FDA News

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FDA, European Medicines Agency to Consider Additional Test Results When Assessing New Drug Safety

Collaborative effort by FDA and EMEA expected to yield additional safety data

In the first use of a framework allowing submission of a single application to the two agencies, the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) worked together to allow drug companies to submit the results of seven new tests that evaluate kidney damage during animal studies of new drugs. The tests measure the levels of seven key proteins or "biomarkers" found in urine that can provide additional information about drug-induced damage to kidney cells, also known as renal toxicity.

The new biomarkers are KIM-1, Albumin, Total Protein, β2-microglobulin, Cystatin C, Clusterin, and Trefoil Factor-3. For decades, both FDA and EMEA have required drug companies to submit the results of two blood tests, called blood urea nitrogen (BUN) and serum creatinine, to evaluate renal toxicity. In addition to those tests, the FDA and EMEA will now consider results from the seven new tests as part of their respective drug review processes. Although a decision by the sponsor to collect information using the new tests is voluntary, if collected, it must be submitted to FDA.

"The development of these and other biomarkers can result in important tools for better understanding the safety profile of new drugs," said Janet Woodcock, M.D., director of FDA's Center for Drug Evaluation and Research. "We hope these biomarkers will lead to human tests that detect drug-induced kidney injury in people earlier than is now possible, and help health care professionals better manage potential kidney damage from drugs."

Woodcock added that such human tests could one day open the door to the approval of more powerful drugs, especially for diseases where renal toxicity currently prevents promising experimental drugs from being approved. With more sensitive tests for renal toxicity, FDA could approve such drugs because health care professionals could closely monitor patients and halt the drug if early signs of renal toxicity appear.

Development of the new biomarkers was led by the Predictive Safety Testing Consortium (PSTC), whose members include scientists from 16 pharmaceutical companies. The PSTC was organized and led by the Critical Path Institute, a nonprofit organization that works to support FDA research collaborations that improve the development of medical products.

Researchers from Merck & Co., Whitehouse Station, N.J., and Novartis AG, Basel, Switzerland, identified the new biomarkers, tested them to prove their accuracy and usefulness, and then shared their findings with the other consortium members for further study. The consortium then submitted applications for use of the biomarkers to FDA and EMEA.

The project is the first in which a group of drug companies has worked together to propose and qualify new safety tests and then present them jointly to the FDA and EMEA for consideration. The FDA and EMEA laid the groundwork for these specific joint-agency biomarker reviews in 2004 when they developed a framework called

the Voluntary Exploratory Data Submission review process.

The new process allowed the PSTC to submit a single biomarker data application to both regulatory agencies, and then to meet jointly with scientists from both agencies to discuss it in detail and to address additional scientific questions posed by the regulators. Each regulatory agency then reviewed the application separately and made independent decisions on use of the new biomarkers.

FDA scientists believe that the seven new tests may provide important advantages over the BUN and creatinine tests. For example, in experiments using rats, the two traditional tests can only detect kidney damage a week after it has begun to occur. The new tests, however, are more sensitive and can detect cellular damage within hours. And while BUN and serum creatinine show that damage has occurred somewhere in the kidneys, the new tests can pinpoint which parts of the kidney have been affected.

The seven new tests were developed and will be carried out initially in rats. These tests were selected because other studies have shown that identical biomarkers are produced in human kidney cells. While the FDA and EMEA will consider these biomarkers in rat studies initially, the PSTC has begun work to further qualify the biomarkers for use in human studies. If successful, the PSTC will present a new biomarker data application to the two agencies to seek acceptance of the human biomarkers.