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Joint response to EMA public consultation

Marketing authorisation flexibilities that enable early access to medicines should only respond to true unmet medical needs and must protect patients' safety

Health Action International (HAI), the International Society of Drug Bulletins (ISDB) and Medicines in Europe Forum (MiEF) are pleased to contribute to the EMA public consultation on the *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* and the *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*^{1 2}

1. The pharmaceutical marketing authorisation procedure is a health protection measure.

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”.³ The importance of maintaining the requirement for solid evidence about benefits and harms before a medicine is approved as the corner stone of pharmaceutical regulation must be emphasised. Pre-market efficacy evidence is an important health protection measure as it protects patients from a potentially harmful exposure to medicines without solid scientific evidence of a benefit to health. The current marketing authorisation procedure emerged as a response to a series of drug-induced disasters and has been in place for more than 50 years. However, several attempts have been made to expand the use of premature and accelerated approvals for new drugs, particularly over the last decade.

The paucity of new medicines that offer even a modest therapeutic advantage stands in stark contrast to the large number of new products that expose patients to unjustified risks. The majority of new medicines are “me-too” drugs and not “innovative” since they do not demonstrate any added therapeutic value.^{4 5} A recent study found that 66% of phase III trials conducted between 2007 and 2010

were terminated for lack of efficacy.⁶ This is a failure that adaptive licensing won't address.

Rather than lowering the requirements for marketing authorisation, the EMA should favour the demonstration of a new drug's **therapeutic advance** when compared to the best available therapeutic option. This would act as an incentive to reorient research and development towards unmet health needs and true therapeutic progress.⁷ It is regulation for innovation.

2. Several mechanisms are already available to allow faster patient access to new medicines.

Over the last 20 years, regulatory approaches have been adopted both in the US and in the EU to ensure that patients have early access to new medicines. In the US, several expedited drug approval schemes have been put in place from 1992 onwards, such as the "accelerated approval" and "priority review" (1992), "fast-track" (1997) and "breakthrough therapy" or "special medical use" (2012). In the EU, mechanisms providing faster patient access to new medicines include "approval under exceptional circumstances" (1993) and "conditional marketing authorisations" (2005).⁸

Approval under exceptional circumstances in the EU covers those medicinal products for which the applicant can demonstrate that comprehensive data on efficacy and safety cannot be provided due to specific reasons foreseen in the legislation (e.g. it could apply to very rare diseases).⁹ Conditional approvals can be granted in the absence of comprehensive clinical data but are subject to specific obligations to ensure that the missing data is provided subsequently, in a short timeframe. According to EU legislation, this mechanism is to be used in exceptional circumstances in order to meet unmet medical needs of patients and in the interests of public health. The submission of less complete data does not preclude the fact that there needs to be a positive risk-benefit balance at the time of conditional approval.¹⁰

In addition to these two schemes, "compassionate use" mechanisms are available in many Member States. They allow physicians and patients to apply for access to an unapproved therapy, or one that is still under consideration for approval if they have a life-threatening condition and approved treatments have failed, or there are no treatments currently approved.

Legitimate when there is an unmet health need. These "expedited" schemes are legitimate when there is a real unmet health need. But just like any other patient, those suffering from rare diseases or life-threatening conditions also deserve drugs approved on the basis of concrete evidence of benefit, not just hope value or interim clinical trial results. As recently stated by seasoned AIDS activists and health researchers: "*patients need knowledge—answers about the drugs they put in their bodies—not just access*".¹¹

Unsuccessful previous attempts to introduce premature new drug approvals in the EU. During the last 15 years, the European Commission has made several attempts to deregulate the framework for new drug approvals in the EU. For example, the proposal for a new pharmacovigilance regulation and directive foresaw the expansion of “conditional marketing authorisations” to all new drugs and not just for unmet medical needs. The aim of the European Commission was to reduce R&D costs and provide pharmaceutical companies with “*a faster return on investment*”.¹² To prevent exposure to insufficiently evaluated medicines and their adverse drug reactions, the European Parliament and the Health Ministers of Member States reiterated the need to ensure that “*a strengthened system of pharmacovigilance does not lead to the premature granting of marketing authorisations*”. Ultimately, the proposal to expand “conditional marketing authorisations” to all new medicines was rejected and is not part of the 2010 pharmacovigilance legislation. (a)^{13 14}

3. No public assessment report is available reviewing the implementation of the accelerated and the conditional marketing authorisation procedures.

While the EMA claims that the documents subject to consultation are based on “*the experience accumulated with Conditional Marketing Approvals*” and “*accelerated assessments*”, no detailed report is available evaluating the implementation of the accelerated or the conditional procedures. The EMA has not published any review, nor shared any quantitative or qualitative data with the public to document eventual shortcomings. It is therefore surprising to read that the Agency is considering implementing, through soft guidelines, several measures that would *de facto* change the existing flexibilities for early market access.

4. Timely access to medicines shall not be to the detriment of patient safety.

Whilst timely access to needed medicines is important, it should not be in detriment of patient safety. In addition, the concept of “innovative medicines” shall be understood to refer to medicines that meet *true* unmet medical needs. The criteria for granting marketing authorisation for medicines should move towards an approach where comparative-trials against the best available treatment are requested and the question of the added therapeutic value is a determining factor in granting approval.

Existing flexibilities for market access (i.e. conditional approval, exceptional circumstances, compassionate use and accelerated assessment) must apply in fully justified circumstances only. Communication to patients and their relatives about the potential benefits of medicines that have been granted a conditional authorisation shall not be overestimated. As important is that the risks from a drug granted conditional authorisation should never be downplayed. Treatment with

a- Another attempt to deregulate the EU regulatory framework occurred in 2002, during the revision of the directive governing EU pharmaceutical regulation (directive 2001/83/EU as modified by directive 2004/27/EU), which introduced a proposal to allow permanent marketing authorisations after an initial authorisation (i.e., no more need to renew approval after 5 years of marketing) (ref. Prescrire Editorial Staff. The most important changes of the new legislation. *Prescrire International August 2004*. Volume 13 N.72. Available at: <http://english.prescrire.org/Docu/DOCSEUROPE/europeSyntheseEn.pdf>.

medicines approved under conditional marketing authorisation needs to be closely monitored and any adverse drug reaction reported and published.

It is also important to emphasise that unmet medical need shall be interpreted as a medical condition that has a significant effect on someone's quality of life or leads to serious morbidity or mortality and for which there is no or no adequate medical treatment available. For example, infectious diseases such as HIV in the 80's, some orphan diseases, cancers without well-established therapy, and so on. The existence of an unmet medical need must be duly justified by the company through sound evidence at the point of marketing application. The EMA's guideline on conditional marketing must reinforce these criteria.

5. A marketing authorisation is not the same as access to a drug.

Especially for orphan drugs, cancer treatments, and more recently also for other treatments (i.e., hepatitis C), the major factor limiting patient access is their **exorbitant prices, which make these drugs simply unaffordable** in the EU.¹⁵ In the meantime, it is important to remember that: *"from the patient's perspective, an unaffordable treatment is no more effective than a non-existent treatment"*.¹⁶

6. Lessons learnt from the last decade about accelerated-access schemes: faster marketing authorisations have implications for health outcomes and patient safety.

Faster patient access to medicines also means increased health risks and fails to guarantee better therapy. The findings from initiatives providing faster patient access to new medicines are even more worrying. In the US, after 16 years of follow-up, researchers have found that drugs approved following legislative changes introduced to speed up the approval process were more likely to be withdrawn or receive new "black-box warnings" than drugs authorised prior to the bill's passage.¹⁷ A black box warning is the FDA's most serious safety warning and often refers to life-threatening risks. According to another study, drugs approved under expedited review were not as thoroughly tested as those that received a standard review.¹⁸ This implies that many hundreds of thousands or even millions of people may be exposed to a drug later considered to be unsafe. In Canada, drugs approved through the priority pathway had a 34% chance of receiving a serious safety warning compared to a 19% chance for drugs approved through the standard pathway.¹⁹

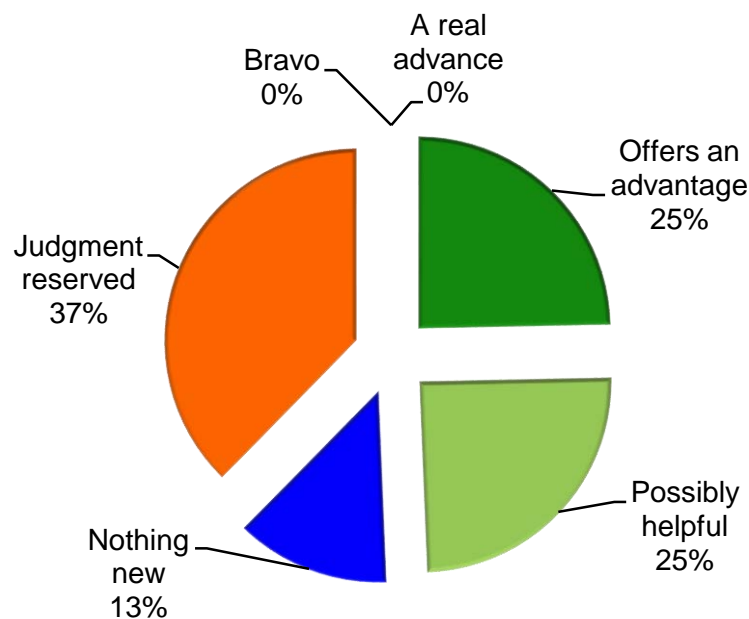
According to data from the European Commission, the **timelines for drug licensing have dramatically shortened over the last 10-20 years**, sometimes posing threats to patient safety.²⁰ Premature licensing is achieved at the expense of proper evaluation, leading to more pharmacovigilance problems down the line.^{21 22}

The EMA should not shorten the timelines for decision-making, as that is likely to speed up approvals based on weak evidence.

Drugs approved under expedited procedures do not necessarily offer a therapeutic advantage to patients. The independent drug bulletin *Prescrire* has assessed 21 drugs “approved conditionally” in the EU since 2006 and rated them as follows: 24% as “not acceptable” (e.g. “*product without evident benefit but with potential or real disadvantages*”); 29% as having “judgement reserved” (e.g. “*rating postponed until better data and more thorough evaluation become available*”); 10% as nothing new, only 19% as “possibly helpful” and only 19% as clearly “offering an advantage” (See **Chart 1**). These results indicate that most medicines approved conditionally do not meet patients’ needs and that for more than one third there is insufficient evidence.

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”.²³ Furthermore, the authors argue that while medicines granted market authorisation under conditional approval could benefit patients who suffer from severe diseases where there is no available treatment, conditionally-approved drugs are not justifiable when effective treatments are already available (e.g. breast and colorectal cancer drugs).

Chart 1. EMA Conditional Approvals (2006-2014) and their Prescrire ratings (per indication)^b



Post-authorisation commitments are often not honoured. Expedited or “conditional drug approvals are often granted by drug regulatory agencies with the requirement that the manufacturer must conduct additional post-market safety or

^b - 24 medicines have been granted conditional approval by the EMA between 2006 and 2014. From these, *Prescrire* has assessed 21 indications.

efficacy studies within a defined timeframe (c). However, years of experience now show that these commitments are often not honoured. A frequent reason provided is that participants are too difficult to recruit.^{24 25 26} Patients are less likely to participate in a clinical trial with all its constraints if the medicine is already available on the market.

In 2007, the US Institute of Medicine reported that many drugs were allowed to remain on the market even though many of the required post-marketing studies had not been completed and confirmatory studies had not shown the expected impact on true health outcomes. In Canada, the Notice of Compliance with conditions (NOC/c) policy allows Health Canada to approve new drugs on the basis of incomplete evidence with the companies promising to do confirmatory studies. A recent study revealed that drugs approved using the NOC/c policy are much more likely to get a post-market safety warning than drugs with a standard approval.²⁷ Furthermore, many of the required post-market studies are still not completed even 10 years after conditional approval was granted.²⁸

It is much more difficult for regulators to remove a drug from the market once it has been approved than to refuse approval in the first place, particularly when regulators have been working closely with companies (scientific advice). In the post-marketing scenario, even in the face of new evidence of higher risks or questionable efficacy, withdrawing drugs can be a lengthy and complicated process, often faced with opposition from patient groups.^{29 30} In addition, shifting the burden of proof from pre-marketing to post-marketing implies that regulators have to rely on the marketing authorisation company to submit additional data to conclude the clinical assessment.

In the EU, the new pharmacovigilance regulation explicitly allows drug regulatory authorities to withdraw marketing authorisations when pharmaceutical companies fail to conduct post-marketing studies.

In short. The current drug approval system already offers opportunities allowing patients who suffer from conditions with an unmet medical need to have early access to a new drug. There are already specific procedures in place to allow earlier access in exceptionally justified cases. Additionally, orphan drugs are not subject to the same efficacy requirements as other new drugs. The current drug approval process does not need to be weakened. It rather needs a critical review.

It is imperative to separate out these exceptional situations from the needs of the general population suffering from a condition where there are already plenty of therapeutic options available (e.g., drugs to treat hypercholesterolemia, cardiovascular conditions, psycho-active drugs, etc.). Faster patient access should

c- Post-authorisation studies are often used as a pretext to market a drug with a poor risk-benefit balance while awaiting further study results. One example is *rimonabant* (formerly marketed as *Acomplia*®), licensed in the EU for the treatment of obesity in 2007. One of its effects was an increase in the number of suicides among users. The European agencies' response was initially confined to setting up a "risk management system". It took about 2 years for *rimonabant* to be withdrawn from the EU market.

not take place at the expense of a thorough evaluation of the efficacy and the safety of new drugs.

Moreover, a market authorisation is not equivalent to ‘patient access’ as the prices of new medicines can be unaffordable to health systems and individual patients. Moves to accelerate regulatory approval could further contribute to a spiral of escalating drug prices and meet the demands of a new pharmaceutical business model: the niche-buster. By targeting specialty markets with no established therapy exists, companies can demand higher prices than the ones that can be demanded in already saturated markets.³¹

7. Post-authorisation evaluation: all but ‘wishful thinking’.

Shifting the burden of evidence from the pre-market period to the post-market period is at best naïve: experience with expedited drug approvals or “conditional marketing authorisations” shows that commitments to post-authorisation evaluation are generally not honoured and sanctions are not enforced (d)^{32 33 34}

Other problems include:

- There are many examples of post-market studies carried out by manufacturers showing no harm, when independent studies have shown the contrary. The pre-market requirements for double-blind randomized controlled trials establish an indispensable level of scientific rigour that is often not present in the post-market period.
- A proposal is put forward based on the use of “big data”: observational studies exploring national health services data. However, this approach has limitations and does not provide the required level of proof.³⁵ Observational studies are of weaker quality than randomised clinical trials as differences in patient characteristics often affect outcomes; and there are fewer methodological standards.
- Lack of incentives for pharmaceutical companies to actually conduct post-marketing studies which could reveal that a drug is less effective or more harmful than initially presumed;
- Public authorities will face opposition from patients when deciding to stop reimbursing a drug or to withdraw its marketing authorisation. According to an example from a US study, “this tension emerged (...) around bevacizumab, which was approved for the treatment of metastatic breast cancer on the basis of surrogate end points under the accelerated-approval pathway. When subsequent studies showed no increase in patient survival, withdrawing the indication took nearly a year and generated substantial opposition. Some insurers even still cover off-label use of the drug for this non-evidence-based purpose”.³⁶

d- The failure of regulatory agencies, governments and the European Commission to impose sanctions after recent infringements (for instance, Roche’s mismanagement of pharmacovigilance data) is indicative of their lack of political will to effectively enforce post-marketing regulations.

According to a recent study on conditionally-approved drugs, the median time taken by companies to meet the specific obligations was four years (range 0.2 to 7.7) and there were delays or discrepancies in the fulfilment of obligations in more than one third of the authorisation procedures.³⁷ In contrast to the approach proposed by the EMA in its consultation document, concrete measures to dissuade, penalties and sanctions should be applied to those marketing authorisation holders which do not comply with their obligations. The EMA must closely monitor marketing authorisation holders and apply sanctions in case of non-compliance (i.e. in the form of fines; removal of conditional approval).

8. Early, scientific and parallel advice = risk of regulatory capture

In both public consultation documents, the EMA proposes close dialogue with pharmaceutical companies. The provision of confidential "advice" to pharmaceutical companies on their development plans for new medicines in exchange for fees is a practice of concern, particularly when the objective is to lower regulatory standards to allow for earlier approval of medicines based on limited data and their subsequent reimbursement. The EMA pilot project on parallel scientific advice with national health technology assessment (HTA) bodies in the European Union (EU) takes place in the context of the Agency's plans on adaptive pathways.³⁸

The provision of confidential scientific advice by regulators to the regulated, in exchange for fees, carries an inherent risk of regulatory capture. This is further accentuated when the members of the committee responsible for providing advice on marketing authorisation procedures are concomitantly involved in the provision and endorsement of scientific advice.

To minimise the risk of regulatory capture, committee members deciding on marketing authorisation should not be involved in the provision of scientific advice. Scientific advice should be transparent to allow independent scrutiny and enhance public trust. Detailed reports of the scientific advice provided by regulators to pharmaceutical companies during drug development and the pre- registration process should be published ideally at the time of decision on trial, or not later than 12 months after the end of the trial. This information cannot be considered commercially confidential information as there is a clear overriding public interest in disclosure.

Instead of providing customised advice to pharmaceutical companies based on regulatory standards that are not guided by therapeutic value, we urge the EMA to write up ad hoc guidelines that help drug manufacturers make development decisions that address genuine public health needs. Potential guideline deviation should be addressed through written exchange only and subject to transparency requirements.

European public assessment reports (EPARs) and similar national regulatory documents should include an additional section summarising scientific advice given

by the EMA at each stage of the development process. This information would not only facilitate better understanding of the data provided, but also allow for an assessment of the role of scientific advice in the approval of new medicines.

9. Transparency: It is imperative to provide and improve the information to the public on accelerated and conditionally-approved drugs.

The EMA's transparency requirements are enshrined in the EU directive 2001/83/EC which regulates pharmaceutical products, as well as in the EU freedom of information Regulation (Regulation 1049/2001) which governs public access to documents in the European Union's institutions and agencies. The accountability and public scrutiny of health authorities' decisions are only possible when the public has access to both the body of evidence and the rationale on which decisions are based.

With respect to accelerated and conditional marketing authorisations, the information provided to the public by the EMA is sparse, particularly during the initial period of marketing authorisation. The European Public Assessment Reports are summaries of discussions and very thin in content. There are also no reports provided during the annual evaluation of conditionally-approved drugs, nor thorough evaluation reports of the Periodic Safety Update Report studies.

To be actively engaged in healthcare and make informed choices about treatment, both professionals and patients have the right to know what to expect from a medicine. This means being aware of the treatment's benefits and harms. Against this background, product information should:

- Easily identify products subject to additional monitoring;
- Easily identify whether a medicine's marketing authorisation has been granted under special conditions or exceptional circumstances;
- Identify recent clinically relevant changes to the product information, in particular those due to safety reasons;
- Enable patients to grasp the meaning of harm-benefit balance;
- Encourage health professionals and patients to report any suspected adverse drug reactions and put in place optimal means for reporting.
- All promotional material should clearly state that products were approved under special conditions or exceptional circumstance

See below for specific comments on the EMA 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.

Specific comments on 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.

Line No. of the first line(s) affected	Comment and rationale; proposed changes
77-78	Remove 'if applicable'. The collection of pharmacovigilance data is a prerequisite of the conditional approval and should be deemed necessary, not optional.
119-120	Remove 'in particular'. The evidence to be reviewed by the EMA in order to evaluate a benefit-harm ratio must consist of clinical trials only to establish a base level of scientific rigour.
151-153	Delete text. Validated surrogate endpoints should not be used to allow unrestricted conditional marketing authorisation (no specific obligations from marketing authorisation holders). Patient safety is at stake.
183, 197, 198	The timelines for completion of obligations (and deadlines) must be publicly accessible to allow public scrutiny. Sanctions must be applied in case of non-compliance.
204	Replace 'may' by 'shall'. Safety monitoring is not an option, but a necessity.
205	Replace 'may' by 'shall'. Safety monitoring is not an option, but a necessity.
255, 259, 266	Replace 'should' by 'shall'. Again, it is not a recommendation, it is an obligation.
273	Replace 'is expected' to by 'shall'. Again, it is not a recommendation, it is an obligation.
283	Replace 'will have to', by 'is to'
291	Add: 'the applicant has the obligation to provide detailed justifications. These shall be made publicly accessible, to allow public scrutiny and for information purposes'.
306	Transparency is needed on the provision of scientific advice. Add: 'the public will have access to reports of the scientific advice provided'.
330	Add: The CHMP shall summarise ' and make publicly available ' its assessment of the request...
345	Replace 'will' by 'shall'
349	Replace 'should' be 'shall'

351	Replace 'will' by " shall'
358	Add: ...following the granting or renewal of a conditional marketing authorisation. These reports shall be ' made publicly available as soon as possible '.
368	Add: " a publicly available opinion... "
396	Add: " a clinical expert statement (to be made public)... "
413	This interim report should be publicly available, as per regulation 1049/2001. Add this provision.

Co-signatory organisations

HAI. Health Action International 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

ISDB. The International Society of Drug Bulletins, 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

MiEF. 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

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