGLE MARKET

Outsourcing is not the only consideration at issue. Many other factors underlie medicine supply issues: fluctuating demand due to long-term factors such as demographic change and short-term factors such as public procurement procedures, pricing strategies and the setting of fixed quotas by the pharmaceutical industry, which are often insufficient in relation to patients' actual needs[25]. In addition, there are various risks that are specific to this distinctive industry, such as delays and failures of production equipment, changes to marketing authorisations which call for a review of production or labelling conditions, a decision from health authorities to suspend a company's accreditation or a quality defect that requires entire batches to be discarded. An impurity on a site, for example, caused the long-lasting shortage of a treatment for tuberculosis in 2019 and 2020[26]. These difficulties can be exacerbated by a lack of visibility and information that makes it harder for manufacturers

21 Staff working document – Strategic dependencies and capacities, European Commission.
22 Resolution of the European Parliament of 17 September 2020 on the shortage of medicines – how to address an emerging problem, see above. See also the opinion piece by Nathalie Colin-Oesterlé: "Pénuries de médicaments, l'Europe doit sortir du coma". L'Opinion, 27 January 2023 (in French).
23 Interview with the author, February 2023, see above.
24 *L'Économie du médicament*, Philippe Abecassis and Nathalie Coutinet, see above.
25 Position Paper on Medicine Shortages, Pharmaceutical Group of the European Union (PGEU).
26 Read the opinion piece by Pauline Londeix and Jérôme Martin in *Le Monde*, 4 March 2022 (in French).

to meet demand on time or by export restrictions that hinder the proper functioning of the internal market. Lastly, certain products are permanently withdrawn from the market by manufacturers who deem them to be no longer sufficiently profitable.

Furthermore, **manufacturers are under no obligation to market authorised medicines across the EU as a whole.** They prefer to target certain markets in accordance with the policies rolled out, population size, the organisation of healthcare systems, administrative procedures and price differentials between Member States, which can sometimes double for the same medicine[27]. "Basically, it is in firms' interest to organise the marketing of their products by firstly selecting the most referenced countries and those with the most liberal price fixing policies, avoiding or delaying marketing in the least referenced countries where prices are lowest"[28]. The WAIT survey conducted by the European Federation of Pharmaceutical Industries and Associations (see above) reveals that out of the 160 medicines approved by the EMA between 2017 and 2020, 147 are available in Germany, 105 in France, 85 in Spain and only 38 in Romania. **Pricing differences have also resulted in the development of parallel imports**, with some distributors purchasing where prices are lowest and selling where they are highest[29].

Intellectual property represents another challenge. Patents play a key role in the pharmaceutical industry and its ability to innovate, which has contributed significantly to raising life expectancy in the last sixty years. For a twenty-year term effective from the date the application is filed, a patent protects the holder from any competition and in return the application must be published within eighteen months. The product is generally available on the market two to three years later, thus ensuring seventeen to eighteen years of market exclusivity[30]. In practice, this timeframe is much shorter. The new molecule must be subsequently subject to research, development and trials for around ten years before the health authorities authorise its marketing to patients. This is why medicines enjoy a "supplementary protection certificate" (SPC) for an additional term of up to five years. Medicines are therefore protected for around fifteen years, before they can be legally copied in generic form.

While it is perfectly legitimate to compensate research due to the significant resources invested, it is less justified to roll out an extensive arsenal of legal instruments, as some companies do, to extend patents beyond the set term, a practice which delays the marketing of generics. Moreover, some of the research is funded by public authorities, directly as subsidies and incentives, or indirectly through coverage and reimbursement systems. "If States co-fund research and purchase medicines, they can incite manufacturers to sign voluntary licence agreements so that production meets demand: this does not detract from the legitimate interests and properties of stakeholders but is a means of promoting access, prices and the sustainability of our social security systems", notes Nathalie Coutinet.

27 Three theoretical price fixing mechanisms co-exist for medicines: cost-based pricing, in which prices are set on the basis of production costs; international benchmarking, in which the price in one or more economically similar or geographically adjacent countries is used as a reference or comparison; and value-based pricing, in which the price of a pharmaceutical product is based on the value of its use as perceived by the consumer. According to a study by Iqvia, the French price for medicines remains one of the lowest in comparable countries. While with gap with the German price is narrowing, the latter remains 9% higher.

28 *L'Économie du médicament*, Philippe Abecassis and Nathalie Coutinet, see above.

29 Parallel imports of medicines entail importing then distributing medicines from one country to another, outside the distribution network established by the manufacturer or their distributor. In 2020, parallel trading was estimated at €6.07 billion, Leem Report (in French).

30 Information sheet published by the Entreprises du Médicament (leem)(in French).

III . Rules that need to be improved to ensure the availability of medicines

I WORKING TOWARDS A NEW EUROPEAN LEGAL FRAMEWORK

While the organisation and provision of healthcare services and medical care fall under the competence of Member States, the EU has a supplementary competence in health policy which authorises it to support and coordinate actions and adopt legislative measures in certain clearly defined areas such as medicines and medical devices[31]. The European Commission is preparing a proposal to overhaul and modernise this current system.

Many objectives were set out in its 2020 pharmaceutical strategy, concerning unmet medical requirements, access to safe and affordable treatment and antimicrobial resistance (a genuine public health issue)[32]. There are as many avenues for achieving these objectives, such as increased research efforts, the overhaul of legislation on rare and paediatric diseases (for which the low population concerned limits return on investment) or stepping up cooperation in health technology assessment (clinical added value, cost effectiveness in comparison to existing medicines). The current European Commissioner for Health, Stella Kyriakides, has expressed the option of incorporating a "PRIME" programme into legislation for priority medicines with a view to speeding up development and authorisation. One priority will be to ensure that therapies are affordable, for example by requiring greater transparency regarding prices and research and development costs or by optimising resources through increased use of generic and biosimilar products.

A modernisation of the pharmaceutical framework would also require improved competitiveness and the industry's long-term ability to innovate, on the basis of a range of instruments including incentives, intellectual property rights and European funding. It will also be necessary to specify the conditions under which a product may be used in an emergency, to speed up certain procedures, such as the renewal of market authorisations, and to favour digitalisation of electronic information to remove language barriers and facilitate cross-border transfers and the updating of the EU register of authorised products. This could be an opportunity to abolish certain inconsistencies: manufacturers are obliged to provide a single code for each box but each country has its own system. Lastly, the potential adverse effects of the production, use and disposal of active pharmaceutical ingredients on the environment and public health must be identified.

The industry and regulators cannot dispense with a discussion on data protection in relation to clinical trials. Such data is disclosed to regulatory authorities to obtain marketing authorisation. A company that markets a medicinal product currently enjoys exclusivity of this data for eight years, to protect the work conducted

31 A legal framework has been introduced and is regularly updated in the EU. It covers in particular: the general rules applicable to medicines (directive 2001/83/EC on the Community code relating to medicinal products for human use and regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency); orphan medicines intended to treat rare diseases (regulation (EC) No 141/2000); medicines for paediatric use (regulation (EC) No 1901/2006); innovative therapies (regulation (EC) No 1394/2007 and directive 2009/120/EC); clinical trials on medicinal products for human use (regulation (EU) No 536/2014); medical devices (regulation (EU) 2017/745 and regulation (EU) 2017/746). • Articles 23bis and 81 of the 2001 directive sets out the general obligations for the supply of medicines with which holders of distribution authorisations must comply and a notification obligation in the event of a product ceasing to be placed on the market, either temporarily or permanently. Implementation varies significantly from one country to another, due to a lack of harmonised criteria for the notification of medicine shortages.

32 Antibiotics: A multi-perspective challenge, cep Input, No 2, 31 January 2013.

upstream. Competitors must then wait another two years to launch the production of a generic and a further year in the event of a new important therapeutic indication. If these timeframes are shortened, this may speed up the marketing of new treatments to meet unmet medical requirements.

I STRENGTHENING THE EU'S HEALTH RESILIENCE

The Commission sees "strategic independence" as a means of securing supply and of stimulating a far-reaching movement that many stakeholders are calling for[33]. There are various ways of making this happen: identifying areas of dependence with an appropriate mapping of needs and production sites, diversifying and securing value chains, building up strategic stocks and encouraging manufacturers to produce and invest in Europe. The industry may be subject to more stringent rules governing supply, notifications of shortages and withdrawals and stock transparency.

In a report published at the end of 2022, the French Senate's European Affairs commission proposed to **define in law the very notions of "medicine shortage" and "critical medicines"**, taking into consideration the therapeutic benefit and the vulnerability of production chains[34]. Another proposal is the creation of a solidarity fund which would help the poorer European nations to meet unmet medical requirements. The issue of shortages also concerns the European Parliament, which has proposed in particular the creation of a **European reserve for certain highly sensitive medicines** and the integration of certain pharmaceutical productions in the framework of the IPCEI (Important Projects of Common European Interest), so that State subsidies may support private investments and step up innovation[35].

MEPs are also in favour of the creation of one or more non-profit European pharmaceutical undertakings. One option could be public-private partnerships or a model based on the US Civica project[36]. "We have reached a point where we must either increase the price of certain generics, because it is very difficult to manufacture them, or shift to **a public generic production** model", explains Nathalie Coutinet. "It is ethically contentious, however, as there would be an appropriation of profits by the private sector when it is highly profitable and public intervention in cases when this is less the case. It is therefore necessary to consider the way in which prices are fixed and profits distributed".

The measures taken in response to Covid-19 must also be underscored. **The European Medicines Agency is now in charge of monitoring shortages** which may occur in a situation of health crisis or in the event of a crisis. An interoperable IT plat-

33 A structured dialogue, co-chaired by the Commission's Directorate-General for Health and the Directorate-General for Internal Market, Industry and Entrepreneurship, was held in 2021/2022 with and between public authorities and stakeholders of the pharmaceutical product manufacturing value chain with a view to identifying the weaknesses concerning critical medicines, raw materials, intermediate products and active ingredients.

34 There is currently no definition of a medicine shortage on an EU level that is not directly related to a situation of public health emergency as provided for in the new European regulation concerning serious cross-border threats to health. It is solely within this framework that the regulation of 25 January 2022 on a reinforced role for the European Medicines Agency defines the shortage as "a situation in which the supply of a medicinal product that is authorised and placed on the market in a Member State does not meet demand for that medicinal product at a national level". • See the report of the French Senate, "La stratégie pharmaceutique pour l'Europe de la Commission européenne" (in French).

35 Sixteen EU Member States, including France, Italy and Poland, signed a manifesto on 2 March 2022 for an Important Project of Common European Interest (IPCEI) in the field of health to support innovation and improve the quality and access to healthcare for European patients, PIIEC (in French).

36 Report by France info on the US *Civica* project (in French).

form on an EU level has been created to facilitate data collection on supply issues, supply and demand. Future measures could be based on these new provisions and expand their scope of action[37].

I EUROPEANS AT A CROSSROADS

The Commission's proposals will naturally be examined in detail by the entire industry. For example, is it necessary to discuss the EU's health sovereignty, a notion dear to France but eyed with caution in various other countries[38]? At a hearing in February 2023 before the European Parliament's special committee on the COVID-19 pandemic, Matthias Bauer, director of the ECIPE (European Centre for International Political Economy) questioned the policies to be implemented, given that "perceptions vary between Member States and industry stakeholders"[39].

The European objective should be to reduce European dependence in the area of health products, which implies a diversification of supply chains, the relocation of certain productions and the creation of a strong industrial base by investing both in the production of essential products and in sectors with a bright future[40]. One avenue may be to **make certain calls for tenders launched by public institutions conditional upon the commitment to produce active ingredients and end products in the EU** and in addition on greater clarifications of required quantities. The appointment of several suppliers in public procurement contracts also limits the risks related to supplier non-performance.

Ensuring a secure supply also calls for a clearer organisation within the EU. Older products have often been registered country by country and do not necessarily have the same indication, dosage or contraindications across the board. It would therefore be much easier to have a marketing authorisation on a European level, together with a single packaging.

Above all, the European Union must draw up a list of essential medicines (perhaps 150 to 200), subject to specific legislative, regulatory, economic or industrial measures. "For each medicine, we would have to look at the entire value chain and decide on a case-by-case basis to develop production within the EU", believes Bruno Bonnemain. "This requires qualified staff to be trained with a view to offsetting the loss of skills caused by relocations. Incentives for investments and research in "internal" processes is also necessary"[41].

37 Improving the availability of medicines authorised in the EU is a key priority of the EMA and the European network of regulatory authorities for medicines. The Agency plays a key role in coordinating the EU's response to supply issues caused by major events or public health emergencies. Faced with the difficulties of the winter of 2022/2023, it encouraged the relevant authorities to use existing regulatory flexibilities such as the exceptional provision of certain unauthorised medicines in a Member State or exemptions to some labelling or packaging requirements. The Agency also identifies shortages in Member States.

38 La souveraineté sanitaire européenne au révélateur de la crise Covid-19. Florent Parmentier, *Diplomatie*, 7 January 2022.

39 Covi comittee meeting.

40 See on this topic the report of the Jacques Delors Institute's Health Working Group.

41 The European regulation on the reinforced role of the EMA provides for the creation of a list of the main therapeutic groups of medicines necessary for emergency treatment in order to contribute to the preparation of the lists of medicines which will be deemed critical in the event of a public health crisis. Outside of this emergency scenario, there are no plans for a list of medicines considered to be critical or of major therapeutic benefit. For example, depending on the situation, there are "medicines of major therapeutic benefit", for which there is no possible substitution, and "medicines of health and strategic benefit", for which a break in treatment represents an immediate danger to the patient's life.

Creating a harmonised EU price would be difficult, given the specific characteristics of each Member State, and could even disadvantage the lowest-income countries. After two years of discussions, the European Commission was forced in 2014 to withdraw a proposal concerning the transparency of measures that govern price fixing, as it predicted a failure to reach an agreement in the Council. However, cooperation between the EU-27 as part of the Networking Meeting of the Competent Authorities on Pricing and Reimbursement is worth fostering, particularly to consider the range of situations in terms of GDP[42]. It would also be interesting to consider a form of coordination of medical assessment on the basis of common criteria and expertise; the constant back-and-forth between national and European levels results in a loss of data, knowledge and resources.

Bolstered by its single market of 450 million inhabitants, the EU could negotiate price ceilings for the most critical products with pharmaceutical companies, which would mitigate the risks of them favouring the highest bidders. It could also **introduce the notion of a "fair and equitable" price**, by requiring greater clarity for research and production investments. For the most critical medicines, one solution would be to have HERA, the new European Health Emergency Preparedness and Response Authority make bulk purchases, as was the case for Covid vaccines. It would be necessary to strike the right balance between two ambitions: strengthening innovation and production capacities in the EU and reducing prices to improve public finances and ensure distribution to the most vulnerable. The challenge will also be financial. Public finances, both national and European, will be necessary to top up research resources in areas of no commercial interest or with too high a risk.

Some measures, which at first glance appear justified, may give rise to adverse effects. This is the case for stock constitution obligations which must be properly gauged to avoid that they contribute to fuelling the shortages they aim to prevent, including to the detriment of neighbouring countries, and that industry players do not pass on the costs incurred to consumers. The stock obligation introduced in France did not prevent supply problems, which even peaked in 2022[43]. The best way would therefore be to build up European reserves, preferably for semi-manufactured products, so that it is possible to respond to a sudden rise in requirements for paracetamol, antiviral drugs, antibiotics and other key products.

Conclusion

The pharmaceutical industry's business model has changed significantly in recent years, shifting from a public heath perspective aimed at providing medicines to as many people as possible to predominantly financial motivations. This encourages Big Pharma companies to cut costs and pull out of the production of mature products, while generic manufacturers are forced to sell their products at prices that are often very low.

The risk for Europe's health autonomy is twofold: start-ups need to raise considerable funds to successfully conduct their research projects and, as they do not find

42 Networking Meeting of the Competent Authorities on Pricing and Reimbursement (NCAPR) is an informal cooperation platform.

43 In France, manufacturers and operators of medicines of major therapeutic interest are required since 2021 to constitute minimum stocks of two months. This timeframe is reduced to one month for other medicines and can be increased to four months by the French National Agency for Medicines and Health Products Safety (ANSM). In addition, pharmaceutical companies must define shortage management plans for all medicines of major therapeutic benefits marketed in France, identify risks and propose solutions. Other European countries also enforce storage obligations, such as Belgium, Finland, Germany, Greece, Portugal and Romania.

sufficient capital in the EU, are turning en masse to venture capital funds located in the USA, while a growing share of low added value active ingredient production is being transferred to third countries, chiefly India and China.

The time has come for the EU-27 to roll out ambitious long-term solutions, even if this disrupts the industry and Member States themselves. Financial sanctions would be a deterrent to non-compliance with notification and supply requirements. In contrast, financial and tax incentives could convince industry stakeholders to relocate some of their production to Europe and/or to build new factories in the EU.

As Professor Massimo Florio stressed to the European Parliament's COVI commission, tomorrow the EU-27 will have to answer a simple yet fundamental question: do they want to become the top player in the world or stay second in line?

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