At FDA, speedier approval could add uncertainty over risks

By Kathy Wren

Officials at the Food and Drug Administration (FDA) must wrestle with a difficult paradox. Since the early 1960s, after the thalidomide tragedy, the agency has been charged with protecting the public from unsafe and ineffective medical products. At the same time, across society, the demand for faster access to new therapies has risen. As patients exhaust treatment options for serious or life-threatening conditions, their tolerance for risk may grow.

In an effort to balance prudence and innovation, the FDA has implemented a variety of new regulatory pathways to expedite the approval of new drugs and medical devices that meet certain conditions. But the benefits of these accelerated approaches must be weighed against their drawbacks, speakers cautioned at a 13 June event at AAAS headquarters in Washington, DC. The meeting was cosponsored by AAAS; the Program on Regulation, Therapeutics, and Law within the Division of Pharmacoepidemiology and Pharmacoeconomics of Brigham and Women’s Hospital/Harvard Medical School; and the National Center for Health Research.

Scientific evidence is paramount to balancing the multiple demands on the Obama Administration, according to FDA Commissioner Margaret Hamburg. “At the end of the day, we have to be guided by science in everything we do. It has to be our compass,” she said in a keynote address.

Several of these speedier approval pathways are specifically designed to allow FDA validation based on studies measuring “surrogate end points.” Certain cholesterol levels, for example, have been proven to adequately reflect a patient’s risk of having a heart attack, so a drug that reduces those levels may be presumed to lower cardiovascular mortality.

Forty-nine percent of the drug approvals by the FDA from 2005 to 2012 were based on surrogate end points, according to a study by Joseph Ross, an assistant professor of medicine and of public health at the Yale University School of Medicine. The numbers varied by medical specialty, with a full 80% of cancer drug approvals relying on these measurements.

As speedier approval pathways allow the use of surrogate measures in a wider variety of conditions, fewer of these measures are subject to the rigorous validation required of earlier FDA-authorized surrogates such as cholesterol levels or systolic blood pressure.

“We need to do better studies to validate whether these surrogates are as good as we think, and not just assume things about them,” said Jerry Avorn, a professor of medicine at Harvard Medical School and chief of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women’s Hospital.

Speakers at the meeting cited study design as another area of concern. While randomized, controlled clinical trials are the gold standard in medical research, this type of study is not always used when testing new medical products for FDA approval. And it is particularly rare for new devices, which are subject to different regulatory procedures from prescription drugs.

More than 90% of all new medical devices are not tested in clinical trials at all, according to Diana Zuckerman, president of the National Center for Health Research. And, when Rita Redberg, a cardiologist at the University of California, San Francisco, School of Medicine, investigated the approval of cardiovascular devices in the high-risk category over an 8-year period, she found that only one-third were approved on the basis of a randomized clinical trial.

In some cases, bypassing a controlled trial may cost lives. An intracranial stent called the Wingspan Stent System was approved for use in stroke prevention on the basis of a 45-person study, according to Redberg. Instead of using a randomized control group, the researchers compared the patients’ outcomes to those in a previous study. The FDA approved the Wingspan stent via the “humanitarian device exemption,” which is intended to encourage the development of devices for treating rare diseases.

Later, a larger, randomized, controlled trial known as the SAMPRISS trial determined that 1 out of every 11 patients who received the Wingspan stent experienced a stroke or died. An FDA committee agreed that these data did not support the stent’s use for stroke, and the agency recommended narrowing the official list of ways that the device should be used.

The SAMPRISS trial was able to gather data effectively because it required anyone using the device to be enrolled in the trial, and it may thus be a good model for future postmarket studies, Redberg suggested.

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