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Joint response to EMA public consultation

A PRIME example of how EMA is pushing for accelerated market approvals, but at what cost for patients?

Health Action International, International Society of Drug Bulletins, Mario Negri Institute for Pharmacological Research, Medicines in Europe Forum, Nordic Cochrane Centre and Wemos are glad to contribute to the EMA public consultation on the *Draft Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME)*.

In this joint response, we highlight concerns with current attempts to weaken marketing authorisation requirements in the EU, most notably through the EMA's adaptive pathways project. The PRIME scheme appears to be a complementary move to entrench the provision of confidential, customised advice to pharmaceutical companies in the regulatory system for expedited approval and coverage of new, expensive medicines which as evidence suggests will rarely bring therapeutic advance but often safety concerns.

Expedited approval schemes should guarantee patient safety and better therapy

EU pharmaceutical legislation provides that, as a general rule, before a medicine is authorised it has to undergo "extensive studies to ensure that it is safe, of high quality and effective for use in the target population".¹ The requirement for the demonstration of solid evidence about benefits and harms before a medicine is approved protects patients' safety. It contributes to medical innovation by requiring companies to generate meaningful clinical data.

Besides the conventional marketing authorisation scheme, the EU has introduced some specific regulatory procedures to allow for early access to new medicines. These include "approval under exceptional circumstances", and "conditional marketing authorisations" and "accelerated assessment". Whilst the use of expedited approval schemes is justified in the context of truly unmet medical needs, early access to medicines must not jeopardise patient safety or clinically relevant outcomes. After all, people suffering from a rare disease or life-threatening condition also deserve medicines that are approved on the basis of concrete evidence of benefit, not merely hope or interim clinical trial results.

Data from the European Commission show that the timelines for drug licensing have dramatically shortened over the last 10-20 years.² A major concern is that premature licensing comes at the expense of thorough evaluation, leading to more pharmacovigilance problems later. US researchers found that drugs approved after legislative changes introduced to speed up the approval process were more likely to be withdrawn or receive a new “black box warning” than drugs authorised before the bill’s passage.³ In Canada, 34% of drugs approved through the priority review received a serious safety warning compared with 19% of those approved through the standard pathway.⁴

Years of experience also show that manufacturers fail to honour post-marketing commitments to provide missing data (e.g. in the context of conditional marketing authorisations) adding to concerns on patient safety.^{5 6} Evidence also demonstrates that mechanisms for early access fail to guarantee better therapy. An assessment from the independent drug bulletin *Prescrire* reveals that amongst 22 drugs “approved conditionally” in the EU from 2006-2014: 27% are “not acceptable” (e.g., “*product without evident benefit but with potential or real disadvantages*”); 28% have a “judgement reserved” (e.g., “*rating postponed until better data and more thorough evaluation are available*”); 9% are “nothing new”, only 18% are “possibly helpful” and only 18% clearly “offer an advantage”. A recent study from Banzi and colleagues covering the same period of conditional marketing approvals states that “the benefit-risk profile of medicines conditionally allowed is rarely reassuring and strong enough to make the expected public health advantage outweigh the risk of limited clinical information”.⁷

Despite the scarcity of clinically superior medicines, pharmaceutical sales more than doubled between 1990 and 2010.⁸ Pharmaceutical expenditure is highly concentrated on expensive me-too therapies. According to a 2015 OECD report, the proliferation of high-cost specialty medicines targeting small populations and/or complex conditions will be a major driver of health spending growth in the coming years. The report finds that whilst some of these medicines are of benefit to patients, others provide only marginal improvements.⁹ The consolidation of a new business model by the pharmaceutical industry - the “niche buster” model – is contributing to increased pressure on health authorities to reduce evidence requirements for marketing authorisation and price-setting.

Clearly, instead of weakening existing mechanisms for medicines’ early market entry expedited approval schemes must:

- address true unmet medical needs (i.e. a medical condition that significantly affects someone’s quality of life or leads to serious morbidity or mortality and for which no adequate medical treatment exists);
- allow thorough marketing authorisation assessments by regulators
- lead to the (conditional) approval of medicines based on clinical trial data that demonstrate an advance over existing treatment options with respect to outcomes that matter to patients;
- be subject to rigorous and proactive pharmacovigilance requirements, including application of dissuasive sanctions in case of non-compliance.

Adaptive pathways: lowering marketing authorisation requirements and shifting even more the burden of proof to post-market

Several attempts have been made, particularly in the last 15 years, to weaken marketing authorisation requirements in the EU. In 2008 the European Commission put forward a legislative proposal to expand “conditional marketing authorisations” beyond situations of unmet medical needs, in the context of the review on pharmacovigilance rules. The Commission aimed to reduce R&D costs and give pharmaceutical companies “*a faster return on investment*”.¹⁰ Instead of supporting this move, the European Parliament and the Council reiterated the need to ensure that “*a strengthened system of pharmacovigilance does not lead to the premature granting of marketing authorisations*”. Ultimately, the Commission’s proposal was not part of the new pharmacovigilance legislation adopted in 2010.^{11 12}

The move towards flexible marketing authorisation schemes for medicines in situations other than those covered by existing expedited approval schemes was also envisaged in the EMA’s Road map 2015, published in 2010.¹³ The EMA referred to a “progressive licensing” scheme that should apply to situations “characterised by a better-defined or more restricted population of good responders, followed by a broadening of the population post-authorisation when more ‘real-life’ data are available”. Supporting this move, European pharmaceutical industry associations and industry-sponsored patient groups wrote to the European Commission in December 2013 calling for adaptive licensing pilots.¹⁴ In March 2014, the EMA launched the adaptive pathways pilot project (also known as adaptive licensing (AL)).¹⁵

The adaptive pathways scheme aims at bringing drugs to the market earlier by starting with a niche indication in a small population group and then broadening use through additional phases of data gathering. Initial licensing would be based on less comprehensive data, relegating much of the demonstration of evidence about a medicine’s effects to the post-marketing phase. Observational studies would also inform decisions about subsequent authorisations.

According to supporters of this model, “a successful AL [adaptive licensing] pathway for any drug will also be dependent on the willingness of patients, health-care providers, payers, and regulators to accept a greater level of uncertainty in the expectation of a drug’s improved benefit and/or improved safety”.¹⁶ For this model to be implemented as envisaged, healthcare technology assessment (HTA) bodies need to be willing to accept lower evidence standards: “adaptive licensing would require (...) to reduce the development misalignment between marketing and reimbursement decisions” and should “allow for early approval and coverage of a new compound (...) based on smaller initial clinical studies”.^{17 18} To reduce such “misalignment” the EMA and HTA agencies are to provide confidential “scientific advice” to pharmaceutical companies in parallel, at an early stage of the development process.

Although the EMA argues that the adaptive pathways approach uses regulatory processes foreseen in the existing legislation, the Agency is currently revising a series of existing guidelines for expedited approval schemes.^{19 20} In addition, it now proposes new schemes such as the Priority Medicines (PRIME), aimed at enhancing the

involvement of regulators and HTAs bodies during drug development processes and speeding up market access – key elements of the adaptive pathways model.²¹

The EMA's PRIME scheme: an undue rush to market entry

The EMA's Reflection paper on PRIME says that this programme aims at “strengthening support to medicines that have the potential to benefit patients who presently have no treatment options, or that may offer a major therapeutic advantage over existing treatments”.²² Through PRIME, the EMA will provide “early and enhanced scientific advice and regulatory support” to pharmaceutical companies to facilitate data collection and enable faster assessment. The PRIME scheme is “limited to products under development which are innovative and yet to be placed on the EU market”.

The concept of “*innovative medicines*” has for long been captured by the pharmaceutical industry and is popular in discussions on adaptive pathways. According to the EMA's glossary, an innovative medicine is a “medicine that contains an active substance or combination of active substances that has not been authorised before”.²³ It is important to emphasise however that from a therapeutic perspective, true drug innovation refers to therapies that bring a meaningful improvement over existing treatment with respect to outcomes that matter to patients.

Under the PRIME scheme, eligibility will rely on how far the medicinal product is expected to address an unmet medical need. According to the EMA's Reflection paper, such justification could include a description of the product's observed and *predicted* [our italics] effects, its clinical relevance and added value and its impact on medical practice. Medicinal products at early stages of the development process may be eligible (based on non-clinical and very early clinical data) in addition to those in clinical stages of development (e.g. exploratory studies). Preliminary clinical evidence should be based on relevant clinical outcomes but also on established surrogate endpoints.

It is important to bear in mind that a low regulatory bar gets in the way of genuine therapeutic innovation, leading to the pursuit of marginal outcomes and a me-too mentality.²⁴ However, regulators are progressively lowering evidence requirements for approval of new medicines, by allowing smaller trials, surrogate endpoints and placebo comparisons.²⁵ Surrogate endpoints do not guarantee that a drug will affect health status in a clinically meaningful way for patients. Nonetheless, they are commonly used, especially in expedited approval schemes.²⁶ A study revealed that between 1995-2004 most cancer drugs were approved in Europe on the basis of surrogate endpoints such as “tumour shrinkage [that] did not translate most of the time into significant survival benefit”.²⁷ Similarly, a recent US study revealed that the great majority of cancer drugs approved between 2008 and 2012 on the basis of surrogate endpoints (86%) had either unknown effects on overall survival or failed to show gains in survival. The authors concluded that most cancer drug approvals have not been shown to, or do not, improve clinically relevant endpoints.²⁸

A characteristic element of the adaptive pathways model that the EMA proposes to further promote under the umbrella of PRIME is the active joint involvement of regulators and HTA bodies in drug development. According to the EMA's Reflection

paper on PRIME, by providing scientific advice, the EMA and HTA bodies would guide companies on development plans from the very beginning, with the ultimate goal of enabling expedited approval and coverage. The EMA even proposes an early appointment of the CHMP Rapporteur to *“enable continuity in a life-cycle approach and support the development of important innovative medicines (...)”*. The Reflection paper continues *“the Rapporteur will support the development by directing applicants towards the EMA scientific advice on data requirements for future MAA as well as raising awareness on the use of early access tools where relevant (...).”*

The provision of scientific advice by regulators to the regulated raises concerns about conflicts of interest and institutional capture. Such concerns are accentuated when the committee responsible for deciding on marketing authorisation/HTA decision is also giving advice through its involvement in the scientific working party. The lack of transparency associated with these interactions undermines regulatory accountability and the fee-for-service procedure *de facto* creates a financial dependence on the pharmaceutical industry. The potential bias of regulators involved in providing advice **and** deciding on marketing authorisation/reimbursement are genuine concerns.

To incentivise the development of health technologies that genuinely respond to patients and society’s needs, address health outcomes and improve public health, the regulatory environment must send a clear signal to the pharmaceutical and medical devices industries by setting the bar higher and demanding the delivery of relevant, comparative evidence of efficacy and safety. This can be generally achieved by publishing detailed joint guidance (by regulatory agencies and HTA bodies) on requirements for data packages that needed to be supplied, choices of comparators, and preferred trial designs.

The PRIME scheme, however, appears to be another move to entrench the provision of confidential, customised advice to pharmaceutical companies in the regulatory system to facilitate expedited approval and coverage of new, expensive medicines, which as evidence suggests will rarely bring therapeutic advance but often safety concerns.

Conclusions

Regulatory flexibilities for early market access should be applied only in fully justified circumstances, and must ensure patient safety and an advance as compared to best available treatment. To promote innovation in the pharmaceutical sector, the regulatory environment must send a clear signal to the pharmaceutical industry by setting the bar higher – and not lower as suggested - and demanding the delivery of relevant, comparative evidence of efficacy and safety. For this purpose, the following recommendations should be considered:

- Demand a robust evaluation of new drugs before marketing authorisation (introducing the demonstration of added therapeutic value); The requirement for demonstration of solid evidence about benefits and harms before a medicine is approved is of particular importance since it can be challenging to identify serious adverse drug reactions during the post-marketing phase.

- Ensure that expedited approval mechanisms are used only in duly justified circumstances (e.g., when there is a true unmet medical need) and that (conditional) approval of medicines is based on clinical trial data that demonstrate an advance over existing treatment options for patients and clinically-relevant outcomes.
- Allow for thorough marketing authorisation assessments by regulators;
- Ensure rigorous and proactive pharmacovigilance requirements, including the application of dissuasive sanctions if post-marketing requirements are not complied with.
- Reinforce the independence of drug regulatory agencies from corporate influence and funding.
- When scientific advice is given, in exceptional circumstances, as a minimum standard:
 - It should not be provided in exchange for direct fees from individual pharmaceutical companies. Instead, it could be funded through general corporate taxation.
 - Patient and consumer advocates, and expert clinicians with direct or indirect conflicts of interest should not be involved in scientific assessment procedures.
 - A separation of roles should exist between regulators and stakeholders involved in the provision of advice and subsequent discussions on marketing authorization or HTA decisions.
 - Regulatory procedures shall take into account a sufficient representation of the range of views that may exist between patient advocacy groups, between consumer groups, and between patients with different conditions or different severity of disease.
 - Public access to documents related to scientific advice shall be ensured. EPARs and national regulatory documents should include an additional section giving comprehensive information about the scientific advice given at each stage of the development process.

Endorsing organisations

Health Action International (HAI) is a non-profit organisation comprising a European network of consumers, public interest NGOs, health care providers, academics, media and individuals working to increase access to essential medicines and improve their rational use through research excellence and evidence-based advocacy. More info: www.haiweb.org. Contact: ancel.la@haiweb.org

The **International Society of Drug Bulletins (ISDB)**, founded in 1986, is a worldwide network of bulletins and journals on drugs and therapeutics that are financially and intellectually independent of the pharmaceutical industry. Currently ISDB has about 80 members representing 41 countries around the world. More info: www.isdbweb.org. Contact: press@isdbweb.org

The **Medicines in Europe Forum** was launched in March 2002 and reaches 12 European Member States. It includes more than 70 member organisations representing the four key players on the health field, i.e. patient groups, family and consumer bodies, social security systems, and health professionals. Such a grouping is unique in the history of the European Union and is testament to the importance of European medicines policy. Contact: pierrechirac@aol.com

The **Mario Negri Institute for Pharmacological Research** is a not-for-profit biomedical research organization founded in 1961 in Milan, Italy. The Institute's research programs span from the molecular level to the whole human being, and the findings help build up the basis for developing new drugs, and making existing ones more effective. The Institute also provides training and takes part in a range of initiatives to communicate information in biomedicine and encouraging more rational use of drugs. More information: www.marionegri.it

The **Nordic Cochrane Centre** is part of the Cochrane Collaboration, an international not-for-profit international network of more than 30,000 dedicated people from over 100 countries preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health care. More information: www.cochrane.org. Contact: pcg@cochrane.dk

WEMOS advocates a world in which everyone can lead a healthy life. We influence (inter)national policy makers in order to take decisions that respect, protect and realize the right to health. Our contribution to policy changes aims at making structural improvements in health for all. We advocate for ethical conduct, coherent and fair policy, and health equity in a global perspective. More information: www.wemos.nl, contact: press@wemos.nl

References

- ¹ Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council
- ² European Commission Directorate General Competition. "Final Report of the Pharmaceuticals Sector Enquiry"; 8 July 2009.
- ³ Frank C et al "Era of faster FDA Approval has also seen increased blackbox warning and market withdrawals" *Health Affairs* 2014; **33**(8): 1453-1459.
- ⁴ Lexchin J "New drugs and safety: what happened to new active substances approved in Canada between 1995 and 2010?" *Archives of Internal Medicine* 2012; 172:1680-1.
- ⁵ US Government Accountability Office "Drug safety – Improvement needed in FDA's postmarket decision-making and oversight process" Report GAO-06-402, 2006. www.gao.gov: 63 pages.
- ⁶ Carpentier D "Can expedited FDA drug approval without expedited follow-up be trusted" *JAMA Internal Medicine* 2014; **174** (1): 95-97.
- ⁷ Banzi R, et al "Approvals of drugs with uncertain benefit–risk profiles in Europe" *Eur J Intern Med* 2015, <http://dx.doi.org/10.1016/j.ejim.2015.08.008>
- ⁸ Naci H, Carter AW, Mossialos E. Why the drug development pipeline is not delivering better medicines. *BMJ* 2015; 351: h5542
- ⁹ OECD. Health at a Glance 2015, Chapter 2. Available at <http://www.oecd-ilibrary.org/docserver/download/8115071ec005.pdf?expires=1450718870&id=id&accname=guest&checksum=343E98E092BF1B49FA61AFE0FB0A26BF>
- ¹⁰ Prescrire Editorial Staff. "European pharmacovigilance: increasingly outsourced to drug companies" *Prescrire Int* 2014; 23 (155): 302-307
- ¹¹ Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance". *Official Journal of the European Union*, 27 October 2012 ; L299/1-L299/4.
- ¹² Regulation (EU) No 1027/2012 of the European Parliament and of the Council of 25 October 2012 amending Regulation (EC) No 726/2004 as regards pharmacovigilance » *Official Journal of the European Union*, 27 October 2012 ; L299/1-L299/4
- ¹³ European Medicines Agency. Road map to 2015. The European Medicines Agency's contribution to science, medicines and health
- ¹⁴ Eurordis Website. "News: Promotion of progressive patient access bears fruit". 11 June 2014. www.eurordis.org/news/promotion-progressive-patient-access-bears-fruit
- ¹⁵ European Medicines Agency. Pilot project on adaptive licensing. 19 March 2014
- ¹⁶ Eichler H-G et al. "Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval" *Clinical Pharmacology & Therapeutics* 2012; **91** (3): 426-437.
- ¹⁷ Eichler H-G et al. "Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval" *Clinical Pharmacology & Therapeutics* 2012; **91** (3): 426-437.
- ¹⁸ Eichler H-G et al. "From Adaptive Licensing to Adaptive Pathways: Delivering a Flexible Life-Span Approach to Bring New Drugs to Patients". *Clinical Pharmacology & Therapeutics* 2015; **97** (3)
- ¹⁹ European Medicines Agency. "Guideline on the scientific application and the practical arrangements necessary to implement the procedure for accelerated assessment pursuant to article 14(9) of regulation (EC) No 726/2004" EMA/CHMP/697051/2014-Rev. 1. Public Consultation launched on 23 July 2015.
- ²⁰ European Medicines Agency. "Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004" EMA/CHMP/509951/2006,Rev. 1. Public Consultation launched on 23 July 2015.
- ²¹ European Medicines Agency (2015). Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME). Draft. EMA/CHMP/55760/2015

²² European Medicines Agency (2015). Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME). Draft. EMA/CHMP/55760/2015

²³ European Medicines Agency. Glossary. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/document_library/landing/glossary.jsp&mid=&startLetter=I

²⁴ Fojo T, Mailankody S, Lo A. Unintended consequences of expensive cancer therapeutics - the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity. The John Conley lecture. *JAMA Otolaryngol Head Neck Surg* 2014;140:1225-36

²⁵ Naci H, Carter AW, Mossialos E. Why the drug development pipeline is not delivering better medicines. *BMJ* 2015; 351: h5542

²⁶ Light D, Lexchin J "Why do cancer drugs get such an easy ride?" *BMJ* 2015; 350: h2068 doi: 10.1136/bmj.h2068

²⁷ Apolone G, Joppi R, Bertele V, et al. Ten years of marketing approvals of anticancer drugs in Europe: regulatory policy and guidance documents need to find a balance between different pressures. *Br J Cancer* 2005;93:504-9.

²⁸ Kim C, Prasad V, 2015. Cancer drugs approved on the basis of a surrogate end point and subsequent overall survival: An analysis of 5 years of US Food and Drug Administration approvals. *JAMA Internal Medicine*.