DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Resea
1401 Rockville Pike
Rockville MD 20852-1448

CBER-98-015

APR 28 1998

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Jeanne Leszczynski Dr. P.H.
Deputy Director
Massachusetts Public Health Biologic Laboratories
305 South Street
Boston, MA 02130

Dear Dr. Leszczynski:

During an inspection of your facilities located at 305 South Street, Jamaica Plain, Boston, MA, 02130 between January 22 and March 4, 1998, our inspectors identified the following violations of Section 501 (a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and Title 21, Code of Federal Regulations (21 CFR), Parts 211 and 600-680:

1. Failure to ensure that equipment is cleaned, maintained, and sanitized at appropriate intervals to prevent malfunction and contamination that would alter the safety, identity, strength, quality, or purity of the drug product [21 CFR 211.67 (a)]. For example:

   a. The effectiveness of the cleaning of the vaccine filling needles did not address the vaccine material that is the most difficult to clean.
   b. The effectiveness of the [redacted] method post-cleaning for the fill needle assembly has not been established.

2. Failure to establish, maintain, or follow written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100] in that the SOP entitled "[redacted]," is incomplete in that the testing procedure does not specify actions to take when results fail to meet the acceptance criteria.

3. Failure to maintain or establish temperature and humidity controls [211.42(c)(10)(ii)] in that temperature and relative humidity acceptance levels for the class [redacted] blood product and vaccine aseptic filling area during filling have not been established. Additionally, during the filling of [redacted] (on September 11, 1997), [redacted] on August 15,

1997) and — (on August 21, 1997), the relative humidity during filling was recorded at levels higher than — (at times as high as —, and there was no investigation [21 CFR 211.192].

4. Failure to establish appropriate time limits for the completion of each phase of production to assure quality of the drug product [21 CFR 211.111] in that the effectiveness of the tanks to maintain the sterility of the bulk solutions for nine months has not been established.

5. Failure to maintain an inventory record of each component and a reconciliation of the use of each lot of such component and of the record to contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component [21 CFR 211.184(c)] in that there are no records indicating the disposition of — out of — vials of tetanus subculture MS59B, — out of — vials of tetanus subculture MT59B, and — out of — vials of tetanus subculture MT59B. In addition, an investigation including conclusions and follow up was not conducted.

6. Failure to establish scientifically sound and appropriate specifications, standards, and sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)] in that there is no justification of repeat testing following initial out of specification analytical results. For example, the procedure entitled "Limulus Amebocyte Lysate Testing (LAL)" indicates that — In addition, the initial test results are not maintained and an investigation is not initiated unless the second set of test results do not meet specifications. The procedure and the LAL worksheet (IPQC-277) are discrepant in that the worksheet states to " — and the SOP states to — In addition, there are no procedures or system in place which outline steps necessary in the documentation and justification of repeat testing following initial out of specification analytical results.

7. Failure to assure that container closure systems provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product [21 CFR 211.94(b)] in that seal integrity studies for vials of blood products (Respigam and Cytogam) filled by your contract filler have not been performed.

8. Failure to assure that the building or buildings used in the manufacture, processing, packing, or holding of a drug product are of suitable construction to facilitate cleaning, maintenance, and proper operations [21 CFR 211.42(a)] in that the floors and walls of

the tetanus production area (tetanus cultivation and toxoiding) are not smooth, hard, and easily cleaned.

9. Failure to assure that each person engaged in the manufacture, processing, packing, or holding of a drug product has training and experience to enable that person to perform the assigned functions [21 CFR 211.25 (a)] in that an employee participated in the vaccination of mice for the potency test for DTP-287 (expiration August 3, 1993) and DTP-290 (expiration August 18, 1995) on January 1, 1998, prior to appropriate training as required by the SOP entitled "Personnel Training in Approved Animal Protocols." There is no documentation that the employee (1) read the appropriate procedure, (2) observed the procedure, and (3) participated in performance of the procedure until deemed proficient by a trainer.

10. Failure of the licensed manufacture to report each adverse experience that is both serious and unexpected as soon as possible but in any case within 15 working days of initial receipt of the information [21 CFR 600.80(c)(1)(I)] in that six of 25 Adverse Event Reports (AERs) received since March 10, 1997, which warranted agency notification within 15 working days of receipt, were not reported within the appropriate time frame.

During the inspection, investigators noted that, without prior agency notification or approval, approximately ——— vials of Diphtheria and Tetanus Toxoid Adsorbed, lot DT-84, were distributed after extending the originally assigned post filling expiration date by approximately 21 months.

We acknowledge receipt of your April 10, 1998, written response which addresses the inspectional observations on the FDA Form-483 issued at the close of the inspection. You will receive our assessment of your response under separate cover. Corrective actions addressed in your letter dated April 10, 1998, may be referenced in your response to this letter.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deviations. We note that similar observations in other product areas were made by our inspectors during previous inspections at your facility. As management, it is your responsibility to assure that deviations corrected in one product system or area are also corrected in other product systems or areas of this facility as well as all facilities under your

control to assure overall compliance with the provisions of the Federal Food, Drug and Cosmetic Act and all applicable regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action includes seizure and/or injunction, license suspension and/or revocation.

You should notify this office in writing, within 15 working days of receipt of this letter, of specific steps you have taken or will take to correct or prevent these deviations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to the following address: U.S. Food and Drug Administration; Center for Biologics Evaluation and Research; HFM-600; 1401 Rockville Pike, Suite 200N; Rockville, MD 20852-1448.

Sincerely,

Steven A. Masiello
Acting Director, Office of Compliance
Center for Biologics Evaluation and Research