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# Development Times, Clinical Testing, Postmarket Follow-up, and Safety Risks for the New Drugs Approved by the US Food and Drug Administration

## The Class of 2008 FREE

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# ABSTRACT

**Importance** The US Food and Drug Administration (FDA) has advanced multiple proposals to promote biomedical innovation by making new drugs available more quickly but with shorter, smaller, and more selective clinical trials and less rigorous end points.

**Objective** To inform the debate about appropriate standards, we studied the development times, clinical testing, postmarket follow-up, and safety risks for the new drugs approved by the FDA in 2008, when most provisions of current law, regulation, and policies were in effect.

**Design** Descriptive study of the drugs classified as new molecular entities using preapproval FDA evaluation documents, agency drug information databases, prescribing information, and other primary data sources.

**Main Outcomes and Measures** Comparison of drugs that received standard review and those deemed sufficiently innovative to receive expedited review with regard to clinical development and FDA review time, the size and duration of efficacy trials, safety issues, and postmarket follow-up.

**Results** In 2008, the FDA approved 20 therapeutic drugs, 8 with expedited review and 12 with standard review. The expedited drugs took a median of 5.1 years (range, 1.6-10.6 years) of clinical development to obtain marketing approval compared with 7.5 years (range, 4.7-19.4 years) for the standard review drugs ($P = .05$). The expedited drugs were tested for efficacy in a median of 104 patients receiving the active drug (range, 23-599), compared with a median of 580 patients (range, 75-1207) for standard review drugs ($P = .003$). Nonclinical testing showed that 6 therapeutic drugs were animal carcinogens, 5 were in vitro mutagens, and 14 were animal teratogens. Other safety concerns resulted in 5 Boxed Warnings; 8 drugs required risk management plans. The FDA required 85 postmarket commitments. By 2013, 5 drugs acquired a new or expanded Boxed Warning; 26 of 85 (31%) of the postmarketing study commitments had been fulfilled, and 8 (9%) had been submitted for agency review.

**Conclusions and Relevance** For new drugs approved by the FDA in 2008, those that received expedited review were approved more rapidly than those that received standard review. However, considerably fewer patients were studied prior to approval, and many safety questions remained unanswered. By 2013, many postmarketing studies had not been completed.

In 1962, the US Congress required as a condition of approval that the benefits of any new drug be proven with substantial evidence from controlled clinical

trials conducted by persons qualified by training and experience.[1] The Food, Drug, and Cosmetic (FDC) Act amendments further required that safety be demonstrated "by all means applicable."[1]

In 2013, these requirements largely survive, although US Food and Drug Administration (FDA) approvals are controlled by scores of amendments, regulations, and guidance documents that specify the testing required for drugs intended for "the diagnosis, cure, mitigation, treatment or prevention of disease."[2]

One group of FDC Act amendments relates to the speed and conditions under which the FDA assesses applications for new drugs. These set review deadlines including "priority reviews" for drugs representing a significant therapeutic advance and "fast-track reviews" for drugs that fill unmet needs for treatment of serious illnesses.[3]

A second group of changes provides for exceptions to the standards for evidence from clinical trials. The requirement that 2 clinical trials of a drug demonstrate a beneficial effect may be waived, and data from a single trial may be sufficient.[1] Under "accelerated approval," data from a single trial and with a surrogate end point thought to predict a beneficial effect are sufficient, but further studies to confirm benefit are required after marketing approval.[3] An FDA guidance adopted an international regulatory harmonization guideline that sets minimum standards for testing drugs intended for long-term or open-ended use at 300 patients observed for 1 year or more without a comparison group.[4]

A third group of changes mandates additional requirements, including postapproval testing of drugs in a pediatric population, legally binding requirements for postmarketing studies, restricted distribution for some high-risk drugs, and a requirement for manufacturers to develop plans to identify and manage drug risks.[5,6]

Under the Obama Administration, the FDA may also change the testing requirements for many drugs prior to approval; the stated rationales are promoting innovation and reducing the time and cost of discovering new drugs. Recent reports and initiatives include a White House report on "Propelling Innovation in Drug Discovery, Development, and Evaluation,"[7] an FDA program to promote biomedical innovation,[8] a proposed "Alternative Development Pathway" to permit shorter, smaller trials of new drugs for serious illnesses,[9] a draft guidance for "enriched trials," which are conducted in a subset of patients where the benefits of a drug can be more readily demonstrated,[10] and reduced efficacy standards for drugs for Alzheimer disease.[11]

To inform the debate about the appropriate standards for testing new drugs, we studied the development times, clinical testing, postmarket follow-up, and safety risks for the new drugs approved by the FDA in 2008, when most provisions of current law, regulation, and policies were in effect.

# METHODS

Because this study relied on publicly available documents previously reviewed for public release by the FDA, institutional review board approval was not obtained.

We studied new molecular entities, which the FDA defines as new active pharmaceutical ingredients that were not previously marketed in the United States. We did not study changes to existing drugs, such as different salts, esters, or dosage forms or new medical uses (indications).

We assessed drug testing and approval through the following primary data sources: Drugs@FDA database for FDA Approved Drug Products (for preapproval testing reviews),[12] the DailyMed Current Medication Information web site (for the current prescribing information),[13] and the FDA database Postmarket Requirements and Commitments to evaluate completion of

postmarketing studies required as a condition of approval.[12] Through the Freedom of Information Act, we also obtained the date human testing was authorized in the original Investigational New Drug (IND) application, as well as supplementary data about completed postmarketing studies. We used data from the National Prescription Audit for 2013 conducted by IMS Health Inc to assess utilization of outpatient drugs.

End point definitions were as follows: total development time was the years between FDA approval of the initial IND to begin human testing for the indication that was eventually approved and the date of marketing approval. Information on preclinical development time was not available. Total FDA review time was the months between submission of the original New Drug Application (NDA) and marketing approval. Food and Drug Administration review time included time needed to respond to requests by the agency for additional information or requirements to conduct additional studies. Exposed patients in efficacy trials was defined as the number of patients receiving the active drug in clinical trials described in the Clinical Studies section of the original approved label. The total number of patients exposed to the active drug was obtained from the safety summary in the FDA Medical Review of the drug. Carcinogen, teratogen, and mutagen signals were defined as any reported abnormalities listed in the Nonclinical Toxicology section of the approved label. A drug could account for a safety signal in 1 or more of these 3 independent categories. Postmarketing commitments were additional studies specifically listed in the FDA letter of NDA approval or were found in the postmarketing commitments database. Expedited approval was 1 or more of the following: priority review, fast-track review, or accelerated approval. Orphan drug status provides tax and patent exclusivity for drugs for rare diseases; such drugs do not automatically qualify for expedited approval.[14,15]

New drugs were classified as outpatient drugs normally dispensed from the pharmacy or inpatient drugs administered in physicians' offices, hospitals or

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