Académie nationale de Pharmacie

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# UNAVAILABILITY OF INDISPENSABLE MEDICINES: ADDITIONAL RECOMMENDATIONS FOR COORDINATED AND PREVENTIVE ACTION BY EUROPE AND THE MEMBER STATES

*Validated by the French Academy Board on 22 June 2021*

## Explanatory memorandum

The unavailability of medicines has been the subject of numerous statements, reports and recommendations; in particular the statements of the French Academy of Pharmacy in April 2013 and June 2018. The 2018 report focused mainly on the situation in France and its recommendations covered actions to be taken in that country. Awareness in France and Europe over the last few months has led to this debate being taken to the European level, considering the experience acquired during to the Covid-19 pandemic.

On 17 September 2020, the European Parliament adopted a resolution entitled "Drug shortages - how to tackle an emerging problem", in line with the position of the Academy, some of whose members were auditioned.

On 25 November 2020, the European Commission published a communication to the Council and the European Parliament on a pharmaceutical strategy for Europe (see its analysis in Appendix 1). In particular, the Commission proposed the creation of a crisis management body, HERA (Health Emergency preparedness and Response Authority), similar to the American BARDA (Biomedical Advanced Research and Development Authority). This body is currently the subject of a pilot project dedicated exclusively to COVID-19 vaccines. However, there are discussions about what HERA should do and under what conditions. One of the concerns of our Academy is that it seems essential to us that this new body, in conjunction with the other European institutions and the Member States, should take charge, in addition to responses to crisis situations, of the coordination and prevention of shortages of essential medicines; these shortages affect certain conventional medicines, which have fallen into the public domain but which nevertheless remain essential (and therefore cannot be replaced) for the treatment of pathologies that threaten the vital prognosis of the patients concerned.

***The French Academy of Pharmacy wishes to supplement its June 2018 Recommendations in view of the following considerations:***

- The European Union's (EU) action must be supported by action from the the Member States', as on the one hand they supervise the existing manufacturing structures for active ingredients or finished products as well as alternative manufacturing solutions at different stages. In addition, it is also the States that manage national registration data and information on supply problems.

However, EU action must also be taken in full cooperation with the European structures already in charge of medicines, such as the European Medicines Agency (EMA) and the European Directorate for the Quality of Medicines (EDQM, Council of Europe);

- The priority for action must be to focus on the medicines most at risk of rupture and the lack of which is likely to lead to a significant loss of opportunity for the patient. Conventional medicines that have already fallen into the public domain, such as anticancer drugs, antibiotics (ATB), corticoids, vaccines, and others, represent the most frequent cases of rupture, and it is essential that they are considered. The COVID crisis has added additional tension (for curares, injectable analgesics, sedatives, etc.);
- Possible under-capacity in the production of finished products is linked to specific pharmaceutical forms (injectables, lyophilizates, etc.) or to particular production conditions (vaccines, ATBs, etc.);
- Manufacturing transfers outside the European Union were historically linked to the specific manufacturing conditions of the medicinal product itself or of the active ingredient(s) of which it is composed (ATBs, antivitamins K, hormones, etc.) or linked to their production cost (in particular for products with a very low selling price) or to environmental specifications or, finally, linked to the rationalization of production.
- The lack of availability of a database recording who makes what, where, in what quantitiesand with what active ingredients, additives, containers, led to the surprise of finding that many corticosteroid manufacturers were all subcontracting to the same manufacturing line, putting all countries in great difficulty when it failed.
- Regulatory, technical, and economic constraints that are too arduous or too long, and slow down the resolution of problems of drug shortages, constituting obstacles to the fluidity of transfers that are sometimes necessary from one country to another to adapt to needs. At the root of these difficulties are the many differences, in particular for medicines that are not registered centrally, concerning specialties that are sometimes almost similar (e.g. with the same active ingredient) but cannot be administratively interchanged without making the necessary regulatory variations. These differences may be related to:
    - legal information and packaging (dosages, posologies, expiry dates, presentation of indications and contra-indications, etc.);
    - registration files such as technical files, analytical methods, manufacturing methods (batch size, etc.), manufacturing sites, and even differences in additives. The expiry dates do not always correspond to the reality of the stability and therapeutic use of the medicines concerned.

It should be noted in this context that the mutual recognition procedure has not been sufficiently effective in achieving full harmonization of formulations, unlike the centralized procedure.

- The constraints of Good Manufacturing Practice (GMP) may hinder this flexibility and the indispensable need to anticipate conditions adapted to manufacturing in crisis situations or to necessary transfers. To date, there are few or no manufacturing protocols defined and validated upstream that could facilitate these technical adjustments.
- The growth in mass purchases by hospitals of these products, added to the administrative complexity, leads to an increase in shortages.
- Pharmaceutical technological innovations are not only relevant for new medicines but are also essential for the continuous improvement of essential mature products, in particular to address environmental issues in production.
- The recently published European documents, both on the EU pharmaceutical strategy and on HERA, and the European Parliament's report which address the issue of supply disruptions.

# Additional recommendations from the French Academy of Pharmacy

- ***Governance:*** designate a steering body that develops a strong joint strategic focus for medicines policy at both EU and Member State levels in a coordinated manner. This governance at EU level should be endowed with sufficient decision-making power to transform a reactive approach into a proactive one that is supported by equally strengthened national actions.

- ***Scope***: under the aegis of the European project to create HERA, in addition to the development of new treatments in the field of emerging pathologies, prioritize old drugs considered to be indispensable; the latter are very often subject to supply shortages (e.g., anticancer drugs, ATB, corticoids, vaccines, etc.);

- ***Essential medicines***: ***pooling the analysis of patient needs between Member States to guide the management of the risk of shortages in cooperation with learned societies and patient associations:*** collecting and consolidating the priorities identified by comparing the risk of a lack of medicines for the patient with the risk of a shortage of supply in order to guide the decisions and actions to be implemented.

- ***Data:*** **at the European level, develop a database that is** easy to search by both European and national strategic actors, referencing the products concerned, including information on formulations, pharmaceutical forms, the supply chain and identifying associated points of weakness (sources of raw materials, manufacturing capacity, packaging, etc.). Encourage national agencies to increase their cooperation with the EMA and EDQM (Council of Europe/European Pharmacopoeia) to make databases interoperable (develop a first pilot project initiated by these agencies and financed at European level in order to be rapidly operational);
- ***Adapt or even complete the existing regulatory framework***, in particular for conventional and essential medicines, in order to
    - Accelerate the alignment of formulations, legal indications and control methods to allow for a smoother flow of medicines between EU countries;
    - Determine, within the framework of GMP, upstream validated protocols facilitating the adjustments necessary for the mutualization of supply chains (batch size adjustment, production transfer, subcontracting);
    - Determine the conditions for improving and accelerating the "variations" procedures while maintaining the financial resources of the agencies (national action) in the spirit of the ICH Q guidelines12.
    - Reconsidering the expiry periods and adjusting them as well as possible, based on stability studies carried out under the aegis of industry, learned societies or national institutions, to allow the optimization of stock conservation in line with their rate of use and therapeutic margin, in particular for essential medicines (following the example of the FDA's reflection).

## Appendix: Medicines Strategy for Europe: Detailed analysis of the strategy announced by the European Commission.

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| | EUROPEAN PHARMACEUTICAL STRATEGY proposed by the Commission (25 November 2020). |
| | French Academy of Pharmacy working group on unavailability of indispensable medicines |
| | 21 June 2021 |

Text under discussion: COMMUNICATION from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions of 25 November 2020[1] entitled "Pharmaceutical Strategy for Europe

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[1] Reference SWD (2020) 286 final/25.11.2020

*Preamble:*

*The European system of pharmaceutical regulation has divided responsibilities between member states and the European Commission. For older medicines, their management is the responsibility of the Member States. It is desirable that France take strong initiatives to mobilize other EU member states to better coordinate actions in line with the recommendations in this document.*
*These new actions could make use of the cooperation mechanisms established in 2016 by the Heads of National Agencies and the EMA in the HMA/EMA Task Force on the Availability of Authorized Medicines for Human and Veterinary Use, which provides strategic support and advice on dealing with disruptions and ensuring continuity of supply of medicines.*
*This enhanced cooperation for the availability of old medicines should be supported by the European Commission's legislative and financial support and should find its place in the creation of the future HERA.*

# 1. CHAPTER 1 (INTRODUCTORY) "MEDICINES - A STRONG ECOSYSTEM AT AN IMPORTANT CROSSROADS"

## 1.1. Too much focus on "innovative" medicines

The introductory chapter of the Pharmaceutical Strategy for Europe focuses on innovation from the outset, and it is difficult to find any mention of the fragility of essential older medicines.

Older molecules, present on the market mainly as generic medicines, are all managed at Member State level. Even if new operators benefit, in order to reach the markets, from European registration procedures by mutual recognition or by 1st coordinated evaluation (decentralized procedure) involving the EMA (secretariat of the Coordination Group for Mutual Recognition and Decentralized Procedures, known as CMDh)[2], the life cycle of these nationally registered medicinal products is the responsibility of the Member States.

In its Communication, the European Commission highlights the major regulatory advances in treatments in which has been involved over the last twenty years[3]. It illustrates its point with the introduction of biotechnology products or antiviral drugs for the treatment of chronic hepatitis C, recent vaccines (notably the first vaccine against Ebola), the arrival of personalized therapies improving the prognosis of certain cancers or advanced therapy drugs (ITDs), i.e. cell and gene therapy drugs.

The Commission is fully in its role in encouraging a new approach by the Union to have an **innovative, strong and competitive pharmaceutical industry, since this is a major weakness identified in particular in relation to the USA**. It rightly insists on the need to adapt the incentive system in order to stimulate innovation in areas where the **need for medicines is not being met**, such as the development of new antimicrobials. It also rightly emphasizes the need to break down

[2] Article 27 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001, as amended, established a coordination group to examine any question relating to a marketing authorization for a medicinal product which concerns at least two Member States, to examine any question relating to pharmacovigilance for medicinal products authorized by the Member States and to examine any question relating to variations to marketing authorizations issued by the Member States. The European Medicines Agency shall provide the secretariat of this coordination group - (OJ L 311, 28.11.2001, p. 67 ff)

[3] Box on page 1 of its chapter 1: Medicines - a strong ecosystem at an important crossroads.

compartmentalization so that the different public authorities responsible for authorization, health technology assessment, health care provision, health insurance and financing work together.

At the end of its analysis, the communication discusses the issue of **critical medicines**. It seems that this notion is confined to emergency medicines (and vaccines) during a health crisis. The preservation of the old portfolio is never identified as an important issue for Europe, and when it discusses, in chapter 4.1, "open" strategic autonomy in relation to the conclusions of the European Council of 2 October 2020, no issue of localization in Europe is raised.

In conclusion, this communication suffers from its focus on innovation without concern for the preservation of portfolios of **medicines that have fallen into the public domain** and especially those of older medicines that are still indispensable today.

## 1.2. Why medicines that have fallen into the public domain should be considered

In our 2018 report[4], we focused on one aspect of the unavailability of medicines: the unavailability of **old and essential medicines that are** still considered necessary for therapy despite the appearance of innovative medicines. In fact, most drugs that "save" lives, even today [and we saw this during the start of the Covid-19 health crisis], are chemical molecules that have long since fallen into the public domain (and were first marketed between the 1950s and 1980s). This is indeed the case for most resuscitation drugs. This is also the case for many anti-cancer and related therapies.

The companies that originated these molecules have either disappeared or merged into larger pharmaceutical groups, which have disengaged over time to focus on developing new, patent-protected innovations.

These "old" but still indispensable molecules are now widely marketed by a new branch of the pharmaceutical industry, the so-called **generic drugs.** Some of the companies producing them appeared *ex nihilo* in the 1990s and 2000s.

**This market for generic medicines** is very sensitive to the law of **supply and demand**. The firms involved compete in a way that is sought after by the public authorities. This competition is amplified in the hospital market, where prices are not controlled. These medicines that have fallen into the public domain are the subject of calls for tender by public and private buyers.

This emergence of "generics" and now "biosimilars" for biotechnology drugs is widely supported as a means of reducing costs for social accounts.

On the other hand, few have realized that the development of the generic market has been concomitant with, on the one hand, **the increase in global demand** and, on the other hand, **the increase in manufacturing costs**; the latter being linked to the constant increase in the level of requirements, the new quality[5] and safety standards for workers and environmental standards. We note that these two aspects are totally absent from the European Commission's text.

The market cannot at the same time succeed in lowering costs and securing sources of supply to avoid relocation and a loss of European autonomy.

As during the thirty glorious years, the continuous supply of medicines had become a given, a non-issue. It took time for the warnings issued by the National Academy of Pharmacy to be heard. We note that our hospital colleagues in 2020 found that some of their calls for tender did not interest any economic operator and remained unanswered.

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[4] The academic report cites 'old' drugs for intensive care, oncology, infectious diseases, neurology, cardiology and paediatrics, which were first marketed between the 1950s and 1980s.

[5] Quality standards that have resulted in an exponential evolution of the requirements set out in "Good Manufacturing Practices

**The current Covid-19 crisis has unfortunately validated the accuracy of the analyses and academic warnings launched three times since 2011.**

Awareness of the difficulties certainly started at the political level before the Covid-19 crisis, but the health crisis acted as an eye-opener. This awareness has probably not been sufficient for essential old drugs, as the "Pharmaceutical Strategy for Europe" shows. Its general economy is largely focused on the medicines of the future and Europe's place in the global innovation scene.

But it should be remembered that there are two strategic objectives:

- one on Europe's place in future innovation
- the other concerning the importance of ensuring a degree of independence to meet the needs of European populations for the manufacture of medicines, those in the public domain.

In the rather tense global geopolitical context in which we find ourselves, one of our priorities should be to ensure that Europe is less dependent on globally dispersed markets. We could set ourselves a common objective of pharmaceutical independence: for example, to achieve a production capacity of 60% of the volume consumed in Europe (raw materials and finished products) **for all the essential molecules that have fallen into the public domain** or will fall into the public domain and ensuring that the remaining 40% are not concentrated in a single geographical sector.

This would mean, for example:

- to have the means to map the supply chains of medicines that have fallen into the public domain (generic medicines and biosimilar medicines) and to facilitate the establishment of operators in Europe for molecules where this is not the case already.
- provide a mechanism, when a new molecule falls into the public domain, to facilitate the establishment of production capacity in Europe (synthetic medicines or biosimilars). We can draw inspiration from a measure of the Strategic Council for Health Industries (CSIS) in the 2000s which allowed the localization of certain molecules by transferring the file from the originator company to a European "generic" operator, with manufacture in Europe.

However, the main obstacle is that, until now, "old" molecules that have been in the public domain for a long time have been managed mainly at Member State level. This makes it difficult to include this subject in the European strategy to prevent shortages and gradual unavailability of medicines, simply because it is a market that the Commission does not understand well or can act on without the support of the Member States, and the latter themselves have generally not defined a long-term strategy in this area.

The continuous supply of essential old medicines will not be ensured in Europe by the mechanisms recently put in place and which are also taken up by the Commission in its Communication (see Chapter 4.1), i.e., the advance declaration of risks of shortages as well as obligations in terms of storage (the latter could even have a perverse effect on these low-priced generic medicines). These are interesting mechanisms, but their scope will remain limited, to the detriment of a prevention policy. A large proportion of recent biotechnology drugs are manufactured in the USA and Japan. Will we take advantage of the fall in patents to relocate production to our European territory? As regards **those medicines that have fallen into the public domain**, whether they are old or recent, our sovereignty can only be achieved through a dynamic, proactive policy that is constant over time. Economic operators must be encouraged to invest on European territory. All the more so as the decision-making centers are now often outside Europe. This requires the definition of a specific policy for an appropriate and dedicated pharmaceutical industrial strategy.

# 2. CHAPTER 2 " DELIVERING FOR PATIENTS: FULFILLING UNMET MEDICAL NEEDS AND ENSURING ACCESSIBILITY AND AFFORDABILITY OF MEDICINES"

## 2.1. "Prioritising unmet medical needs"

This chapter mainly considers measures for R&D and market access for "innovative" medicines such as antimicrobials, and for rare diseases or for small populations (paediatrics). The measures have little or no impact on medicines in the public domain, and therefore no impact on essential older medicines. However, if needs are to be met by new medicines, care must be taken to ensure that currently met needs are not undermined in the future.

## 2.2. "Ensuring patients' access to medicines"

### 1. Flagship initiatives focused largely on biosimilars

Again, **securing the supply of essential old medicines that have fallen into the public domain** is not sufficiently addressed.

The Commission mainly refers to the issue of new entrants in terms of biosimilar medicines. For example, it mentions generics in a paragraph devoted almost exclusively to biosimilar medicines. In this paragraph, it explains that its aim is to remove the obstacles that delay their arrival on the market.

However, no mechanism for **locating the production of these biosimilars on European territory is proposed. We can therefore expect the same problem of non-localization on European territory in the future.** Indeed, molecules derived from biotechnology are relatively little manufactured in Europe. We will therefore remain dependent on third countries in this key sector.

In this area, it would be necessary to create **production capacity** in Europe for these molecules that have fallen into the public domain when they are considered indispensable for the European patient.

### 2. Other actions targeting innovative approaches to drug procurement under the Big Buyers initiative

The Commission calls on **public purchasers to** design **smart and innovative procurement** procedures, introducing conditions other than price alone.

When it proposes that public purchasers add a criterion based on '*environmentally friendly production*', it seems to ignore the fact that hospital budgets are very tight and that it is pointless to ask hospitals or clinics alone to pay for this virtuous policy. These environmental values do indeed have a cost, which led industrial operators to relocate production in the 2000s to countries that were less vigilant on this subject, in order to offer European public purchasers medicines at acceptable costs. It is therefore clear that this issue should be at the heart of a general strategy, with incentive proposals that are not the sole responsibility of hospitals.

Furthermore, the European text does not address a certain number of issues concerning hospital tenders. To ensure continuous supply, manufacturers must be able to anticipate needs over a fairly long period. This also makes it possible to keep the manufacturing tool operational thanks to a relatively constant manufacturing volume, which becomes impossible when the number of invitations to tender is disproportionate (national scale) with periodic changes of great amplitude, which can, in the event of loss of a contract, cause the manufacturer to withdraw from the market.

In order to benefit from a large enough number of industrial operators, it is necessary to look for modalities allowing in particular (see our 2018 report):

- preservation of the industrial tool and even technological innovation to optimize it;
- reduction of industrial upsets (reduction of market volumes to avoid abrupt changes);
- extension of the duration of contracts.
- longer periods of time between agreement on a contract and its implementation.
- optimized allotment of markets. (Segmentation of demand into several lots allows several manufacturers to respond to a call for tender for the same product)

### 2.3. "Ensuring affordability of medicines for patients and health systems' financial and fiscal sustainability"

The Commission discusses the financial and budgetary sustainability of health systems. It quite rightly points out that expenditure on medicines in hospitals is increasing rapidly (20-30% of hospital budgets) and, above all, is increasing faster than expenditure on retail purchases. But here again, no account is taken of the fact that, in the face of the growth of innovative medicines (a market that is not very competitive and often derived from biotechnology), whose prices are high, **old medicines, and especially chemically synthesized medicines, are often the adjustment variable**.

**It is** important to remember that *pricing, payment and public procurement policies* should not lead to a gradual reduction in the number of **operators in the generic market for essential older medicines.**

## 3. CHAPTER 3 " SUPPORTING A COMPETITIVE AND INNOVATIVE EUROPEAN PHARMACEUTICAL INDUSTRY"

### 3.1. "Providing a fertile environment for Europe's industry"

These measures do not take into account the specificities of older medicines.

### 3.2. "Enabling innovation and digital transformation"

The European document addresses this important issue but the analysis suffers from not having identified that, even for **the "non-innovative" industry,** i.e., that which produces generic medicines, **the need for technological innovation** exists, both to maintain competitiveness and to improve the robustness of manufacturing processes.

The various surveys conducted by the ISPE (International Society for Pharmaceutical Engineering) have shown that, in many cases, this is due to a lack of investment in production tools or quality management systems that the production tool gradually deteriorates and sometimes leads to the closure of the least profitable production lines, without taking into account their therapeutic usefulness.

The Commission wants to see the emergence of a **skilled and specialized workforce.**

While this measure will also have an impact on the generic industry, it will not secure supply through technological innovation.

In order to facilitate possible relocations and to maintain, or even improve, the existing production tool, it is necessary to develop measures to this end. This is one of the reasons why the French National Academy of Pharmacy, in its 2018 report, proposed, for example, "*a production tax credit to encourage the relocation of industrial facilities for active ingredients and pharmaceutical forms, particularly injectable ones, including, if necessary, the redevelopment of compatible environmental processes*".

If efforts to improve processes and standards (especially GMP and environmental standards) cannot be sustained, then the idea of a strategy towards greater European independence is effectively abandoned.

Imported medicines that do not face the same environmental constraints will certainly remain cheaper for a long time.

For example, the European pharmaceutical industry is currently investing in the contribution of digital 4.0 and artificial intelligence to improve the maintenance of equipment, improve lead times and also the performance of certain repetitive and delicate controls (e.g. particle contamination) in order to consolidate the manufacturing and batch release processes and avoid the often long maintenance periods with production stoppages.

However, the risk is that the manufacturers who will have access to it will be those who have the means to invest (the innovation industry) and it is feared that this will be inaccessible to the generic industry.

Innovation must be supported throughout the product life cycle and European operators must take advantage of this strategy to secure production in Europe for the benefit of European patients.

## 3.3. "A sound and flexible regulatory system"

**This chapter is important because concrete regulatory measures could have an impact on older/generic medicines.**

**Most of the measures proposed by the Commission are very sensible, such as**

- a single evaluation process in all Member States for active substances used for different generic medicines (Active Substance Master Files, Certificates of Suitability to the European Pharmacopoeia) to facilitate their authorization and life cycle management;
- Better use of electronic product information (ePI) to facilitate the provision of information on medicines to health professionals and patients in the multilingual environment of the EU. This could include the possibility of using QR codes to replace paper leaflets. The possibility of having a "European" packaging that can be used everywherecomes to mind. However, the Commission does not explicitly mention the following;
- the reaffirmation of the desire to simplify and rationalize the procedures for authorizing and monitoring medicinal products. As an example, **the process of variations in marketing authorizations**. The ICHQ12 process goes in the same direction and should be promoted by Member States;
- building on the COVID-19 experience, by considering the introduction of what is known in regulatory jargon as "rolling assessment";
- an interesting measure concerning medicines already on the market that still have potential: "*the Commission supports initiatives to improve the regulatory knowledge of academic researchers and non-profit stakeholders through scientific and regulatory advice, so that the clinical data they generate can be used for the* ***reallocation of off-patent medicines*** *to new therapeutic uses. Industry engagement and partnership in this process will be encouraged*.

It would also have been useful to show the value of working on the rationalization of formulations and dosages of old formulations, which would facilitate portfolio management and increase the possibilities of troubleshooting between Member States when a generic drug is out of stock.

# 4. CHAPTER 4 " ENHANCING RESILIENCE: DIVERSIFIED AND SECURE SUPPLY CHAINS; ENVIRONMENTALLY SUSTAINABLE PHARMACEUTICALS; CRISIS PREPAREDNESS AND RESPONSE MECHANISMS"

## 4.1. "Secure the supply of medicines across the EU and avoid shortages"

►Avoiding **shortages**

Here the Commission addresses the increasingly frequent shortages of ***products that have been on the market for many years and are in widespread use.***

All the measures in this chapter go in the right direction, with the objective of making **critical medicines** safe.

The Commission uses the term ***critical medicines***. In fact, this designation of critical medicines refers to recent experience with supply problems in the context of the health crisis, particularly in emergency/resuscitation medicines. Of course, we must not limit ourselves to this very short-term aspect of the current crisis but look at all therapeutic classes.

The notion of "critical" would need to be clarified, but insofar as the Commission indicates (see box *below*) that it plans to facilitate *"joint procurement"* for these products, it is possible to think that this designation does not cover exactly the same range as that defended by the Académie nationale de Pharmacie with the notion of *old essential medicines*.

However, the objectives pursued may be of secondary benefit to the safety of certain *essential older medicines*.

►**Strategic** autonomy

It should be noted that the Commission, echoing the conclusions of the European Council of 2nd October 2020, refers to an **open strategic autonomy** (sic) **of the Union**. **The word "open" suggests that the aim is not to achieve full autonomy**. It is difficult for the European authorities to announce measures that could be in contradiction with WTO agreements.

Selected extracts

[...]

*"Strengthening the **Union's open strategic autonomy** in the field of medicinal products requires actions to identify strategic health dependencies and to propose measures to reduce them, including possibly diversifying production and supply chains, ensuring strategic stocks and encouraging production and investment in Europe.*

[...]

*Legislative measures could include stricter obligations on industry to ensure the supply of medicines, earlier notification of shortages and withdrawals, increased transparency of stocks throughout the supply chain and a stronger coordinating role for the EMA in monitoring and managing shortages.*

*These measures will be complemented by enhanced cooperation between Member States, for example to improve procurement approaches and strategies, joint procurement for critical medicines and EU-wide cooperation on tools and instruments for national pricing and reimbursement policies. For low volume or limited use products, new models for commercial contracts and/or payment will be essential.*

*[...]*

*The pandemic has shown that public authorities often do not have access to comprehensive information on the structure of production and supply chains. An appropriate response to a crisis requires resilient and sufficiently diverse supply chains that operate in a predictable and resource-efficient business environment. »*

►**Greater anticipation of disruptions**

With regard to the establishment of a legislative framework, the proposal to enable the Authorities to be aware of the risks of breakdowns more quickly, in order to react better, is interesting.

France already has a very precise framework in this area. A recent Decree (No. 2021-349 of 30 March 2021) (following the law of 26 January 2016) specifies the conditions for determining safety stocks intended for the national market (2 months for medicinal products of major therapeutic interest, or even more in special cases).

This is still a reactive policy, not an anticipatory one (in quality management, one would say that one takes the problem on the "corrective action" side without accompanying it with "preventive action").

This will not fundamentally change the situation. A shortage will have to be managed.

This will give the Authorities more time to organize imports of foreign medicines (from other Member States and from third countries) and to compensate for the announced shortages, but it will not resolve the intrinsic fragility of Europe and will not secure the viability of certain old medicines whose profitability is running out.

►The **sources of shortages**

The Commission cites what it considers to be the sources of frequent shortages:

- marketing strategies [*Sic* - no further details];
- parallel trade ;
- the scarcity of certain active substances and raw materials;
- the weakness of public service obligations;
- supply quotas;
- issues related to pricing and reimbursement.

It is symptomatic that it does not also identify:

- certain tendering policies;
- the impact of the multiplicity of formulations and labelling for the same INN, which does not allow factories to optimize and rationalize - which multiplies the risk of errors - prevents delayed differentiation, to make the European market more fluid and encourages the removal of formulations in certain markets;
- the impact of changes in GMP standards (the impact of the forthcoming modification of Appendix I on injectables is of concern to the specialists and manufacturers concerned), without flexibility of approach for implementation, which may lead some manufacturers to abandon certain types of manufacture or to discontinue forms/dosages.

  These points should be taken into consideration.

The Commission also reports that it has launched a study to identify the root causes of shortages as a basis for assessing and revising existing legislation.

►**Stock** transparency **and supply chain transparency**

The Commission is very much focused on **increased transparency on stocks throughout the** supply chain. When we know the reasons for the shortage of oral corticosteroids in France[6], which

[6] For prednisone and prednisolone, there was a problem with the manufacture not of the active ingredient but of the finished product. The main production came from a single French manufacturer. Part of the production also came from a Greek company. There were two problems at the same time: on the one hand, a production capacity problem of the French company faced with the quality problem of the Greek company. In addition, there were carry-over phenomena: a tension

revealed that out of 10 operators (10 competing specialties), 9 used the same manufacturer, we can consider that knowledge of stocks would have been ineffective in preventing the drug shortage. Therefore, having better transparency on stocks, even if supplemented by an obligation to declare in advance any risk of shortage, will not be decisive in curbing the phenomenon.

Above all, there is a need for greater transparency **in supply chains**. On this subject, the Commission refers to "**a voluntary process**". On the contrary, it should be made compulsory, especially for critical or essential medicines (as defined by the NPA).

**This information is available** in the pharmaceutical inventory reports that all manufacturing establishments in Europe are required to submit. France has extended this obligation **to operators** (see extract from Fact Sheet B[7] below, page 11). This obligation should be extended to all European holders. The Member States and the EMA would then hold and consolidate, almost in real time, this information for all medicinal products marketed (at least critical medicinal products) on each market.

**B.3. Produits exploités dans l'année incluant la liste des médicaments d'intérêt thérapeutique majeur (MITM*) faisant l'objet ou non d'un plan de gestion des pénuries (PGP**)**

| Dénomination de la spécialité | CIS | Dénomination commune (DCI) | Type d'AMM | Titulaire de l'AMM | Site(s) de production / sites de production alternatif(s) | Site(s) de conditionnement primaire | Site(s) de condi-tionnement secondaire | Site d'impor-tation | Site(s) de contrôle | Site(s) d'échan-tillothèque | Site(s) de certification | Substance active | Site(s) de fabrication de la substance active | MITM (oui/non) | PGP (oui/non) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | |

* définis à l'article L. 5111-4 du CSP
** défini à l'article L. 5121-31 du CSP

**Ce tableau téléchargeable sur le site de l'ANSM est à annexer à la fiche B EXPLOITANT**

In the above-mentioned case of corticosteroids, the information was held by the ANSM but not used because the reports were in non-usable PDF format. **A database** should be created at Member State level that is updated annually by the holders (or operators in France) and is interactive at European level, at least for critical or essential medicinal products according to the AnP. Member States should be encouraged to coordinate on this issue and European funding should be made available to allow them do so.

It should be possible to provide a database listing the operators in the supply chain by specialty with a unique code for each supplier of active ingredients and for each pharmaceutical plant. Each State would have its own database, and the EMA could interrogate each database to reconcile the data by active substance/operator pair and form/dosage pair of medicinal products/counterfeiters in order to find out their location. This cross-sectional analysis would make it possible to better identify supply risks in order to guarantee the EU's autonomy, at least for essential products.

Moreover, by having this information on supply chains, the Commission could negotiate from an expert position in the WTO.

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## 4.2. "High quality, safe and environmentally sustainable medicines"

In this chapter, it is interesting to note that the Commission aims to analyze *"the regulatory impact **of new** emerging **manufacturing methods** such as decentralized or continuous manufacturing. These*

on one of the products led pharmacists and prescribers to switch to another form, sometimes with over-ordering by certain wholesalers and pharmacists. By domino effect, we found ourselves with products in tension throughout the chain

[7] https://ansm.sante.fr/page/soumettre-letat-annuel-dun-etablissement-pharmaceutique

*methods generate new manufacturing models, favoring master manufacturing over industrial manufacturing. While speeding up production times, they create new challenges in terms of appropriate quality, inspection and monitoring.*

However, the Commission does not mention cases of almost exponential increase in demand for critical medicines in case of crisis (those that meet the needs of the health crisis at the time). It can be assumed that this will be considered in the context of the creation of HERA.

►The **multiplier coefficients**

In March 2020, in France, at the time of the so-called "first wave" of the pandemic, the consumption of anaesthetic-intensive care drugs was multiplied by a factor of 3 to 90 depending on the drug, in only two or three weeks (GERS/DGS data summarized in the small table below, by major therapeutic classes).

| Classes or types of products | Multiplier coefficient in the last week of March compared to the first week of March |
|---|---|
| Curares | 9 |
| Adrenalin | 5 |
| Hypnotics | 3 à 8 |
| Antibiotics | 3 à 8 |
| Morphine | 3 |
| Hydroxychloroquine | 90 |
| Azithromycin | 30 |

These figures clearly illustrate that, unless there is adequate organization and good anticipation plans, it is unrealistic to expect to be able to cope easily with such increases in needs.
Moreover, as in this case, many of the critical medicines are in the form of injectable preparations, which often have a manufacturing cycle of several weeks.
The subcontracting of manufacturing also has to cope with the constraints of production planning, which is often done with an anticipation of 12 to 18 months.

In addition, the question of the availability of production tools arises, in a global context of insufficient production capacity for injectables and lyophilized products. Recent experience has again shown that the availability of additives and packaging materials (ampoules, bottles, viasl, caps, lids, packaging, etc.) is also a limiting factor.

Thus, anticipating stockpiles of medicines at the level of these multiplier coefficients in their final, ready-to-use pharmaceutical form is unrealistic for several reasons:

- ✓ In their final form, most parenteral drugs have a relatively short shelf life (**between 18 months and 3 years**);
- ✓ the volumes would be considerable; however, storage facilities under controlled temperature conditions are few and far between (or even already saturated, whatever the country concerned);
- ✓ Managing dormant stocks requires, in order to avoid drug loss when the products expire, very difficult management to reintroduce them into the general hospital flow without disrupting the supply plans managed by the hospitals' in-house pharmacies, plans that obey constraints set in advance in the specifications signed with the suppliers following calls for tender;

- ✓ Few countries, if any, could afford such an investment, such a financial commitment, without significantly increasing the debts of States and social protection bodies, with long-term impacts on people's standard of living and therefore ultimately on their health.

It is therefore strongly recommended to think outside the box by resorting to scenarios of overstocking of finished products.

The Commission, contrary to Recommendation 30 of the recent report of the European Parliament[8], does not propose to "*create one or more non-profit European pharmaceutical establishments of general interest, capable of producing medicinal products of strategic health interest for health care, in the absence of existing industrial production, in order to complement and guarantee the security of supply and to prevent possible shortages of medicinal products in case of emergency [...]*". [9]

It is considering the HERA solution (point 4.3). However, the question remains as to how to compensate quickly for any "on demand", whether temporary or longer. How can it be ensured that existing firms or other public institutions (such as certain large central hospital pharmacies) can quickly compensate?

**Adaptability through risk management**

Firstly, this means that manufacturing facilities should be identified that could compensate for batches of medicines of predetermined dosage forms, without compromising on the final quality. Plants in Europe capable of manufacturing dosage forms as diverse as immediate release tablets, sustained release tablets, orodispersible tablets, conventional injectable forms, freeze-dried forms, etc. would need to be identified. Furthermore, there should be the capacity to quickly implement a set of processes in an accelerated way as soon as the break is "announced" or even already observed. However, this requires a few weeks, or even a few months... and it is precisely this notion of reactivity, diversity of forms and skills that presupposes an organization and a "adapted" quality management system. This adaptation, this reactivity, is not in the initial "DNA" of the GMP corpus, built stone by stone since the 1980s.

One of the first examples of this inadequacy in the context of crisis and scarcity of the product is offered by Appendix 15 of these GMP. This appendix 15 stipulates that "*a minimum of three consecutive batches manufactured under routine conditions may constitute a validation of the* manufacturing *process*" before batches can be released to patients. This requirement alone constitutes an insurmountable barrier to any reactivity in the event of a crisis since, in this eventuality, it would be necessary to be able to take over within two to three weeks, which is incompatible with this validation/qualification process that takes several months.

However, the initial paradigms are evolving towards a new conception of quality management, since the negotiation of the ICH [10]Q8, ICH Q9, ICH Q10 Guidelines. With these new guidelines, the objective of

[8] REPORT on drug shortages - tackling an emerging problem (2020/2071(INI)) by the European Parliament, Committee on the Environment, Public Health and Food Safety Rapporteur: Nathalie Colin-Oesterlin - 22 July 2020

[9] These are of course the finished products and not the active ingredients.

[10] The International Conference on Harmonisation. The International Conference on Harmonisation of Criteria for the Registration of Pharmaceuticals for Human Use (ICH) was established in 1990 by the pharmaceutical regulatory authorities and pharmaceutical companies of the European Union, Japan and the United States to define and harmonise some of the standards to be applied in the development of new medicines. The ICH was originally a tripartite initiative involving the six regulatory and industry organisations in Europe, the United States and Japan. To date, the conference has published more than 45 reference texts that specify the technical requirements for specific steps in the drug development and registration process. Harmonisation is achieved through the development of guidelines *via* a scientific consensus process between representatives of regulatory agencies and industry experts working side by side. In October 2015, this informal consultation space was restructured and the ICH Association was founded, allowing any country wishing to join this "harmonisation council" to participate in the drafting of texts. The mission of the ICH is now to achieve greater harmonisation throughout the world with regard to the quality, safety and efficacy of medicines and to enable registration by the authorities in the most efficient way possible, avoiding redundancy as

the Health Authorities is to achieve "*maximum efficiency and flexibility in pharmaceutical production, capable of producing quality products without excessive regulatory oversight*".

These three guidelines, and those that follow (ICH Q 11 and 12 in particular), are not yet "enforceable", even though ICH Q9 and ICH Q10 have been introduced into the French GMP guide as a documentary and optional measure.

An "optimized" quality management system (QMS), based on risk analysis, should be put in place, which would allow the proposal of strategies for quality management and quality risk management that differ from the established practices of the last three decades.

These times should also be shortened in this case, without compromising the expected outcome, i.e., product quality and patient safety. A manufacturing process needs to be validated in order to be able to deliver safe batches in two to three weeks.

It is noted that Appendix 15 above stipulates that "*a different number of batches may be justified taking into account the fact that the manufacturing methods used are standard, or that similar products or processes are already used on the site*". Furthermore, pilot industrial batches could validly replace industrial batches if they have been subject to a good risk analysis.
On the basis of these new approaches, there is nothing to prevent the establishment, for each of the critical medicinal products, or even for a broader list of essential old medicinal products, of **specific advance protocols, allowing rapid industrial transposition to other manufacturing sites and by other operators than those initially registered**.
The idea would then be to propose an approach that favours the preparation of "*mock-up*" files, to borrow a word from the computer vocabulary, anticipating, for each manufacturing process, the control elements to be followed, in order to ultimately allow the release of batches on the basis of predefined criteria, as well as the general elements serving the adaptability of the tool (validation of cleaning processes, etc.).

For these essential medicines, it is therefore desirable that a debate be initiated rapidly at European level with the agencies of the Member States in order to arrive at a body of recommendations applicable to these particular situations of transposition/transfer of production and to issue proposals for industrial transposition and batch release protocols. This mechanism could be extended to medicinal products for which a shortage situation has been recognized as having already been encountered.

These reflections must not only look at **the manufacturing elements** but **also at the way of proving the equivalence of the manufactured drugs with the formulations on the market**, if the firms integrated into this emergency system did not have the agreement of an "originator" manufacturer to work on its formula.

### 4.3. " Enhancing Europe's health crisis response mechanisms"

In this paragraph, the Commission advocates the establishment of a European Health Emergency Response Authority (HERA). This body would be able to coordinate operations along the value chain, once the problems to be solved in the event of a crisis, i.e., an event that is difficult to anticipate, have been identified.

The ambiguity lies in the scope of action of this Authority. HERA's main objective is to fill gaps in the EU's crisis preparedness and response infrastructure and to strengthen operations along the value chain. It is

much as possible in order to save resources. The ICH Association has been based in Switzerland to enable collaborative work with the WHO

obviously essential that HERA, like BARDA in the United States, should also address the problems of endemic shortages of old medicines. For this to happen, the interfaces with existing bodies such as the EMA, the EDQM, etc. must be clearly defined.

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