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CBER-98-018

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

JUN 12 1998

Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Karl Kyle
International Biologicals, Inc.
1619 Bassett Street
Piedmont, OK 73078

Dear Mr. Kyle:

The Food and Drug Administration (FDA) conducted an inspection of International Biologicals, Inc., 1619 Bassett Street, Piedmont, Oklahoma, on April 16 and 17, 1998. During the inspection, the FDA investigator identified violations of Section 501 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), Section 351 of the Public Health Service Act (PHS Act), and Title 21, Code of Federal Regulations (21 CFR), parts 600-680 and 211. These documented violations include, but are not limited to, the following:

1. Failure to ensure that all manufacturing steps are performed so that the product will contain only the allergenic and other substances intended to be included in the final product and to provide a ventilation system that will prevent the dissemination of microorganisms from one manufacturing area to another [21 CFR 600.11(a) and 680.2(a)] in that:
 - a. the laminar flow hoods located in the inoculating and Quality Analysis rooms of the mold facility have not been validated for air flow efficiency or filter integrity;
 - b. air flow has not been established in the mold inoculation and harvesting areas;
2. Failure to determine that the method of operation of sterilization equipment ensures the destruction of contaminating microorganisms [21 CFR 600.11(b) and 680.1(b)(2)(ii)] in that the autoclave in the mold facility has not been validated for sterilization effectiveness and heat distribution.
3. Failure to maintain standard operating procedures (SOP) that will ensure the identity of the seed culture, prescribe adequate processing of molds, and specify the acceptable limits and kinds of contamination [21 CFR 680.1(b)(2)(iii)]. For example:

- a. The SOP entitled _____ states that the air quality monitoring of the mold lab should be performed once a week. However, the Mold Lab Air Quality record disclosed that air quality monitoring was not performed during the weeks of 2/27/97 - 1/12/98, and 2/23/98;
 - b. The SOP entitled _____ was not followed. For example:
 - (i) Autoclaved medium was not incubated at least _____ days at room temperature so as to check for sterility prior to use in production as prescribed in the section entitled "Media Preparation and Sterilization". Mold Production records indicate that lots M4006, M4007, and M4008 were used prior to the required three day sterility check period;
 - (ii) Harvested material was not _____ as outlined in the section entitled "Harvest"; and
 - (iii) Culture plates are not incubated for _____ days as outlined in the sections entitled "Viability Testing" and "Bioburden Test". The Mold Production records for *Penicillium notatum*, lots F1747, F1748 and F1749, disclosed that the molds were incubated for greater than _____ days.
 - c. There were no procedures outlining the frequency for calibrating the scales used in mold production.
 - d. There were no manufacturer's operating manuals available nor were there SOPs established that outlined the maintenance and maintenance schedule for the autoclave sterilizer.
4. Failure to maintain records, concurrently with the performance, of each step in the manufacture and distribution of products, in such a way that at any time successive steps in the manufacture and distribution of any lot may be traced by an inspector and to document each significant step in the manufacture, processing, packing, or holding of source materials, in that the exact drying temperatures, while drying molds, are not recorded on the Mold Production records [21 CFR 600.12(a), 680.2(f) and 211.188].

Neither this letter nor the list of inspectional observations (Form FDA-483) which was issued to you at the conclusion of the inspection are meant to be an all-inclusive list of violations occurring at your facility. We remind you that it is your responsibility as a source material supplier to ensure that your operations are in full compliance with all applicable Federal laws and regulations.

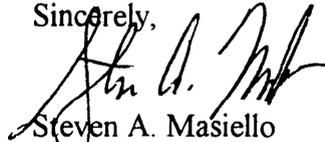
You should take prompt action to correct these violations, and those noted during previous inspections. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action includes seizure and/or injunction.

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International Biologicals, Inc.

Please notify this office in writing of the steps you will take to correct or prevent the listed violations. Your response should be sent to me at the following address: Food and Drug Administration; Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200N; Rockville, MD 20852-1448.

If you have any questions or comments regarding this letter, please contact me at 301-827-6201.

Sincerely,



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