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

Thomas J. Moore, AB; Curt D. Furberg, MD, PhD

**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. The Food, Drug, and Cosmetic (FDC) Act amendments further required that safety be demonstrated “by all means applicable.”

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.”

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.

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. 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. 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.

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.

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,” an FDA program to promote biomedical innovation, a proposed “Alternative Development Pathway” to permit shorter, smaller trials of new drugs for serious illnesses, 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, and reduced efficacy standards for drugs for Alzheimer disease.

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), the DailyMed Current Medication Information web site (for the current prescribing information), and the FDA database Postmarket Requirements and Commitments to evaluate completion of postmarketing studies required as a condition of approval. 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.

New drugs were classified as outpatient drugs normally dispensed from the pharmacy or inpatient drugs administered in physicians’ offices, hospitals or other medical facilities, or diagnostic tests. We excluded diagnostic tests from...
most analyses because their testing requirements substantially differ from the requirements for drugs. Drugs were designated as intended for short-term use if the expected therapy period was 6 months or less and for open-ended use if the expected length of treatment could be more than 6 months.

Both investigators jointly determined whether a drug was intended for outpatient or inpatient use and for short-term or open-ended use. Medical uses and risks for specific drugs were taken from each drug’s 2012 prescribing information.

**Statistical Analysis**
The data were analyzed with the R Package for Statistical Computing (http://www.r-project.org). For study variables, we calculated the mean, median, and range and compared the means of continuous variables with the Welch 2-sample $t$ test.

**Results**

**Drugs Approved**
In 2008, the FDA approved 24 new drugs—10 inpatient drugs, 10 outpatient drugs, and 4 diagnostic tests. Characteristics of the inpatient and outpatient drugs are given in Table 1.

Table 1. New Drugs Approved by the Food and Drug Administration in 2008*

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name (Manufacturer)</th>
<th>Therapeutic Use</th>
<th>Years to Market</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inpatient drugs: short-term use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alvimopan</td>
<td>Entereg (Cubist Pharmaceuticals Inc)</td>
<td>GI recovery after GI surgery</td>
<td>9.8</td>
</tr>
<tr>
<td><em>Bendamustine</em></td>
<td>Treanda (Cephalon Inc)</td>
<td>Chronic lymphocytic leukemia</td>
<td>4.8</td>
</tr>
<tr>
<td>Clevidipine</td>
<td>Clevidipex (Fresenius Kabi)</td>
<td>IV blood pressure reduction</td>
<td>6.1</td>
</tr>
<tr>
<td>Fospropofol</td>
<td>Lusedra (Eisai Inc)</td>
<td>Sedation in anesthesia</td>
<td>7.5</td>
</tr>
<tr>
<td>Methylenealtrexone</td>
<td>Relistor (Salix Pharmaceuticals Inc)</td>
<td>Opioid-induced constipation</td>
<td>6.0</td>
</tr>
<tr>
<td><strong>Plexifor</strong></td>
<td>Mozobil (sanofi-aventis)</td>
<td>Non-Hodgkin lymphoma/multiple myeloma</td>
<td>10.6</td>
</tr>
<tr>
<td><strong>Inpatient drugs: open ended use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certolizumab</td>
<td>Cimzia (UCB Inc)</td>
<td>Crohn disease</td>
<td>4.7</td>
</tr>
<tr>
<td>Degarelix</td>
<td>Firmagon (Ferring BV)</td>
<td>Advanced prostate cancer</td>
<td>7.5</td>
</tr>
<tr>
<td><em>Rilonacept</em></td>
<td>Arcalyst (Regeneron Pharmaceuticals Inc)</td>
<td>Crysopyrin-associated periodic syndrome</td>
<td>3.7</td>
</tr>
<tr>
<td>Romiplostim</td>
<td>Nplate (Amgen Inc)</td>
<td>Thrombocytopenia</td>
<td>6.7</td>
</tr>
<tr>
<td><strong>Outpatient drugs: short term use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difluprednate</td>
<td>Durezol (Alcon Laboratories Inc)</td>
<td>Pain and/or inflammation after ocular surgery</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Outpatient drugs: open ended use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>Prestiq (Pfizer Inc)</td>
<td>Major depression</td>
<td>5.9</td>
</tr>
<tr>
<td><em>Eltrombopag</em></td>
<td>Promacta (GlaxoSmithKline)</td>
<td>Thrombocytopenia</td>
<td>4.1</td>
</tr>
<tr>
<td><em>Etravirine</em></td>
<td>Intelect (Johnson &amp; Johnson)</td>
<td>Human immunodeficiency virus</td>
<td>6.2</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>Toviaz (Pfizer Inc)</td>
<td>Overactive bladder</td>
<td>6.7</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Vimpat (UCB Inc)</td>
<td>Prevention of seizures</td>
<td>9.6</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>Banzel (Eisai Inc)</td>
<td>Seizures in Lennox-Gastaut syndrome</td>
<td>19.4</td>
</tr>
<tr>
<td>Silodosin</td>
<td>Rapaflo (Actavis Pharma Inc)</td>
<td>Benign prostatic hyperplasia</td>
<td>10.2</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>Nucynta (Johnson &amp; Johnson)</td>
<td>Moderate to severe pain</td>
<td>8.0</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>Xenazine (Lundbeck Inc)</td>
<td>Huntington chorea</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Abbreviations: GI, gastrointestinal; IV, intravenous.

* Expedited approval is indicated by bold face with italic font.

* Years from authorization to test in humans to marketing approval.

* Short-term use, expected therapy is 6 months or less; open-ended use, expected therapy is longer than 6 months.

Among the new drugs were 7 orphan drugs for rare diseases that received favorable tax treatment and increased patient exclusivity under the FDC Act. Rufinamide (Banzel; Eisai Inc) was approved for Lennox-Gastaut syndrome, a form of epilepsy with a patient population numbering in the hundreds. Also approved were 2 orphan drugs for second-line use in immune thrombocytopenic purpura, with an estimated population of 16 000, and tetrabenazine (Xenazine; Lundbeck Inc), a monoamine oxidase (MAO) depletor for Huntington chorea, a subset of uncertain size of approximately 18 000 patients with Huntington disease. Overall, 6 of 8 drugs deemed innovative enough to qualify for expedited approval were for small patient populations.
Development and Approval Times

Among the 20 therapeutic drugs, a median of 6.5 years (range, 1.6-19.4 years) elapsed from FDA authorization to initiate testing in humans to market approval. The FDA approval process, including time for manufacturers to provide additional information, lasted a median of 10.9 months (range, 4.1-36.4 months) and accounted for 14.1% of total development time.

Both development and approval times differed among the 12 standard review drugs and the 8 drugs with 1 or more forms of expedited approval (8 priority reviews, 3 fast-track, and 2 accelerated approvals; 3 drugs were part of more than 1 expedited category). The expedited pathway drugs took a median of 5.1 years (range, 1.6-10.6 years) to obtain marketing approval compared with 7.5 years for the standard review drugs (range, 4.7-19.4 years) ($P = .05$). Food and Drug Administration review times were shorter for expedited drugs compared with the standard review group, a median of 7.7 months (range, 4.1-35.2 months) for expedited drugs, compared with 13.2 months (range, 9.5-36.4 months) for standard reviews, although the mean differences were not significant ($P = .15$).

Testing

In the controlled trials that were conducted to establish substantial evidence of benefit, the drugs were tested in a median of 352 patients (range, 23-1207) for the active drug; the size of the control groups varied. These data are given in Table 2. The expedited pathway drugs were tested in a median of 104 patients for the active drug (range, 23-599); the standard review drugs were tested in a median of 580 patients (range, 75-1207). The difference in the mean number of patients was significant ($P = .003$).

Overall, 5 of 20 drugs (25%) were tested for efficacy in a single trial, 11 of 20 (55%) had 2 efficacy trials, and 4 drugs were tested in more than 2. None of the 8 expedited pathway drugs were tested in more than 2 trials; 3 were approved on the basis of a single efficacy trial.

Among the smallest efficacy trials were those for 2 orphan drugs: rilonacept (Arcalyst; Regeneron Pharmaceuticals Inc), an interleukin-1 blocker, was tested in 23 patients receiving the active drug, and tetrabenazine, an MAO depletor, was tested in 54 patients receiving the active drug. Three drugs had more than 1000 patients in efficacy trials—desvenlafaxine with 1207 patients, fesoterodine with 1120 patients, and alvimopan (Entereg; Cubist Pharmaceuticals Inc) with 1096 patients.

The total number of patients exposed to an active drug during testing includes clinical pharmacology studies, uncontrolled studies, and other specialized studies. For the expedited drugs, a median of 626 patients (range, 313-1161) were exposed, compared with 2133 (range, 430-4110) for standard review drugs. The difference was also significant ($P < .001$).

Safety

The 20 drugs had a wide spectrum of known safety issues at time of approval including Stevens-Johnson syndrome (romiplostim [Nplate; Amgen Inc]), abuse liability (tapentadol [Nucynta; Johnson & Johnson]), lacosamide (Vimpat; UCB Inc), serious opportunistic infections (certolizumab), severe fetal harm (bendamustine [Treanda; Cephalon Inc]), suicidality (desvenlafaxine, lacosamide, and tetrabenazine), medically significant cytopenia (certolizumab), and serious hepatotoxicity (eltrombopag [Promacta; GlaxoSmithKline]). At time of approval, the drugs had 1 or more of the following safety risk indicators: 5 of 20 drugs had a Boxed Warning indicating a significant safety risk, 8 drugs required special risk management plans, and 8 had a warning or contraindication for hypersensitivity.

Requirements for Postmarketing Studies

The risks of cancer and birth defects for new drugs are assessed prior to approval in animal and in vitro studies, with uncertainties about how the results might apply to humans. In these nonhuman studies, 6 drugs had signals for...
animal carcinogenicity, 5 were mutagens in vitro or in animals, and 14 were animal teratogens (Table 2). Pediatric studies are not required prior to approval, and were waived for 9 drugs, deferred for 1, and required after approval for 10. Specific unanswered questions were outlined in required postapproval studies. Overall, the FDA required 85 postmarketing studies for 19 of the 20 drugs. Silodosin (Rapaflo; Actavis Pharma Inc), a treatment for benign prostatic hyperplasia, had no required postapproval studies; the FDA, however, required enhanced postmarket surveillance of serious hepatic events. None of the trials conducted prior to approval assessed the efficacy of the drug beyond 24 weeks, including those for medications intended for open-ended use. After approval, the FDA required the collection of efficacy data beyond 24 weeks for desvenlafaxine and bendamustine.

**Status of the Drugs in January 2013**

As of January 2013, all 20 drugs were still marketed; 3 of the 10 outpatient drugs were on an IMS Health list of the 400 most frequently dispensed outpatient drugs: the antidepressant desvenlafaxine (ranked 223 with 825,000 dispensed outpatient prescriptions in the first quarter of 2013), and the opioid tapentadol (ranked 384 with 241,000 prescriptions), and the topical difluprednate (Durezol; Alcon Laboratories Inc) (ranked 392 with 227,000 prescriptions). Of these 3 drugs, only difluprednate had received expedited approval. Both drugs granted accelerated approval (etaravine [Intelence; Johnson & Johnson] and eltrombopag [Promacta]) were granted full approval after completing 2 confirmatory studies that were ongoing at the time of initial approval.

Substantial additional risks were discovered in the 4-year period after approval: 5 drugs acquired a new or expanded Boxed Warning, bringing the total number of drugs with such warnings to 7; 1 drug had new contraindications; and 4 drugs had additional warnings or precautions. Tapentadol, an opioid, had the most new risks, with 4 items in a new Boxed Warning, 3 new contraindications, and a more restricted indication. As of January 2013, 26 of 85 (31%) of the postmarket study commitments were fulfilled and another 8 (9%) had been submitted for FDA review. The postmarket studies had original projected completion dates ranging from a few months to the year 2020 (dates were missing for 6 studies). Of the studies scheduled for completion by 2013, 34 of 48 (71%) were completed or submitted. Additional postmarket study detail is given in Table 2.

**Discussion**

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. As many safety questions were not answered prior to drug approval, some patients may have been exposed to safety risks that had not been well characterized.

Among the 8 drugs deemed innovative, only 1 (difluprednate) ranked among the 400 most frequently dispensed outpatient drugs in 2013. However, 6 of the 8 drugs deemed innovative were orphan drugs intended for small patient populations. Among the other 12 drugs, 3 were metabolites or prodrugs of existing drugs, and the FDA did not judge the remaining 9 as significant therapeutic advances.

Our study has limitations. As the typical postmarket major regulatory safety action occurs a median of 11 years after approval,16–37 our 4-year follow-up period could only capture some of the additional risks that are likely to be detected for the drugs approved in 2008. The year studied, 2008, was typical of drugs approved between 2008 and 2010 for 3 characteristics: number of new drugs, number of orphan drugs, and number of priority reviews.

By definition, the FDA judged that all the drugs it approved in 2008 had benefits that outweighed the known risks; subsequent information about additional risks has not led the FDA to remove any of the drugs from the market. The agency managed safety risks that became evident after approval with warnings and label changes.

The testing of new drugs has shifted from a situation in which most testing was conducted prior to initial approval to a situation in which many innovative drugs are more rapidly approved after a small trial in a narrower patient population, with extensive additional testing conducted after approval. Our findings suggest that the shift has made it more difficult to balance the benefits and risks of new drugs. Further systematic assessment of the standards and procedures for testing new drugs is needed.

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**AUTHOR CONTRIBUTIONS:** Mr Moore had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Both authors.

**Acquisition of data:** Moore.

**Analysis and interpretation of data:** Moore.

**Drafting of the manuscript:** Moore.

**Critical revision of the manuscript for important intellectual content:** Both authors.

**Statistical analysis:** Moore.

**Study supervision:** Furberg.

**Conflict of Interest Disclosures:** None reported.

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**REFERENCES**

Can Expedited FDA Drug Approval Without Expedited Follow-up Be Trusted?

Daniel Carpenter, PhD

**Invited Commentary**

Like blood itself flowing through the human circulatory network, several billion prescriptions and hundreds of billions of drugs course every year through the vast web of factories, wholesale suppliers, hospitals, physicians’ offices, pharmacies, medicine cabinets, and pill boxes that together compose the health system in the United States.¹ That network comprises a vast social machine; besides money, the main lubricant is trust premised on evidence. Physicians prescribe drugs in part because they know they have been tested and that their initial safety and efficacy has met the approval criteria of the US Food and Drug Administration (FDA).² When a generic medication is prescribed, the physician trusts, consciously or unconsciously, that basic conditions of quality manufacturing and bioequivalence have been met. In most instances, the physician does not see the evidence but assumes that someone else, principally the FDA, has rigorously reviewed the underlying data.

The system can fail in many ways, but 2 of the ways are false trust and lack of trust. If regulation fails and physicians and the public do not have evidence-based trust in drugs, fewer drugs are prescribed, patients do not receive therapies that might help them, investment drops accordingly, and the social foundations of the health system are weakened.³ In the absence of sound, independent evidence and underlying trust, just about everything can go wrong.

In this issue of *JAMA Internal Medicine*, Moore and Furberg⁴ report on the development time, clinical testing, and safety risks of new drugs approved by the FDA. Moore and Furberg⁴ looked back to 2008, the calendar year before President Barack Obama took office. They examined the 20