# Study examines reasons for delay, denial of new drugs by FDA

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Several potentially preventable deficiencies, including failure to select optimal drug doses and suitable outcome measures for a study, accounted for significant delays in the approval of new drugs by the Food and Drug Administration (FDA), according to a study in the January 22/29 issue of *JAMA*.

"The road from medical product discovery to marketing is typically long and costly. The interval between initial clinical testing and product approval has been estimated to average 8 years and only 1 in 6 drugs entering clinical trials ultimately obtains U.S. Food and Drug Administration approval," according to background information in the article. Many drugs do not receive approval not because they are unsafe or ineffective, but because the information supplied is unsatisfactory to make that determination. Delays and failures that occur late in development affect the availability of innovative new drugs and increase the costs of drug development.

Leonard V. Sacks, M.B.B.Ch., of the U.S. Food and Drug Administration, Silver Spring, Md., and colleagues reviewed marketing applications for all new molecular entities (NMEs; active ingredients never before marketed in the United States in any form) first submitted to the FDA between 2000 and 2012. Using FDA correspondence and reviews, the researchers investigated the scientific and regulatory reasons approval of NMEs were delayed or denied.

Of the 302 identified NME applications, 151 (50 percent) were

approved when first submitted and 222 (73.5 percent) eventually achieved marketing approval. Of the 151 first-cycle failures, 71 (47.0 percent) eventually obtained approval in a median (midpoint) of 435 days following the first unsuccessful submission.

Among the reasons for failure to initially receive approval:

- Uncertainty about the optimal dose to maximize efficacy and to minimize safety risks;
- Populations that were studied did not reflect the populations likely to use the drug;
- End points used in clinical trials were unsatisfactory;
- Inconsistent results for multiple predefined end points in clinical studies;
- Inconsistencies in efficacy for portions of the study population.

There were 20 drugs (13.2 percent) that despite showing superiority to placebo were considered to have inadequate efficacy compared with the standard of care.

The frequency of safety deficiencies was similar among never-approved drugs compared with those with delayed approval. However, efficacy deficiencies were significantly more frequent among the never-approved drugs than among those with delayed approvals. Among the 48 drugs with initial efficacy concerns alone, only 31.3 percent were eventually approved compared with 61.5 percent of the 39 drugs with safety concerns alone.

"Failures late in drug development are costly, often involving the commitment of many study participants and personnel. It is advantageous to identify products that fail as early as possible in the development process to avoid these issues. For those drugs that require resubmission before approval is obtained, delays are taxing on the

industry and regulators, and patients may have to wait for access to promising, and sometimes lifesaving, new treatments," the authors write.

"Our findings may be helpful to clinicians and policy makers in interpreting the extensive literature reporting the design and outcome of clinical trials, which in turn may have an effect on practice. For drug developers and clinical investigators, our findings suggest areas of deficiencies in new drug applications in which strategies for drug development could be improved. Early and frequent dialogue between the FDA and drug sponsors addressing critical aspects of study design (including the selection of study populations, study end points, and drug doses) has the potential to reduce delays in the approval of new drugs."

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