Supplemental Online Content

Shahzad M, Naci H, Wagner AK. Association between preapproval confirmatory trial initiation and conversion to traditional approval or withdrawal in the FDA accelerated approval pathway. *JAMA*. doi:10.1001/jama.2023.0625

eAppendix

This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix

Sample and Data Sources

We used an FDA database of indications with accelerated approval between September 2002 and December 2018 including information about the indication, the date of accelerated approval and the status of the approval (indication confirmed/withdrawn/not yet converted) on December 31st 2021.[1] We then linked each approval to the Drugs@FDA[2] database which publishes the accompanying approval letter with details regarding whether a protocol has already been submitted for the confirmatory trial and what the date for the final report submission to the FDA will be. We were able to complete this exercise for all but 4 approvals. We further dropped 6 approvals related to levofloxacin (Levaquin) since there were no confirmatory trial requirements for those applications. We then used the information in the approval letters to match approvals to confirmatory trials from ClinicalTrials.gov[3] (detailed algorithm for matching provided below). We were able to find at least 1 confirmatory trial for all indications except 3 in ClinicalTrials.gov. For these indications, Google searches suggested that trials had not been initiated at time of approval.

Algorithm used for mapping confirmatory trial requirements to clinical trials in ClinicalTrials.gov

1) When the National Clinical Trial ID (NCTID) was provided in the approval letter, it was used to match confirmatory trial requirements to clinical trials in ClinicalTrials.gov.
2) When NCTID was not provided but name of trial or protocol number was provided, we searched ClinicalTrials.gov to identify the corresponding study.
3) When no identifying information was provided, we used characteristics listed in the approval letter to match to clinical trials in ClinicalTrials.gov. We ensured that treatment arms, randomization, and phase (if provided) were identical. When there were multiple matches, we used patient numbers and start and end dates to guide selection.
4) If still not conclusive, we used labels of confirmed indications to identify new information added on the date of the confirmation. We considered that new information to be coming from the confirmatory trial and used that information for steps 1-3.
5) If still not conclusive, we searched Google for any confirmatory trial information and used that for steps 1-3.
6) The trial start date associated with each NCTID record was considered the start date of the trial. An indication was considered to not have a confirmatory trial started pre-approval if any of the confirmatory trials had starting months later than the month of the accelerated approval.

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[1] FDA. CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint. Accessed September 12, 2022. https://www.fda.gov/media/151146/download
[2] Drugs@FDA: FDA-Approved Drugs. Accessed September 12, 2022. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
[3] Home - ClinicalTrials.gov. Accessed October 11, 2022. https://clinicaltrials.gov/ct2/home