DEPARTMENT OF HEALTH & HUMAN SERVICES

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

March 10, 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. 43-3525, dated August 16, 1993

Dear Mr. Gregory:

During October 4 through 13, 1999, the Food and Drug Administration ("FDA") conducted an inspection of Parkedale Pharmaceuticals, Inc. ("Parkedale"), located at 870 Parkedale Road, Rochester, Michigan. Based upon FDA's review of the inspection, the records collected during the inspection, and your written response 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 Current Good Manufacturing Practice ("CGMP") regulations set forth at 21 C.F.R. Parts 210 and 211 and thus are adulterated within the meaning of 21 U.S.C. Section 351(a)(2)(B). As acknowledged in your letter dated February 26, 1998, to Mr. Douglas Ellsworth, FDA District Director, New Jersey District, Parkedale is a successor corporation under the referenced Consent Decree of Permanent Injunction ("Consent Decree"). In accordance with paragraph XVI of the Consent Decree, FDA hereby notifies Parkedale that it must cease and discontinue manufacturing, processing, packing, labeling, and distributing all lots of Influenza Virus Vaccine pending performance, and FDA review and acceptance, of certain actions described in detail below.

As you know, this is the third letter issued to Parkedale by FDA pursuant to paragraph XVI of the Consent Decree that has included deficiencies in the manufacture of Influenza Virus Vaccine. The first letter, dated August 14, 1998, resulted from the observations noted during FDA's March 23 to April 16, 1998 inspection, and discussed widespread deviations from CGMP. Some of the deficiencies noted were similar to those found during the current inspection, including inadequate cleaning validation and inadequate procedures for environmental monitoring in areas where Influenza Virus Vaccine is manufactured. The second letter, dated August 25, 1999, resulted from the observations noted during FDA's inspection of May 3 to 13, 1999, and discussed numerous significant CGMP deficiencies in the manufacture of Influenza Virus Vaccine, including in-process

testing for bioburden and potency, container/closure integrity, sterile media fills, and environmental controls. Again, some of the significant GMP deficiencies noted were similar to those found during the current inspection. While we acknowledge your efforts in the past to correct the deficiencies cited by FDA, we have concluded that your overall corrective action plan is unacceptable and incomplete, and that Parkedale must correct the significant CGMP deficiencies disclosed by the current FDA inspection before it may continue the production and distribution of Influenza Virus Vaccine.

ASEPTIC PROCESSING

FDA's current inspection of Parkedale revealed numerous significant deficiencies in the aseptic processing of Influenza Virus Vaccine. The investigators documented that the manufacturing process is not adequately validated and does not demonstrate a stepwise reduction in bioburden. Rather, numerous monovalent strain lots of the B/Yamanashi component that demonstrated low levels of bioburden following inactivation with formaldehyde, subsequently became contaminated with high levels of bioburden later in the manufacturing process. For example, eight monovalent strain lots contained over 100 colony-forming units (cfu) per milliliter (ml) of contaminating organisms immediately prior to the final filtration steps with ——— filters. These lots of in-process product were used to formulate finished product lots of Influenza Virus Vaccine. The lots of vaccine passed final product sterility tests and were distributed.

In addition, FDA discovered that the ——— filters used to render the product sterile have never been validated for bacterial retention using in-process product or an appropriate surrogate. In your September 3, 1999 letter to FDA you stated, "Parkedale qualified the filtration process in terms of bacterial retention. The study utilized ——— ——— as the challenge organisms for the ——— filter." However, our investigators documented that Parkedale has never performed microbial retention studies and the qualification study referenced was performed by one of the filter manufacturers. The filter manufacturer did not use Parkedale's Influenza Virus Vaccine or in-process product or an appropriate surrogate to conduct the referenced study.

FDA is concerned because Parkedale failed to recognize, investigate, and take appropriate corrective action in response to elevated levels of bioburden. We note that your September 3, 1999 letter to FDA reported an alert limit of — cfu/ml and action limit of, "exceeding alert limit on three consecutive bioburden samples" for post — and prefiltration product pools. However, monovalent strain lots that exceeded the newly established bioburden limits were used to formulate trivalent vaccine after your September 3, 1999 commitment. We also note your November 15, 1999 letter to FDA in which you further modified the alert and action limits for these in-process products. Your letter states that an investigation will be initiated in the event that the action limit is exceeded, however, you failed to explain the actions to be taken. For example, it is unclear whether monovalent strain lots that exceed the action limit will be quarantined and/or excluded from production. FDA is also concerned about Parkedale's reliance

upon the ——— filtration step to provide sterility assurance for final vaccine product manufactured using monovalent strain lots contaminated with high levels of bioburden, without ever having validated the filtration step.

While we acknowledge your promises of improvements in control of the environment in the — column room, you have not adequately addressed the — columns as sources of bioburden. For example, the ——— and the ——— are reused repeatedly and only changed between strains or if the flow rate decreases to a certain level. The sanitization of the ——— media and ——— has not been adequately validated and the number of uses of the — column has still not been established. You state in Parkedale's November 15, 1999 letter that the — "column sanitization validation will be completed during the 1999/2000 Fluogen manufacturing season," and you acknowledge that "formal qualification of the——— filtration columns has not previously been completed." This response is unacceptable to FDA.

Further, FDA investigators documented nine instances where environmental monitoring of viable particulates in the — column room exceeded the action limit and no action was taken. Instead of taking corrective action, the excursions were "accepted" by the quality assurance (QA) unit based on the subsequent filtration steps and the fact that the finished vaccine products passed sterility testing. It is our view that review of final product sterility testing results does not constitute adequate corrective action. Parkedale neither increased the number of sampling sites or the frequency of sampling. Additional cleaning was not performed and the source of the environmental contamination was not investigated.

POTENCY TESTING

The current FDA inspection revealed that the standard operating procedure (SOP) titled, "Influenza Virus Vaccine (SOP 1200, Version 4)," that provides procedures for the evaluation of in-process, finished product, and stability ——— potency testing data for Influenza Virus, is not always followed in that retesting and re-reading of test results have occurred. In addition, this procedure is inadequate because it does not include any references to the internal formulation "guidelines" or "targets" used as part of Parkedale's formulation strategy. For example, the investigators documented that vaccine lot number 02979 was tested numerous times for potency in July and August 1999, after the initial tests failed to meet the internal "guidelines" for all three components. Subsequently, Parkedale lowered the guideline for the B/Yamanashi component to ——— (mcg) (from ———) in late September 1999, released the lot, and selectively reported only some of the testing data in its October 8, 1999 letter to FDA. FDA is concerned that Parkedale continues the practice of extensive retesting for potency when the initial test results are below the internal guidelines/targets. We are also concerned that decisions regarding the extensive retesting appear to have been made with the knowledge of the quality control unit and management personnel.

PARAGRAPH XVI NOTIFICATION

Based on the above observations, FDA has concluded that the conditions under which Influenza Virus Vaccine is manufactured do not comply with CGMP. Under the terms of paragraphs XVI and XVII of the Consent Decree, Parkedale must immediately cease operations with respect to 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. FDA will not issue such notification unless and until Parkedale completes the following actions:

1. Parkedale shall within 30 days of receipt of this letter, submit an outline of all critical steps, and the test methods used to evaluate those critical steps, in the manufacturing process of Influenza Virus Vaccine. FDA will review the critical process steps submitted and provide comments. Contemporaneous with FDA's review, Parkedale shall continue to establish and implement manufacturing process validation protocols within a time frame acceptable to FDA.

2. Parkedale shall perform microbial retention validation studies of all ——— filters using in-process Influenza Virus Vaccine product. The challenge organism(s) should be small enough to challenge the retentivity of the filter and simulate the smallest microorganism that may occur in production.

3. Parkedale shall:
   a) establish bioburden specifications for in-process products based on historical data and scientific judgment;
   b) quarantine in-process products that fail to meet the established bioburden specification; and
   c) establish procedures for investigating bioburden failures and determining the final disposition of in-process products that fail to meet bioburden specifications.

4. Parkedale shall immediately revise and implement the environmental monitoring program for critical and controlled environments to include investigations and specific corrective actions to be taken when action levels are exceeded.

5. Parkedale shall:
   a) immediately revise its potency testing ——— and laboratory investigation procedures so that excessive retesting and re-reading are prohibited;
   b) retrain all laboratory and quality assurance personnel on the revised potency testing and laboratory investigation procedures; and
   c) implement the revised procedures.

Following conformance with the terms of item 1 and completion of items 2 through 5 above, Parkedale may resume manufacturing, processing, packing, and labeling, but not

distribution, of Influenza Virus Vaccine. A responsible corporate officer shall certify conformance and completion of items 1 through 5 in writing to FDA prior to resumption of these operations. In addition to items 1 through 5, Parkedale must take the following actions within 120 calendar days of this notification with submissions to the agency on a quarterly basis thereafter:

6. Parkedale shall perform adequate validation studies of the purification processes for Influenza Virus Vaccine performed in buildings 46 and 8, and based on those findings, revise specifications referenced in the batch production records and procedures. Parkedale shall establish the acceptable number of uses of the ——— and ——— used in the —— and —— columns based on the results of these studies.

7. Parkedale shall:
   a) establish and implement a cleaning validation program that includes all aspects of the Influenza Virus Vaccine manufacturing process; and
   b) validate the sanitization of ——— and —— used in the —— and ——— columns.

8. Parkedale shall conduct proper media fills. Media fills will be conducted appropriately and correctly according to current guidelines, in that, all media filled vials will be incubated and examined; all positive vials will be recorded; production activities will be simulated; and records of reconciliation will be accurate.

Following completion of items 2 through 8 and prior to any distribution of finished Influenza Virus Vaccine, FDA will verify satisfactory completion of the above corrective actions and substantial compliance with CGMPs. In accordance with paragraph XVII of the Decree, FDA will issue to Parkedale written notification permitting resumption of all operations, including distribution, upon FDA's determination that Parkedale is in substantial compliance.

CORRESPONDENCE

FDA has reviewed Parkedale's letters dated August 26, and September 3 and 13, 1999, which respond to FDA's letter dated August 25, 1999, and provide a quality master plan outline, a summary of the status of corrective actions, process validation protocols for Fluogen and Aplisol, and a summary of the WFI system enhancements. We are also in receipt of your letters dated August 31, September 16, 28, and 29, October 7, November 4, and December 6, 1999, which contain the monthly potency data for the 1999-2000 Fluogen lots, the revised Fluogen formulation strategy, and the revised stability protocol for commercial lots of Fluogen manufactured for the 1999-2000 season. Additionally, we have reviewed your November 15, 1999 response to the Form FDA 483 issued at the close of the inspection on October 13, 1999. As stated earlier in this letter, we have concluded that your overall corrective action plan is unacceptable and incomplete and our comments and requests for further information and clarification are detailed below.

November 15, 1999 Letter

In your November 15, 1999 response you acknowledge that the bioburden data collected by Parkedale does not adequately demonstrate the step-wise reduction of bioburden during the manufacturing process for Influenza Virus Vaccine. While we generally agree that enhanced environmental controls and continued bioburden monitoring of in-process product are important, we have the following comments:

1. You state that the —column room will be "environmentally monitored — during operational activity. Thereafter, the — Column Room will be environmentally monitored — during operation activity." This revision of the frequency of monitoring appears to require substantially less environmental monitoring of the — column room than is described in SOP Number 3110, Version 2.0, titled "Environmental Microbiological Monitoring Program – Buildings 8, 43 & 46." Version 2.0 of this procedure requires —

Please explain the rationale for decreasing the environmental monitoring of the — column room.

2. You state repeatedly that a Notice of Event (NOE) and an investigation will be initiated when action levels are exceeded in the environmental monitoring program and the in-process product bioburden monitoring program. This response is unacceptable because you fail to provide immediate, specific corrective actions that will be taken.

September 3, 1999 Letter

Observation 1.A. – You state that all Fluogen bulk vaccine tanks are outfitted with vent filters that are integrity tested before and after use, and that these filters are left "open during bulk vaccine storage because of the temperature changes associated with these transfers." Please explain how vent filters are "left open" without compromising the sterility of the bulk vaccine.

You state that the data contained in your letter dated July 9, 1999, supports your decision to remove the nitrogen blanket from the bulk storage tanks. We note that the scope of the experiment was limited to the effect of the nitrogen purge on the potency of the B/Yamanashi strain stored at two different temperatures during a four week test period. Please comment.

Observation 1.F. – You state that, based on the data submitted in your July 9, 1999 letter to the FDA, you have determined that neither the free formaldehyde nor the oxygen head space concentration had an impact on potency. However, the data presented in Attachment 3 of the July 9, 1999 letter does not appear to be correlated to potency values

for each lot. In fact, the potency of eight of the lots listed in Attachment 3 fell below the release specification by the nine month stability measurement. Please comment.

Observation 1.L. – As discussed earlier in this document, we disagree with your statement that Parkedale "has evidence to support the progressive reduction of bacterial load with each manufacturing step." Also, the proposed bioburden specifications (alert and action limits) are unacceptable, as discussed during the September 23, 1999 meeting between the FDA and Parkedale.

Observation 21B – Your response is unacceptable because it does not address the issue of sampling being representative of water usage. Water should not be sampled after flushing of the drop points unless the drop points are always flushed prior to the water being drawn for use in routine manufacturing.

September 13, 1999 Letter

The retrospective validation report and the prospective validation protocol are inadequate for process validation purposes. In addition to Observations 8 and 9 of the Form FDA 483 issued on October 13, 1999, the agency's specific comments are outlined below. Issues related to Tuberculin process validation will be addressed by the agency under separate cover.

Influenza Virus Vaccine Process Validation

There were numerous deviations during manufacture of the final drug product for lots used for the retrospective analysis. All deviations encountered during a retrospective analysis should be extensively investigated for potential impact on the validity of the process. Our specific comments include the following:

1. Several of the batches analyzed retrospectively (02288F, 02298F, and 02888F) had attribute failures (defects in final containers). These lots were " —— manually reworked" and deemed satisfactory. There is no mention of an investigation into these failures including corrective action taken to prevent recurrence, and a detailed description of the rework procedure was not included.

2. Batch 02988F exceeded the initial —— inspection reject rate of —— The acceptance of the lot was based partially on the "nature of product to have temporary high rejection rates." There is no explanation of this statement and an investigation report including corrective actions taken to prevent recurrence was not included.

3. Batch 02198 failed "USP sterility." It appears that a double retest was performed which also failed. An investigation concluded that the first and second failures were a result of faulty aseptic technique. The first and second

tests were invalidated. A third test was performed, passed, and was identified as a "satisfactory double volume initial test for the batch." The batch was released by the Quality Review Board. An investigation report was not included. The investigation report should contain the following information:

a) The evidence for invalidating the initial failing result (9/21/98) and allowing the first double retest to proceed; and

b) The evidence for invalidating the second failing result (9/25/98), first double retest, and allowing the double volume retest to proceed on 10/2/98.

4. The retrospective analysis did not include any of the manufacturing steps prior to the monovalent intermediates. While it is acknowledged that there may be some variation from strain to strain, this analysis should be extended to include all steps in the manufacture of the bulk drug substance.

5. Retrospective analyses are particularly useful in correlating operating parameters (e.g., time, temperature) to successful or unsuccessful outcomes for any given process step. The retrospective validation report does not identify the operating parameters and expected outcomes for each step in the manufacturing process. The retrospective analysis should be extended to include identification of the critical operating parameters and outcomes.

6. A prospective or concurrent process validation study should be designed to evaluate the process at its limits of operation. Therefore, operating parameters (e.g., time, temperature) should be clearly identified in the protocol and their limits challenged during the execution of the study. Validation studies should also include the evaluation of additional process parameters (e.g., potency, and bioburden) than would normally be measured during routine production in order to adequately assess and validate the process. The validation protocol should outline all process parameters that are to be measured for each step with appropriate acceptance criteria. Please revise your validation protocol accordingly.

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. A responsible corporate officer shall certify receipt of this notification in writing to FDA within 5 working 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.

Sincerely,

Raymond V. Mlecko
Director
Detroit District Office