Study examines FDA influence on design of pivotal drug studies

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An examination of the potential interaction between pharmaceutical companies and the U.S. Food and Drug Administration (FDA) to discuss future studies finds that one-quarter of recent new drug approvals occurred without any meeting, and when such meetings occurred, pharmaceutical companies did not comply with one-quarter of the recommendations made by the FDA regarding study design or primary outcome, according to a study in the November 26 issue of *JAMA*.

To enhance protocol quality, federal regulations encourage but do not require meetings between pharmaceutical companies and the FDA during the design phase of pivotal studies assessing drug efficacy and safety for the proposed indication. These meetings often generate FDA recommendations for improving research, although companies are not bound to follow them, according to background information in the article.

Steven Woloshin, M.D., M.S., of the Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, N.H., and colleagues reviewed and analyzed approximated 200 FDA documents (memos; meeting minutes; filing checklists; and medical, statistical, and summary reviews) for 35 new drugs approved between February 1, 2011, and February 29, 2012. The researchers identified all FDA comments and analyzed recommendations about pivotal study design or primary outcomes and characterized the effect of recommendations on study quality.

Of 35 new drug approvals, companies met with the FDA to discuss

pivotal studies for 28. The FDA made 53 recommendations about design (e.g., controls, doses, study length) or primary outcome for 21 approvals. Fifty-one recommendations were judged as increasing study quality (e.g., adding controls, blinding, or specific measures and frequency for toxicity assessments, lengthening studies to assess outcome durability) and two as having an uncertain effect. Companies complied with 40 of the 53 recommendations. Examples of non-compliance include a request for randomized trials of brentuximab and crizotinib, but the companies conducted uncontrolled studies. Other cases included primary outcome choice (e.g., progressionfree instead of overall survival) and drug (active comparator) doses tested.

Companies can also request FDA review of pivotal trial protocols. If FDA endorses the protocol it agrees not to object to any study design issues when reviewing the drug for approval. Companies requested protocol review for only 21 of the 35 new drug approvals - and FDA endorsed the protocol for 12.

The authors write that instituting mandatory FDA review of pivotal trial protocols with the power to issue binding recommendations could be an effective way to optimize study quality. They believe that such review may be even more important with increasingly flexible approval pathways. "An independent FDA-commissioned report suggested that stronger early FDA involvement could avoid deficiencies that delay approval of effective drugs and more clearly identify ineffective or harmful ones."

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