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REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL

on the experience acquired with the procedures for authorising and supervising medicinal products for human use, in accordance with the requirements set out in the EU legislation on medicinal products for human use

1. INTRODUCTION

At least every 10 years[1], the Commission must publish a general report on the experience acquired from operating the procedures for medicinal products for human use laid down in Regulation (EC) No 726/2004[2] and in Chapter 4 of Title III of Directive 2001/83/EC[3]. There are different procedures in the EU for granting a marketing authorisation for medicinal products. This report covers the centralised, decentralised and mutual recognition procedures. It does not cover the purely national procedure for authorising medicines for human use in a single Member State[4].

This report links to the pharmaceutical strategy for Europe[5] and will inform its implementation, with regard to possible legislative and non-legislative measures. It also complements the ongoing revisions of: (i) the EU regulations on medicines for rare diseases and on medicines for children[6]; and (ii) the Regulation on the European Medicines Agency's fee system[7].

2. REGULATORY FRAMEWORK AND CONTEXT

Objectives of the framework

The EU regulatory framework for medicinal products has three main objectives, set out in the bullet points below.

- Its first objective is to guarantee a high level of health protection for the people of Europe. It seeks to do this in two main ways. Firstly, the framework aims to provide patients as swiftly as possible, with high quality, safe and effective medicinal products – both innovative and off-patent. Secondly, it aims to increase monitoring of medicinal products after they have been authorised thanks to strengthened procedures for monitoring and pharmacovigilance.
- Its second objective is to both: (i) complete the single market in pharmaceutical products, taking account of the implications of globalisation; and (ii) support the competitiveness of the European pharmaceuticals sector.
- Its third objective is to rationalise and simplify the regulatory system as much as possible, thus improving its overall consistency, efficiency and transparency in running procedures and decision-making.

[1] Article 86 of Regulation (EC) No 726/2004 and of Article 38(2) of Directive 2001/83/EC.
[2] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136, 30.4.2004, p.1.
[3] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p.67.
[4] Section 2 gives further details on the different procedures for marketing authorisation of medicinal products for human use in the EU.
[5] COM(2020) 761.
[6] Joint evaluation of Regulation (EC) No 1901/2006 on medicinal products for paediatric use and Regulation (EC) No 141/2001 on orphan medicinal products (SWD(2020) 163 final).
[7] Evaluation of the European Medicines Agency's fee system (SWD(2019) 335 final).

Marketing-authorisation procedures

Since the first piece of EU pharmaceutical legislation in 1965, the EU has aimed at two overarching objectives: ensuring a high level of public health protection and removing obstacles to the free movement of pharmaceuticals. Council Directive 65/65/EEC[8] established the fundamental principle of EU pharmaceutical legislation that no medicinal product may be placed on the EU market unless a marketing authorisation has been granted for that product. The authorisation of medicines builds on three key criteria: quality, safety and efficacy. This helps to ensure that products administered to patients are of suitable quality and provide a positive benefit-risk balance.

Since 1965, a large body of legislation has been developed. There has been a progressive harmonisation across the entire European Economic Area (EEA) of the requirements for: (i) granting marketing authorisations; and (ii) post-marketing monitoring. The two main legal acts currently regulating marketing authorisation procedures for medicinal products in the EEA are Regulation (EC) No 726/2004 and Directive 2001/83/EC, as amended. There are four different procedures to obtain a marketing authorisation: a **centralised procedure**; a **decentralised procedure;** a **mutual recognition procedure**; and a purely **national procedure**.

The centralised procedure allows the applicant to gain a single authorisation with EEA-wide effect[9]. The application is assessed by the European Medicines Agency (EMA) through its scientific Committee for Medicinal Products for Human Use (CHMP) and the authorisation granted by the European Commission. The centralised procedure for medicines for human use has two different 'scopes'. The first scope is a mandatory scope that covers: (i) medicines developed by certain biotechnological processes; (ii) advanced therapy medicines; (iii) medicines for rare diseases; and (iv) new medicines for specific diseases, e.g. cancer, AIDS and diabetes. The second scope is an optional scope that covers, for example: (i) medicines in other disease areas; (ii) medicines containing a new active substance; or (iii) existing medicines presenting a significant innovation.

The other procedures allow the applicant to gain a national authorisation in only one Member State market (purely national procedure) or several Member States' markets (decentralised procedure and mutual recognition procedure).

The mutual recognition procedure applies when the applicant already holds a national authorisation for a medicinal product in one Member State and wishes to obtain a national authorisation for the same medicinal product in other Member States.

[8] Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products, OJ 22, 9.2.1965, p. 369.

[9] In accordance with the EEA agreement, a national procedure/step to give the EU marketing authorisations effect is necessary for Norway, Iceland and Liechtenstein.

The decentralised procedure is for products not yet authorised in any Member State and where the applicant wishes to obtain a national marketing authorisation in more than one Member State.

The initial marketing authorisation procedures are framed by two types of activities, set out in the bullet points below.

- **The first type of activities are pre-authorisation activities**. These are activities that take place before an application for marketing authorisation has been made. They include: (i) seeking and receiving scientific advice; (ii) assessing applications for orphan designations; (iii) agreeing on paediatric investigation plans; and (iv) other formal and informal activities to support the development of medicines and prepare applications for marketing authorisations.
- **The second type of activities are post-marketing activities**. These include pharmacovigilance activities (continuous safety monitoring), referrals and variations to marketing authorisations.

European medicines regulatory network

To fulfil their obligations in authorising and supervising medicines, a partnership has been formed by the Commission, the EMA, and the national competent authorities in the Member States. This partnership is commonly referred to as the 'European medicines regulatory network'. In this network, the parties have different roles as set out below.

- The EMA is responsible for the scientific evaluation, supervision, and safety monitoring of medicines in the EU. The EMA also coordinates scientific expertise from across the EU.
- The national competent authorities are responsible for granting national marketing authorisations and supervising medicines in the respective Member States. They also provide expertise to the network.
- The European Commission grants EU marketing authorisations following assessment by the EMA. It also monitors and oversees the network's activities. In addition, it is responsible for ensuring that EU law is applied correctly.

The parties work in close collaboration with all the stakeholders involved in developing, manufacturing, distributing and administering medicines. This collaboration aims to ensure that the objectives of the legislation are achieved.

3. BACKGROUND ANALYSIS STUDY

The Commission engaged an external contractor to provide a supporting study for this report.

Study on the experience acquired from operating the procedures for authorising and monitoring medicinal products for human use[10]

The study assessed the extent to which the current marketing-authorisation system for medicines met its objectives in the period 2010-2017. More specifically, the study:

- collected available data and evidence on the operation of the centralised procedure, the decentralised procedure, and the mutual recognition procedure;
- assessed the effectiveness (achievement of objectives set by the regulatory framework) and efficiency (relationship between the resources used and the changes made, which included an examination of the administrative and regulatory burden) of the procedures and the system in place, including an assessment of the functioning of the European medicines regulatory network;
- summarised the results of its analysis and drew useful conclusions based on lessons learnt from the experience acquired from the marketing authorisation procedures;
- compared the current situation with the findings of the 2010 study and followed up on the implementation of the recommendations made in 2010;
- identified options for possible actions that may need to be taken to remove any existing barriers and obstacles to optimal performance, and analysed the pros and cons of each option.

As part of the study, relevant stakeholders were consulted on their experience with the system and on its strengths and weaknesses. Consultation activities included:

- interviews with representatives of the EMA, the Commission, the European Parliament, the pharmaceutical industry, umbrella organisations, patient groups, and healthcare professional organisations;
- attending meetings of the CHMP and the Coordination Group for the Mutual Recognition and Decentralised Procedures – human (CMDh);
- a written questionnaire sent to national competent authorities, followed by follow-up telephone interviews;
- an online survey sent to committees' experts;
- eight Member-State case studies (Czechia, Denmark, Estonia, Germany, Italy, Portugal, Spain and Sweden).

Review of the study report

The Commission circulated this contractor's study among the Member States, the EMA and the CMDh. The comments it received clarified inconsistencies and inaccuracies in the study. However, the comments also suggested to investigate further certain potential efficiency gains and to adapt the current procedures and guidelines to innovation and progress in science. For instance, the comments called for: (i) greater coordination

[10] *Insert link when published.*

between national competent authorities, the EMA, and health technology assessment (HTA) bodies; and (ii) actions to streamline procedures to reduce administrative burden. The comments also pointed to issues not appropriately investigated in the study, but which will be further addressed in the evaluation of the pharmaceutical legislation as part of the pharmaceutical strategy for Europe.

4. RESULTS FROM THE STUDY ON THE ASSESSMENT OF AUTHORISATION AND MONITORING PROCEDURES

Effectiveness

Overall, data provided by the contractor's study indicate that the current system of EU procedures for marketing authorisation and monitoring of medicinal products for human use, meets the objectives laid down in the legislation. In particular, the current system guarantees a high level of health protection for the people of Europe. The system also broadly meets its objectives of completing the internal market in pharmaceutical products and of creating a regulatory framework that supports the competitiveness of the European pharmaceutical sector.

Rapid scientific developments have resulted in new challenges for the system. The system has therefore become more complex through the setting-up of: (i) new committees via new EU legislation; (ii) supportive expert working parties; and (iii) other additional EU legal requirements. The rapid scientific developments continue to challenge the system, and solutions to these challenges will be proposed through the implementation of the pharmaceutical strategy for Europe.

In the period 2010-2017, activities in the network have generally increased. As a result, most national competent authorities have allocated more resources to EU-level activities. The increased fee income of the EMA (+81%) is also an indicator of increased activities, given that the fees are paid by applicants to apply for and maintain marketing authorisations. The number of initial marketing authorisation applications under the centralised procedure remained stable at around 90-100 applications per year. Nevertheless, these new applications add to the ever-growing portfolio of authorised products that the EMA, the network and the Commission must manage. This has led to constant growth in the number of post-marketing procedures and related supervisory and monitoring activities. The number of variations to marketing authorisations granted under the centralised procedure increased from about 4 100 in 2010 to approximately 6 200 in 2017 (+ 51%)[11].

In addition, the number of procedures for orphan, paediatric and advanced therapy medicines have increased substantially in 2010-2017. The advanced therapy medicinal products classification requests increased from 20 requests submitted in 2013 to 46

[11] Based on publicly available EMA annual reports: https://www.ema.europa.eu/en/about-us/annual-reports-work-programmes

submitted in 2017 (i.e. an increase of 130%), while orphan designations submitted every year grew from 174 to 260 (up 49%), and all paediatric investigation plan procedures increased from 318 to 421 (up 32%).

The number of finalised mutual recognition and decentralised procedures has fluctuated between 1 640 procedures in 2010 and 1 515 procedures in 2017. In 2014, there was a dip to 1 046 procedures[12]. The CMDh plays an important role in the mutual recognition and decentralised procedures, both pre- and post-authorisation. It fosters harmonisation, for example by examining disagreements between Member States and providing general guidance on the procedures. In the study period, the number of referrals for the mutual recognition and decentralised procedures has decreased over time through dialogue, cooperation and harmonisation in the CMDh. The number of referrals to the CMDh fell from 17 in 2010 to 11 in 2017, with a peak of 27 referrals in 2012. The number of referrals from the CMDh to the CHMP fell from 7 in 2010 to only 1 in 2017[12].

Requests to the EMA from developers of medicines for scientific advice and protocol assistance increased by more than 40% between 2010 and 2017. The contractor's study recognised that the EMA has ensured a well-functioning process overall.

Support to small and medium-sized enterprises (SMEs) has increased from 366 requests for scientific advice to the EMA in 2013 to 436 in 2017. In that period, SMEs consistently accounted for around 30% of all requests at EMA level.

Even though the level of activity increased, the system has remained effective overall. The system relies on resources and expertise from the Member States, and benefits from mechanisms that ensure internal coordination within the system. The EMA plays an effective coordination and scientific support role, adapting organisational structure and working methods to ensure efficiency gains in response to the increased level of activity.

There was greater harmonisation and coordination among Member States after the enlargements of the EU. More and more Member States began taking an active role in procedures as: (i) (co-)rapporteur; (ii) part of a multi-national assessment team in the centralised procedure; or (iii) reference Member State in the mutual recognition and decentralised procedures.

Market surveillance and safety monitoring have been strengthened. One of the main reasons for this was the implementation of the revised pharmacovigilance legislation in 2012, which led to: (i) the establishment of the Pharmacovigilance Risk Assessment Committee; and (ii) coordinated signal management. There has been continuous development of the mechanisms to report adverse drug reactions. Patients have played a particularly significant role in this, with patient-submitted adverse drug reactions reaching the number of about 90 000 in 2017[13]. The review procedure for adverse drug

[12] CMDh statistics 2017.
[13] EMA, Annual Report 2017.

reactions identifies potential risks and gives the EMA, the Commission and national competent authorities the possibility to take necessary regulatory steps. The identification of these potential risks could be further improved by integrating real-world data into the procedures. This would require building expertise on big data, pharmacoepidemiology and statistics.

Efficiency

The study found that the efficiency of the current system can be improved. The main elements for improvement are outlined below and will be further explored and addressed in the implementation of the pharmaceutical strategy for Europe.

Even before the COVID-19 pandemic, some of the experts who participated in the study survey indicated that there was insufficient capacity to address emergency needs and shortages through post-marketing procedures. Experts said that the system is unable to react quickly and flexibly, due to: a) the lack of EU legislation to address emergency needs (e.g. for medicine shortages); and b) the cumbersome coordination approaches between Member States and between committees, which should be streamlined and formalised.

The recently adopted legal proposals under the European health-union package[14] will help to address emergency needs. In addition, the pharmaceutical strategy for Europe[5] will explore how to minimise the risk of medicine shortages through specific measures such as: (i) stronger obligations for supply; (ii) earlier notification of shortages and withdrawals; (iii) greater transparency of stocks; and (iv) stronger EU coordination mechanisms to monitor, manage and avoid shortages. Furthermore, the pharmaceutical strategy for Europe will consider measures that improve the availability of medicines throughout the EU. This will also have a (preventive) impact on shortages.

The contractor's study suggests that, beyond the authorisation process regulated by the EU pharmaceutical legislation, coordination between the EMA, national competent authorities and HTA bodies could be improved. This would help to ensure that medicines become accessible to patients more quickly. Since 2010, there has been an increase in procedures for the joint issuing of scientific advice by the EMA/national competent authorities on the one hand and HTA bodies/pricing authorities/ reimbursement authorities on the other. Joint scientific-advice procedures would allow the design of clinical trials and real-world data studies to generate evidence with multiple uses. Not only could this evidence be used to support marketing authorisations, it could also be used to support pricing and reimbursement decisions at national level. This would ensure faster access for patients to medicines. As a result, greater cooperation between these parties will make the system more efficient to the benefit of patients, improving their access to medicines.

[14] European health-union package: COM(2020) 724, COM(2020) 725, COM(2020) 726, COM (2020) 727.

To reduce administrative burden and free valuable time and capacity for both regulators and industry, the regulatory framework should be simplified. This could be achieved by streamlining certain procedures and processes. To streamline authorisation procedures and optimise the authorisation framework, collaboration with – and inspiration from – other mature systems in other parts of the world could be considered.

Variations to the terms of a marketing authorisation include very different types of amendments. For example, variations can: (i) add a new therapeutic indication to a product; (ii) modify information on contraindications; or (iii) change the address of a marketing authorisation holder. National competent authorities, the EMA and industry stakeholders share the view that variations create a high workload for all three parties and that simplification is necessary. Efficient business processes are therefore very important.

The contractor's study also raises the possibility of continuing to improve coordination between the EMA committees. In particular, the study suggested coordination that would improve the consistency of outcomes, by better aligning procedures amongst committees for the delivery of the final scientific opinions and recommendations by the EMA. The ongoing revision of the regulations on medicines for rare diseases and on medicines for children is already assessing possible solutions to: (i) better coordinate, when necessary, the work of the concerned committees; and (ii) simplify and streamline certain procedures.

Applications for centralised authorisation submitted by SMEs have increased over the study period 2010-2017. However, the proportion of products not receiving authorisation is higher for applications by SMEs than applications submitted by larger companies. The contractor's study indicates that this may be due to the complexity, cost and accessibility of the procedure. SMEs also lack staff and money, and are therefore challenged by the quality and clinical requirements for obtaining a marketing authorisation. In addition, SMEs may not necessarily bring to the market themselves the medicines they have developed. This is because promising medicines are often acquired by larger pharmaceutical companies at a late stage of development.

Significant progress in the support provided to SMEs has been observed in the study period 2010-2017 thanks to:

- a dedicated support function and incentives for SMEs (e.g. regulatory guidance and fee incentives) put in place by the EMA;
- support from national competent authorities to industry – including SMEs – by providing them with early advice.

Further ways to support SMEs will be explored as part of the pharmaceutical strategy for Europe.

Digital transformation is changing the health sector. However, digital expertise and infrastructure are not yet sufficiently available across the Member States and the

network. Development of expertise and infrastructure is particularly needed in big data and the use of artificial intelligence.

All stakeholders agreed that EU telematics systems also play an important role in contributing to the efficiency of the system. However, the stakeholders also identified room for improvement. National competent authorities pointed to a very complex governance system for EU telematics. Some stakeholders said that EMA telematics systems and national systems were not fully compatible, leading to duplication of work. Various stakeholders and national competent authorities remarked that the network was falling behind in the development of EU-wide IT systems. This is due to competing priorities between the need to set up new IT systems required by legislation and the need to maintain existing systems with the resources currently available. This may result in decreased efficiency in the near future if not addressed in a timely and agile manner.

National competent authorities, the EMA and experts reported that the system has difficulties handling products that lie on the borderline between medicines and medical devices that are not easily classified in one or the other category (i.e. products where the primary mode of action cannot be easily determined). Improved coordination between the sectors is necessary, so as not to hamper innovation in the EU. Difficulties are also caused by borderlines between medicines and other product categories (i.e. substances of human origin, biocides and food supplements).

The EMA committees and working parties need to build further access to new areas of expertise in order to intergrade the latest scientific and technological knowledge into the development and evaluation of novel medicines. This is particularly true in areas such as advanced therapy medicinal products where the development of expertise in the national competent authorities is of increasing importance, considering the substantial pipeline of products.

5. INITIAL LESSONS LEARNT FROM COVID-19 AS REGARDS AUTHORISATION AND MONITORING PROCEDURES

The COVID-19 pandemic highlighted both limitations and strengths of the European medicines regulatory system. It also showed opportunities to improve the system.

The EU delivered fast assessment and authorisation of COVID-19 vaccines and therapeutics thanks to rapid scientific advice and rolling review by EMA of scientific evidence as it becomes available and expedited decision-making procedures by the European Commission. Remote inspections and remote clinical trials enabled the system to keep delivering under the constraints of the pandemic, but also made possible to test alternative ways of working. Conditional marketing authorisations were granted for COVID-19 vaccines and other medicines in view of the emergency situation.

Member States provided access at national level to COVID-19 medicines in advance of their (conditional) authorisation, through compassionate-use[15] mechanisms on the basis of harmonised advice provided by EMA. This has been done for remdesivir before the conditional marketing authorisation was granted, dexamethasone and medicines consisting of monoclonal antibodies against SARS-CoV2[16].

To efficiently respond to the emergency, regulatory flexibilities were introduced, for instance for requirements for labelling and on timelines and languages for consultation during the decision making process. Those flexibilities were explained in several guidance documents published by the Commission[17], EMA[18] and the Heads of Medicines Agencies[19].

The pandemic also reinforced the importance of early dialogue with medicine developers and academia to keep the EMA and the experts of the EU network abreast of emerging new technologies and to prepare for their review, which facilitated the fast approval of COVID-19 vaccines and therapies. The COVID-19 EMA pandemic Task Force[20] brought together the best expertise from the network and ensured a fast and coordinated response to the pandemic, from the provision of early advice to developers to steering scientific discussions at key milestones. This lesson learnt has already been taken up in the proposal of the Health Union package to strengthen EMA's mandate[21], where it is proposed to formally establish such a task force at EMA to lead the scientific response to any future public health emergency. The same proposal also includes mechanisms for crisis management and for monitoring and mitigation of shortages.

The pandemic added an extremely high pressure on the European medicines regulatory network, stretching its resources. Mitigation measures were taken to ensure business continuity[22]. Member States reported unprecedented workload, both for the assessment and for the pharmacovigilance of COVID-19 vaccines and therapeutics. The heavy workload could be sustained for a short period without serious impact on normal business and with remarkable results as regards the efficient support provided to COVID-19 medicine and vaccine developers and the timely authorisation of four

[15] https://www.ema.europa.eu/en/human-regulatory/research-development/compassionate-use
[16] https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/article-53-opinions
[17] E.g. vaccinesstrategy_labellingpackaging_en.pdf (europa.eu) and guidance_regulatory_covid19_en.pdf (europa.eu).
[18] EMA guidance can be found here: Guidance for medicine developers and other stakeholders on COVID-19 | European Medicines Agency (europa.eu).
[19] Heads of Medicines Agencies: COVID-19 (hma.eu).
[20] COVID-19 EMA pandemic Task Force: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/emas-governance-during-covid-19-pandemic#covid-19-ema-pandemic-task-force-section.
[21]COM (2020) 725.
[22] EMRN COVID19 BCP (europa.eu).

COVID-19 vaccines. However, this requires further monitoring to ensure that the right steps are taken to sustain and strengthen the capacity of the network.

The possibility to integrate, with adjustments, the tools and flexibilities, applied during the COVID-19 pandemic, into the normal business is already being considered and will be further assessed, including impact on resources, in the context of the evaluation of the general pharmaceutical legislation under the pharmaceutical strategy for Europe.

6. CONCLUSIONS

The current report and the supporting study demonstrate that overall the EU has a well-functioning authorisation system for medicines. However, it also highlights issues that could be improved. Moreover, the study pre-dates recent disruptive events that had a direct impact on the marketing authorisation procedures and business continuity, such as Brexit and the COVID-19 pandemics. Lessons from these experiences should inform any follow-up action. Some initial lessons learnt from the COVID-19 pandemic are discussed in section 5 above.

The implementation of the pharmaceutical strategy for Europe[5], which covers challenges to the medicines framework and a wide range of issues along the life-cycle of medicines, provides an opportunity for a holistic response to the issues outlined above.

The implementation will explore several issues, such as: (i) how to address shortages of medicines; (ii) how to streamline procedures and life-cycle management, including those for variations; (iii) how to increase cooperation between sectors and relevant parties along the life-cycle of medicines; and (iv) how to ensure relevant expertise in the network. This will also benefit SMEs by reducing the administrative burden for industry and increasing cooperation between medicines regulators, HTA bodies, pricing and reimbursement authorities.

Some actions would require changes in the legislation, whereas others can be achieved by non-legislative means (e.g. through guidelines and enhanced coordination). Evidence for the need for specific legislative actions will be gathered through an evaluation of the pharmaceutical legislation under the pharmaceutical strategy for Europe.

The work of the implementation of the pharmaceutical strategy for Europe[5] will be undertaken in close collaboration with: (i) the EMA; (ii) Member States and national competent authorities; (iii) representatives of patients' and healthcare professionals' organisations; (iv) academia; (v) industry; and (vi) other relevant stakeholders.