

fenac — three drugs previously removed from the U.S. market by the FDA because of the increased risk of acute liver failure. Given that telithromycin is neither clinically superior to other drugs prescribed for respiratory tract infections nor uniquely life-saving, physicians, patients, and third-party payers might wish to reconsider their choice of antibiotic for such infections.

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The views expressed are those of the author and do not necessarily reflect those of the FDA.

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## Judging the Safety of Aprotinin

**TO THE EDITOR:** I was troubled by the recent, near-unanimous decision of the Food and Drug Administration (FDA) Cardiovascular and Renal Drugs Advisory Committee publicly advocating the safety of aprotinin<sup>1</sup> — despite considerable evidence to the contrary,<sup>2-4</sup> including our recent study<sup>2</sup> and the FDA's own initial 1993 warning regarding “kidney toxicity.”<sup>5</sup> We learned after the Advisory Committee's meeting of newly disclosed records of 67,000 patients, yielding data that were consistent with our warnings (renal failure, stroke, and heart failure)<sup>2</sup> and that were inconsistent with the positions of the committee and Bayer.<sup>1,6</sup>

In defending the committee's decision, Dr. Hiatt makes allegations in this issue of the *Journal* regarding our “transparency” (FDA access to our data).<sup>7</sup> In fact, there is no question that our independent, nonprofit research groups (the Ischemia Research and Education Foundation [IREF] and the Multicenter Study of Perioperative Ischemia [McSPI] research group) made every effort to have the FDA review in detail all of the source and derivative data from our study<sup>2</sup> and all associated documentation and operating procedures.

In February 2006, after publication of our article,<sup>2</sup> the FDA asked that we present our data to them. We agreed and sent a team of IREF scientists to the FDA. The FDA and Bayer then asked that we send them our database, because they each wanted to combine our data with

Bayer's data and then perform a number of unspecified analyses. We agreed to the FDA proposal, making three requests: that patient privacy and legal trust be preserved, that the methods used to mix our patient data with the Bayer patient data be specified, and that in addition to their analyses, the FDA independently analyze our data, comment on each finding of our study published in the *Journal*,<sup>2</sup> and make the results known to the public. In May (4 months before the Advisory Committee meeting), frustrated by the delay and concerned that our data would not be reviewed, I abandoned all three requests and informed the FDA that we would provide our database and any and all source data for its review. Hearing no response, after several weeks, I wrote to the FDA and again asked for a review of our data. However, the FDA refused, and we were told that a review was not necessary. As I publicly stated to the Advisory Committee on September 21, 2006, we stand by our offer to the FDA to provide for review any and all data regarding our publication without constraint or condition.

The FDA and its Advisory Committee should take a conservative, protective stance when independent evidence regarding drug safety presents itself. Instead, they appear to be protecting the drug rather than the patient.

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**TO THE EDITOR:** We wish to address some issues related to data access discussed at the September 21, 2006, meeting of the FDA Cardiovascular and Renal Drugs Advisory Committee. The major topic for this meeting was a consideration of the safety findings from two publications relating to the use of aprotinin injection (Trasylol, Bayer).<sup>1,2</sup>

Karkouti et al. reported that aprotinin increased the risk of renal dysfunction as compared with another hemostatic drug. Mangano et al. reported that, for some patients, aprotinin increased several risks, including those of renal failure and myocardial infarction, as compared with other hemostatic drugs or no drug. Both studies used propensity-scoring methods to correct for imbalances in treatment groups.

Given the nature of these studies, the FDA believed it important to conduct an independent evaluation of the statistical methods. The FDA asked both authors for access to their data and supportive documents in order to conduct this evaluation. Dr. Karkouti supplied full access to

the data sets for his study, with no limitations on the extent of analyses that FDA staff could perform. Dr. Mangano imposed restrictions, including his physical presence at the FDA while the FDA representatives inspected and analyzed the data, and limitations on the nature of the analyses the agency could perform. Furthermore, he required the FDA to make a determination of the validity of the published findings and conclusions rather than assess the methods alone. Under these terms, the FDA could not perform a substantive, independent evaluation of his statistical methods.

The experience with aprotinin illustrates some of the challenges of obtaining access to proprietary data sets. Nevertheless, the reports from Karkouti et al. and Mangano et al. represented laudable efforts, and the ensuing discussions at the committee meeting highlighted the value and limitations of observational data.

We anticipate seeking further public comment once we have reviewed all relevant data, including the recently noted observational study by Bayer. We welcome unrestricted access to all relevant information, including that obtained from proprietary data sets.

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