European Commission public consultation on the revision of European pharmaceutical legislation: Prescrire's response

- The European Commission has launched a major revision of European pharmaceutical legislation. In November 2023, it opened its proposals to public consultation, to which Prescrire has responded.
- While Prescrire welcomes several of the proposals, some of them need to be further developed. Others are counterproductive or even dangerous, and should be rejected.
- It is unfortunate that, in its proposals, the Commission did not see fit to act on the persistent, substantiated calls from a range of different stakeholders in recent years to strengthen regulatory standards by requiring marketing authorisations for new drugs to be based more firmly on robust evidence and on randomised comparative trials versus standard treatment.
- After a disappointing vote in the European Parliament, it is now up to the European Council to improve the proposals in order to facilitate access to useful, effective and affordable medicines.
- The regulatory framework must raise the bar for the requirements and fundamental principles of standard marketing authorisations, while allowing flexibility under exceptional circumstances (as occurred with covid-19 vaccines) by permitting limited exceptions to these fundamental principles.

The European Commission portrays its legislative proposals as an attempt to respond to several pharmaceutical policy challenges (1). These include safeguarding the continuity of the drug supply chain and efforts to prevent drug shortages; ensuring that drugs are available across all European Union (EU) member states; combatting antibiotic resistance; developing drugs for unmet medical needs; and maintaining a competitive pharmaceutical industry in the EU.

This article closely reproduces the response Prescrire sent to the European Commission on 8 November 2023 as part of the public consultation on the proposed reform to European pharmaceutical legislation. It includes suggestions for ways in which the European Council might improve the proposals, with the interests of patients in mind, during their work in 2023 and 2024.

Marketing authorisations: require comparative trials versus standard treatment

The European Commission has not used the opportunity provided by the reform of European pharmaceutical legislation to protect patients by improving the quality of evidence required to obtain marketing authorisation. In the interests of patients, it is important that the evaluation of new medicines be founded on robust, reliable, comparative clinical trials using clinical outcomes relevant to patients.

Yet, for many years, there have been growing calls from health authorities, health technology assessment agencies, health professionals, researchers, third-party payers, and patient and consumer groups to introduce more stringent marketing authorisation requirements, on the grounds that the current requirements are not robust enough to support informed decision-making in clinical practice (2,3). In order to help health professionals choose between treatment options, these requirements need to be based on evaluation data relevant to patients.

Prescrire supports the Commission's proposals to reduce the duration of the data exclusivity period for marketing authorisations from 8 to 6 years, which will enable earlier market entry for generics, and to encourage companies to conduct comparative trials by offering them an additional 6 months of data exclusivity for doing so. This is a welcome first step, but it needs to be supported by other regulatory measures.

The legislation should stipulate that, as a general rule, marketing authorisation applications should include results from at least two comparative trials versus the standard treatment, where one exists. The standard treatment should be determined in a fully transparent manner by joint scientific committees involving both the European Medicines Agency (EMA) and national health technology assessment agencies such as France's National Authority for Health (HAS).

All stakeholders would benefit from the introduction of more stringent regulatory standards for marketing authorisations for new drugs, based on robust evidence and requiring randomised comparative trials to be conducted versus standard treatment.

These changes would speed up decision-making on health technology assessments, price setting and reimbursement; support informed decision-making in clinical practice; make it possible to identify and highlight new drugs that represent a genuine therapeutic advance; and reduce the waste of precious resources on uninformative trials.

Ensure transparency about public funding

The Commission's proposed requirement for marketing authorisation holders to declare any public funding they receive for their research and development (R&D) activities would be an important step forward. But in order to be fully transparent, these data would need to include both direct funding and indirect funding (such as tax credits).

Prescrire proposes centralising this information with the EMA and making it publicly accessible via its website, listed by country and by medicinal product.

Prioritise robust evaluation data over boosting innovation and competition

The Commission's proposals to shorten the evaluation period of the harm-benefit balance by drug regulatory agencies from 210 to 180 days, and to abolish the 5-yearly renewal of marketing authorisations, would have a detrimental effect on patient health. Prescrire advises the European Parliament and Council to reject these proposals and maintain the existing regulations.

The scientific evaluation period should not be shortened. The scientific evaluation of marketing authorisation applications is one of the essential tasks of the EMA, with support from national drug regulatory agencies, and should under no circumstances be portrayed as an administrative hurdle. Rigorous evaluation requires expertise, time and complete independence. Failing to allow enough time for evaluation may result in decisions that put patients at risk and increase the agencies' post-authorisation workload.

Instead of shortening the evaluation period, the new regulations should require marketing authorisation applicants to ensure that all the necessary data and documents are included in their marketing authorisation application, so that the evaluation process can move forward without lengthy interruptions.

The 5-yearly renewal of marketing authorisations should not be scrapped. The 5-yearly renewal of each marketing authorisation should be seen as an opportunity to thoroughly analyse the available data on the medicine's efficacy, if any, in improving clinical outcomes, and its adverse effect profile, taking into account the way in which it is used in clinical practice across EU member states.

The 5-yearly renewal of marketing authorisations should provide the agencies with an opportunity to withdraw drugs with an unfavourable harm-benefit balance, along with drugs for which the companies responsible have not provided the results of the requested post-authorisation studies within the allotted timeframe.

Require greater transparency about the scientific advice the EMA gives companies before they apply for marketing authorisation. Following the recommendation from the European ombudsman, the EMA should ensure that there is a separation between those responsible for providing pharmaceutical companies with scientific advice and those who are subsequently involved in evaluating a marketing authorisation application for the same drug (4). For greater transparency, details of the scientific advice should also be provided in the European public assessment report (EPAR).

Rolling reviews should only be used in a public health emergency. Rolling reviews, also called phased reviews, can be useful for evaluating new drugs in a public health emergency, as demonstrated with the covid-19 vaccines. But this experience also showed that rolling reviews are very draining on resources, with a knock-on effect on the EMA's other activities. These include aspects of the agency's transparency policy and the publication of clinical data, which the EMA does not consider to be key priorities (5).

Prescrire therefore recommends only using rolling reviews in public health emergencies.

Temporary emergency marketing authorisations should not be introduced. During the covid-19 pandemic, conditional marketing authorisations and phased reviews were used to expedite the market entry of covid-19 vaccines in the EU. Prescrire does not support the introduction of a new accelerated marketing authorisation pathway modelled on that of the United States (US). We also note that the US Emergency Use Authorization pathway has come in for a great deal of criticism. If the EU does decide to introduce such a pathway, it should be subject to the same transparency rules as those set out in Regulation 2022/123 on the reinforced role for the EMA in crisis preparedness, notably in Article 17 on public information regarding clinical trials and marketing authorisation decisions.

Regulatory "sandboxes" should not be introduced. The "regulatory sandboxes" proposed by the Commission would allow the EMA to substantially depart from standard regulatory procedures without prior approval from the European Parliament and Council. In practice, these sandboxes would create a new route to market entry for certain pharmaceutical products, bypassing current regulations. They would thus open the door to the

deregulation of marketing authorisation procedures in the EU.

Improve the information in patient leaflets and on packaging, while maintaining the provision of paper leaflets. Prescrire is calling for the patient leaflets supplied in drug packaging to be maintained in paper form, accompanied as appropriate by access to an electronic version. Plans to scrap paper leaflets, even gradually, are premature and dangerous, since many people are not able to easily access the internet, in particular older people, vulnerable patients and those living in areas with suboptimal internet access. In addition, the Commission's proposal that such a decision be made by the European Commission without approval from the European Parliament and Council is inappropriate.

With regard to the content of patient leaflets, they should also describe any risks that have not yet been confirmed, but are listed in the risk management plan.

Packaging assessments should be described in the EPAR, and should cover all of the informative elements included on the labelling (pictograms and dosing schedules), measurement or administration devices and the patient leaflet. As is the case with patient leaflets, packaging mock-ups should be made publicly available at the time of marketing authorisation, in order to enable independent evaluation of their quality and capacity to ensure patient safety.

The patient leaflet and the summary of product characteristics (SmPC) intended for use by health professionals should include information about the quality of evidence on which the marketing authorisation is based, and about the remaining uncertainties regarding the drug's efficacy and adverse effects, in both the short and long term.

Prescrire strongly opposes the Commission's move to be assigned sole competence over revisions to Annex II of the Directive, thereby bypassing the legislative reform procedure and the oversight of the European Parliament and Council. This is a sensitive, vitally important annex, as it sets out the standards and protocols for drug trials.

Combat antibiotic resistance without unnecessarily increasing healthcare costs

Prescrire does not support the Commission's proposals to reward the development of new antibiotics with "transferable data exclusivity vouchers" that can be used for other drugs. These vouchers would enable pharmaceutical companies to extend the data exclusivity (and thus the duration of their market monopoly) for drugs of their choice. As these drugs are likely to be their most profitable and most expensive products, the voucher system would further exacerbate the problem of drug affordability.

To combat the development of antibiotic resistance, the Commission has set out proposals to ensure that antibiotics are dispensed in line with the quantity specified by the prescription. For safety reasons, the revised legislation should require antibiotics dispensed in specific quantities to be packaged in correctly labelled pre-cut unit-dose blister packs, in order to limit the risk of errors. The Commission's recommendations for improving the legibility of the labelling and patient leaflets should be introduced as regulatory requirements in a specific annex to the Directive.

Tackle shortages: require pharmaceutical companies to hold contingency stocks, with sanctions for those that fail to comply

The Commission has put forward several proposals designed to strengthen the continuity of supply and to address drug shortages, including through the introduction of shortage prevention plans.

Member states should also be able to require pharmaceutical companies to establish contingency stocks for critical drugs, and to impose deterrent sanctions on marketing authorisation holders that do not comply with their obligations regarding supply chain continuity.

With regard to the shortage prevention plans to be submitted by marketing authorisation holders, Prescrire would like the EMA to evaluate their suitability, and for the results of these evaluations to be made publicly accessible. Companies submitting prevention plans that do not include serious proposals for addressing supply chain vulnerabilities should be subject to corrective measures and/or be sanctioned.

EMA funding: independence and transparency

The EMA is among the drug regulatory agencies primarily funded by fees paid by pharmaceutical companies. In 2021, approximately 90% of the EMA's income came from this source, with just 10% provided by the EU budget.

In recent years, in the wake of the EMA's move to Amsterdam and the covid-19 pandemic, the agency has failed to fulfil certain duties that it considers to be "negative priorities" (5). These include activities relating to transparency and providing access to documents containing the highly detailed clinical data on which its decisions are based.

Prescrire is calling on the European Parliament and Council to ensure adequate public funding for the EMA's work on transparency, so that it can provide rapid access to data and documents. Periodic safety update reports (PSURs), packaging mock-ups, risk management plans, as well as all of the reports from the EMA's pharmacovigilance risk assessment

committee (PRAC), should be an integral part of the EPAR and published systematically. It is unacceptable for external parties to be unable to access the clinical data held by the PRAC for months on end.

Maintain the additional monitoring system for specific drugs

Prescrire is calling for the existing legislation on "additional monitoring" of recently approved drugs (identified by a black triangle in the patient leaflet and the SmPC) to be maintained, in order to facilitate rapid identification of any new adverse effects.

Prescrire opposes the Commission's proposal to abolish these measures, and advises the European Parliament and Council to keep the existing regulations in place.

Respect the fundamental rights of women to access contraception and elective abortion

In light of the ongoing restrictions in some countries regarding women's health and their fundamental rights, Prescrire proposes removing from the Directive the unhelpful and unwarranted statement underlining member states' sovereignty over legislation on contraception and elective abortion.

Give the EMA a bigger role in the regulation of medical devices

To discourage pharmaceutical companies from exploiting the medical device status for health products resembling medical products (which affords patients less protection), the EMA should be given a bigger role in this area, accompanied by an appropriate increase in its resources.

In particular, the EMA should ensure that clinical trials of these medical devices have shown that the product has no pharmacological, immunological or metabolic effects. If this is not the case, the product in question should either be required to secure marketing authorisation or be withdrawn.

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Update

The vote in the European Parliament (EP) Committee on the Environment, Public Health and Food Safety (ENVI) took place on 19 March 2024. The vote in EP Plenary is due to be held in April 2024. Prescrire will report on the result of the EP vote in a forthcoming issue.

References

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