PROPOSALS OF THE FRENCH ACADEMY OF PHARMACY
FOR THE REFORM OF EU PHARMACEUTICAL LEGISLATION

The French Academy of Pharmacy (AnP) welcomes the Commission's consultation to support the evaluation and impact assessment of the revision of the EU pharmaceutical legislation[1]. The AnP, a legal entity under French public law, is a member of the European Federation of Medical Academies (FEAM). The AnP has nearly 560 full members, national correspondents, associate members, foreign members and honorary members, divided into six sections according to their discipline or sector of activity. It responds to requests from public authorities and alerts health professionals and the general public to any public health issue related to medicines, medical devices and other health products, biology and environmental health. It organizes monthly meetings open to the public and publishes reports and recommendations on its website (https://www.acadpharm.org) covering most chapters of the Commission's questionnaire.

On 26 April this year, the Academy provided the European Commission with its comments on the creation of the Health Emergency Authority (HERA), some of which are in line with the present proposals. Given the dates set for this consultation, from 28 September to 21 December 2021 the Academy has focused its proposals on 4 themes which concern several objectives of the questionnaire, and require a grouped response to these questions, namely :

- Introduce a mandatory European Clinical Authorization ("IND") for clinical trials of medicinal products under the EMA.
- Accelerate the procedures for variations to authorization dossiers according to their criticality.
- Initiate a genuine European policy on essential medicines.
- Strengthen the authority of the qualified person, particularly for manufacturing.

In the future legislative reform, the AnP would like the directive instrument to remain preferred, as it allows good adaptation to national health realities. The AnP reserves the right to come back to these questions depending on the timetable for the presentation of the Commission's legislative proposals, which will be published in the last quarter of 2022. It is desirable that all new legislative initiatives, including implementing legislation, in addition to the check of the subsidiarity criterion, be subject to an analysis of their impact on the European Union's autonomy and supply of essential medicines.

1. Centralized clinical authorisation ("European IND")

[1] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation/public-consultation_en

13th of December 2021

AnP proposals for a "European IND”
Chapters of the Commission's questionnaire: Effectiveness of EU pharmaceutical legislation; incentives for innovation; Adapting the regulatory framework for new products to the future; Improving access to medicines.
Regulatory aspects: Amend Articles 4 (prior authorization) and 5 (filing of an application) of Regulation (EU) No 536/2014 to establish a European clinical trial authorization for medicinal products under the centralized procedure. Amend Regulation (EC) No 726/2004 (EMA & centralized procedure) to establish a Clinical Trials Committee and an Ethics Committee at the EMA.

In Europe, the EMA's scientific opinions have, since 1995, marked progress in the dialogue between authorities and researchers. This initial progress has now reached its limits. This dialogue deserves to be better structured in order to ensure the continuity of the evaluation within life cycle of medicinal products covered by the centralized European procedure, from the pre-authorization phase of clinical trials to post-authorization monitoring (pharmacovigilance).

The Covid-19 crisis has demonstrated that the drug evaluation process benefits from a continuous process, which should start well in advance of the submission of an ideally complete file. For centralized procedure medicinal products, consistency between the EMA's scientific opinions, national decisions to authorize clinical trials and the subsequent opinions of the Committee for Medicinal Products for Human Use is far from ideal, with unavoidable delays. This is a serious handicap for innovative European companies compared to the US situation. The entry into force in 2022 of the Clinical Trials Information System (CTIS) provided for in Regulation (EU) No 536/2014 does not guarantee consistency and continuity between national and European procedures. The EMA's role remains limited to the administration of the portal of the new system, which moreover appears to be too cumbersome and bureaucratic for trials initiated by academic research and small biotechnology firms.

The FDA's "IND" (Investigational New Drug [application]) arrangements allow single point of contact and consistency of decision making from Phase I clinical trials to marketing authorization in the USA. It includes in a coordinated and continuous way assessors and inspectors. It imposes

a global scheme of trial protocols on companies, well in advance of any European decision. And finally, it is much more responsive to a strong therapeutic need. The FDA process is sequential, comprising progress meetings and thematic meetings, formal, with minutes, and informal, with participation of assessors, inspectors and applicants. Thus, the FDA can be met at all stages of the clinical trial phases, and avoids desynchronization between the clinical, chemical and manufacturing controls.

The EMA's "Prime" scheme, which makes it possible to obtain a rapporteur at an early stage for priority medicinal products, is certainly an improvement, but only for a limited number of medicinal products. Centralizing the authorization of clinical trials for medicinal products intended for European marketing authorization would be a much more decisive and beneficial step forward for European clinical research. The current scientific opinion could be maintained for the "pre-IND" phase. To this end, Regulation (EU) No 536/2014 on clinical trials should be amended to give the European Commission, on the advice of the EMA, the power to authorize any clinical trial concerning a medicinal product falling under the centralized procedure. Regulation (EC) No 726/2004 on the EMA could establish a Clinical Trials Committee and an Ethics Committee.

After submission of the application to the EMA, the rapporteurs of these two committees should preferably be appointed from among the members of the countries concerned by the proposed trials. Strict deadlines for the appraisal, the modalities of coordination with the relevant inspectorates and the amounts of fees will have to be specified. It will be important for the EMA to ensure the continuity and consistency of assessments from the central authorization of clinical trials to the marketing authorization of the medicinal product concerned. In addition, procedures should be adapted to the needs of academic research and small biotechnology companies. This European clinical authorization must not call into question the procedures health technology assessment (HTA) procedures for the reimbursement of medicines by national reimbursement of medicines by national social security bodies.

2. Flexibility and acceleration of certain variation procedures.

AnP proposals to improve variation procedures
Chapters of the Commission's questionnaire: Efficiency of EU pharmaceutical legislation; incentives for innovation; Adapting the regulatory framework for new products to the future; Improving access to medicines.
Regulatory aspects, adaptation to ICH Q12 requirements of the following texts:

Regulation (EC) No 726/2004 (centralized procedure), in particular Articles 14bis, 16 and 16bis.
Regulation (EU) No 712/2012 on variations.
Directive 2001/83/EC on the Community code relating to medicinal products for human use, in particular Articles 22ter, 23ter, 44 and 45.
Extend the responsibility for PQs to the marketing authorization holder (Art 48/49, 52 of the Directive) and make good manufacturing and distribution practices, etc., enforceable against him.

The recent pandemic has shown the importance of being able to rapidly carry out certain necessary improvements (manufacturing sites, suppliers, analysis methods, batch sizes, storage conditions, etc.) to better adapt to the needs of European patients and avoid shortages.

The marketing authorization holder will have to submit, upstream, to the authorities responsible for marketing authorization, including the assessment of the risks related to critical or non-critical changes. Control by a well-controlled quality system, available for inspection and under the authority of the qualified person[2] , will ensure this. This should allow for a faster implementation without prior authorization, of changes according to objective criteria of criticality and their control. The regulatory framework for these changes will have been validated in advance by the marketing authority and will be facilitated by a more systematic upstream dialogue with the authorities. These improvements will ensure better access to medicines and may avoid delays and possible production stop or batch recalls. These changes are recommended in particular by the guideline Q12 of the International Council for Harmonization of Pharmaceutical Requirements (ICH). In order to be operational, this guideline must be integrated into the regional legislation of the countries participating in ICH. The United States, Japan and Canada have already implemented it. It is up to the European Union to do the same so as not to penalize production on its territory.

Due to globalization, the verification of risk assessment studies by national authorities in Europe is possible for manufacturing sites that are subject to recognition of inspections within the EU or outside the EU as a result of agreements with the EU. This verification is more problematic, unless specific and rigorous inspections, for other producing countries, notably India and China. The development of a more extensive system of international cooperation on inspection should be encouraged and supported by the parties concerned by ICH to achieve mutual confidence in inspection reports in the medium term. This would save resources, facilitate the implementation of ICH Q12 and the necessary exchange between inspection systems.

[2] In France, the Pharmacien Responsable », see chapter 4.

3. Engage the EU and stakeholders in an essential medicines policy

AnP proposals for a European essential medicines policy
Chapters of the Commission's questionnaire: Effectiveness of EU pharmaceutical legislation; unmet medical needs; improving access to medicines; competitiveness of European markets to ensure affordable medicines; reallocation of medicines; security of supply of medicines; quality and manufacturing of medicines.
Regulatory aspects: Amend the following provisions to facilitate cross-border cooperation in response to unavailability. Regulation (EC) No 726/2004 (centralized procedure) creation of a "Committee for Essential Medicinal Products" to prepare monographs and coordinate data collection in conjunction with the European Pharmacopoeia. Directive 2001/83/EC on the Community code for medicinal products for human use: simplified registration, with increased harmonization for medicines designated as "essential", including legal information.

The unavailability of medicines has been the subject of public statements by the French Academy of Pharmacy in April 2013, June 2018 and June 2021, as well as in its above-mentioned comments of 26 April on the creation of HERA. According to the Academy, the priority for action should be to focus on the medicines most at risk of shortage and whose lack is likely to lead to a significant loss of chance for the patient: conventional medicines that have already fallen in the public domain such as anticancer drugs, antibiotics, corticoids, curares, analgesics, sedatives, vaccines, etc., representing the majority of sources of shortages. The COVID crisis has added additional tensions (curares, injectable analgesics, sedatives, etc.). The AnP highlighted the difficulties linked to the lack of harmonization of so-called "essential" medicines under decentralized procedures.

In June 2021, the AnP had noted the multiple differences between almost similar medicines not registered by the centralized procedure:

● Legal information and packaging (dosages, formulations of indications and contraindications).

● Registration records: dosing methods, manufacturing methods (batch size, ...), manufacturing sites, difference in excipients. 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.

● Necessary constraints on good manufacturing practice that may hamper this flexibility and the need to anticipate the particular 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.

In order to encourage cross-border cooperation to deal with unavailability, the European legislator could commit the EMA, national authorities and the European Pharmacopoeia in an "essential medicines policy" for the European Union. Among all essential medicines, this new policy should target a growing number of so-called "essential medicines" for which Member States accept the need for further harmonization, in the interests of public health and greater EU health autonomy. While it is not possible to centralize all medicinal products under the essential medicines policy, measures[3] could be taken to facilitate and simplify access to these medicines before and during their registration in the decentralized and mutual recognition procedures.

The EMA would be responsible for identifying, together with the Heads of National Agencies, these "essential" medicines (medicines and active ingredients) according to common criteria on the basis of data available to all authorities concerned, including the European Pharmacopoeia. Consultation with industry, wholesalers and hospital and community pharmacists, as well as patient representatives and scientific societies. The European Directorate for the Quality of Medicines and HealthCare (EDQM, European Pharmacopoeia, Council of Europe) has a key global role in ensuring the quality of medical products and their components. The monographs of the Pharmacopoeia are made mandatory in EU legislation. EDQM has a good knowledge of the supply chain, notably through inspections of active ingredients manufactured in third countries. In addition to the intensification of links with the EMA, EDQM should be fully integrated into future HERA networks. The European Health Programme could provide the important resources needed for interactive data sharing resources, including data from the certification of European Pharmacopoeia monographs. This could help the new European Health Emergency Response and Preparedness Authority (HERA) to prevent shortages of essential medicines, by detecting and responding quickly to health emergencies. The European Essential Medicines Policy should make it possible to identify at any time existing strategic stocks and to pool them if necessary, under the conditions set by the interested Member States.

The EMA could collaborate with the European Pharmacopoeia to develop more European monographs of essential medicines (finished products and active ingredients) by standardizing formulations, manufacturing processes, control methods and stability periods according to the type of

[3] A precedent in terms of legislative tools exists for herbal medicinal products, although the basic issue is quite different.

packaging. This cooperation could be financially supported in the same way as the European Commission provided financial support to EDQM for biological standardization when Directive 89/342/EEC on immunological medicinal products was adopted.

An ad hoc committee of relevant European and national partners, located at the EMA could define the standardized elements of information to be included on the packaging and package leaflet of these medicinal products, including an electronic package insert. The use of the electronic package leaflet could be developed through the use of a quick response code (QR code). Medicines identified as essential should have privileged access to harmonized procedures for national authorizations, as provided for in Articles 30.1 and 30.2 of the Community Code for medicinal products for human use.

4. Authority of the Qualified Person

AnP proposals on the authority of the qualified person
Chapter of the Commission's questionnaire: Quality and manufacturing of medicines; security of supply; effectiveness of EU pharmaceutical legislation.
Regulatory aspects: Amend the following aspects of Directive 2001/83/EC on the Community code for for medicinal products for human use: - Joint liability of the manufacturing authorization holder and the qualified person: Articles 46, 48 and 49, 52 - Joint liability of the marketing authorization holder (Article 6) and the qualified person for information (Article 12) and pharmacovigilance (Article 104). - Joint liability of the distribution authorization holder and the qualified person: Articles 77 and 79.

Since Directive 75/319/EEC, good manufacturing practice has evolved considerably and has been extensively codified at European level. There is a need to strongly assert the shared responsibility of the general management of companies and the Qualified Person, so as not to leave the Qualified Person alone when faced with difficult situations and without adequate resources to fulfil their role. The responsibility of the Qualified Person does not exonerate the company's management from its "product liability". The manufacturing authorization holder must have a pharmaceutical quality system incorporating good manufacturing practice and risk management, the effectiveness of which is the full

responsibility of the company's management. In view of the increasing complexity of manufacturing processes, the Qualified Person must have experience and general competence in manufacturing practices and quality risk management as defined in Article 48 of the European Medicines Code. He/she must be able to be assisted by persons who have specific competence in the type of manufacture. In order to be able to exercise authority, the qualified person must have access to all the documentation and resources necessary to make independent decisions throughout the life-cycle of the medicinal products for which they are responsible.
By analogy, Qualified Persons for information and pharmacovigilance, placed under the authority of the marketing authorization holder, must have independent access to all documentation and resources necessary to exercise their authority fully. Their personal liability does not exonerate the company's management from its general "product liability". The same applies to the qualified person responsible for implementing good distribution practices of medicines.

In the face of a health crisis such as Covid-19, pharmacists in France have played a decisive role, from manufacturing and wholesale distribution to dispensing at the pharmacy or hospital. At the industrial level, the French legislator wanted the exercise of pharmaceutical responsibility be assumed at each stage by a named person, the responsible pharmacist, who is the main contact for the authorities for any quality and safety of the provision of medicines. The industrial pharmacist of the industry is in a position to make independent and informed decisions personally. As a director or co-director of the pharmaceutical company, he or she has authority over all the people involved in pharmaceutical activities: manufacturing, advertising, medical information, pharmacovigilance, batch monitoring and recalls, distribution and storage, import, export, marketing authorization, labelling, transport conditions, etc.