DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Detroit District
1560 East Jefferson Avenue
Detroit, MI 48207-3179
Telephone: 313-226-6260

September 27, 2000

BY FACSIMILE AND CERTIFIED MAIL – RETURN RECEIPT REQUESTED

Jefferson J. Gregory, R.Ph., J.D.
President, Chief Executive Officer
Parkedale Pharmaceuticals, Inc.
870 Parkedale Road
Rochester, MI 48307-1740

Re: Consent Decree of Permanent Injunction, United States v. Warner-Lambert Company, Civil Action No.93-3525, entered August 17, 1993 in the United States District Court for the District of New Jersey ("Consent Decree")

Dear Mr. Gregory:

The Food and Drug Administration ("FDA") has reviewed Parkedale's letter dated July 11, 2000, which responds to FDA's letter of June 6, 2000. FDA has also reviewed Parkedale's July 11 and July 24, 2000 responses to the Form FDA 483 issued at the close of the limited FDA inspection of the Influenza Virus Vaccine operation conducted June 26 to 29, 2000. As you know, this inspection was performed pursuant to FDA's March 10, 2000 Paragraph XVI notification in order to verify satisfactory completion of items two through eight of the March 10, 2000 letter and compliance with CGMPs. Based upon FDA's review of the inspection, the records collected during the inspection, and your written responses to the observations, we have concluded that the methods, facilities, and controls used by Parkedale in the manufacture, processing, and packing of Influenza Virus Vaccine are not established, operated, and administered in compliance with 21 U.S.C. Section 351(a)(2)(B) and 21 C.F.R. Parts 210 and 211 (CGMP). Therefore, in accordance with paragraph XVI of the Consent Decree, FDA hereby notifies Parkedale that it must again cease and discontinue manufacturing, processing, packing, labeling, and distributing Influenza Virus Vaccine.

FDA's June 2000 inspection of Parkedale revealed continuing CGMP deficiencies in production and process controls for Influenza Virus Vaccine. During the inspection, the investigators discovered that [redacted] monovalent strain lots of A/New Caledonia had been rejected due to egg safety test failures. The egg safety test is performed to verify that inactivation of viable influenza virus has been accomplished. FDA has serious concerns regarding Parkedale's investigation and the actions taken in response to these egg safety test failures. Our concerns are outlined below.

1. For some of these lots, Parkedale created a retest protocol to "retest each lot at the point [redacted] past the completion of the previous test and to continue testing at [redacted] intervals until the sample meets the specifications of the test." FDA strongly objects to Parkedale's retest protocol and the documented rationale that, "...generally at [redacted] when the egg safety test was repeated on the same sample, the results were then within specification. This is believed to be due to a slow kill rate of the virus for the particular samples." It is our view that Parkedale's practice constitutes testing the monovalent strain lots into compliance, a practice that undermines the principles of process validation and good manufacturing practice, and could possibly result in the presence of live influenza virus in the in-process monovalent concentrate.

2. In response to the egg safety test failures, Parkedale changed the inactivation time for the A/New Caledonia strain from [redacted] days. FDA has serious concerns regarding Parkedale's initial failure to establish the inactivation time for this new strain of influenza virus. The kinetics for viral inactivation for every new strain should be studied and established prior to production and not in response to egg safety test failures. In addition to changing the inactivation time, Parkedale also changed the method of mixing from a [redacted] of the solution bottle to a mixing step using a [redacted] mixer. It is unclear, however, whether the change was adequately validated. FDA reminds you once again that changes in manufacturing must be reported to CBER pursuant to 21 CFR 601.12.

3. Finally, FDA has discovered that at least one of the "rejected" lots, 46578, that failed the egg safety test was incorporated into monovalent concentrate lot 47115 and submitted to CBER for lot release. We interpret the submission of this monovalent concentrate to mean that Parkedale intends to market the trivalent vaccine formulated with this lot. For the reasons discussed in numbers 1 and 2 above, FDA questions the suitability and safety of monovalent concentrates prepared using strain lots that failed the egg safety test. The final disposition of the remaining [redacted] monovalent strain lots that failed the egg safety test and were recommended for rejection by Parkedale's Cross Functional Investigation (CFI) Team, is unknown.

The investigators also documented that the pooling laboratory, a classified area used to pool monovalent concentrates and formulate trivalent vaccine, had been quarantined due to mold contamination in the environment. The environmental monitoring results revealed that multiple plate exposures from the upper surface of the pooling tank were contaminated with mold. Each test result exceeded the action limit established for mold [redacted] respectively), which was identified as [redacted] Because of the mold contamination, [redacted] lots of monovalent concentrate [redacted] were quarantined in accordance with the established procedures.

Given the circumstances, which included multiple excursions so severe as to warrant quarantine of the classified area and the products, FDA was surprised to discover that the

[redacted]lots had been submitted to CBER for lot release in June 2000, when your July 24, 2000 letter characterized the lots as "in quarantine pending final disposition by Quality Assurance." Our review of Parkedale's SOP "3010 Deviation Investigation Procedure, version 7.0", and SOP "3110 Environmental Microbiological Monitoring Program – Buildings 8, 43, & 46, version 4.0" indicates that these environmental monitoring results clearly exceeded the action limit, and the corresponding products should have been "rejected."

FDA is also concerned about decisions made by Parkedale's management with respect to other monovalent strain lots that were characterized as "rejected" due to environmental monitoring excursions in your July 11, 2000 letter. For example, our investigators obtained records of a Quality Review Board meeting on February 20, 2000, in which numerous "rejected" lots were recommended for "further processing" based on product bioburden results, final filtration through a[redacted]micron filter, and "a refiltration operation." FDA is not aware of an approved reprocessing procedure that includes refiltration of monovalent strain lots.

Regarding your process validation efforts with respect to the reuse of [redacted] in the [redacted] columns, FDA acknowledges your statement that historical data were not available to provide the relevant background information. Inspectional information reveals that the concurrent validation study to evaluate the reuse of [redacted] was initiated on or about May 20, 2000, with the first data recorded on May 22, 2000. The protocol collected by the investigators, however, indicates that Parkedale has not established acceptance criteria for [redacted] used in the study. Rather, the protocol states that, "[t]he [redacted] concentration acceptance limits will be determined after a thorough review of the collected data from pooled fraction samples." Further, the protocol states that, "[e]valuation of collected data ... will determine whether [redacted] acceptance limits are required." These findings call into question the scientific basis of the study and are of concern to FDA.

Regarding the microbial retention validation studies of all [redacted]micron filters used in the manufacture of Influenza Virus Vaccine, we acknowledge the revised schematic of the filtration process and the clarification that "Step 1 (pre-filtration)" was not part of the [redacted] study. FDA continues to have concern regarding the practice of switching the [redacted] filters numerous times during the pre-filtration process due to clogging. We acknowledge Parkedale's revision to the batch record that now limits the number of filter switches to [redacted] Parkedale states the criteria for changing filters is based on "observations of decreased filtrate rate," however, you also state in your July 11, 2000 letter that the flow rate is not controlled except with pressure. Therefore, it is unclear how the "decreased filtrate rate" is observed or measured. Additionally, Parkedale has not explained how the filters are switched without compromising the sterility and integrity of the product. Based on these concerns, FDA has concluded that the filtration step intended to render the product sterile has not been adequately validated.

Based on our review of Parkedale's letters dated July 11 and 24, 2000, and the deviations documented during the inspection, FDA does not accept your April 13, 2000 certification that Parkedale has conformed with and has satisfactorily completed items one through five contained in FDA's March 10, 2000 Paragraph XVI notification. This decision reflects the agency's determination that Parkedale continues to have systemic CGMP problems that have not been satisfactorily addressed.

PARAGRAPH XVI NOTIFICATION

FDA has concluded that the methods, facilities, and controls used in the manufacturing, processing, packing, and labeling of Influenza Virus Vaccine are not established, operated, and administered in compliance with 21 U.S.C. Section 351(a)(2(B) and 21 C.F.R. Parts 210 and 211, and as a result, the product is adulterated. Under the terms of paragraphs XVI and XVII of the Consent Decree, FDA hereby notifies you that Parkedale must immediately cease manufacturing, processing, packing, labeling, and distributing Influenza Virus Vaccine until it receives written notification from FDA that Parkedale appears to be in compliance with 21 U.S.C. Section 351(a)(2)(B) and 21 C.F.R. Parts 210 and 211. Additionally, FDA has concluded that the safety, purity, potency, identity, and quality of in-process Influenza Virus Vaccine in your inventory cannot be assured. We recommend, therefore, that you initiate appropriate steps for the proper disposition of the inventory.

Prior to the resumption of any operations, FDA must verify compliance with current good manufacturing practice. In accordance with paragraph XVII of the Decree, the cessation of operations must continue until Parkedale receives written notification from FDA permitting Parkedale to resume all Influenza Virus Vaccine operations, including distribution, upon FDA's determination that Parkedale is in compliance with CGMP.

We advise you that both of the biologics license application supplements recently submitted by Parkedale, regarding changes to the heating, ventilation and air conditioning system (STN 103783-5001) and an alternate buffer for use in selected manufacturing steps (STN 103783-5000) are being reviewed in accordance with FDA's established procedures.

Parkedale must immediately comply with this notification. Failure to do so will result in FDA's consideration of assessing liquidated damages against Parkedale as provided for in paragraphs XX and XXI of the Consent Decree. You are further instructed to inform FDA of the status of Parkedale's actions taken in compliance with this notification, including the disposition of Parkedale's inventory. A responsible corporate officer shall certify receipt of this notification in writing to FDA within five business days. Copies of your responses should be sent concurrently to my attention and to Mr. Steven A. Masiello, Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610.

This letter constitutes notice of a significant failure to comply with 21 U.S.C. Section 351(a)(2)(B) and 21 CFR Parts 210 and 211 under paragraph XXII of the Consent Decree.

If you have questions about this notification or wish to request a meeting with FDA, please contact Mr. Masiello at (301) 827-6190.

Sincerely,

Raymond V. Miecko
Director
Detroit District Office