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Senior Medical Officer

Adaptive pathways

Reply to Prof. Silvio Garattini, Peter C. Gøtzsche, Tom Jefferson MD MSc FFHPM MRCGP, Joan-Ramon Laporte, Joel Lexchin MD, Donald W. Light, Martin McKee CBE MD DSc FRCP FFPH F MedSci, Professor of European Public Health, Jean-Louis Montastruc, Sir Richard Thompson

To the authors,

Thank you very much for your letter of 13 May 2016. The Agency values contributions from stakeholders on its initiatives, as feedback and open debate are essential for adapting and fine-tuning concepts and approaches and ensuring that they meet stakeholders' expectations.

From the inception of adaptive pathways, the Agency has encouraged debate, especially in the scientific community; the concepts and ideas behind adaptive pathways were presented in scientific publications and discussed extensively in scientific conferences. Since 2014, some of these ideas have been trialled in a pilot. We agree with many of the points made by the authors and believe that many of them in fact define the concept.

Adaptive pathways is a concept of medicines development intended for medicines that address patients' unmet medical needs. It seeks to maximize the positive effect of new medicines by balancing timely access for patients likely to benefit most from a new medicine with the need for adequate, evolving information on their benefits and risks.

However, adaptive pathways is not a new route of approval for medicines, but makes use of existing review tools and is subject to the same principle: only those medicines for which the balance of benefits and risks for a defined patient population is found to be positive at the time of initial approval will receive a recommendation for a marketing authorisation. This means that the same benefit-risk standards will apply as for any other new medicine.

We fully agree that adaptive pathways is not meant to apply to all medicines, but only to those likely to offer help for a patient population with an unmet medical need and to which the principles of adaptive pathways can be applied, e.g. targeting the development of a medicine to a well-defined group of patients in need to enable smaller, faster clinical trials that are likely to yield results earlier.

We also fully agree that a key feature of adaptive pathways is its "life-span approach" to learning. As part of this, all involved stakeholders agree upfront on a plan of post-licensing knowledge generation for a medicine before it is authorised, and the marketing authorisation holder commits to carrying out this plan, which is a legally binding regulatory obligation. The benefit-risk profile and, when required by

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the relevant national bodies, the ‘value’ of a medicine will be re-assessed and revised as more knowledge is gained.

Another key aspect of adaptive pathways is its focus on bringing together all relevant stakeholders - patients, healthcare professionals, regulators, HTA bodies and payers. Dialogue with those involved in the development of medicines is important throughout the life span of the medicine: early on to help determine which medicines could be appropriate for adaptive (iterative) development; then to jointly agree a data generation plan to meet the needs of regulators, HTA bodies and payers and, later on, when the medicine has reached patients, to ensure the use of the medicine (i.e. how it is prescribed) is well monitored and managed.

Cooperation between stakeholders and a strong pharmacovigilance system are the basis for organising and planning the systematic monitoring of the safety and the overall performance of a medicine in clinical practice, a unique feature of adaptive pathways that no other development setting foresees at present.

In their letter, the authors list a series of assumptions, with some comments and proposals. We respond to each of these in the two tables below. The first table contains six key ideas and proposals together with our replies. The second table relates to what the authors perceive as eight assumptions made by EMA, their comments on these assumptions and we include a reply to each of these.

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Table 1

	Key ideas for the adaptive pathways concept
1.	Drugs to be submitted to the adaptive pathway must be selected on clear and shared criteria based on the impact of the target disease or health problem.
	Reply: *We agree.*
2.	An assessment schedule based on the Target Product Profile approach must be publicly agreed.
	Reply: *A 'Target Product Profile' (TPP) is a strategic development tool, which summarizes a drug product's development goals, including tests and studies, ideally as expressed in terms of its labelling concepts. It has been described as "beginning with the end in mind".* *EMA does not work with formal TPPs but the overall idea of "beginning with the end in mind" is close to the adaptive pathways concept. Yet, adaptive pathways goes even beyond TPPs in that it does not limit itself to the development plan up to the point of (initial) authorisation but considers at an early stage studies which will be needed during the on-market phase. We fully concur with the authors' statement "Before the use of an adaptive pathway leads to authorisation, any subsequent plan to generate evidence must be agreed and legally binding on all parties, following an agreed protocol". (see point 4 below)*
3.	Scientific terms should be used correctly, as there is potential for misinterpretation. The term "real world evidence" is a euphemism for observational evidence as it comes from observations which always precede experiment and production of empirical evidence.
	Reply: *We agree that scientific terms should be used correctly. "Real-World data" is a term used to describe healthcare-related data that is collected outside of randomised clinical trials. "Real-World Evidence" is used by EMA to mean evidence coming from registries, electronic health records (EHRs), and insurance data either in specific observational studies or through continued monitoring of use, benefits and risks.* *Monitoring the safety and benefit-risks of regulated products is a major part of EMA's mission to protect public health.* *In medicines regulation – pre- and post-authorisation – decisions should be based on experiment and empirical evidence in the form of pivotal trials and real-world observations.* *(Please see also table 2, our reply to comment 8 below)*
4.	Before the use of an adaptive pathway leads to authorisation, any subsequent plan to generate evidence must be agreed and legally binding on all parties, following an agreed protocol. This is because of the need to ensure accountability for the considerable sums of public money which have been invested and will be invested in the process and because of the role that patients will play in the emergence of evidence on drugs that are still being evaluated. This is a form of co-development with great potential benefits, but there is a need for communication of the

	Key ideas for the adaptive pathways concept
	uncertainty involved to those who will be receiving the treatment, who occupy an intermediary position between patients and research subjects.
	Reply: *We agree on all accounts; this is at the heart of the adaptive pathways concept. However, under the existing EU legal framework post-authorisation obligations are only legally binding on the marketing authorisation holders.*
5.	Any adaptive pathways registration should have an initial roll-out plan clearly describing the potential beneficiary population(s) and the factual information on the uncertainty of the pathway to be conveyed to users.
	Reply: *We agree.*
6.	In keeping with the high traditions of EMA, we expect all documents relating to adaptive pathways to be made public expeditiously. This is because your initiative is so far mostly based on interpretation of current problems and their proposed solutions.
	Reply: *We agree. All documents relating to products that will be authorised in keeping with the adaptive pathways concept will be made public as per the current EMA transparency policies.* *A compiled report of the currently ongoing "adaptive pathways pilots" will be published shortly on the EMA website, respecting the "safe harbour" nature of the individual preliminary discussions.*

Table 2

In their letter, the authors list eight assumptions they believe EMA has made. These assumptions are accompanied by comments. The authors support these assumptions and comments with a number of references from the literature. These can be found in the original letter from the authors.

	Perceived assumptions	Authors' comments on perceived assumptions
1.	New drugs & biologics are more effective and safer than existing ones. (new and innovative are synonymous)	The assumptions are not based on any solid evidence. The definition of "innovative" is unclear.
	Reply: *We agree that "innovative" means no more than "new". The term is neutral with respect to whether a given "innovative" product is more (or less) effective and/or safe than existing treatment options. Experience shows that many new products are an improvement over existing therapies but others are not.* *The aim of adaptive pathways is to bring potentially* ***beneficial*** *treatments to the right patient group as early as appropriate [IMI ADAPT SMART]. Therefore, an assessment of the likely benefit over existing treatment options, not of "newness", has to precede a decision to follow adaptive pathways.* *Note that EMA received 60 applications from sponsors for its ongoing adaptive pathways pilot program, but selected only 20. We aim to "pick the winners", in the interest of patients with unmet medical needs.*	
2.	Current mechanisms for market and post market regulation stifle innovation and delay market entry of innovative new drugs. This is bad for all parties.	Fast track registration processes are being applied to drugs that are not first in class and potentially less innovative.
	Reply: *Current drug development and authorisation pathways are less than ideal for some novel products, and patients with a range of serious diseases express a desire for earlier access to beneficial new treatments. Not adapting the current research, authorisation and access path would indeed be bad for those patients who are in urgent need of better treatments. Note that "innovative" is not key, but promise of added benefit is. (see response to #1)* *Analysis of EMA's choice of products for fast-tracking procedures reveals that the decision criterion was* ***sufficient early evidence of relevant patient benefit*** *to justify fast-tracking (see EMA Annual reports 2014 and 2015] and European Public Assessment Reports [EPARs] related to individual products).*	
3.	Early market entry (whether with rapid procedures or with the proposed adaptive licensing - like routes) is beneficial to society.	Early market approval is sometimes associated with a higher rate of post marketing safety warnings. The literature contains a high prevalence of authors with declared conflicts of interest who present findings in a positive light

	Perceived assumptions	Authors' comments on perceived assumptions
	Reply: *Early market entry (whether with rapid procedures or with the proposed adaptive licensing-like routes) is beneficial to patients in need as described above, provided that preference is given to products with sufficient early evidence of benefit (see above).* *An analysis of products authorised in the EU concluded that "Using the Exceptional Circumstances and Conditional Approval procedures does not lead to more post-marketing safety alerts or safety-related withdrawals when used for drugs with unmet medical needs" [Arnardottir et al. Br J Clin Pharmacol. 2011 Sep;72(3):490-9].* *However, it will be important to ensure that robust pharmacovigilance is in place for products authorised through an adaptive pathway, as for all new products. This is because we can and should learn a lot about the benefits and risks of a new medicine in the early post-authorisation period. The EU pharmacovigilance system has recently been extensively strengthened to reinforce safety monitoring and action and new products are authorised with legally binding commitments for studies and risk minimisation.*	
4.	Reversibility: patients who have been on new fast drug X are going to be happy to switch back to old drug Y if X fails regulatory or post-market hurdles and physicians act on post-marketing warnings on harms and restrictions of use.	Once early market entry is achieved on the basis of preliminary evidence, it may be difficult to temper demand, even if the drug is revealed to be less effective or more harmful than initially believed.
	Reply: *We are aware of disappointing experiences in the past; indeed, physicians have not always acted on post-marketing warnings on harms and restrictions of use. However, recent experience with prospectively designed Risk Management Plans shows that, if appropriately managed, restrictions/warnings can be successful.* *[http://www.encepp.eu/encepp/openAttachment/studyResult/13665;* *http://www.encepp.eu/encepp/openAttachment/studyResult/11488.]* *A key component of the adaptive pathways concept is to place particular emphasis on steering prescribing/utilisation to be in line with the state of knowledge about benefits and risks of a medicine.*	
5.	Surrogate outcomes (for which there is no confirmation of a direct link to the clinical outcome of interest) are acceptable.	The current system may be approving many costly, toxic drugs that do not improve overall survival
	Reply: *Experience has shown that while some surrogate outcomes translated into favourable clinical outcomes, others did not. The issue is well recognised but is not peculiar to adaptive pathways.* *A central tenet of adaptive pathways is* ***repeat cycles of evidence generation*** *and assessment. Where applicable, this would include a pre-agreed plan to establish a link to the clinical outcome when a product is initially authorised on the basis of an endpoint that is not of direct clinical relevance to patients.*	

	Perceived assumptions	Authors' comments on perceived assumptions
6.	Current or proposed mechanisms for market and post market regulation are up to changing, reversing or limiting initial bad decisions.	The current system is slow to react even when use of the drug is associated with increased mortality. Post-marketing commitments are not adhered to.
	Reply: *We disagree with the comment on slow reaction of the system. The EU Pharmacovigilance Legislation which came into operation in 2012 has brought about major improvements in the regulators' ability to monitor products on the market and to react fast to incoming signals. Every novel product's launch is now accompanied by a legally binding risk management plan agreed between the sponsor and the regulator.* [http://www.nature.com/nrd/journal/v13/n5/full/nrd3713-c1.html] *We reject the statement that "Post-marketing commitments are not adhered to." An EMA-led study of post-marketing requirements concluded that compliance with the request of the CHMP to conduct [post-marketing] studies is generally very good albeit with some aspects for improvement. [Blake et al. pharmacoepidemiology and drug safety 2011; 20: 1021–1029]*	
7.	"Something is better than nothing" is acceptable.	An inert comparator does not provide sufficient information on the performance of a drug, and may be unethical and also misleading, as placebo controlled trials have rarely been adequately blinded because drugs often have conspicuous side effects.
	Reply: *We do not hold that "Something is better than nothing". It would be unethical and incompatible with the role of regulators to "sell hope instead of help" [Bianco & Sipp. Nature 2014; 510, 336–337]. This is why adaptive pathways places strong emphasis on sufficient early evidence of relevant patient benefit and close monitoring of patient benefit after launch.* *There are many arguments for or against placebo- or active-controlled studies; the adaptive pathways concept is neutral with regards to this issue. We agree with the general comment that many randomised trials have been misleading and RCTs are not an infallible methodology.*	
8.	Our information systems can support the process with unbiased (or minimally biased) up to date information such as observational data	This is just a selection of the enormous body of evidence calling into question the reliability of observational data to test hypotheses (Note: the list of references can be found in the letter)
	Reply: *We are aware that observational studies have produced non-reproducible or contradictory results; however, so have other methodologies, including RCTs. The adaptive pathways concept therefore emphasises the need for planned collection of observational data where evidence from trials may need to be complemented. This collection is based on expert methodological advice and multi-stakeholder input. Furthermore, repeat cycles of evidence generation are emphasized to quickly refine or correct past decisions where needed.*	

	Perceived assumptions	Authors' comments on perceived assumptions
	The adaptive pathways concept holds that the full spectrum of knowledge generation tools should be used to inform decision-making, including RCTs and observational data. When considering the totality of evidence, inferences based on observational studies may need to be more circumspect, in light of the non-randomised nature of study findings.	