Revision of European pharmaceutical legislation: an opportunity to transform the system of R&D incentives

Since 2020, the European Commission has been undertaking a major revision of European pharmaceutical legislation. Its proposals have generated numerous contributions from a variety of different stakeholders (**a**)(1,2). Following the vote in the European Parliament in April 2024, it is now up to European Union member states, via the European Council, to have their say on the Commission's proposals for revision of the legislation. Agreement on the final legislation will then be reached via "trilogue" interinstitutional negotiations between the Commission, Parliament and Council (3,4).

A report by the European Parliament's Panel for the Future of Science and Technology sets out options for major changes to the pharmaceutical research and development (R&D) system (5). We have previously echoed the Panel's proposal to create a "European drug infrastructure" (2).

Improving access to drugs and encouraging pharmaceutical innovation

The report by the European Parliament's Panel for the Future of Science and Technology provides an overview of the general objectives of pharmaceutical policy, describes the inadequacies of the current model for incentivising pharmaceutical R&D, and finally puts forward a series of policy options representing different degrees of change from the current situation (5). This report, which was written by a group of Italian academic economists, includes analyses and proposed technical measures that may be unfamiliar to healthcare professionals, but are well known to people with an interest in R&D incentives.

Excerpts from the report's insightful analyses, followed by the Panel's constructive policy options, are published below. The headings, subheadings and notes have been added by Prescrire's Editors.

"The current system fails to strike a balance between innovation and access. (...) The current pharmaceutical system of innovation and care rests on two fundamental conditions: i) the ability to develop new innovative drugs; and ii) the possibility for patients to access them.

Different actors with different ethos and capabilities are involved in the development of new drugs over long periods. Public and private institutions contribute to the early stages of innovation, whilst the private sector dominates the later stages of development.

To launch a new drug on the market, clinical trials are required to prove the drug's safety and efficacy. Data from these trials are used by regulatory authorities in the authorisation process. In the EU context, pricing and reimbursement decisions fall under the responsibility of national authorities. In contrast, most industry decisions are taken with a global perspective.

Against this backdrop, the development of new medicines takes many years and is fraught with uncertainty, with a large proportion of new drug candidates never reaching the market owing, for instance, to a lack of safety or efficacy. To ensure that innovation efforts are rewarded, intellectual property rights (IPRs) play a key role for private investors, by granting monopoly rights to the patent holder. However, while supporting innovation efforts, IPRs create a potential barrier to access (availability and affordability), so that the two key conditions mentioned above – innovation and access – can become difficult to reconcile. This makes it challenging to strike a balance between providing sufficient incentives to invest in research and development (...) and ensuring price levels at which new products are accessible and affordable (...).

In addition, the set of incentives provided is not suitable to stimulate research across all areas, with expected market value being among the main determinants of the direction of R&D investments. To ensure access, it is also important not to introduce undue delays to the possibility for generics/biosimilars to enter the market.

In this context, the STOA Panel [Panel for the Future of Science and Technology] of the European Parliament launched the present study to examine the impact of regulatory mechanisms on public health, as determined by access and innovation for patients. The study also explores alternative frameworks that could be adopted to achieve a proper balance between [access and innovation] (**b**). Particular attention is paid to unmet medical needs (UMN), including drugs for rare diseases, the development of antibiotics to address the growing burden of resistance, and medicines for paediatric use.

a- *In our French edition, we also published excerpts from a declaration by the Minister of Health for the Netherlands, who called for cooperation between EU member states in demanding that pharmaceutical companies focus their R&D efforts more on patients' and society's needs (ref 6).*

b- *"Static and dynamic efficiency" in the original text (ref 5).*

The need for major reform

(…) Reforms to the current system of incentives are demanded, to better balance the need to sustain innovation and to ensure access to medicines.

Market exclusivities are a barrier to access. Market exclusivities (including patents and their extensions, and regulatory exclusivities) have an important role in stimulating private sector R&D activities. Under the current system, where the private sector plays a prominent role in R&D investment, several innovations have been brought to the market with significant impacts on life expectancy and quality of life.

Nevertheless, unless explicitly targeted (as is the case for market exclusivity granted to orphan medicinal products, or patent extension for paediatric clinical trials), the ability of exclusivities to address UMN is limited, because the size of the reward is linked to the size of the relevant market.

As a side effect, such exclusivities may have a negative impact on patient access, owing to (sometimes excessively) high prices or limited availability. In the case of patents, concerns have been raised that they may delay scientific progress. In some cases, exclusivities have been used strategically, to delay the entry of generics/biosimilars upon expiry, thereby limiting competition. (…)

Anti-infective drugs: various possible mechanisms. The proposed reform of the pharmaceutical regulation would introduce a transferable (data) exclusivity voucher (TEV), to be granted for the development of priority antimicrobials. The voucher could be redeemed by its holder for another product [Editors' note: thus extending its commercial monopoly], or sold. By focusing on a specific therapeutic area, the voucher could be expected to stimulate research into eligible conditions. Evidence on this measure is limited as, to the best of our [the STOA's] knowledge, this would be its first implementation.

Vouchers have been used in the United States in selected areas, but these take the form of priority review vouchers [Editors' note: for drug approvals], which allow faster market access.

Concerns have been raised about TEVs, including the distribution of rents they imply, the impact on patients in other therapeutic areas, the sustainability for national pharmaceutical budgets, and the risks of increased uncertainty around the end of exclusivity periods.

However, it is recognised that some urgent action is needed to stimulate research for the development of antimicrobials, and TEVs have the advantage of being easy to implement in the EU, requiring virtually no coordination among Member States and no upfront payment from the health system. Although more difficult to implement in the EU context, subscription models may be an interesting alternative (**c**).

Non-market mechanisms are an option, and have been used previously. Advance purchase agreements (APAs) [Editors' note: a promise in advance to buy a certain quantity of health products, as used with the covid-19 vaccines] and subscription models (SMs) [Editors' note: a promise in advance to buy a quantity of products corresponding to the needs of a particular population, for a period of several years, as used in several US states and in Australia for the early direct-acting antivirals used to treat hepatitis C virus (HCV)] have been invoked in the context of UMN, where rewards based on exclusivities fail to stimulate sufficient research effort.

Such APAs and SMs could also reduce uncertainty related to market dynamics. In particular, SMs have the ability to de-link revenues from quantity, which is essential to stimulate research for UMN. This could also be achieved through innovation prizes (milestone payments and market entry rewards, with the latter being preferred because they reward solely products with proven therapeutic effect).

A difficulty relating to the introduction of APAs, SMs and prizes is that a product's characteristics and the value of a 'right reward' need to be defined ex-ante. In the EU context, it may also be challenging to reach consensus on the dimension of each country's contribution.

Tax credits may be useful to support sponsors in the early stages of development, but are currently not feasible at EU level.

Greater use of a public approach and public tools. Public-oriented approaches such as open science, public-private partnerships (PPPs) and public R&D infrastructures are also considered in this study as a complement to a strong and competitive private industry.

In the open science model research outputs are made freely and publicly available. The model has mainly been adopted in clinical areas characterised by a very limited market size and for drug repurposing, with successful results.

Such PPPs may or may not adopt an open science model. They have proved effective in the development of pre-competitive research topics and product development, as well as in enhancing access. As an advantage, PPPs provide transparent information on R&D costs.

Public R&D infrastructures can lead to improved access to products and better alignment between R&D choices and public health priorities. To this end, governments could take a more active role in specific areas where investment is likely to remain insufficient even in the presence of a well-designed system of incentives for the private sector, by investing throughout the entire innovation chain. This would

***c-** It is on the basis of the drawbacks of the "transferable (data) exclusivity vouchers" set out in this paragraph that Prescrire and numerous other civil society representatives have argued against their inclusion in the European pharmaceutical legislation (ref 1). But no amendment to this effect was adopted by the European Parliament in April 2024 (ref 3).*

give the public sector more decision-making power over development choices, prices and distribution of publicly funded innovations.

Daring to change the model

The study suggests five policy options in addition to the 'baseline' case, or policy option 0 – current regulatory framework. This is the baseline scenario, intended to reflect the current situation and serve as a benchmark against which to assess the alternatives.

Coordinating drug purchasing at the European level. Policy option 1 – strengthening EU coordination in IPR and procurement. EU coordination in IPR is increasing with the recent institution of the 'unitary patent' [Editors' note: valid across the EU] and the proposal to create a 'unitary supplementary protection certificate'.

This option proposes extending coordination to procurement. An EU procurement authority could be established alongside an EU pharmaceutical fund. This would allow for centralised price negotiation and definition of an 'EU price', while prices paid by the Member States to the EU fund could take into account ability to pay (proxied by suitable measures to be agreed upon). Countries could be given the option to opt-out of the coordinated procurement. An experimental phase could be envisaged where coordinated procurement is limited to selected products/areas.

This policy would require significant up-front investment and broad consensus among Member States. However, it could be beneficial for patients, who would benefit from earlier access to new products and reduced disparities in availability between countries; for the pharmaceutical industry, the option could improve efficiency by reducing the costs associated with national market access procedures; for national regulators/payers, and by reducing transaction costs associated with pricing and reimbursement decisions.

Limiting profits. Policy option 2 – adjusting current incentives to limit excess profits. This option aims to reduce over-protection of R&D investment and the scope of pharmaceutical company profits and facilitate access to medicines that have either been financed with public funds, or where the innovation already received substantial compensation. To be implemented, this policy would require both greater transparency on public funding and/or private sector R&D costs, as well as the definition of a fair level of profits. To the extent that this policy option would reduce exclusivities and prices, it could also bring benefits in terms of patient access.

Curtailing market exclusivities. Policy option 3 – redesigning incentives. This option involves a revision of existing incentives, and proposes some new solutions.

The option confirms the role that patents and SPCs [supplementary protection certificates] play under the current framework, but would reduce the scope of data exclusivity and market protection. This option also aims to stimulate R&D directed towards UMN by proposing the use of SMs managed at the EU level as an additional tool for ultra-rare diseases (i.e. diseases with particularly low prevalence among those formally defined as rare), and in the context of antimicrobials, de-linking revenues from quantities sold. Efforts to study repurposing of existing medicines would also be incentivised by providing an extension to market protection.

Creating a European public R&D infrastructure. Policy option 4 – European infrastructure for pharmaceutical R&D. This option would involve the establishment of a public R&D infrastructure focused on UMN, to better match public health needs with R&D investment and to stimulate the dissemination of results [Editors' note: open science].

The European infrastructure could also be active in conducting independent superiority trials [Editors' note: more robust than 'non-inferiority' trials, which are not designed to demonstrate whether or not a drug offers a therapeutic advantage] and repurposing studies. The time needed to set up the infrastructure and the significant up-front investment required could pose a challenge, however.

Greater public involvement in oversight of the pharmaceutical sector. Policy option 5 – a comprehensive approach. This option is the most ambitious and combines policy options 1, 3 and 4, and would involve greater EU coordination on IPR and procurement (PO1 [policy option 1]), a redesign of the incentives (reducing the duration of existing exclusivities, whilst introducing new incentives targeted at UMN – PO3), and the creation of a European infrastructure for pharmaceutical R&D (PO4), complementing private initiatives and by focusing on areas where the private sector is under-investing, relative to public health needs. This combination could allow synergies to be exploited and reduce systemic risk through the diversification of the actors involved in the entire R&D chain.

Policy option 5 is the suggested option. This is because the hurdles identified in the study would require a general reform of incentive schemes and tailored solutions for UMN, which would involve determined EU action and a broader involvement of public actors."

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Selected references from Prescrire's literature search

1- Prescrire Editorial Staff "Impending changes to European pharmaceutical regulations. Part I. Civil society's analysis of the Commission's proposals: major changes ahead, improvements needed" *Prescrire Int* 2022; **31** (243): 302-304.

2- Prescrire Editorial Staff "Impending changes to European pharmaceutical regulations. Part II. The European Parliamentary Research Service in favour of a European Medicines Infrastructure" *Prescrire Int* 2023; **32** (244): 23-25.

3- Prescrire Editorial Staff "European pharmaceutical legislation: too many opportunities missed" *Prescrire Int* 2024; **33** (264): 255.

4- Prescrire Editorial Staff "Revision of European pharmaceutical legislation: a disappointing vote in the Parliament" *Prescrire Int* 2024; **33** (264): 278-279.

5- Panel for the Future of Science and Technology "Improving access to medicines and promoting pharmaceutical innovation" November 2023: 107 pages.

6- Kuipers E "Towards needs-driven innovation and healthcare policies" *Eurohealth* 2023; **29** (3): 12. World Health Organization. Regional Office for Europe. https://iris.who.int/handle/10665/375422.

Too many scientific articles continue to be cited after their retraction

● About 60 out of 100 000 articles are retracted after publication. Unfortunately, those who read or cite them are not always aware of their retracted status.

Has the scientific article that you were about to read been retracted by the journal or the authors who originally published it? While the likelihood of this occurring may be low, it is on the rise. A study has found that between 1985 and 2014, the retraction rate of scientific articles increased from about 4 to 60 per 100 000 published articles (1). Another study has shown that between 2000 and 2020, the retraction rate increased from 11 to 45 per 100 000 articles for publications with a corresponding author affiliated with a European institution (2). And as the authors of the first study observe, too often these articles continue to be cited with no reference to their retracted status. This includes publications based on data produced through scientific misconduct, which was the most common reason for retracting articles in the fields of biology and medicine in 2020 (1).

In their discussion of the causes of this phenomenon, the authors note that many articles remain accessible with no reference to their retraction. Firstly, journal publishers do not always correctly identify retracted articles on their websites. Although the Committee on Publication Ethics (COPE) has issued guidelines to help them do so, these recommendations still need to be applied. Secondly, scientific articles are often available from a range of different online platforms, including preprint servers (in advance of potential acceptance post-peer review), bibliographic databases and publishers' websites (1).

In April 2021, the study authors selected 500 retracted articles from the PubMed database and checked whether they were properly identified as having been retracted in the Web of Science, Google Scholar, ResearchGate, Scopus and Sci-Hub databases, and on publishers' websites. The proportion of articles not identified as having been retracted ranged from between 25% to 70%, depending on the database. The highest non-identification rate was found in Sci-Hub, which is used extensively in low-income countries (1).

A resource specifically dedicated to listing retracted articles does exist, however: the Retraction Watch Database. This database can also be consulted by reference management software such as EndNote® and Zotero® to automatically warn users if an article listed in their digital library has been retracted (1,3).

The authors conclude by calling on the entire scientific publishing community to commit to improving the situation, in order to ensure that data from retracted articles are no longer used to inform healthcare decisions (1).

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References 1- Boudry C et al. "Poor visibility of retracted articles: a problem that should no longer be ignored" *BMJ* 2023; 381: e072929, 4 pages. **2-** Freijedo-Farinas et al. "Biomedical retractions due to misconduct in Europe: characterization and trends in the last 20 years" *Scientometrics* 2024; 129: 2867-2882. **3-** Prescrire Editorial Staff "Queries and Comments - Retraction of a published article: what are the consequences for evaluation data?" *Prescrire Int* 2023; 32 (247): 108-110.