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Press Release

EMA's report on adaptive pathways: little data and much ado about nothing

The European medicines agency (EMA) launched its controversial “adaptive pathways” pilot project in 2014, with its main advocates writing profusely about its promises and the fact that it would revolutionize medicines’ evaluation and approval. The concept consists in letting drugs onto the market as soon as possible, based on results from surrogate end points obtained during stage 2 clinical trials, and to complement the clinical assessment with “real world data”, i.e. patients’ experiences. Such a process involves consultations with patient representatives and drug companies, as well as early parallel scientific advice from the EMA and health technology assessment agencies.

Many expected to see data from the experience gained with the pilot. EMA announced its report for 2015 and postponed its release several times, with some sources mentioning autumn 2016 as a likely date. It was published on August 3rd (1), just a few days before a very critical article on adaptive pathways was published by the *BMJ* in which the authors argue that EMA made neither a scientific nor an ethical issue for adaptive pathways (2).

Strong hints at disappointing results

This report includes little to no new factual data. No information is shared about the drugs’ indications, the type of clinical trial data to be submitted, or which patient representatives were consulted. The agency notes that among the seven pilot proposals considered, “...*some did not progress beyond the initial discussions because the subsequent scientific advice on more detailed protocols cast doubt on the feasibility and methodological robustness of the development plan.*” (page 3)

A safe harbour for manufacturers; rocky seas for the public

Despite this strong hint at failure, no further information is provided. The agency claims that, “*Discussions on a possible adaptive pathways approach in the pilot have taken place at the early stages of medicine development (i.e. Phase I and II), and as is the case for all scientific*

advice discussions, deal with commercially sensitive information. This report does therefore not contain detailed information on the products and issues discussed in the “safe harbour setting”; “(page 9). In other words, the report provides no information to allay any public concerns about the weaker standards for market approval under “adaptive pathways”.

EMA highlights inadequacies of proposed ‘real world’ evidence

An especially controversial aspect of “adaptive pathways” is greater reliance on “real world data” (a euphemism for observational studies at best and probably other data with lesser level of evidence), rather than more rigorous randomised controlled trials, which are the scientific standard. The EMA’s report contains no further details about how these studies are to be designed. The only comments on the industry’s plans are far from reassuring: *“The majority of the plans were vague in terms of the purpose of collection of real world data to supplement RCTs, and on the practical elements for implementation there was insufficient detail in the submitted proposals to explore the refinement of the safety profile, and even less about to what extent efficacy could be confirmed or augmented in the post-authorisation phase. A critical discussion on the quality, potential for bias, and reliability of the data acquired in the post authorisation setting, and their suitability for regulatory and HTA [Health Technology Assessment] purpose, was lacking. The few submitted proposals relied mostly on a traditional registry paradigm, geared towards the confirmation of conditional marketing authorisation or the reimbursement/effectiveness link”.* (page 14).

Burdensome and resource-intensive for both the EMA and HTAs

Another key point of the adaptive pathway project is to involve HTAs in the provision of parallel scientific advice. But HTAs do not seem that enthusiastic: *“Generally, HTAs which had the conceptual interest and the resource capability engaged in the pilot once approached by the company, but the fit within existing mechanisms and procedures has proven burdensome in terms of resources (both for EMA and HTAs), due to the number of simultaneous applications received, the concomitant pressure on resources exercised by the dramatic increase in the volume of parallel regulatory-HTA scientific advice requests in the same time period, and the flexible and iterative nature of the discussions, which was difficult to accommodate into streamlined existing workflows.”* (page19). Some HTA bodies have openly rejected basing their evaluations on unreliable data (3) . Yet that is not mentioned in the EMA report.

With next to no returns...

The EMA further notes that, "...*The aim of adaptive pathways is to design development plans that support regulators' benefit-risk assessments and HTA bodies' assessment of value. However, the submission of plans on value proposition and reimbursement strategies has been limited in most cases.*" (page 20).

Reading between the EMA's lines -- in the absence of any real information -- the pilot is clearly a failure and should be retracted. If "commercial sensitivities" prevent detailed reporting to the public, it is doubly a failure. **No fundamental shift to regulation should be based on such secrecy.**

References:

- 1- European Medicines Agency "Final report on the adaptive pathways pilot" 28 July 2016. EMA/276376/2016: 23 pages. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/08/news_detail_002586.jsp&mid=WC0b01ac058004d5c1
- 2- Davis C, Lexchin J, Jefferson T, Gøtzsche P, McKee M. "Adaptive pathways" to drug authorisation: adapting to industry? *BMJ* 2016;354:i4437.
- 3-IQWiG "Adaptive pathways: EMA still leaves open questions unanswered" 9 August 2016. Available at: <https://www.iqwig.de/en/press/press-releases/press-releases/adaptive-pathways-ema-still-leaves-open-questions-unanswered.7492.html>

About the organisations:

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 pharmaceutical industry. Currently ISDB has around 80 members in 41 countries around the world. More info: www.isdbweb.org; Contact: info@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 **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