The Food and Drug Administration Amendments Act and Postmarketing Commitments

Because rare but potentially serious adverse events of prescription drugs are often discovered only after market approval, observational postmarketing studies constitute an important part of the US drug safety system. In most instances prior to 2007, the US Food and Drug Administration (FDA) could only request that drug manufacturers voluntarily agree to conduct postmarketing safety studies. An Office of Inspector General report in 2006 found inadequacies in drug companies’ fulfillment of these postmarketing studies and weaknesses in FDA’s regulatory authority to enforce these commitments. In 2007, Congress passed the Food and Drug Administration Amendments Act (FDAAA), which authorized the FDA to require postmarketing studies for a prescription drug’s approval and mandate adherence to study deadlines. We examined how fulfillment of these postmarketing studies has changed over time.

Methods | We extracted data on the status of all postmarketing studies for both biological license and new drug applications from the FDA annual reports published in the Federal Register. Each report specifies the number of studies for that year in each status category: pending (not yet started), ongoing, delayed, terminated, submitted, released, and fulfilled. Descriptions of each category appear in the Box. We reviewed the status of all studies reported by the FDA from 2007 to 2011.

Results | The total number of postmarketing studies was 1841 in 2007, 1901 in 2008, 2227 in 2009, 1774 in 2010, and 1781 in 2011 (Table). The total number of studies required under the FDAAA was 0 in 2007, 46 in 2008, 153 in 2009, 279 in 2010, and 387 in 2011. There were 3 distinct trends in postmarketing studies during this period.

First, the number of studies not yet started decreased from 1044 (56.7%) in 2007 to 775 (43.5%) in 2011, whereas the number of studies required under the FDAAA but not yet started steadily increased each year since 2007 to 271 (15.2%) studies in 2011.

Second, there was an opposite trend for completed studies that fulfilled the postmarketing obligation, which increased from 122 (6.6%) in 2007 to 224 (12.6%) in 2011. There were no fulfilled FDAAA studies during this time.

Third, delayed studies increased from 125 (6.8%) in 2007 to 241 (13.5%) in 2011. By 2011, there were 19 studies required under the FDAAA that were delayed (1.1%).

Discussion | Because of heightened public scrutiny of the status of postmarketing studies, we expected uninitiated studies to decrease and fulfilled studies to increase since 2007. Indeed, our analysis found the number of studies not yet started declined during this 5-year period, and the number of studies fulfilling obligations nearly doubled. These trends

Table. Postmarketing Commitments by Status for New Drug Applications and Biological License Applications for Fiscal Years 2007-2011

<table>
<thead>
<tr>
<th>Postmarketing Commitments, No. (%)</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not started by manufacturera</td>
<td>1044 (56.7)</td>
<td>936 (49.2)</td>
<td>874 (39.2)</td>
<td>728 (41.0)</td>
<td>775 (43.5)</td>
</tr>
<tr>
<td>Under FDAAA jurisdictionb</td>
<td>0</td>
<td>42 (2.2)</td>
<td>120 (5.4)</td>
<td>207 (11.7)</td>
<td>271 (15.2)</td>
</tr>
<tr>
<td>Ongoing</td>
<td>271 (14.7)</td>
<td>302 (15.9)</td>
<td>308 (13.8)</td>
<td>279 (15.7)</td>
<td>275 (15.4)</td>
</tr>
<tr>
<td>Under FDAAA jurisdictionb</td>
<td>0</td>
<td>4 (0.2)</td>
<td>28 (1.3)</td>
<td>50 (2.8)</td>
<td>64 (3.6)</td>
</tr>
<tr>
<td>Submitted for FDA evaluation</td>
<td>238 (12.9)</td>
<td>356 (18.7)</td>
<td>389 (17.5)</td>
<td>236 (13.3)</td>
<td>199 (11.2)</td>
</tr>
<tr>
<td>Under FDAAA jurisdictionb</td>
<td>0</td>
<td>0</td>
<td>5 (0.2)</td>
<td>16 (0.9)</td>
<td>33 (1.9)</td>
</tr>
<tr>
<td>Total delayed</td>
<td>125 (6.8)</td>
<td>133 (7.0)</td>
<td>217 (9.7)</td>
<td>200 (11.3)</td>
<td>241 (13.5)</td>
</tr>
<tr>
<td>Under FDAAA jurisdictionb</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6 (0.3)</td>
<td>19 (1.1)</td>
</tr>
<tr>
<td>Total terminatedc</td>
<td>4 (0.2)</td>
<td>9 (0.5)</td>
<td>16 (0.7)</td>
<td>12 (0.7)</td>
<td>10 (0.6)</td>
</tr>
<tr>
<td>Under FDAAA jurisdictionb</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total concludedd</td>
<td>159 (8.6)</td>
<td>165 (8.7)</td>
<td>423 (19.0)</td>
<td>319 (18.0)</td>
<td>281 (15.8)</td>
</tr>
<tr>
<td>Under FDAAA jurisdictionb</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Study commitments fulfilled</td>
<td>122 (6.6)</td>
<td>143 (7.5)</td>
<td>324 (14.5)</td>
<td>254 (14.3)</td>
<td>224 (12.6)</td>
</tr>
<tr>
<td>Total</td>
<td>1841 (100)</td>
<td>1901 (100)</td>
<td>2227 (100)</td>
<td>1774 (100)</td>
<td>1781 (100)</td>
</tr>
<tr>
<td>Under FDAAA jurisdictionb</td>
<td>0</td>
<td>46 (2.4)</td>
<td>153 (6.9)</td>
<td>279 (15.7)</td>
<td>387 (21.7)</td>
</tr>
</tbody>
</table>

Abbreviations: FDA, Food and Drug Administration; FDAAA, Food and Drug Administration Amendments Act.

a These studies are described as pending in the Federal Register notices.
b Studies that the FDA has required under its authority from the FDAAA.
c Applicant ended the study before completion, but has not yet submitted a final study report to the FDA.
d Include those released by the FDA from the obligation to be conducted, as well as those submitted to the FDA that the agency has determined satisfy the study obligation (fulfilled).
help address concerns expressed by the Institute of Medicine that many postmarketing studies before the FDAAA were not implemented or fulfilled. Despite these improvements, though, more than 40% of studies had not yet been started in 2011. In addition, the number of studies with delays doubled to approximately 1 in 8 as of 2011, and the proportion of all studies that have been fulfilled remains low.

Our investigation has limitations. First, it was not designed to statistically isolate the FDAAA’s effect on fulfillment rates for postmarketing commitments. Second, our analysis does not examine the content and outcome of specific commitments because much of this information is not publicly available. Nevertheless, despite some gains in studies initiated and fulfilled, our analysis reinforces continued concerns about the status of prescription drug postmarketing studies in the United States. Most of these studies reported since 2007 were requested by the FDA before the FDAAA’s enactment, which could explain the extent of delayed and unfulfilled studies during this period.

For those newer studies required under the FDAAA, which are steadily increasing each year, the FDA must enforce the law against companies failing to comply with study requirements. Under the FDAAA, the FDA can issue warning letters and initiate litigation for significant failures, including seizures and injunctions. These regulatory actions can help ensure the timely conduct and submission of adequate studies, which will ultimately strengthen the FDA’s ongoing monitoring of prescription drug safety.

Kevin Fain, JD, MPH
Matthew Daubresse, MHS
G. Caleb Alexander, MD, MS

Author Affiliations: Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Fain); Center for Drug Safety and Effectiveness, Johns Hopkins University, Baltimore, Maryland (Daubresse, Alexander).

Corresponding Author: G. Caleb Alexander, MD, MS, Johns Hopkins Bloomberg School of Public Health, 615 N Wolfe St, W6035, Baltimore, MD 21205 (galexand@jhsph.edu).

Author Contributions: Dr Alexander 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: Fain, Alexander. Acquisition of data: Fain, Daubresse. Analysis and interpretation of data: Fain, Daubresse, Alexander. Drafting of the manuscript: Fain, Daubresse. Critical revision of the manuscript for important intellectual content: Fain, Daubresse, Alexander. Statistical analysis: Fain. Obtained funding: Alexander. Administrative, technical, or material support: Daubresse. Study supervision: Fain, Alexander.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Mr Fain reported working in the Office of Chief Counsel at the US Food and Drug Administration (FDA) from 1995 until 2010. Dr Alexander reported being an ad hoc member of the FDA’s Drug Safety and Risk Management Advisory Committee; serving as a paid consultant to IMS Health; and serving on an IMS Health scientific advisory board (this arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies). Mr Daubresse did not report any disclosures.

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Box. Postmarketing Requirements and Commitments: Status and Fulfillment Categories

Pending: The study has not been initiated (ie, no patients have been enrolled or animals dosed), but does not meet the criterion for delayed (ie, the original projected date for initiation of patient accrual or initiation of animal dosing has not passed).

Ongoing: The study is proceeding according to, or is ahead of, the original schedule. The Food and Drug Administration (FDA) considers a study to be ongoing until a final study report is submitted to the FDA, as long as the activities are proceeding according to the original study schedule. If patient accrual or animal dosing has started but is not complete, and the projected date for completion of that milestone has passed, the study should be categorized as delayed.

Delayed: The progression of the study is behind the original study schedule. Delays can occur in any phase of the study, including patient enrollment, analysis of study results, or submission of the final study report to the FDA. Even though the original study schedule (not a revised schedule) serves as the basis for defining a study as delayed, each phase of the study will be considered in its own right. If the applicant has 1 delayed phase, but gets back on schedule during the next phase, the delayed status will no longer apply.

Terminated: The applicant ended the study before completion, and has not yet submitted a final study report to the FDA.

Submitted: The applicant has concluded or terminated the study and has submitted a final study report to the FDA, but the FDA has not yet notified the applicant in writing that the study commitment has been fulfilled or that the commitment has been released.

Fulfilled: The applicant has submitted the final study report for the commitment, and upon review of the final study report, the FDA is satisfied that the applicant has met the terms of the commitment.

Released: The FDA has informed the applicant that it has been released from its obligation to conduct the postmarketing study because the study is either no longer feasible or would no longer provide useful information.

The fulfilled and released commitments will be displayed on the FDA website for not more than 1 year from the date the commitments are fulfilled or released.
COMMENT & RESPONSE

Aldosterone Inhibition in Patients With Heart Failure With Preserved Ejection Fraction

To the Editor  The Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF) study 1 tested the hypothesis that aldosterone inhibition with spironolactone would result in improvement in maximum exercise capacity (peak \( \dot{V}O_2 \)) or diastolic function \( (E/e') \), each a co-primary end point. Whereas resting \( E/e' \) was reduced by spironolactone, exercise capacity was not. The method of patient selection may have contributed to a false-negative result. We believe that this study illustrates the fundamental problems with the current concept of heart failure (HF) with preserved ejection fraction (EF) and, in particular, the role of exercise in this syndrome.


The study by Dr Edelmann and colleagues 1 investigated the effects of spironolactone on diastolic function in patients with symptomatic diastolic HF. Under the broad definition of improvement of diastolic function, the authors included echocardiographic variables indicative of both relaxation (first phase of diastole, active) and compliance (second phase, passive) of the left ventricle. For precision, reduced left ventricular compliance (ie, determining the increase in ventricular filling pressures) is always associated with but not equivalent to a deficit of relaxation.

The study was based on the observation of a significant effect of the active therapy on \( E/e' \), which is an indirect index of left ventricular filling pressure. The mean \( E/e' \) of patients in the study at baseline was in the gray zone 2 (a large area of overlap between normal and increased filling pressures). This suggests that a significant proportion of patients may have had normal filling pressures. Furthermore, the mean left atrial volume (LAV) indexed was less than 28 mL/m² for both groups and not significantly modified after treatment. This LAV index size, which is in the normal range according to current recommendations, 3 also could indicate left ventricular filling pressures in the normal range.

The data presented in Table 3 in the article show a significant reduction in \( E/e' \) compared with placebo that was related to the small but significant increase in \( e' \) without a clear reduction in the transmitral E wave. This suggests that after