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Joint briefing paper

"Adaptive licensing" or "adaptive pathways": Deregulation under the guise of earlier access

Executive summary

● "Adaptive licensing" (AL), also called "adaptive pathways" (AP) or Medicines Adaptive Pathways to Patients (MAPP), is described as "(…) *a prospectively planned, flexible approach to regulation of drugs and biologics*". Presented as a new "concept" and even as a new "paradigm", it aims to allow medicines onto the market faster, based on lower evidence requirements than under a conventional marketing authorisation. The main claimed benefits of AL are that patients will gain "earlier access" to new medicines and that companies will benefit from "*an earlier revenue stream (…) and less expensive and shorter clinical trials*" (1).

● "Adaptive pathways" raise numerous concerns from a public health perspective. The organisations that endorse this statement have closely monitored developments in EU pharmaceutical regulation for many years and put forward a critique of the "adaptive pathways concept".

● First, we highlight the importance of maintaining the requirement for solid efficacy evidence before a medicine is approved for marketing as the cornerstone of pharmaceutical regulation. The requirement for pre-market efficacy and safety evidence is an important health protection measure, as it prevents harmful exposures unless there is solid scientific evidence supporting a potential benefit to health. The marketing authorisation procedure emerged as a response to a series of drug-induced disasters and has been applied for nearly 50 years. There have been several attempts, particularly over the last decade, to expand the use of "premature" and "accelerated" approvals to all new drugs.

● Second, we outline the main lessons learnt from current initiatives providing faster patient access to new medicines. This overview includes a short insight into the new business paradigm of the pharmaceutical industry - the "niche-buster" model -which contributes to greater pressure on health authorities to reduce evidence requirements for marketing approval and price-setting.

● Third, our critical assessment of the adaptive licensing/pathways "concept" reveals potential consequences to patients' safety by shifting, even more, the burden of evidence from pre-marketing to post-marketing. Post-authorisation commitments are often not honoured. This approach can lead to widespread exposure and population harm before a medicine is removed from the market. Implementing adaptive pathways could lead to a situation where premature marketing authorisations become the rule, even when no genuine public health need exists, therefore putting EU citizens' health unnecessarily at risk. Even if a public health need is identified, lowering requirements for efficacy means that products that are unlikely to meet that need will still be introduced.

● The European Medicines Agency's (EMA) pilot project, launched in March 2014 has not been endorsed by the European Parliament and Council. It undermines the democratic process as it aims to change current practices without a proper discussion or legal basis. It paves the way for the deregulation of marketing approval procedures and increases industry's control over other healthcare actors, such as health technology assessment (HTA) bodies, prescribers and patients.

● Finally, faster market access and escalating drug prices are not proper incentives for real drug innovation. On the contrary, to ensure access to medicines for unmet medical needs, we offer pragmatic recommendations to:

– Demand a robust evaluation of new drugs prior to marketing authorisation (introducing the demonstration of added therapeutic value);
– Ensure that conditional and expedited approval mechanisms are only used in duly justified circumstances (e.g., when there is a true unmet medical need);
– Uphold the rights of EU citizens to obtain compensation from drug- or medical device-induced harm;
– Ensure greater transparency of clinical data, including pharmacovigilance data from regulatory agencies;
– Reinforce the independence of drug regulatory agencies from corporate influence and funding;
– Support needs-driven R&D models as an alternative to corporate-driven R&D.

Adaptive licensing" or "adaptive pathways": Deregulation under the guise of earlier access

"Adaptive licensing" (AL), also called "adaptive pathways" (AP) or "medicines adaptive pathways to patients (MAPP), is described as "*(…) a prospectively planned, flexible approach to regulation of drugs and biologics*" (1,2). Presented as a new "concept" and even as a new "paradigm", it aims to grant marketing authorisations based on lower evidence requirements than under a conventional marketing authorisation.

The main claimed benefits of AL are that patients would have "earlier access" to new medicines and that companies would benefit from "*an earlier revenue stream (…) and less expensive and shorter clinical trials*" (1). From a public health perspective, such an approach generates many reasons for concern, outlined below.

The organisations that endorse this statement have closely monitored developments in EU pharmaceutical regulation for many years. This experience informs the following critique of the "adaptive pathways concept".

Foreword: marketing authorisations are the corner stone of pharmaceutical regulation

In 1965, in the aftermath of the *thalidomide* (Contergan°) disaster, the European Union (EU) adopted directive 65/65/EC, which established that pharmaceutical companies are only allowed to sell their products after obtaining a marketing authorisation from regulatory authorities. In order to obtain such a marketing authorisation, companies need to demonstrate that their medicine has a favourable benefit-harm balance for a specific indication or condition. Clinical trial evidence is required to demonstrate efficacy to treat a condition, or relieve a symptom, or prevent future ill health, without disproportionate adverse reactions. However, demonstration of therapeutic advantage over existing therapies is not required (**a**)(3,4).

The aim of the pharmaceutical marketing authorisation procedure is to protect public health. There are many examples of medicines that failed to be approved when safety problems overrode their hypothetical or even non-existent efficacy. For instance, the development of the lipid lowering drug, *torcetrapib*, was stopped in 2006 when, following phase III clinical trials, patients taking the drug had a higher mortality rate. The combination *phentermine/topiramate* was rejected by the European Medicines Agency (EMA). A recent study found that 66% of phase III clinical trials conducted between 2007-2010 were terminated for lack of efficacy (half of these trials were against placebo) (5). The current system is far from optimal and, frequently, poorly-assessed drugs with meager benefit-harm profiles enter the European market, then are subsequently withdrawn when serious safety problems arise. For instance, *rimonabant* (formerly marketed as Acomplia°) was licensed in the EU for the treatment of obesity in 2007. The rate of suicides increased amongst users and the medicine was only withdrawn in 2009. Another example is a combination of *laropiprant* and *nicotinic acid* (marketed as Tredaptive°), which was approved in 2008 to lower blood cholesterol, but actually caused serious adverse effects without cardiovascular benefit and was removed from the market in 2013. These examples prove that the current regulatory framework for market approval needs to be strengthened, rather than weakened.

Several modalities are already available to allow faster patient access to new medicines. Over the last 20 years, several regulatory approaches have been adopted both in the United States (US) and the EU to ensure that patients have early access to new medicines.

In the US, several expedited drug approval schemes were 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) (6). In the EU, modalities providing faster patient access to new medicines include "approval under exceptional circumstances" (1993) and "conditional marketing authorisations" (2005) (6).

Additionally "compassionate use" mechanisms are available in many Member States. They allow individual 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 other approved treatments have failed, or there are no treatments currently approved. "Compassionate use" schemes allow selected patients to access unapproved treatments in exceptional circumstances. France's temporary authorisation/recommendation for use (ATU/RTU) provides a broader "temporary use" permit for unapproved uses with minimal evidence of efficacy, where there is a pressing medical need and the regulatory agency has evaluated the evidence of efficacy and considered it adequate (7).

Legitimate when there is an unmet health need. These "expedited" schemes are legitimate when there is a real unmet health need (a medical condition that

*a- New drugs are therefore often approved based on evidence from clinical trials comparing the new drug versus placebo and not versus the best available existing therapy. This can lead to inferior therapy and threaten patient safety: the anti-inflammatory drug rofecoxib (Vioxx°) triggered serious cardiovascular adverse reactions but was not more effective than other well-established anti-inflammatory drugs) (ref. Prescrire Editorial Staff. "How to avoid future Vioxx" Prescrire Int 2005; **14** (77): 115-117.*

has a significant effect on someone's quality of life or leads to serious morbidity or mortality and for which there is no adequate medical treatment available (e.g., infectious diseases, such as HIV in the 1980s, orphan diseases, cancers without well-established therapy, etc.). But like other patients, those suffering from rare diseases or life-threatening conditions also deserve drugs that are approved on the basis of concrete evidence of benefit, not just hope 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*" (8). Expedited schemes cannot replace the regular market authorisation procedure; instead, they should provide an alternate means for access under exceptional circumstances.

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*" (9). 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 (**b**)(9,10,11).

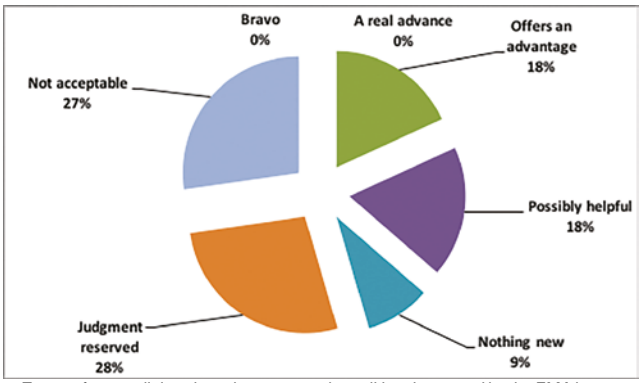
Lessons learnt from the last decade about accelerated-access schemes

Evidence from the US and the EU collected over the last decade indicates that even the regulatory standards for "regular" drug approval are quite low: clinical trials are conducted on a selected group of patients. In the EU, for medicines approved between 2000 and 2010, the median of patients studied before approval was 1708 for standard medicines and 438 for orphan medicines (12). An analysis of all new molecular entities approved in 2008 in the US found that there was a median of 2133 patients exposed to the drug in the pre-market period for standard review drugs [range 430 to 4110], or a median of 1266 if both standard and expedited review drugs are considered (13). Moreover, the clinical evaluation is often based on surrogate (or intermediary) outcomes, which are not always clinically relevant (14). The deficiencies in the regulatory standards for regular drug approvals are not a reason to adopt the increasingly weaker standards that adaptive licensing entails.

Faster patient access 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, researchers have found that drugs approved following 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 prior to the bill's passage (15). A black box warning is the US Food and Drug Administration's (FDA) most serious safety warning on drug labelling and often refers to life-threatening risks. According to another study, drugs approved under expedited review were not as thoroughly tested as those with a standard review (13). This implies that many hundreds of thousands or even millions of people may be exposed to a drug under conditions 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 (16).

Not only safety is a concern; drugs approved under expedited procedures do not necessarily offer a therapeutic advantage to patients. The independent drug bulletin, *Prescrire*, has assessed 22 drugs "approved conditionally" in the EU since 2006 and rated them as follows: 27% as "not acceptable" (e.g., "*product without evident benefit but with potential or real disadvantages*"); 28% as having "judgement reserved" (e.g., "*rating postponed until better data and more thorough evaluation become available*"); 9% as nothing new, only 18% as "possibly helpful" and only 18% as clearly "offering an advantage" (See Chart 1; and Table 1, page 4). These results indicate that most medicines

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



a- Twenty-four medicines have been granted conditional approval by the EMA between 2006 and 2014. From these, Prescrire has assessed 22 indications. See Table 1 page 4.

*b- 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 further need to renew approval after five years of marketing) (ref. Prescrire Editorial Staff. The most important changes of the new legislation. Prescrire Int 2004; **13** (72): 158. Available at: http://english.prescrire.org/Docu/DOCSEUROPE/europeSyntheseEn.pdf).*

Table 1. European Medicine Agency Conditional Approvals (2006-2014) and their Prescrire ratings (per indication)

Active Substance (INN)	Therapeutic Area	Year of Approval	Prescrire Rating	Status
Sunitinib*	Gastrointestinal stromal tumours carcinoma	2006	Offers an advantage	Converted to regular MA
Sunitinib*	Renal cell carcinoma	2006	Judgment reserved	Converted to regular MA
Darunavir	HIV Infection	2007	Offers an advantage	Converted to regular MA
Panitumumab	Colorectal cancer	2007	Not acceptable	Still conditional
Raltegravir	HIV infection	2007	Offers an advantage	Converted to regular MA
Stiripentol*	Myoclonic epilepsy, juvenile	2007	Offers an advantage	Converted to regular MA
Etravirine	HIV infection	2008	Possibly helpful	Converted to regular MA
Aztreonam*	Respiratory tract infections cystic fibrosis	2009	Nothing new	Converted to regular MA
Lapatinib	Breast cancer	2008	Possibly helpful	Still conditional
Ofatumumab*	Chronic lymphocytic leukemia	2010	Possibly helpful	Still conditional
Pazopanib	Renal carcinoma	2010	Not acceptable	Converted to regular MA
Pazopanib	Soft tissue sarcoma	2010	Not acceptable	Converted to regular MA
Everolimus*	Astrocytoma associated with tuberous sclerosis	2011	Possibly helpful	Still conditional
Fampridine	Multiple sclerosis	2011	Not acceptable	Still conditional
Brentuximab*	Hodgkin and systemic anaplastic large-cell lymphoma	2012	Judgment reserved	Still conditional
Crizotinib	Anaplastic lymphoma-kinase (ALK) positive advanced non-small-cell lung cancer	2012	Judgment reserved	Still conditional
Pixantrone	Non-Hodgkin B cell lymphomas	2012	Nothing new	Still conditional
Vandetanib	Medullary thyroid cancer	2012	Not acceptable	Still conditional
Bosutinib*	Chronic myeloid leukemia	2013	Judgment reserved	Still conditional
Vismodegib	Advanced basal-cell carcinoma	2013	Judgment reserved	Still conditional
Ataluren*	Duchenne muscular dystrophy	2014	Prescrire's evaluation not published yet	Still conditional
Bedaquiline fumarate*	Pulmonary multidrug resistant tuberculosis	2014	Judgment reserved	Still conditional
Cabozantinib*	Metastatic medullary thyroid carcinoma	2014	Not acceptable	Still conditional
Delamanid*	Pulmonary multidrug resistant tuberculosis	2014	Prescrire's evaluation not published yet	Still conditional

* Orphan drug

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"(17). 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). Another study revealed that in the past two decades, drugs approved by the FDA have been associated with an increasing number of expedited development or review programs; and although expedited programs should be strictly limited to drugs providing noticeable clinical advances, this trend was being driven by drugs that were not first in class and thus potentially less innovative (18).

Post-authorisation commitments often not honored. 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 efficacy studies within a defined timeframe (**c**). However, years of experience now show that these commitments are often not honoured. A frequent justication is that participants are too difficult to recruit (19,20,21). 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 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 (19). 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 (22). Furthermore, many of the required post-market studies are still not completed even 10 years after conditional approval was granted (23).

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 (24,25).

In addition, shifting the burden of proof from pre-marketing to post-marketing implies that regulators have to rely on the marketing authorisation holder 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 (10, 11). However, that has never happened since the legislation was implemented. As stated by supporters of the approach that places a heavier reliance of post-approval monitoring: "*This may be difficult to achieve politically in some healthcare environments and may not be acceptable for patients*" (2).

In short. The current drug approval system offers opportunities that allow 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. In additional, 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; instead, it 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 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.

Impact of the new "niche buster" model on regulatory requirements

A blockbuster is a drug that generates annual sales of over US$1 billion. The blockbuster business model dominated the 1990s and 2000s. It relied on developing medicines that would treat common diseases maximising the number of users.

Around the mid-2000s, this model became a victim of its own success. The market was saturated with redundant "me-too" drugs (26). Payers became more selective about which drugs they were prepared to fund and increasingly relied on health technology assessment (HTA) bodies to appraise the comparative value of new medicines, as explained below (27).

The "niche buster" model. Over the last 10 years (since the mid-2000s), drugs produced through biotechnology to treat rare diseases and various forms of cancer have blossomed. By targeting specialty markets where no established therapy existed, pharmaceutical companies were able to demand higher prices than in otherwise saturated blockbuster markets. Some niche drugs have progressively gained approval for additional therapeutic indications, generating annual revenues of over US$1 billion, and leading to the term "niche buster" to describe this emerging business model (28).

All medicines to become orphan drugs? Policies such as the EU Regulation on Orphan Medicinal Products adopted in 2000, which encourage the production of drugs for "orphan" diseases by ensuring marketing exclusivity and data protection, are at the core of the niche buster model. "Orphan drug" is a regulatory status supposed to encourage the development of treatments for rare diseases (29). According to these policies, marketing approval is to be granted based on

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 amongst users. The European agencies' response was initially confined to setting up a "risk management system". It took about two years for rimonabant to be withdrawn from the EU market.

pared-down evaluation (small trials of short duration). Astronomical drug prices are frequent and accepted (28).

According to evidence from the US: "*In recent years, the trend in drug development has moved from blockbuster drugs towards pharmaceutical products that meet the needs of patient populations with particular conditions. These "niche" populations are smaller and have a more urgent need for treatment. This has led to increasing pressure on regulatory agencies to accelerate drug approval*" (30).

In addition, advances in biotechnology and in genetic testing to identify sub-groups of patients have further contributed to blurring the boundary between rare and common diseases (**d**)(31).

In short. As research and development (R&D) has shifted towards orphan drugs, pressure has increased to reduce the regulatory requirements for marketing approval (28). This industrial and regulatory context must be borne in mind when analysing the recent push for "adaptive licensing" or "adaptive pathways". Adaptive licensing aims to lower the bar for market authorisation of new drugs (as explained below) and to pave the way for a new market where complementary medical devices and medicines are developed and marketed in tandem ("test-drug pair") (2).

"Adaptive licensing" or "adaptive pathways": Shifting the burden of evidence from pre-marketing to post-marketing, shifting health and financial risks to society

In 2010, the European Parliament and Council (Health Ministers of Member States) voted against the legislative proposal to expand the use of conditional marketing authorisations for all new medicines (See Unsuccessful previous attempts to introduce "premature" new drug approvals in the EU, page 4). Apparently, in its drive towards "adaptive pathways", the EMA has adopted the European Commission's priority of securing an "*earlier revenue stream*" for pharmaceutical companies. In fact, "*adaptive licensing is envisioned as the ultimate replacement for the current development and authorisation model and as such should be applicable to most new products*", not only to address unmet medical needs, as is currently foreseen through the EU conditional marketing authorisation or compassionate use programmes (1).

EU citizens to become guinea pigs without the ability to seek compensation if they are harmed: A win-win for manufacturers' revenues and a lose-lose for citizens and national governments. Adaptive licensing relies on marketing authorisations based on lower evidentiary requirements. This could include, for instance, taking on board surrogate endpoints to the detriment of clinically relevant outcomes in order to save companies' costs and time. The evaluation of a drug's harms and benefits is to be rolled out once the medicine is already on the market (1). It is candidly explained: "*The potential benefits [of adaptive licensing] for companies would be an earlier revenue stream than under a conventional licensing pathway and less expensive and shorter clinical trials*" (**e**)(2).

However, showing an impact on surrogate endpoints is no guarantee that a drug will impact health status in a clinically meaningful way for patients (**f**)(14). Most notably, the delinking of "*the populations in which the fundamental efficacy hypothesis and the overall safety hypothesis are tested*" means that a medicine's harm-benefit balance will not be properly assessed prior to the exposure of the general patient population to a new drug.

Pharmaceutical companies and the creators of the "adaptive licensing concept" realise that such a pathway is likely to put public health at risk. They therefore propose an additional measure be included in the concept: "***a prohibition on product liability suits during the initial marketing period***" by injured patients or payers. This blanket prohibition is to be achieved by "*communicating the higher than usual level of uncertainty to patients and providers*" (**g**)(1). In other words, patients will be subject to greater levels of uncertainty, harm and lack of benefit, but will not be able to sue if something goes wrong. This disingenuous measure clearly defends the interests of the manufacturers. Patients and healthcare professionals will not only have to agree to use a medicine that has not been adequately tested, but if patients suffer harmful effects, they would also be financially vulnerable. In the case of adverse events, the healthcare system would also have to cope with increased medical interventions, hospitalisations, and, potentially, with increased morbidity and mortality. If patients have a life-threatening disease without available treatment, or for which other treatments have already failed, they and their families are in a desperate and vulnerable position. This "liability prohibition" takes advantage of the desperation of unprotected patients, which is clearly unethical (**h**).

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d *- One method used to blur boundaries in "personalised medicine" is to segment common diseases into subtypes, even though evidence for their clinical meaningfulness might be weak.*

e- *According to the Massachusetts Institute of Technology (MIT) Center for Biomedical Innovation (CBI), "the close partnership between the two Centers [CBI and the MIT Center for International Studies] are mirrored in [Dr Eichler's] work, which will be cutting across national boundaries and biomedical industry stakeholders" (ref. "Senior EMA official joins CBI as visiting scholar – Hans-Georg Eichler, European Medicines Agency, joins MIT Center for Biomedical Innovation and MIT Center for International Studies" 18 November 2010; http://cib.mit.eu: 2 pages.).*

f- *Methodological shortcuts, such as combining endpoints or distinct events, increase the likelihood of obtaining statistically significant differences, particularly when trials are small or when treatments are likely to be similarly effective. But it makes it increasingly difficult to obtain clear-cut answers from those clinical trials.*

g- *It should be noted that, while the "adaptive licensing" concept aims to shift the burden of evidence from pre-marketing clinical trials to post-marketing studies and to obtain information on the "real use" of medicines, there is very little focus on pharmacovigilance activities in the conceptual papers that introduce the "adaptive licensing concept" (1,2).*

h- *Article 15 of the Helsinki declaration states clearly that: "Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured."*

Post-authorisation evaluation: all but 'wishful thinking'. Lessons must be learnt from the past decade's experience with expedited drug approvals or "conditional marketing authorisations": commitments to post-authorisation evaluation are generally not honoured (see above on page 4-5) and sanctions are not enforced (23,32,33). The failure of regulatory agencies, governments and the European Commission to impose sanctions after recent infringements (for instance, Roche's grave mismanagement of pharmacovigilance data) is indicative of their lack of political will to effectively enforce post-marketing regulations. Other problems include:

– 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 randomised controlled trials establish an indispensable level of scientific rigour that is often not present in the post-market period;
– A proposal being 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 (34). Observational studies are of weaker quality than randomised clinical trials because 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 that could reveal a drug is less effective or more harmful than initially presumed;
– Public authorities being faced with 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 still cover off-label use of the drug for this non–evidence-based purpose" (35).

In contrast to the approach proposed within adaptive pathways, researchers from the US warrant caution and highlight that when a decision is not easily reversible, decision theory suggests that more care should be taken in reaching the initial determination (35).

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 (17). In contrast to the approach proposed by the EMA, concrete measures to dissuade penalties and sanctions should be applied to marketing authorisation holders that 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 and/or revoking of conditional approval).

EMA's pilot project: Circumventing democratic process?

The adaptive licensing concept aims to replace the current development and authorisation process/model in its entirety (**i**). In March 2014, the EMA publicly launched an "adaptive licensing" pilot project with "*discussions conducted in a safe harbour environment and all submissions strictly confidential*" (36). This "safe harbor" builds on a previous initiative started in 2006, which was led and financed by GlaxoSmithKline (GSK), AstraZeneca and Roche. The EMA has profiled its pilot as a patient-centred project, as a way to provide "*accelerated access to innovative medicines for patients in need*" (6), but adaptive licensing supporters are already asking: "*(…) what would it take to establish this mindset for many or all other therapies?*" (2,37). The pilot concept, its discussions, selection process and all decisions around it have been carried out behind closed doors with no opportunity for public scrutiny.

The EMA's pilot project claims to be an exploratory initiative, which "*builds on existing regulatory processes and intends to extend the use of elements that are already in place, including scientific advice*". Nevertheless, industry has welcomed it as an omen of things to come (38,39). Once the EMA implements the pilot and the pharmaceutical industry reaps its benefits, it is likely to inform lobbying efforts to weaken the current European marketing approval procedures and trigger a legislative review.

Increased control by industry of other sectors: HTA bodies, prescribers and patients

If implemented, adaptive pathways (AP) will increase pharmaceutical companies' control over other sectors, including health technology assessment agencies (HTA), prescribers and patients.

Health technology assessment (HTA) bodies. HTA agencies provide independent advice to governments and insurers that guide reimbursement decisions. If a product is considered not to be cost-effective and reimbursement is denied, companies' revenues suffer, making HTA a priority target for industry. According to supporters of adaptive pathways, "*to be successful, adaptive licensing would require (...) to reduce the development misalignment between marketing and reimbursement decisions*" and should "*allow for early approval and cove-*

i- *According to the MIT CBI website, "NEWDIGS [the New Drug Development Paradigm initiative, a think tank group established at the Massachusetts Institute of Technology (MIT); see page 8] provides a unique opportunity for disruptive innovation at the level of the overall system, rather than simply improving the current environment."*

"Adaptive licensing/pathways": Industry-driven from inception to implementation

The adaptive licensing concept was first shaped by the New Drug Development Paradigm initiative (NEWDIGS), a think tank group established at the Massachusetts Institute of Technology's (MIT) Center for Biomedical Innovation (CBI) in the US, financed and strongly influenced by the pharmaceutical industry (**a**) (1,2).

Getting institutional support from the EMA and the European Commission. According to the MIT CBI website, "*NEWDIGS investigated the feasibility of adaptive licensing between 2010-2013 (…) Findings have been widely disseminated (…) and have helped to inform the European Medicines Agency (EMA) [adaptive licensing] pilot program*", probably taking advantage of the fact that the EMA's Chief Medical Officer had joined CBI as a visiting scholar (2).

As the "concept" of "adaptive licensing" matured, joint efforts of industry-sponsored patient groups and European pharmaceutical trade associations further consolidated the aspirations of EMA officials and led the European Commission to accept a pilot project on adaptive licensing, which was officially launched by the EMA in March 2014 (3, 4, 5).

Targeting "patients expectations". "Patients expectations" – from rare diseases' patients – were identified as a key driver of adaptive licensing (2). According to the website of EURORDIS, the association representing Rare Disease Patients in the European Union: *"(…) in October 2013, (…) some 80 high-level stakeholders (…) discuss[ed] the advantages and challenges of Progressive Patient Access. Sustained interaction between EURORDIS and the EMA, the European Commission, and Health Technology Assessment (HTA) bodies, culminated in a letter that was co-signed by the European Patient Forum, the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Association for Bioindustries (EuropaBio) and sent to the European Commission in December 2013 calling for Adaptive Licensing pilots. The European Commission was supportive and, in response, the EMA announced in March 2014 the launch of a pilot project on Adaptive Licensing (…)*" (3).

Preparing the ground for legislative review. Very rapidly, the Innovative Medicines Initiative, a public-private partnership between the biopharmaceutical industry and the European Commission, announced plans to undertake a project that would help the development of "*tools to facilitate and support exploratory [adaptive licensing] pilot projects*" (6).

a- *The CBI merged with the Program on the Pharmaceutical Industry (POPI) in 2008 (ref. "About CBI" Website http://cbi.mit.edu/about-cbi/ consulted on 1 July 2014: 1 page). Johnson & Johnson, Pfizer, Sanofi, inter alia, are all full members of the CBI.*

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rage of a new compound (…) based on smaller initial clinical studies" (1). In order 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 development. Yet, a serious risk of institutional capture exists when secret early-stage interactions with pharmaceutical companies take place (**j**)(17). This procedure could bind HTA bodies to their initial advice and limit their decisions afterwards. Another avenue that has been proposed to override the authority of HTA bodies and payers is to negotiate managed entry agreements (MEA) (2). These are contracts between payers and pharmaceutical companies to share financial risks associated with uncertainties around the cost-effectiveness of new drugs, gain "flexibility", and, most notably, accommodate changes to the scope of the covered population. Both of these proposals would reduce HTA agencies' impact to grant or deny reimbursement based on robust efficacy and safety evaluations.

Prescribers. In line with the "adaptive licensing concept", approval will first be granted for a niche indication, usually involving use in a small population and prescribing by a restricted group of physicians and then followed by additional phases of evidence gathe-

j- *In the EU, since 2005, within the framework of scientific advice procedures, pharmaceutical companies pay the EMA a service fee in exchange for early confidential guidance on the minimal clinical requirements needed to obtain a marketing authorisation. If the pharmaceutical company follows the EMA's advice, the EMA can, in practice, be considered a "co-developer" of the medicine, making it increasingly difficult to deny a marketing authorisation, even if trial results are disappointing (ref.17). Such an institutional conflict of interest is further amplified by individual conflicts of interests, as members of the Committee Responsible for Market Authorisation (CHMP) can also participate in scientific advice working groups and officially endorse scientific advice in their capacity as CHMP members.*

Table 2. The underlying myths of adaptive licensing

Adaptive licensing "problem statement"	In reality…
There are **not enough "innovations" being developed**	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 have an added therapeutic value (1, 2). A recent study has found that 66% of phase III trials conducted between 2007-2010 have been terminated for **lack of efficacy**. This is a failure that adaptive licensing does not address (3). Rather than lowering the requirements for market authorisation for new drugs, as proposed in adaptive licensing, the European Medicines Agency should opt for the compulsory demonstration of a new drug's **therapeutic advance** when compared to the best available therapeutic option. This would act as an incentive to re-orient research and development towards unmet health needs and true therapeutic progress (2).
"Innovative" medicines are not **quickly available** to patients (approval procedures are not sufficiently flexible)	Several **modalities are already available to provide faster patient access to new medicines** when there is an unmet health need (e.g., conditional approvals, approvals under exceptional circumstances, compassionate use schemes, such as temporary authorisation/recommendation for use, etc.) (4). 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 ([5]). Premature licensing is achieved at the expense of proper evaluation, leading to more pharmacovigilance problems down the line (6, 7). Especially for orphan drugs, cancer treatments, and, more recently, for other treatments (i.e., hepatitis C), the major factor limiting patient access is **the exorbitant prices of medicines, which make these drugs simply unaffordable** in the European Union (8). 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*" (9).
Adaptive licensing allows for "***life span management***" of new drugs, in contrast to "*single gated licensing decision [ordinary marketing authorisation scenario]*"	The adaptive licensing "concept" puts, in reality, very little focus on pharmacovigilance activities. Under the conventional scenario, **approvals are systematically reassessed** after five years of marketing, giving ample opportunity for "lifespan management". Moreover, post-marketing efficacy and safety studies and periodic benefit-risk assessment reports (formerly "periodic safety update reports", or PSURs) are being used to accumulate knowledge even after approval is granted.
R&D costs are too high	The pharmaceutical industry generated higher profit margins than any other industrial sector in 2013, and is likely to have remained the most profitable sector in 2014. However, **money is not reinvested in R&D, but mainly redistributed to shareholders** (9). The cost of a new drug discovery is claimed to be $1,3 billion (€1billion), but this figure, which comes from the industry-supported Tufts Center, is at least a four-fold overestimation (**a**). North American researchers have recalculated the Tufts Center figures using a comprehensive methodology to include less expensive drugs in their calculation and take into consideration drugs partly produced with public funds or tax credits. They found a **mean cost closer to US$ 90 million per new drug and a median cost of US$ 60 million** (10).

Notes:
a- Half of that $1,3bn comes from estimating how much profit would have been made if the money had been invested in an index fund of pharmaceutical companies and half of the remaining $0.65bn is paid by taxpayers through company deductions and credits (9).

References (Table 2)
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ring. Supporters of adaptive licensing argue that "off-label use" can be effectively prevented. However, there are no guarantees that that will be the case. No legal provisions are foreseen in the European Legislation to tackle "off-label use". In addition, *"greater emphasis [on physicians] by regulators, payers and industry on targeted drug utilisation"*, will make physicians responsible if patients suffer harm and seek compensation (2).

Patients. *"Access to patients' electronic medical records and direct contact with patients"* are considered as crucial enablers of adaptive licensing implementation, thus establishing avenues for companies to access patients' personal data, contact patients directly and further promote their products to foster patient loyalty to a particular branded medicine under the guise of better treatment compliance or "education" programmes (2). These plans echo the controversial proposals on "infor-

mation to patients" withdrawn in May 2014 (**k**) (40,41). Recent developments are diametrically opposed to direct communication to patients by pharmaceutical companies, and recognise that patients need independent, nonconflicted sources of information and advice. These *direct communication* provisions would take advantage of the vulnerability of patients with serious, life-threatening illnesses.

In short. While it is clear that pharmaceutical companies stand to gain from adaptive licensing, the actual benefits of adaptive licensing to patients, health systems, payers and healthcare professionals are far from obvious (read also Table 2, "The underlying myths of adaptive licensing") (42).

On the contrary, there are strong reasons for concern: adopting adaptive pathways could lead to a situation where premature marketing authorisations become the rule rather than the exception, putting patients' safety at risk even when no genuine public health need is identified. Moreover, shifting the burden of evidence from pre-marketing to post-marketing is at best naïve: experience with expedited drug approvals or "conditional marketing authorisations" shows that commitments to post-authorisation evaluation are often not honoured.

In addition, the EMA's pilot project, launched in March 2014, seems to be a perfect way of circumventing the democratic process by presenting the European Commission, Parliament and Council with a *fait accompli*. It is likely that adaptive pathways will be used as a springboard to lobby for a legislative review aimed at:

– weakening current marketing approval procedures;
– increasing industry's control over other healthcare actors, namely:
  - Influencing HTA bodies' decision-making on pricing and reimbursement;
  - Increasing access to patients' personal data and allowing new avenues for direct-to-consumer advertising.

Most strikingly, an intervention by an industry head of research and development during EMA's 20th anniversary seminar revealed another advantage for pharmaceutical companies: Adaptive licensing will allow companies to enjoy longer patent protection by increasing the time on the market of a patented drug (43).

Reorienting European medicines policy: Towards a regulation where patients come first

Looking back at the evidence accrued over the last 30 years, fast-track drug approvals and high prices have not worked effectively as incentives for drug innovation (28,44,45). In order to ensure real access to medicines for unmet medical needs, rather than supporting deregulatory moves, such as "adaptive licensing/pathways", the priorities of future policy developments should:

– **Demand robust evaluation of new drugs before granting marketing authorisation** by requiring comparative trials against the reference treatment. These must be in line with the ethical standards of the Declaration of Helsinki in order to demonstrate added therapeutic value (therapeutic progress) and to avoid exposing patients to otherwise avoidable harm (**l**)(3,46);

– **Apply conditional and expedited marketing authorisation procedures only when there is a true unmet medical need; early approval should be subject to the demonstration of a positive harm/benefit balance**;

– Drug regulatory agencies must **closely monitor pharmaceutical companies' pharmacovigilance activities** to avoid data being misinterpreted or withheld. Access to reports of suspected adverse drug reactions should include narrative summaries of individual cases;

– Defend **EU citizens' right to obtain compensation for harm** caused by medicinal products or medical devices. Medicines and medical devices are not mere commodities, but products that inherently carry high risks. They should therefore be outside the scope of Directive 85/374/EEC on liability for defective products (47,48,49);

– Ensure greater **transparency of clinical data** in line with the Clinical Trials Regulation, which clearly states that clinical trial data is not commercially confidential information. Anonymised individual patient data ("raw data") should be made available to allow reanalysis of clinical trial results. In compliance with Regulation (EC) 1049/2001, the EMA must also be compelled to set up, without further delay, a public online register of documents held by the Agency;

– Reinforce the **independence of drug regulatory agencies and wean them from pharmaceutical companies' financing and influence**. Public funds should be allocated for their activities to replace the current fee-for-service system. Conflicts of interest and revolving door practices of experts and EMA

*k- In December 2008, despite clear opposition to direct-to-consumer advertising (DTCA) by the European Parliament in 2003, the European Commission proposed allowing direct communication to patients by pharmaceutical companies under the guise of improving "information to patients". The adoption of EU Commission proposals (a directive and a regulation) was halted by the Council that pointed out that "the proposals will not provide sufficient guarantees that the prohibition of advertising of prescription-only medicinal products to the general public will not be circumvented" (ref. Prescrire Editorial Staff. "Direct-to-consumer advertising of prescription drugs: European Commission persists in putting industry's interests first" Prescrire Int 2013; **22** (134): 24-27).*

*l- Demonstration of additional therapeutic value was enforced as a marketing authorisation criterion in Norway, prior to its harmonisation with EU standards in 1996. A study revealed that "This approach led to Norway having seven non-steroidal anti-inflammatory drugs on the market compared with 22 in the Netherlands.'' Ref: Dukes M, Lunde I. The regulatory control of non-steroidal anti-inflammatory agents. European Journal of Clinical Pharmacology 1981; **19**: 3-10.*

agents should be avoided, rather than poorly "managed" (50);

– The role of medicines' agencies as co-developers raises concern. It is paramount to ensure that early dialogues between manufacturers, regulators, HTA bodies and patients refrain from aligning drug regulatory agencies and HTA assessments towards weakened standards for marketing authorisation and reimbursement. As a minimum precaution, **'customised' scientific advice should become transparent to curtail regulatory capture** and a clear separation of roles between the committees providing scientific advice and those evaluating the marketing authorisation is needed (27). The drug regulatory agencies' role of "supporting innovation" should not be understood as "avoiding market failure" and "optimising industry's return on investment". Such an interpretation creates an inherent conflict with the key mandate of public health authorities to assess and regulate medicines and medical devices. Provisions to assure added therapeutic value and clinically relevant outcomes are essential to guide drug development processes that meet the needs of patients and public health;

– Support **needs-driven R&D models other than corporate-driven R&D**. R&D should be seen as an investment for society and therefore supported through public funds and also carried out by other actors free from commercial interests (51).

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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.

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