A cynic might say that it is hard to take the mammoth 21st Century Cures bill seriously. It passed Congress at the very end of the session in December, the culmination of four years of discussion. So in one sense, many of its provisions were vetted, at least politically, which is another way of saying they didn’t raise serious objections in any quarter. The votes in the House (392–26) and Senate (94–5) were testimony to that. It can often be said that, when it comes to congressional legislation, “no controversy equals minimal significance.”

The nearly 1,000-page bill is a hodgepodge of loosely worded speculative provisions across many health care/federal programs, most of them at the Food and Drug Administration (FDA) and National Institutes of Health (NIH). When the House Energy and Commerce Committee began holding hearings on the bill four years ago, the legislation was viewed as a vehicle for allowing, or, if one prefers, forcing the FDA to permit pharmaceutical companies to gain approval of new indications for existing drugs with evidence assembled short of expensive clinical trials and short of conventional “endpoints.” Over the years, the vehicle was expanded to include funding for the Cancer Moonshot supported by Vice President Joe Biden and some other programs at the NIH. As the bill lumbered toward passage in early December, it was larded with new provisions in areas such as mental health and opioid addiction.

The FDA provisions are the most ballyhooed and are where the bill started. Here, the legislation encourages the FDA to approve new drugs based on real-world evidence (RWE) and surrogate endpoints, such as biomarkers. The term RWE refers to findings about a drug that are gleaned by looking at patient health records, whether obtained in a clinical trial or not, and marrying them with health insurance claims data and/or product registries to reach a conclusion about whether an already-approved drug should be approved for a new indication. The FDA already issued a guidance document on RWE used for medical device approval in 2016, so it is not clear what the bill requires the FDA to do that it is not already doing. Moreover, the top leaders of the FDA published an article in the New England Journal of Medicine on December 8, 2016, committing to move forward with the use of RWE, including publishing draft guidance on pharmaceuticals as a follow-on to its guidance on medical devices. The provision in the bill simply requires the FDA to evaluate the use of RWE.

The bill defines RWE “as data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.” The implication that randomized clinical trials can be done away with concerns some health researchers, such as Sanket Dhruva, MD, FACC, a cardiologist and health services researcher at the Yale University School of Medicine. “Specifically saying that clinical trials, the gold standard in drug and medical device approval, do not have to be used takes a step in the wrong direction,” he says. “There certainly is tremendous potential with RWE, but we must validate the evidence as being rigorously collected and reliable.”

Dr. Dhruva worries about the bill’s endorsement of the use of “drug development tools” in the drug approval process. Here, the bill defines those tools as: “a) a biomarker; b) a clinical outcome assessment; and c) any other method, material, or measure that the [Department of Health and Human Services] Secretary determines aids drug development and regulatory review for purposes of this section.” Dr. Dhruva also worries about the FDA moving away from requiring drug manufacturers to prove that a drug actually benefits a patient by making his or her life longer and/or better. He cites the controversial use of endpoints in the recent FDA approval of eteplirsen (Exondys 51, Sarepta Therapeutics) based on the use of a surrogate measure (in this case, muscle dystrophin levels). In an article published by the Journal of the American Medical Association, Aaron S. Kesselheim, MD, JD, MPH, of the Program on Regulation, Therapeutics, and Law (PORTAL) at Harvard Medical School, and similarly situated colleague Jerry Avorn, MD, wrote:

However, the accelerated approval pathway through which eteplirsen was authorized requires that a surrogate endpoint must be reasonably likely to predict clinical benefit of the drug, and this standard is challenged by the minimal changes seen in the dystrophin levels. Speeding drugs to market based on such biomarker outcomes can actually lead to a worse outcome for patients, even those with life-threatening diseases, if a product confers no meaningful benefit and carries a risk of adverse effects and a high cost. Immediately after approval, the manufacturer announced a price of $300,000 per year for eteplirsen.

The FDA approval process measures were sought by the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Advanced Medical Technology Association, the drug and medical device manufacturers’ trade groups, and some patient groups, too. The PhRMA released a statement saying:

The legislation includes pro-patient, science-based reforms, which enhance the competitive market for biopharmaceuticals and drive greater efficiency in drug development. It also increases FDA’s regulatory
that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcomes, of the use of a drug.¹

It may turn out that the Cures bill results in deep culture changes in the FDA drug and medical device approval processes. Certainly, the Trump administration will be more expansive in its interpretations of the provisions than the Clinton administration would have been where rulemakings are required. But the vagueness of some of the provisions and the general public concern about out-of-control drug prices, shared by Republicans and President Trump, probably mitigate against the Cures bill bestowing too many of what might be viewed as rich gifts on the drug industry.

REFERENCES


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