

## Reform of the EU Pharmaceutical Legislation

### *Statement by the European Society of Cardiology*

The [European Society of Cardiology](#) (ESC) welcomes the overarching goal of the EU Pharmaceutical Legislation Reform to make medicines more available, accessible, and affordable, addressing existing disparities in patient access to innovative medicines. We also praise the Commission for taking action to enhance security of supply and to address environmental risks, which are raising growing concerns in the medical community and society at large.

With this statement, we express our support for the objectives of the reform and for specific measures included in the proposals. On the other hand, we would like to shed light on remaining issues and possible side-effects and suggest possible improvements. As a general remark, we call policymakers to ensure that availability and affordability stand in one line with innovation in the development of the new framework.

#### ***Modulation of incentives***

The ESC praises the European Commission for proposing an updated framework meant to fill the current gaps in the pharmaceutical sector and to encourage the achievement of desirable goals from a public health perspective. In particular, we fully support the need to address disparities in patient access across Europe, as well as the existing issues in the affordability of medicinal products.

Nevertheless, the modulation of incentives in the current form targets specific market failures in areas like orphan diseases and antimicrobial resistance but fails to tackle the remaining unmet needs in other fields, such as chronic conditions or non-communicable diseases, which pose a considerable threat to individual and population health, regardless of their designation. In particular, the ESC is concerned that the proposed scheme could unintentionally lead to a further slowdown of cardiovascular research and innovation and continued positioning of priorities in pharmaceutical development towards other therapeutic areas that optimize probability of market success and are more likely to reach rapid regulatory approval.

Although cardiovascular disease (CVD) remains the leading cause of death and morbidity in Europe, research and development in this area is far out of proportion to its burden and lagging behind with respect to other therapeutic areas. Out of 89 positive opinions for the authorization of new medicines issued by the European Medicines Agency (EMA) in 2022, none were in the CVD area<sup>1</sup> and only 4% of the trials started between 2017 and 2022 were for CVD, with respect to 24% in oncology<sup>2</sup>. Potential drivers for this low level of innovation include longer and more expensive clinical trials and low regulatory priority. Absence of large programmes of public funding into academic research may also threaten the pipeline for innovative treatments.

The lack of targeted incentives addressing these unmet needs risks worsening this trend. The cardiologists will be left without new instruments to save more lives and patients will be losing battle with Europe's number one killer. In addition, we point out that as CVD alone costs the EU approximately 282 billion euros<sup>3</sup> on an annual basis. Fostering innovation in high-prevalence chronic diseases would also alleviate healthcare system's budgets in the long run.

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<sup>1</sup> Human Medicines Highlights 2022, EMA, 2023: [https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2022\\_en.pdf](https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2022_en.pdf)

<sup>2</sup> EFPIA Pipeline Innovation Review, 2022: [https://www.efpia.eu/media/676661/iqvia\\_efpia-pipeline-review\\_final-report\\_public-final.pdf](https://www.efpia.eu/media/676661/iqvia_efpia-pipeline-review_final-report_public-final.pdf)

<sup>3</sup> Ramon Luengo-Fernandez, Marjan Walli-Attai, Alastair Gray, Aleksandra Torbica, Aldo P Maggioni, Radu Huculeci, Firoozeh Bairami, Victor Aboyans, Adam D Timmis, Panos Vardas, Jose Leal, Economic burden of cardiovascular diseases in the European Union: a population-based cost study, *European Heart Journal*, 2023;, ehad583, <https://doi.org/10.1093/eurheartj/ehad583>

The ESC welcomes Commission proposal addressing unmet medical needs related to the lack of access to affordable medications and the need to accelerate market entry of generic compounds. On the other hand, shortened exclusivity periods may de-incentivize investment in bringing certain categories of novel drugs to market. This presents a paradox and misalignment between incentives for innovation and public health needs of European citizens, which is of particular relevance for cardiovascular diseases and should be addressed by appropriate measures.<sup>4</sup>

On these bases, the ESC calls for the *introduction of an additional period of regulatory data protection for medical products targeting highly prevalent chronic conditions characterized by high mortality and morbidity, requiring large scale trials and long-term follow-up and where innovation is stagnating*. The European Medicines Agency (EMA) could provide guidance, with the support of learned societies, experts from national competent authorities, health technology assessment bodies and payers.

In addition to the aforementioned problem with shortened exclusivity in slow-progressive conditions, we may expect a decrease in the funding of post-marketing trials by the industry, which would also result in the lack of important long-term information on safety and efficacy. Therefore, adequate funding of independent post-marketing clinical trials needs to be ensured. At the same time, the accelerated authorization of generics and biosimilars will increase the need for *comparative trials*, for which additional funding should be allocated. Academia can play a key role in the conduct of such independent post-marketing studies.

Several incentives are tied to definitions which are currently unclear and open to different interpretations (i.e., “significant clinical benefit”, “relevant and evidence-based comparator”, “exceptional therapeutic advancement” and “meaningful reduction in disease morbidity and mortality”). We call for decision-makers to *clarify these definitions, allowing measurable assessments and a correct application* during the authorization process of drugs and ensure an adequate participation of healthcare professionals in their periodic interpretation, also considering clinical practice guidelines.

Finally, we urge negotiators to maintain and possibly enhance the regulatory streamlining and regulatory support provisions in the other sections of the proposal to achieve a balanced outcome and prevent that the reduction in the baseline regulatory data protection period results, paradoxically, in higher prices of innovative medicines, as well as in research and development activities shifting to other regions.

### ***Unmet Medical Needs***

The ESC strongly supports the need to foster research in the area of unmet medical needs (UMN), but considers the definition provided in the draft Directive to be too narrow. The limits of the current definition are also reflected in the very low number of medicinal products in some therapeutic areas, including cardiology, that were granted access to the PRIME scheme so far, despite the remaining unmet needs<sup>5</sup>. UMN are observed also in chronic and progressive conditions, in large populations, impacting populations health and quality of life. The definition of UMN should cover specific settings (e.g., common vs. rare conditions, preventive vs. therapeutic approaches, paediatric vs. adult setting) but at the same time remain sufficiently adaptable to respond to currently unidentified or neglected conditions. As such UMN may affect would require specific adaptations. The ESC recommends a *more flexible approach to UMN suitable for the future of cardiovascular medicine*, also considering the wider definition adopted by other regulatory bodies, including

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<sup>4</sup> Piotr Szymański, Eva Irene Bossano Prescott, Franz Weidinger, The first European Union approval of a new medicine to treat cardiovascular diseases in 2023: why is it important to collaborate with the European Medicines Agency?, *European Heart Journal*, 2023;, ehad426, <https://doi.org/10.1093/eurheartj/ehad426>

<sup>5</sup> [https://www.ema.europa.eu/en/documents/report/prime-analysis-first-5-years-experience\\_en.pdf](https://www.ema.europa.eu/en/documents/report/prime-analysis-first-5-years-experience_en.pdf)

the Food and Drug Administration (FDA)<sup>6</sup>. UMN related to chronic and prevalent diseases, which pose a significant burden to public and individual health, should also be included. The criteria to identify medical products addressing an UMN should not be confined to a meaningful reduction” in disease morbidity or mortality but include other dimensions of great importance for patients, such as *quality of life, the severity of unwanted drug effects and short- and long-term complications of the disease process*. Healthcare professionals and patients’ organisations should be consulted for the development of the definition and of the scientific guidelines to be drafted by the EMA for its application.

### ***Regulatory streamlining and sandboxes***

The ESC praises the European Commission for the several measures introduced to streamline and digitalize the regulatory process, speeding up access for patients, including the reduction of the scientific evaluation period from 210 to 180 days and the enhanced scientific and regulatory support. Concerning the structure and governance of EMA, we applaud the significant simplification effort and the proposed increase in the representation of patients and health care professionals at the CHMP and PRAC. In this respect, we call for wider involvement of experts not on an individual level but rather as representatives of medical societies, with the aim of providing regulators with collective views. This is particularly important as clinical practice throughout Europe is shaped by international learned societies, such as the ESC among others, publishing clinical practice guidelines which are in the case of CVD universally endorsed by national societies in all European countries, deeply affecting delivery of healthcare services including innovative technologies and recently approved drugs.

The EMA shall formally assume the task of periodically monitoring the trend in research and in the number of newly authorised medicines across therapeutic areas to identify existing gaps and explore possible regulatory solutions, consulting healthcare professionals’ organisations. Such an assessment could also constitute the basis for the launch of targeted research projects with adequate European Union funding, including investments in registry infrastructure.

*Expedited regulatory pathways* – extending the current scheme - *tailored scientific advice and protocol assistance* could be other possible solutions to the low number of trials and newly authorized drugs in some chronic conditions characterized by a remaining high-prevalence and mortality. In these areas healthcare professionals or medical societies may assist the EMA in offering their clinical expertise and competency.

Given the unpredictable nature of scientific progress, we praise the proposed establishment of regulatory sandboxes to sustain innovation and advance proactive regulatory learning and recommend involving healthcare professionals’ organizations in their development.

### ***Transparency and affordability***

The ESC supports the proposed transparency requirement regarding public financial support received for research and development, agreeing that greater transparency would help maintain or improve access to affordable medical products. We remark that the obligation should apply also to funding received at the national level. To further improve affordability of medicines, we call for greater transparency on the overall incurred research and development costs.

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<sup>6</sup> <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track>

The granting of additional 6-months of RDP if a relevant comparator is used in clinical trials and the application of the Bolar exemption – including to support the marketing authorization of generics and biosimilars and for pricing and reimbursement activities – are also expected to improve affordability.

Last, we call for legislators to ensure that if a medical product receives an orphan designation following repurposing, access for well-established use in non-orphan indications is not hampered by unduly price increases, like occurred in the case of mexiletine<sup>7</sup>.

### ***Supply security and shortages control***

The ESC praises the European Commission for taking action to enhance security of supply across Europe and improve the control of medicines shortages. The latter are a growing problem that puts healthcare professionals under pressure and patients at risk. Shortage prevention plans, a Union list of critical medicines and a stronger coordinating role for EMA and additional powers to Member States and the European Commission are all desirable measures, with the following remarks:

- The timeframes for early notification requirements in case of withdrawal seem rather short, particularly in the case of lack of good and easily accessible pharmacological alternatives.
- The European Union list of critical medicinal products should be developed in cooperation with learned societies taking into consideration the recommendations included in the clinical practice guidelines regarding indications for use of certain medication groups.
- In case of suspension, cessation, or withdrawal, the risk assessment should be evaluated and validated by an external panel of experts.
- The composition of the Steering Group on Shortages and Safety of Medicinal Products needs a wider representation of patients, healthcare professionals and academia.

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<sup>7</sup> Pieter G Postema, Peter J Schwartz, Elena Arbelo, Wilbert J Bannenberg, Elijah R Behr, Bernard Belhassen, Josep Brugada, Pedro Brugada, A John Camm, Ruben Casado-Arroyo, Ellen 't Hoen, Carla E M Hollak, Stefan Kääh, Pier D Lambiase, Antoine Leenhardt, Silvia G Priori, Vincent Probst, Bas C Stunnenberg, Jacob Tfelt-Hansen, Baziel G M Van Engelen, Christian Veltmann, Sami Viskin, Arthur A M Wilde, Continued misuse of orphan drug legislation: a life-threatening risk for mexiletine, *European Heart Journal*, Volume 41, Issue 5, 1 February 2020, Pages 614–617, <https://doi.org/10.1093/eurheartj/ehaa041>