RESEARCH LETTER

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>
<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 manufacturer&lt;sup&gt;a&lt;/sup&gt;</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 jurisdiction&lt;sup&gt;b&lt;/sup&gt;</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 jurisdiction&lt;sup&gt;b&lt;/sup&gt;</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 jurisdiction&lt;sup&gt;b&lt;/sup&gt;</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 jurisdiction&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6 (0.3)</td>
<td>19 (1.1)</td>
</tr>
<tr>
<td>Total terminated&lt;sup&gt;c&lt;/sup&gt;</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 jurisdiction&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total concluded&lt;sup&gt;d&lt;/sup&gt;</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 jurisdiction&lt;sup&gt;d&lt;/sup&gt;</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 jurisdiction&lt;sup&gt;d&lt;/sup&gt;</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.

<sup>a</sup> These studies are described as pending in the Federal Register notices.

<sup>b</sup> Studies that the FDA has required under its authority from the FDAAA.

<sup>c</sup> Applicant ended the study before completion, but has not yet submitted a final study report to the FDA.

<sup>d</sup> 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.

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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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Role of the Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.


5. US Food and Drug Administration. Postmarketing requirements and commitments: annual reports in Federal Register (FY2002-FY2012). http:
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 tested the hypothesis that aldosterone inhibition with spironolactone would result in improvement in maximum exercise capacity (peak \( V_{\text{O2}} \)) or diastolic function (\( E/e' \)), each a co-primary endpoint. 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 definition of HF with preserved EF used by the investigators relied on the presence of breathlessness (New York Heart Association class II), a preserved EF (>50%), and evidence of resting diastolic dysfunction (grade ≥1). Objective evidence of exercise limitation was necessary at baseline (via cardiopulmonary exercise testing) and resting spirometry was performed as a means to exclude those with respiratory limitation. Approximately half of the patients met diagnostic criteria of the European Society for Cardiology for HF with preserved EF, although the initiation of this study preceded the publication of these guidelines.

Even though mean baseline peak \( V_{\text{O2}} \) (16.4 mL/min/kg) indicated significant exercise limitation, the mean expired volume per unit time/volume of expired carbon dioxide (\( V_{E}/V_{\text{CO2}} \)) slope was 30.3. This implies that exercise limitation was not primarily cardiac in origin in approximately half of the patients. The \( V_{E}/V_{\text{CO2}} \) slope has physiological, diagnostic, and prognostic implications; a value of less than 30 is considered normal without adjustment for age and sex, whereas patients with HF typically far exceed this threshold. In this study, the normal mean \( V_{E}/V_{\text{CO2}} \) slope suggests that many of these patients may have been primarily deconditioned and that pathophysiological heterogeneity may have been a major confounder.

Heart failure with preserved EF should be considered a disorder in which therapeutic efficacy will primarily be seen in functional capacity. Phase 2 mechanistic trials are therefore likely to continue to use ergometric end points. However, the full physiological potential of cardiopulmonary exercise testing should be used to ensure a cardiac origin of limitation, thus validating the diagnosis of HF with preserved EF and increasing study power. In contrast, current guidelines emphasize resting echocardiographic indices, which are an insufficient basis on which to attribute a cardiac origin to dyspnea. If these fundamental issues are not addressed in trial methods, we believe negative findings will continue to predominate.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Singh reported receiving a grant from the British Heart Foundation. Dr Frenneaux reported holding a patent for perhexiline for heart muscle diseases. Dr Neil reported no disclosures.


To the Editor The study by Dr Edelmann and colleagues 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 (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, 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