Medicinal products receiving expedited approval in Europe may not provide intended clinical benefit

September 10 2019

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The approval of new pharmaceutical products addressing an unmet need or public interest may be speeded up if medicine regulators at the European Medicines Agency agree to assess them through expedited assessment pathways, including conditional marketing authorization (CMA) and accelerated assessment (AA). In the pivotal trials supporting products assessed by expedited pathways, surrogate endpoints (e.g., those based on a blood test or a radiological change) reduce drug development time compared with waiting for the intended clinical outcomes (i.e., benefits in how patients feel or function or how long they survive). However, it is not known how often regulatory approval is based on a surrogate endpoint instead of a clinical outcome, or how accurately the surrogate endpoints used in pivotal trials correspond to improvement in clinical outcomes. To address this gap in knowledge, McGettigan and colleagues used European Public Assessment Reports (EPARs) to identify the primary endpoints in the pivotal trials supporting products authorized through CMA or AA pathways from 2011 through 2018.

Most of the expedited approvals studied (46/51, 90%) were based on surrogate endpoints, none of which has been shown to reliably predict clinical outcomes (i.e., non-validated surrogate endpoints). Among a total of 49 products with surrogate endpoints reported, most were rated as being reasonably likely (n=30, 63%) or of having biological plausibility (n=45, 94%) to predict clinical outcomes. The information provided by the regulator for prescribers and patients did not consistently explain that the approval for the product was based on trials that reported surrogate endpoints rather than clinical outcomes.

The authors note that these findings apply to just two expedited pathways and may not be generalizable to products authorized through the standard pathway. Still, according to the authors, EPARs and summary product characteristic documents, including patient information leaflets, need to state consistently the nature and limitations of endpoints in pivotal trials supporting expedited authorizations so that prescribers and patients appreciate shortcomings in the evidence about actual clinical benefit. For products supported by non-validated surrogate endpoints, postauthorisation measures to confirm clinical benefit should be imposed by the regulator on the marketing authorisation holders.

More information: Schuster Bruce C, Brhlikova P, Heath J, McGettigan P (2019) The use of validated and nonvalidated surrogate endpoints in two European Medicines Agency expedited approval pathways: A cross-sectional study of products authorised 2011-2018. *PLoS Med* 16(9): e1002873. doi.org/10.1371/journal.pmed.1002873