DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FEB 2 5 1999

The Honorable Henry A. Waxman
Ranking Minority Member
Committe on Government Reform
and Oversight
House of Representatives
Washington, D.C. 20515-0529

Dear Mr. Waxman:

Thank you for your letter of December 18, 1998 consigned by Representatives John D. Dingell and Sherrod Brown, concerning the safety of the drug, Rezulin (troglitazone), approved by the Food and Drug Administration (FDA or the Agency) for type II diabetes. Approved by FDA on January 29, 1997, Rezulin was the first of a new class of drugs offering the possibility of reducing or eliminating diabetic patients' dependence on insulin by making better use of their own insulin production. Your letter requests information about the approval and post-approval surveillance concerning the drug. The following are the Agency's responses to your questions:

1. How many deaths and cases of serious liver damage are attributable to, or associated with, Rezulin since its January 30, 1997 approval? How many have been reported directly to the FDA? How many were reported to the FDA by Rezulin's manufacturer, Warner-Lambert? Please provide the date of each report.

FDA has completed individual analyses for cases reported to the Adverse Event Reporting System (AERS) with either a fatal outcome or requiring a liver transplant, but we are still processing the reported non-fatal, non-transplant cases. Of the 100 reported cases of liver adverse events with a fatal outcome, we considered 33 cases to be associated with the use of Rezulin, 8 of which occurred in Japan. Five additional cases of serious liver damage in which the patients survived, but required a liver transplant, also were associated with Rezulin use. A breakout of these 38 cases is as follows: hepatic failure (38) -- 5 survived with transplant; 2 died following transplant; 31 died without transplant.

To determine the above figures, a computer search of AERS for all liver adverse events associated with Rezulin since its approval on January 29, 1997 through February 3, 1999 retrieved 838 *possible* cases. Of these cases, Warner-Lambert reported 724 cases; 114 cases were reported directly to FDA from other sources. The AERS line listing produced by the search only provides the reporting year, not the exact date for each report. (See enclosed at Tab A.)

The 838 cases included liver adverse events with an AERS-defined serious outcome of any or a combination of the following: death, disability, hospitalization, life-threatening situation or "others." Included among these 838 cases were 100 deaths. The 838 cases retrieved by the computer search were further evaluated to determine the strength of the link between Rezulin and serious liver damage.. In some of these cases, the reported clinical data were incomplete, so there is no certainty that the drug caused the reported reactions. A given reaction may actually have been due to an underlying disease process or to another coincidental factor. Further, cases were screened to avoid duplicate records. Additional data responsive to the above question is enclosed at Tab A.

2. **It is widely recognized that adverse reactions are underreported to the FDA through its MedWatch program and other postmarketing surveillance systems. Does the agency have an estimate of how significant this underreporting might be in the case of Rezulin?**

No. The Agency believes, however, that in the case of Rezulin underreporting may have been less substantial because the medical community was alerted to the need for increased liver function monitoring for this product. It is FDA's experience that when there has been increased publicity on a particular drug, there tends to be an increase in the number of reports received in the surveillance system.

FDA has long acknowledged that incidents of adverse drug reactions are underreported to the FDA Medical Products Reporting Program, MedWatch. There are no federal laws or regulations that require hospitals or other health care providers to report suspected pharmaceutical-related adverse events to FDA or to the product manufacturer, although they are strongly encouraged to do so for those events deemed serious. Reporting by individual healthcare providers is voluntary. Manufacturers and distributors of FDA approved pharmaceuticals (drugs and biologics) and medical devices, plus pharmaceutical

packers and device user facilities, however, all have mandatory reporting requirements to FDA. If they receive voluntary reports from healthcare providers or consumers, or become aware of reports, they are required to report these to FDA.

FDA does not have comprehensive estimates of the number of post-marketing adverse reactions concerning Rezulin or most drugs. Unlike clinical trial data, which are obtained under strictly controlled conditions where the exact number of patients receiving the drugs and the number of patients with suspected adverse reactions is known, spontaneously reported information is uncontrolled, and therefore, subject to the possible influence of a number of biases that can affect reporting and dependent on the initiative of the independent health care providers. Suspected cases spontaneously reported to any surveillance program, which would comprise the numerator of an equation, generally represent only a small portion of the number that actually have occurred. Compounding these numerator limitations is the lack of precise denominator data, such as user population and drug exposure patterns.

Despite the limitations of spontaneous reporting, however, FDA's program for the surveillance of regulated medical product safety provides vital information of clinical importance as it did so with Rezulin. It generates "signals" of potential serious, rare, and unexpected problems that warrant further investigation.

3. Warner-Lambert's December 1 "Dear Doctor" letter downplays the disclosure of three new deaths from liver failure associated with Rezulin, stating, "You will be reassured to know that the additional reports received since early November do not indicate a greater frequency of liver injury or potential for serious harm than had been previously estimated."

   Did the FDA approve or review this letter before its nationwide distribution? Does it concur with this assessment of Rezulin's safety, particularly in light of the labeling changes mandated by the agency?

FDA staff did not review or approve the December 1, 1997, "Dear Healthcare Professional" letter of Parke-Davis (a division of Warner-Lambert). After the letter was issued, we expressed our concern that the seriousness of the hepatotoxicity was downplayed. Accordingly, FDA asked Parke-Davis to send another "Dear Healthcare Professional" letter together with a copy of

the revised physician labeling and the FDA, December 1, 1997, "Talk Paper." That follow-up letter was issued by Parke-Davis on December 15, 1997. Parke-Davis sent FDA a draft of the December 15, 1997 letter before it issued, but did not ask for a 'formal review." Documents reflecting this request are enclosed at Tab B.

4. Since January 30, 1997, the FDA has added a bold-face warning of Rezulin's danger of liver damage, and required three major changes in Rezulin's labeling. Each labeling change has called for increased testing of patient liver functions. In light of the rising number of patient deaths and cases of liver damage, does the Agency continue to believe that testing of liver function is an adequate means of preventing future fatalities and serious adverse reactions?

The Agency believes that the increased testing of liver functions as recommended in the revised labeling for Rezulin will improve the monitoring of potential adverse effects resulting from taking Rezulin. The majority of reported deaths related to Rezulin occurred in patients who were not properly monitored. Additional monitoring should reduce the incidence of both deaths and serious adverse reactions. FDA's monitoring of adverse event reports involving Rezulin is ongoing. The Agency will continue to evaluate whether additional steps need to be taken concerning the drug. The additional labeling provides information both for the physician and the patient, which enables both to make better judgments as to available treatment options. At this time, after careful reevaluation, we believe that the benefits of the drug outweigh the risks.

5. What proportion of patients are complying with the liver function tests mandated in Rezulin's revised labeling? Given the serious health risks to patients of noncompliance, are the FDA or Warner-Lambert monitoring such compliance? What steps are FDA and Warner-Lambert taking to ensure patient compliance?

We currently have no data to permit us to estimate, nor generally the means to monitor, the level of physician-patient compliance with the program of liver function test monitoring recommended in Rezulin's labeling. Such testing compliance is part of the physician-patient relationship. We have worked with Parke-Davis to develop literature for physicians, pharmacists and patients which is related directly to the labeling changes.

FDA will continue to monitor the situation closely under the MedWatch reporting system.

The Agency has announced that at its next meeting the Endocrinologic and Metabolic Drugs Advisory Committee, which originally reviewed this drug, will review the experience with Rezulin since marketing approval, as well as the benefits and risks of Rezulin for patients with type II diabetes mellitus. This Advisory Committee meeting will be held on March 26, 1999, 8 a.m. to 5 p.m. at the Holiday Inn Bethesda, Versailles Room I and II, 8120 Wisconsin Avenue, Bethesda, Maryland, and is open to the public.

In an effort to obtain all available information for the Advisory Committee meeting, the Office of Postmarketing Drug Risk Assessment, within the Center for Drug Evaluation and Research, is working with one of its cooperative Agreement Program sites to design and conduct an observational epidemiologic study. The primary goal of this study is to measure the rate of baseline and monthly liver function test monitoring and correlate it with the time-intervals defined by successive "Dear Healthcare Professional" letters. Data collection started in December 1998 in order to maximize the sample size for the study despite the inherent time lags in the processing of billing claims within the health plan database. Because the monitoring recommendations first appeared in the labeling in December 1997, the Agency hopes to have complete claims data for the first six months of 1998 and partial claims data available for the last six months of 1998 to help assess voluntary adherence to these recommendations.

The following steps, in the form of information made available to the medical community and the general public, have been taken by the Agency and Parke-Davis to help ensure patient and practitioner compliance. Since the initial approval of Rezulin on January 29, 1997 the following have been provided:

January 30, 1997 - FDA "Talk Paper" announcing the approval of Rezulin and detailing certain precautions concerning the product.

October 28, 1997 - A "Dear Healthcare Professional“ letter was issued by Parke-Davis regarding prescribing information changes and the incidence of idiosyncratic hepatocellular injury observed in type II diabetes patients being treated with Rezulin.

November 3, 1997 - FDA "Talk Paper“ issued concerning the changes in prescribing information for Rezulin.

December 1, 1997 - FDA issued a "Talk Paper" concerning the need for increased patient monitoring for signs of liver injury and warning of potential liver toxicity for patients taking the diabetes drug, Rezulin.

December 1, 1997 - A "Dear Healthcare Professional“ letter was issued by Parke-Davis regarding FDA's November 19, 1997, labeling changes for Rezulin. The letter detailed the additional liver monitoring recommendations.

December 15, 1997 - A revised "Dear Healthcare Professional" letter was issued by Parke-Davis together with a copy of the revised physician labeling and the FDA, December 1, 1997, Talk Paper.

July 28, 1998 - A "Dear Healthcare Professional" letter was issued by Parke-Davis concerning the more stringent liver enzyme monitoring recommended in FDA's labeling changes for Rezulin.

Enclosed at Tab C are copies of the above documents.

6. **Why was Dr. Gueriguian removed from the review of Rezulin?**

7. **Did Dr. Gueriguian recommend against the approval of Rezulin? Please provide copies of any memoranda, email, notes, or other documentation of Dr. Gueriguian's recommendations regarding Rezulin's safety, approval, or potential conditions of use.**

FDA is unable to provide responses to these questions based on the confidential nature of the information which is not releasable under the Freedom of Information Act (FOIA) (5 U.S.C. S552) and FDA's implementing regulations. The issues also involve personnel matters which are not subject to disclosure under the same Act and regulations.

8. **What was the response of Dr. Gueriguian's superiors in the Division of Metabolic and Endocrine Drug Products (DMEDP) and Center for Drug Evaluation and Research (CDER) to such recommendations? Please provide copies of any memoranda, email, notes, or other documentation of such responses.**

9. **The Los Angeles Times describes a September 1996 meeting between DMEDP staff and representatives of Warner-Lambert, in which Dr. Gueriguian voiced reservations regarding Rezulin. Please provide any transcripts, memoranda, notes, or other documentation of this meeting and any subsequent communication from Warner-Lambert concerning this meeting.**

Although the Agency is not able to provide specific responses to these questions for the reasons noted in the above response, we would like to provide general information concerning the review of Rezulin. Dr. Gueriguian did not complete his review of Rezulin and thus such review materials are not included in the new drug application file that is releasable to the public. The Agency did conduct a thorough review of Rezulin subsequent to the incidents described above. The materials relating to the new drug application (NDA) review are enclosed at Tab D.

10. **Please provide any memoranda, email, notes or other documentation of concerns expressed by DMEDP staff prior to Rezulin's approval on January 30, 1997 regarding the product's potential risks of cardiovascular or liver damage.**

Documents responsive to this request are enclosed at Tab E and Tab D.

11. **On or prior to the December 11, 1996 meeting of the Endocrinologic & Metabolic Drugs Advisory Committee, did Dr. Solomon Sobel, Dr. Alexander Fleming, Dr. Robert Misbin or other DMEDP or CDER staff recommend to the committee members that regular liver function tests be a condition of Rezulin's approval? Did they recommend any other restrictions on the use of Rezulin as a condition of approval?**

FDA staff did not recommend to the Advisory Committee members that regular liver function tests be a condition of Rezulin's approval. In general, we do not make recommendations to the Advisory Committee. We ask the Committee members to give their recommendations to FDA. Safety matters were discussed by FDA staff at the December 11, 1996, Advisory Committee Meeting (see transcript, pages 186-217), as were restrictions on the labeled indication (see transcript, pages 239-241 and 319-322), but no specific restrictions on the use of Rezulin were recommended as a condition of approval. The complete transcript of this

Advisory Committee meeting is enclosed at Tab F. Documents responsive to this request are enclosed also at Tab D.

12. **Please provide copies of any medical reviews of Rezulin written prior to December 11, 1996 for the use by the Endocrinologic and Metabolic Drug Advisory Committee, and any transcripts, memoranda, notes, or other documentation of the December 11 committee deliberations on Rezulin.**

Documents responsive to this request are enclosed at Tab D and Tab G.

13. **Rezulin was approved in the United Kingdom on July 31, 1997 and withdrawn from the market on December 1, 1997 after reports of six deaths and 130 cases of liver damage associated with Rezulin. Please provide copies of any memoranda, email, notes, or other documentation of the FDA's evaluation of the U.K.'s Medicines Control Agency decision to withdraw Rezulin from the market.**

Documents responsive to this request are enclosed at Tab H.

14. **Did Dr. Richard Eastman, Director, Division of Diabetes, Endocrinology and Metabolism, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), have any communications with the Division of Metabolic and Endocrine Drug Products regarding the approval of Rezulin? Please provide copies of any memoranda, email, notes, or other documentation of any such communications.**

There were no communications between Dr. Richard Eastman and the Division of Metabolic and Endocrine Drug Products regarding the approval of Rezulin.

Some of the documents were redacted pursuant to the Freedom of Information Act (FOIA) (5 U.S.C. S522) and FDA's implementing regulations. Enclosures are included only with the letter to Representative Dingell due to the volume. We hope this information is useful. A similar letter has been sent to your cosigners.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

cc: The Honorable Tom Bliley
Chairman, Committee on Commerce

The Honorable Michael Bilirakis
Chairman, Subcommittee on
Health and Environment