Dear Prof. Rasi and Dr. Eichler,

Thank you for developing the idea of adaptive pathways. We think that it is an idea with great potential benefit for society. It is no coincidence that you developed the idea, given the pivotal role your Agency has played in promoting transparency and the potential benefits of data access.

We had a look at some of the assumptions your proposal is based on. This is the list which we came up with:

1. New drugs & biologics are more effective and safer than existing ones (and “new” and “innovative” are synonymous).
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.
3. Early market entry (whether with rapid procedures or with the proposed adaptive pathways - like routes) is beneficial to society.
4. Reversibility: patients who have been on new fast drug X are going to be happy to switch back to old drug Y if drug X fails regulatory or post-market hurdles and physicians act on post-marketing warnings on harms and restrictions of use.
5. Surrogate outcomes (for which there is no evidence of a direct link to the clinical outcome of interest) are acceptable.
6. Current or proposed mechanisms for market and post market regulation are effective in changing, reversing or limiting initial bad decisions.
7. “Something is better than nothing” is an acceptable principle.
8. Our information systems can support the adaptive pathways process with unbiased (or minimally biased) up to date information such as observational data.

The evidence on which these assumptions is based does not seem very convincing to us [Annex A] and there seems to be a lot of uncertainty in their potential operational application. We therefore eagerly await publication of all the documents relating to your adaptive pilot. As drugs are such an important potentially beneficial element of health care, we suggest a few changes and slight modifications to your concept. Most of these ideas come from the highly successful orphan disease area:

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.
2. An assessment schedule based on the Target Product Profile approach must be publicly agreed.
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.
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, there is a need for communication of the uncertainty involved to those who will be receiving the treatment, who occupy an intermediary position between patients and research subjects.
Any misunderstanding may reduce the accruing of potential benefits from your initiative.

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.
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.

We hope that HTA bodies will take notice of the potential benefits of your initiative and set, where possible, appropriate reimbursement commensurate with the quantity and quality of evidence produced. Likewise, we expect that the EMA will duly inform the public of how it has applied sanctions to companies who have failed to comply with post-marketing requirements.

We also hope that the results of your potentially beneficial initiative will be made public, like all science is. We look forward to your reply.

With best wishes (in alphabetical order),

Prof. Silvio Garattini, Director IRCCS - Istituto di Ricerche Farmacologiche Mario Negri, Italy

Peter C. Gøtzsche, Professor, Director, MD, DrMedSci, MSc
Nordic Cochrane Centre, Copenhagen, Denmark

Tom Jefferson MD MSc FFHPM MRCGP,
Honorary Research Fellow, Centre for Evidence Based Medicine, Oxford, United Kingdom

Joan-Ramon Laporte, Director, Fundació Institut Català de Farmacologia (FICF)

Joel Lexchin MD, Professor, School of Health Policy and Management, York University Toronto, Canada

Donald W. Light, Visiting Professor, University of Cambridge

Martin McKee CBE MD DSc FRCP FFPH F MedSci
Professor of European Public Health, London School of Hygiene and Tropical Medicine
London, United Kingdom

Jean-Louis Montastruc, Professor of Medical Pharmacology, Member of the French National Academy of Medicine, University of Toulouse

Sir Richard Thompson, immediate - president, Royal College of Physicians, London, UK

Annex A

Assumptions at the basis of adaptive regulation and selected relevant evidence

Serial	Assumptions	Evidence	Comments
1.	New drugs & biologics are more effective and safer than existing ones. (new and innovative are synonymous)	Djulbegovic et al. New treatments compared to established treatments in randomized trials. Cochrane Database of systematic reviews 2012, Issue 10. Art. no.: mr000024. DoI: 10.1002/14651858.mr000024.pub3. Lexchin. Postmarket safety in Canada: are significant therapeutic advances and biologics less safe than other drugs? A cohort study. BMJ Open 2014;4:e004289. Lexchin. Health Canada's use of its priority review process for new drugs: a cohort study. BMJ Open 2015;5:e006816. New drugs and indications in 2014. Prescrire International 2015;159:132-6. Garattini and Bertele. Efficacy, safety and the cost of new anticancer drugs British Medical Journal, 2002;325:269-271. Garattini and Bertele. Efficacy, safety and cost of new drugs acting on the central nervous system, European Journal of Clinical Pharmacology 2003;59: 79-84. Garattini and Bertele. Efficacy, safety and cost of new cardiovascular drugs: a survey, European Journal of Clinical Pharmacology 2003;59:701-706.	The assumptions are not based on any solid evidence. The definition of "innovative" is unclear
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	Kesselheim et al. Trends in utilization of FDA expedited drug development and approval programs, 1987-2014: cohort study. BMJ 2015;351:h4633. Lexchin. Post-market safety warnings for drugs approved in Canada under the Notice of Compliance with conditions policy. British Journal of Clinical Pharmacology 2015;79:847-859. Naci et al. Raising the bar for market authorisation of new drugs, BMJ 2012;344:e4261. Gambardella et al. *Global Competitiveness in Pharmaceuticals. A European Perspective*. Report Prepared for the Directorate General Enterprise of the European Commission,	Fast track registration processes are being applied to drugs that are not first in class and potentially less innovative

		November 2000**.**	
3.	Early market entry (whether with rapid procedures or with the proposed adaptive licensing - like routes) is beneficial to society.	Lexchin J. Post-market safety warnings for drugs approved in Canada under the Notice of Compliance with conditions policy. British Journal of Clinical Pharmacology 2015;79:847-859. Valiyeva et al. Effect of regulatory warnings on antipsychotic prescription rates among elderly patients with dementia: a population-based time-series analysis. CMAJ 2008;179:438-46. Friedman et al. Relationship between conflicts of interest and research results. Journal of General Internal Medicine 2004;19:51-56. Als-Nielsen et al. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events? JAMA 2003;290:921-8.	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
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.	Prasad. Translation failure and medical reversal: Two sides to the same coin, European Journal of Cancer, 2016; 52: 197-200 Prasad et al. A Decade of Reversal: An Analysis of 146 Contradicted Medical Practices, Mayo Clin Proc, 2013; 88(8):790-798 Tatsioni et al. Persistance of contradicted claims in the literature, JAMA 2007; 298(21):2517-2526 Smalley et al. Contraindicated use of cisapride: impact of Food and Drug Administration regulatory action. JAMA 2000; 284: 3036–9. Willy et al. A study of compliance with FDA recommendations for pemoline (Cylert). J Am Acad Child Adolesc Psychiatry 2002: 41: 785–90. Graham et al. Liver enzyme monitoring in patients treated with troglitazone. JAMA 2001; 286: 831–3. 69. Graham et al. Troglitazone induced liver failure: a case study. Am J Med 2003; 114: 299–306. Darrow et al. New FDA Breakthrough-Drug Category — Implications for Patients. N Engl J Med 2014; 370:1252-1258.	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.
5.	Surrogate outcomes (for which there is no confirmation of a direct link to the clinical outcome	Svensson et al. Surrogate outcomes in clinical trials: a cautionary tale. JAMA Internal Medicine 2013;173:611-12. Kim et al. Cancer Drugs Approved on the Basis of a Surrogate End Point and Subsequent	The current system may be approving many costly, toxic drugs that do not improve overall survival

	of interest) are acceptable.	Overall Survival: An Analysis of 5 Years of US Food and Drug Administration Approvals. JAMA Internal Medicine 2015;175:1992-4. Echt et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the Cardiac Arrhythmia Suppression Trial. N Engl J Med. 1991;324(12):781-788. Barter et al. ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med. 2007; 357(21):2109-2122. IQWiG. Validity of surrogate endpoints in oncology: executive summary. IQWiG Reports. Cologne: IQWiG, 2011. Fleming and Powers. Biomarkers and Surrogate Endpoints In Clinical Trials. Statistics in medicine. 2012;31(25):2973-2984. doi:10.1002/sim.5403. Fleming. Surrogate Endpoints and FDA's Accelerated Approval Process Health Aff January 2005 vol. 24 no. 1 67-78 Krumholz and Lee. Redefining Quality – Implications of Recent Clinical Trials N Engl J Med 2008; 358:2537-2539 Floyd and Psaty. The Potential Risks of Expedited Approval of Drugs for Acute Bacterial Infections. JAMA Intern Med. 2014;174(9):1436-1437. doi:10.1001/jamainternmed.2014.3055. Yudkin et al. The idolatry of the surrogate BMJ 2011; 343:d7995 Prasad et al. The Strength of Association Between Surrogate End Points and Survival in Oncology: A Systematic Review of Trial-Level Meta-analyses. JAMA Intern Med. 2015;175(8):1389-1398. doi:10.1001/jamainternmed.2015.2829. Tzoulaki et al. JPA. 2013. Bias in associations of emerging biomarkers with cardiovascular disease. JAMA Intern. Med. 173(8):664–71 Ciani et al, Comparison of treatment effects sizes associated with surrogate and final patient relevant outcomes in randomised controlled trials, BMJ 2013; 346:f457;	

		Ioannidis et al. Comparison of effect sizes associated with biomarkers reported in highly cited individual articles and in subsequent meta-analyses. JAMA 305(21):2200–10 Gøtzsche et al. Beware of surrogate outcome measures. Int J Technol Ass Health Care 1996;12:238-46.	
6.	Current or proposed mechanisms for market and post market regulation are up to changing, reversing or limiting initial bad decisions.	Darrow et al. New FDA Breakthrough-Drug Category —Implications for Patients. New England Journal of Medicine 2014;370:1252-8. Moore and Furberg. "Electronic Health Data for Postmarketing surveillance: a vision not realized" Drug Saf 2015; 38:601–610. Fain et al. The food and Drug Administration Amendments Act and Postmarketing Commitments. JAMA 2013; 310 (2): 202-4. Onakpoya et al. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. BMC Medicine (2016) 14:10. Seife. Research misconduct Identified by the US Food and Drug Administration. Out of sight, out of mind, out of the PeerReviewed Literature. JAMA Intern Med. 2015; 175(4):567-577.	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.
7.	"Something is better than nothing" is acceptable.	Goldberg et al, Availability of comparative efficacy data at the time of drug approval in the United States JAMA 2011;305:1786-9 Van Luijin et al Superior efficacy of new medicines? Eur J Clin Pharmacol 2010;66:445-6 Misbin. Comment on the Ethics of Placebo-Controlled Trials in Patients with Type 2 Diabetes Mellitus', The Journal of Clinical Endocrinology & Metabolism, 1996;84(2): 823. Hróbjartsson et al. Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non- blinded outcome assessors. BMJ. 2012; 344: e1119.	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.
8.	Our information systems can support the process with unbiased (or minimally biased) up to date information such as observational	Woodcock. Evidence vs. Access: Can Twenty-First-Century Drug Regulation refine the Trade-offs? Clin Pharm & Therapeutics 2012;91(3):378-80. Tuccori et al. Pioglitazone use and risk of bladder cancer: population based cohort study, BMJ 2016;352:i541 Montori. Selecting the right drug treatment for	This is just a selection of the enormous body of evidence calling into question the reliability of observational data to test hypotheses

	data	adults with type 2 diabetes, BMJ 2016;352:i1663 Moore and Furberg. “Electronic Health Data for Postmarketing surveillance: a vision not realized” Drug Saf 2015; 38:601–610. Hemkens et al. Agreement of treatment effects for mortality from routinely collected data and subsequent randomized trials: meta-epidemiological survey. BMJ. 2016 Feb 8;352:i493.	