The US Food and Drug Administration (FDA) “is responsible for protecting the public health by assuring the safety, efficacy, and security” of drugs and medical devices and for helping provide the public with the “science-based information” it needs to use drugs and devices to improve health. Under the current Code of Federal Regulations (CFR), new drug approval is typically based on demonstration of efficacy in 2 or more randomized clinical trials (RCTs), often in comparison with placebo; high-risk device approval appears to be based on considerably weaker evidence of safety and efficacy. Given the continued progress of science, approval of a new drug or device implies to physicians and the general public that the product represents an advance over older treatments. The current FDA standards for approval fail to assess whether newly approved drugs and devices are less efficacious or less well-tolerated than existing alternatives. This raises the possibility that patients may be harmed by receiving a newly approved treatment instead of an alternative with established efficacy and safety.

Current FDA Approval Requirements

The CFR requires the FDA to approve new drug applications that meet specified criteria for approval. The efficacy criterion permits the FDA to reject an application if “there is a lack of substantial evidence consisting of adequate and well-controlled investigations...that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.” The CFR language pertaining to device approval is similar.

These regulations can be interpreted as meaning that the FDA may not reject an application on the basis of efficacy if the treatment demonstrates a statistically significant benefit over placebo (justifying label claims of efficacy), even if the new treatment appears to be less efficacious than established treatments or produces benefits of questionable clinical significance. With effective marketing, patients may receive a new treatment instead of a more efficacious older treatment, thereby potentially subjecting patients to excess risk of poor outcomes. In addition, excess costs are likely to be generated by the often higher costs of new treatments and the need for additional treatments that may have been avoided if the most efficacious treatment had been used.

Comparative Effectiveness Research and Product Labeling

Comparative effectiveness research has recently gained attention and federal funding, although the vast number of comparative effectiveness questions, the high costs of RCTs, and industry influence may limit the potential benefits of federally funded comparative effectiveness research. Alexander and Stafford have recently recommended that the FDA “generate [comparative effectiveness] data prior to the widespread adoption of a drug or treatment,” and “incorporate the principles of comparative effectiveness research throughout the process of [FDA] approval and regulation.” This should reduce the downstream needs for federally funded comparative effectiveness research and for attempts to reduce the use of inferior but already adopted treatments.

Stafford et al proposed changing the CFR to require reporting what is known about the comparative effectiveness of a new treatment in its label and marketing materials. This proposal would help the FDA ensure the availability of critical science-based information and would promote transparency in marketing new treatments. However, the comparative effectiveness research that might result, motivated in part by desire to market a specific product, could be of limited value or even counterproductive. For example, companies might choose to compare their drug with a second- or third-line drug, disadvantage the active control via dosing modifications (eg, using a relatively low or high dose of comparator to reduce its efficacy or tolerability, respectively), underpower a trial to show a difference between treatments, or any number of other design and reporting modifications that have been described in industry-sponsored active-comparator trials. Alternatively, companies may prefer to allow a product’s label to state that little is known about the comparative efficacy of the product.

What is needed then is strict FDA oversight of required active-comparator trials, which could be designed and powered to demonstrate superiority, equivalence, or noninferiority.
The public health benefits of protecting patients from receiving new, inferior treatments should withstand legal challenges based on manufacturers’ economic interests. While manufacturers might attempt to circumnavigate new approval requirements by encouraging off-label use, this problem exists whatever approval requirements are used. Over time, clinicians might become accustomed to using comparative efficacy and tolerability information, so off-label prescribing might decrease in situations in which on-label prescribing is available.

Conclusions

Legislative revision of the CFR is needed so the FDA can ensure that new but inferior treatments do not replace established treatments. Approval decisions based on trials with both active treatment groups and placebo control groups would also improve clinicians’ and the public’s understanding of the role of new treatments, reduce the amount of taxpayer-funded comparative effectiveness research needed, and may even reduce health care costs. Collaboratively designed active-comparator clinical trials could help the FDA and industry work together to improve the health of the public.

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REFERENCES