## Drug evidence watch: a process to the benefit of public health

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Medicines regulators, such as the UK MHRA and the European Medicines Agency, have statutory duties to ensure the safety, quality and efficacy of medicines, medical devices, and blood products. To do this, and to safeguard the health of the population, drug regulators are alert to safety signals for licensed medicines. Pharmacovigilance systems monitor and act on new data as it emerges, regardless of data provenance (whether from company-sponsored studies or from non-company sources) 1. However, this effective monitoring process does not capture data showing efficacy in new medical uses for existing medicines. We propose that regulators institute a ‘drug evidence watch’ process to track emerging data showing efficacy of drugs in new indications. Where pharmacovigilance can lead to label changes, we suggest that the drug evidence watch includes a form of ‘efficacy vigilance’ that could lead to label extension.

Currently, the monitoring of efficacy data for new indications of a licensed drug is fully dependent on the drug companies. This situation creates two major issues when data supporting a new indication are developed by other actors. First, because only a marketing authorisation holder (MAH) can file for label extension (a form of type II variation), this requires the transfer of data from non-company studies to companies, for example adult pemphigus vulgaris was added to the label for rituximab after the transfer of clinical trial data from the academic sponsor to the MAH 2. Although companies may not have been involved in how these data were generated, they must take full responsibility for them – a risky situation from their perspective. Second, assuming the successful transfer of data, the company will also need to decide whether submitting a type II variation is financially sound and consonant with their commercial strategy. These decisions are mainly based on the projected revenue for the new indication versus the costs associated with the type II variation 3. The costs are related to the filing of the application (e.g. €94k for the application to EMA) and the workload to generate the application dossier, to the potential request by regulators to generate additional evidence, and to additional company workload if the extension of indication is granted.

The projected revenue for new indications incorporates data on two key parameters: disease prevalence and remaining patent life. Rare diseases and off-patent drugs are therefore negatively affected by the low, or very low, projected revenue. In a welcome attempt to correct for this bias in the context of an emergency, EMA announced in September 2020 (3 months after the results of the RECOVERY dexamethasone arm) that it was endorsing the use of dexamethasone in COVID19 patients on oxygen or mechanical ventilation, though EMA could not do anything to change the label 4. In the UK, the MHRA had invited MAHs for dexamethasone to apply for type II variation.

There are instances where new indications for off-patent drugs do end up on label, but this is patchy and unpredictable. For example, acute idiopathic pericarditis is on-label for colchicine in France but not the UK, and bleeding trauma is on the label of tranexamic acid in Pakistan but nowhere else, (in the UK it used off-label following a NICE evidence summary for the use of unlicensed and off-label medicines). For dexamethasone and COVID19, EMA’s statement might have been instrumental in adding COVID19 on the label of some of the dexamethasone products available. In the UK, 14 of 26 eligible dexamethasone products had labels updated to include COVID19. In the cases of colchicine, tranexamic acid and dexamethasone, evidence comes from well-conducted academic randomised controlled trials 5–7.

We believe that a regulatory pathway to label extension for off-patent drugs, at the EMA and MHRA, should be explicitly outlined so that it can be applied when new efficacy evidence emerges. Detailed guidance documents, including the level of evidence and type of data needed to submit, would frame the process. Level of evidence could include guidance on the type of trial and the most appropriate end-points required in the new indication, it may also clarify the use of case series or registries in ultra-rare diseases for example. Types of data required may indicate situations in which new safety data is warranted or cover the use of animal model data for the drug in the new indication.

This would effectively be a public-interest label extension pathway. The aim would be to create the conditions whereby a MAH would find it conducive to apply for a type II variation for an extension of indication. For example, the pathway may lead to preparatory work on producing evidence dossiers, collecting data, undergoing scientific advice, and generating fee-reductions for the label extension application. It would make the process of applying for a label extension as efficient and as low-cost as possible for the MAH. Other forms of incentive could also be explored, for example tax breaks or fee reductions for other regulatory services.

Identifying new medical uses could be ‘outsourced’ to non-commercial third parties such as scientific/medical societies or collaborative groups. We hypothesize that, with a pathway in place, these third parties would endeavour to ensure that the trials they support and/or conduct lead to the greatest access and impact for patients. The EMA and MHRA would simply need to apply the processes they currently have in place for type II variations for extension of indication.

While off-label use of a medicine may be appropriate in some circumstances 8, in general it has several drawbacks including liability issues, problems with reimbursement and lack of prospective data collection 9. There may also be supply issues when a drug is no longer used for its original indication. A drug evidence watch process that incorporates label extension would address these issues. This would result in improving access to new and efficacious treatments and may also lead to health system savings as many of the drugs are available at low cost. In the long-term, it will greatly lessen the problem of off-label use, which is unintentionally exacerbated by the current regulation.

While several examples currently exist, we highlight three test cases for this pathway: Tranexamic acid for trauma victims 10; Rituximab for multiple sclerosis 11; Sorafenib for post-transplant maintenance in FLT3-ITD AML 12,13.

It may be argued that our proposal will ultimately benefit the MAHs, who may benefit financially from the work of academics, clinicians and regulators in producing the evidence to support the addition of new indications for existing medicines. However, in many cases the repurposed drugs are widely available as generics, at relatively low cost, and the additional revenue will be slight, particularly for rare diseases. The main beneficiaries will be patients and health systems able to access new treatments to meet existing unmet needs.

Recent regulatory developments in the context of post-COVID pandemic planning are supportive of what we propose. The role of the EMA has been reinforced in crisis preparedness using new regulations 14. Article 18 includes provision for the EMA to request information and data from MAHs, and to make use of additional health data generated from outside of clinical studies. This is effectively a drug evidence watch process in the context of a pandemic. It enables a more proactive EMA role in ensuring citizens get access to safe and effective drugs. Such measures may appear commensurate with pandemic health emergencies, but there are also very high unmet needs in other areas of medicine that are deserving of urgent regulatory solutions. We fear that safe and effective new treatments using existing licensed medicines may languish and remain inaccessible to patients unless we also innovate in regulatory pathways. Our proposal requires no major change to pharmaceutical legislation or regulation, instead it refines existing pathways to deliver an easily implemented change that can potentially unlock new treatments for patients in need.

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*We declare no competing interests.*

1 Guideline on good pharmacovigilance practices (GVP) - Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). ; : 144.

2 European Medicines Agency,. MabThera Assessment Report. (2019). https://www.ema.europa.eu/en/documents/variation-report/mabthera-h-c-165-ii-150-epar-assessment-report-variation\_en.pdf (accessed March 15, 2023).

3 Hernandez JJ, Pryszlak M, Smith L, *et al.* Giving Drugs a Second Chance: Overcoming Regulatory and Financial Hurdles in Repurposing Approved Drugs as Cancer Therapeutics. *Front Oncol* 2017; **7**: 273.

4 EMA. EMA endorses use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation. Eur. Med. Agency. 2020; published online Sept 18. https://www.ema.europa.eu/en/news/ema-endorses-use-dexamethasone-covid-19-patients-oxygen-mechanical-ventilation (accessed Dec 6, 2022).

5 CRASH-2 collaborators, Roberts I, Shakur H, *et al.* The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet Lond Engl* 2011; **377**: 1096–101, 1101.e1-2.

6 Adler Y, Charron P, Imazio M, *et al.* 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2015; **36**: 2921–64.

7 RECOVERY Collaborative Group, Horby P, Lim WS, *et al.* Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021; **384**: 693–704.

8 Ladanie A, Ioannidis JPA, Stafford RS, Ewald H, Bucher HC, Hemkens LG. Off-label treatments were not consistently better or worse than approved drug treatments in randomized trials. *J Clin Epidemiol* 2017; published online Nov. DOI:10.1016/j.jclinepi.2017.11.006.

9 Verbaanderd C, Rooman I, Meheus L, Huys I. On-Label or Off-Label? Overcoming Regulatory and Financial Barriers to Bring Repurposed Medicines to Cancer Patients. *Front Pharmacol* 2019; **10**: 1664.

10 Roberts I, Shakur-Still H. Tranexamic acid for trauma in the USA: is prejudice a barrier to saving lives? *The Lancet* 2022; **399**: 1675–7.

11 Svenningsson A, Frisell T, Burman J, *et al.* Safety and efficacy of rituximab versus dimethyl fumarate in patients with relapsing-remitting multiple sclerosis or clinically isolated syndrome in Sweden: a rater-blinded, phase 3, randomised controlled trial. *Lancet Neurol* 2022; **21**: 693–703.

12 Xuan L, Wang Y, Huang F, *et al.* Sorafenib maintenance in patients with FLT3-ITD acute myeloid leukaemia undergoing allogeneic haematopoietic stem-cell transplantation: an open-label, multicentre, randomised phase 3 trial. *Lancet Oncol* 2020; **21**: 1201–12.

13 Burchert A, Bug G, Fritz LV, *et al.* Sorafenib Maintenance After Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia With FLT3-Internal Tandem Duplication Mutation (SORMAIN). *J Clin Oncol Off J Am Soc Clin Oncol* 2020; **38**: 2993–3002.

14 Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices (Text with EEA relevance). 2022 http://data.europa.eu/eli/reg/2022/123/oj/eng (accessed Dec 7, 2022).