

MAKING **MEDICINES AUTHORISATION PROCEDURES** WORK FOR PATIENTS



APPROVAL PATHWAYS

The study “Approval of cancer drugs with uncertain therapeutic value: a comparison of regulatory outcomes in Europe and the United States” by Salcher-Konrad et al.¹, compares outcomes of medicines marketing authorisation procedures for the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) for 21 cancer-drug pairs.

Both the EMA and FDA can opt for a conditional approval pathway that requires the collection of additional evidence. These are called Conditional Marketing Authorisation and Accelerated Approval, respectively. The authors highlight several issues with these procedures. Based on these findings and our previous and current work on pharmaceutical research & development (R&D), transparency and market authorisation requirements, Health Action International (HAI) has developed a set of policy recommendations.

These recommendations aim to promote transparency and high standards for evidence on medicines marketing authorisation procedures, which would ultimately lead to better quality medicines with real added therapeutic value.

ADDED THERAPEUTIC VALUE

A systematic evaluation of EMA oncology approvals in 2009–2013, showed that evidence of clinically relevant therapeutic value on survival or quality of life was submitted for only a small number of (regularly and conditionally) approved cancer drugs². Instead, many clinical trials used surrogate endpoints, such as response rate endpoints, progression-free survival (PFS) or recurrence-free survival. Where studies did find there was a benefit to quality of life and survival—compared to existing treatments or a placebo—it was, in many cases, doubtful whether this benefit was clinically meaningful.

We need more safeguards to ensure pharmaceutical companies evaluate their products in a meaningful way.

- The design of cancer drug trials should be improved to ensure they involve relevant endpoints related to quality of life and survival.
- Companies should conduct research to better understand which outcomes are clinically meaningful for patients.
- Companies should compare their outcomes, not merely with a placebo, but with most effective existing treatments to ensure we know that the product truly adds to the medicine market.

AUTHORISATION STANDARDS SHAPING THE MEDICINES MARKET

Approval standards vary between the EMA and FDA, illustrated by the often-differing responses to applications for the same medicine.¹ In 57% of the 21 investigated cancer-drug pairs, the drug received conditional approval by one agency and regular approval by the other. However, there was great overlap in the pivotal trials that formed the basis for regulatory decisions, with the same evidence being used in 81% of the 21 pairs. Also, evidence standards seem to have decreased, with EMA and FDA more often granting regular access to medicines with limited data on efficacy and safety. The fact that single-arm studies and studies using surrogate endpoints more often result in regular drug approval creates an environment that incentivises pharmaceutical companies to apply for market authorisation for medicines with limited proven effectiveness.

What this means is that currently pharmaceutical companies are not developing medicines with most clinical value to patients, but instead are developing medicines designed primarily to meet the regulatory evidence standards needed to be approved for market authorisation.

The inconsistency in authorisation decisions between the EMA and FDA and diluting evidence standards are of serious concern.

- EMA and FDA should show more caution when granting regular access to a medicine and take into account that chances are high that no research will take place post-authorisation.
- Regular approval should only be granted if there is strong evidence that the medicine is safe, effective, and offers benefits compared to current treatment options.

TRANSPARENCY IN CLINICAL TRIAL REPORTING

In October 2018, the EMA issued the Access to Documents Policy (policy 0043) to promote transparency and public access to all documents originated, received or held by the EMA³. This was the first time a medicines agency had taken the initiative to provide public access to reports of clinical studies.

At the moment, the EMA is facing multiple challenges to this policy. In particular, the 2018 case of PTC Therapeutics International versus EMA is currently reopening the conversation: a recent opinion issued by the Court of Justice of the European Union's Advocate General Hogan on this case supports the presumption of commercial confidentiality, which puts at risk the hard-won transparency of clinical trial data⁴.

Transparency will allow for thorough scrutiny of study quality and risks of bias, and will allow for uptake and use of new knowledge by others. This prevents the unnecessary duplication of costly studies both in terms of public resources and human costs.

- Companies and research institutions should make the reports of all their clinical trials, including all relevant information on the design, development and results (including Clinical Studies Reports) publicly and easily available.
- The 'Access to Documents' policy of the EMA is a significant step but the organisation should protect the spirit of this policy and make concrete steps towards a more proactive implementation.

NEXT STEPS

HAI will work to promote the recommendations of this report as part of our mission to ensure access to medicines for everyone, everywhere.

REFERENCES

1. M Salcher-Konrad, H Naci and C Davis. Approval of cancer drugs with uncertain therapeutic value: a comparison of regulatory decisions in Europe and the United States. The Milbank Quarterly 2020. doi:10.1111/1468-0009.12476 .
2. C Davis, H Naci , E Gurpinar, et al. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals. 2009-13. BMJ 2017; 359: j4530.
3. EMA. European Medicines Agency policy on access to documents. October 2018. Via: https://www.ema.europa.eu/en/documents/other/policy/0043-european-medicines-agency-policy-access-documents_en.pdf
4. InfoCuria Case-law. Case T-718/15. February 2018. Via: <http://bit.ly/2Z2lgcy>

OTHER RESOURCES

- HAI report on 'Clinical Trials in the European Union: A Roadmap to Greater Transparency'. Available here: <https://haiweb.org/publication/clinical-trials-transparency/>
- Report of HAI/TranspariMED event at the European Parliament on clinical trial transparency, November 2019. Available here: <https://haiweb.org/clinical-trial-transparency/>
- HAI blog on bias in clinical trials supporting approvals of new cancer trials, September 2017. Available here: <https://haiweb.org/cancer-drug/>
- HAI response to EU Ombudsman consultation on EMA engagement with manufacturers for marketing of medicines, January 2019. Available here: <https://haiweb.org/publication/ema-engagement-with-manufacturers-marketing-medicines/>

For more information: +31 (0) 20 412 4523 – jaume@haiweb.org – **HAIWEB.ORG**



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