DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable John D. Dingell
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-0115

MAR 1 2007

Dear Mr. Chairman:

Thank you for the letter dated February 16, 2007, co-signed by Ranking Minority Member Joe Barton, and Chairman of the Subcommittee on Oversight and Investigations, Bart Stupak, and Ranking Minority Member Ed Whitfield, to Michael O. Leavitt, Secretary of Health and Human Services, requesting information and documents related to telithromycin (Ketek). Secretary Leavitt asked that the Food and Drug Administration (FDA or the Agency) respond on his behalf. This is a partial response.

Information contained in the enclosures includes information that is trade secret, commercial confidential or other privileged information protected from disclosure to the public under the Freedom of Information Act (Title 5, *United States Code* [U.S.C.] 552), the Trade Secrets Act (18 U.S.C. 1905), the Privacy Act (5 U.S.C. 552a), and Food and Drug Administration (FDA or the Agency) regulations. The Committee should not publish or otherwise make public any such information. We would be glad to discuss with the Committee staff the protected status of any specific information. As you instructed in your letter, we have redacted the documents to remove patient identifiers.

As has been discussed with Committee staff, we had previously asked for a broader set of Ketek-related documents from the FDA Centers, Office of Commissioner, and the Office of Regulatory Affairs field operations in connection with a similar congressional request. To expedite our response to your request, we are reviewing that set of documents for documents responsive to your request. In cases where there were large numbers of documents containing patient privacy identifiers, we redacted an example of those particular documents and have indicated how much more of that same type of document we have in our files that would be responsive to your request. For example, we have enclosed patient medical history and informed consent documents. We wrote on the top of the enclosed such documents that we have 16 more inches of the same type of documents for other study patients.

We have repeated your questions in bold type followed by our answers.

[W]e hereby request that the Department provide to the Subcommittee....all records relating to:

1. The integrity of data associated with the planning, coordination, implementation, or review of Study 3014. This does not include 3014 itself;

Answer: See Tabs A, B, C, D, and E.

2. Questions or concerns with respect to Study 3014 arising between July 24, 2002, when the study was presented to the FDA, and January 8, 2003, the second meeting of the Advisory Committee;

Answer: See Tabs A, B, D, and E.

3. Communications between representatives, including but not limited to independent contractors, of the FDA and Sanofi-Aventis regarding Study 3014;

Answer: See Tabs A and B.

4. Investigations conducted by the FDA's OCI and DSI related to Study 3014;

Answer: Tabs A, B, C, and D.

5. Compliance or lack of compliance with Good Clinical Practices (GCP) in association with the Ketek new drug application;

Answer: See Tabs A, B, C, D, and E.

6. The use of foreign adverse data to satisfy the safety concerns of the Advisory Committee without even reconvening the Advisory Committee. This does not include the body of any large study or analysis of the data supplied by Sanofi-Aventis to the NDA file except for any executive summary of each such study or analysis.

Answer: See Tab B.

1. Identify all persons who worked on any aspect or matter related to the review or investigation of Study 3014.

Answer: See Tab F.

2. Has the FDA ever withheld data integrity problems from an Advisory Committee in association with the review of other drugs?

Answer: FDA uses advisory committees to gain expert advice about scientific and public health issues and/or regulatory decisions. In preparing for an advisory committee meeting, scientific team leaders, supervisors and managers – seasoned regulatory scientists with drug development and public health expertise – exercise scientific judgment in synthesizing issues to be brought before advisory committees. This process is designed to ensure that, in general, an advisory committee considering an issue is provided with sufficient data and information to fully discuss the issues.

In general, FDA will withhold data integrity problems from an Advisory Committee when it knows that such problems exist and that the Agency will not be using data from such studies to support the application. For example, in many cases where data integrity violations are identified at study sites, the Division of Scientific Investigation (DSI) will recommend elimination of data from the violative site from the study. Only if the findings appear to be systemic or a site represents a large portion of the study's enrollment is the entire study disqualified. Also, in large studies, sometimes individual study sites may be disqualified but the rest of the study may be used to support an application.

In the case of Study 3014, at the time of the January 8, 2003, Advisory Committee meeting, FDA did not know that the entire trial would be excluded from consideration in the approval of the Ketek new drug application (NDA). This determination to exclude Study 3014 from consideration could not have been made prior to the meeting of the Advisory Committee on January 8, 2003, because the review division did not receive a final recommendation from DSI regarding the reliability of data from Study 3014 until March 25, 2004.

In addition, the Advisory Committee was not informed about the data integrity concerns associated with Study 3014 during the January 8, 2003, meeting because the Agency did not have definitive information to provide and it could not disclose the existence of an ongoing investigation. The first official DSI evaluation dated January 21, 2003, became available two weeks after the open public meeting of the Advisory Committee. The DSI evaluation described issues with the referred study sites and recommended that the Kirkman-Campbell data not be used in support of an NDA pending further investigation and resolution. Even in that report, the DSI classification for the two remaining sites was still pending. There was no mention of any systemic problems with data integrity or a need to consider elimination of the entire study. Also, no determination of fraud was made at that time, though the report stated that the Office of Criminal Investigation's investigation of the Kirkman-Campbell site was ongoing.

We will continue to work with Committee staff on this request, and may provide additional responsive materials to these and other questions if they are identified. An identical letter has been sent to your co-signers without enclosures. Thank you for your interest in this matter. If you have further questions, please let us know.

Sincerely,

Stephen R. Mason
Acting Assistant Commissioner
for Legislation

Enclosures