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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

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

WARNING LETTER

CBER-08-01

January 24, 2008

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Joerg Reinhardt
Chief Executive Officer
Novartis Vaccines and Diagnostics
350 Massachusetts Avenue
Cambridge, MA 02139

Dear Mr. Reinhardt:

The Food and Drug Administration (FDA) conducted an inspection of Novartis Vaccines and Diagnostics Gmbh & Co. KG, located at Emil-von-Strasse 76, D-35041 Marburg, Germany between September 20 and September 27, 2007. During the inspection, FDA investigators documented a number of significant deviations from current good manufacturing practices (CGMP) in the manufacture of your Rabies Vaccine (RabAvert) and Diphtheria and Tetanus Toxoids Adsorbed concentrate (without preservative). These deviations from CGMP include deviations from the applicable requirements of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as well as requirements of your biologics license application approved under section 351(a) of the Public Health Service Act (PHS Act) and Title 21, Code of Federal Regulations (21 CFR) Part 601.

At the close of the inspection FDA issued a Form FDA 483, Inspectional Observations, which described a number of significant deviations in the manufacture of your Rabies Vaccine (RabAvert) and Diphtheria and Tetanus Toxoids Adsorbed concentrate (without preservative). Specific areas of concern include, but are not limited to:

PRODUCTION AND PROCESS CONTROLS

1. The sterility of media lot # [redacted] used in the RabAvert vaccine upstream process could not be assured, yet final product lots that used media lot # [redacted] were further processed and submitted to FDA for lot release. For example, two contamination events were linked to the use of media lot # [redacted]

   A. RabAvert [redacted] lot # [redacted] was observed contaminated on 16 October, 2006 with *Candida guilliermondii*.
   B. RabAvert [redacted] lot # [redacted] passed sterility testing on 19 October 2006. However, on June 20, 2007, as part of an investigation into inactivation failures,

[redacted] lot # [redacted] was retested for safety and sterility and found non-sterile. Fifty percent of the [redacted] volume was retested and failed sterility on July 7, 2007. The contaminant was identified as *Candida guilliermondii*.

The root cause for sterility failures of both lots [redacted] and [redacted] was determined to be "low levels of contamination of individual bottles of media lot #[redacted] with *Candida guilliermondii* during aseptic filling of the media lot" yet 15 additional [redacted] lots that came into contact with media lot #[redacted] did not undergo a second sterility test as was performed during the investigation of previously manufactured [redacted] lots.

2. "Master Plan Stability of Media, MPS-001" is inadequate in that the media/buffers assigned to each group were not defined, and the rationale for determining which media or buffer represented the worst case for each group was not documented in the study. Also, the actual storage containers were not represented for media and buffer solutions used in the production of Rabies Vaccine. For example, [redacted] Medium was evaluated under MPS-001 in 2004. This medium was stored in a [redacted] for [redacted] months at [redacted] Currently, Rabies Vaccine [redacted] Medium is stored in a [redacted] for up to [redacted] months at [redacted]

3. Stability study Q312-001, which was conducted to establish an expiry period for Diphtheria and Tetanus Toxoids Adsorbed concentrate (without preservative), is inadequate in that containers and closure systems used for stability sample storage are not representative of the final container. In study Q312-001, stability samples for sterility testing were stored in a [redacted] while a [redacted] was used for all other stability tests. The final container is a [redacted] sealed with a [redacted] with attached [redacted]

4. Validation study for the use of [redacted] connectors for the media formulation area of building [redacted] is inadequate in that the final report did not address the reason for the deviations or the potential effect of the deviations on the study. For example:

A. The final report inaccurately stated that media filled [redacted] were incubated according to the protocol, for [redacted] days at [redacted] and [redacted] days at [redacted] The samples were actually held for [redacted] days at [redacted] and for [redacted] days at [redacted]

B. The final report did not completely address the deviation in the batch record for the media fill study in which media was observed leaking at the [redacted] connection to the [redacted] connection [redacted] The reason for the leak was attributed to [redacted] but the impact of this event to the process validation was not addressed.

5. You failed to follow written procedures to assure proper inactivation of the rabies virus suspension. SOP 100084-06 defines Phase I of the inactivation process which requires a minimum inactivation time of [redacted] hours at [redacted] The viral inactivation incubation time at [redacted] was approximately [redacted] hours for RabAvert rabies viral harvest for batches [redacted]

INVESTIGATION OF FAILURES

6. Sterility Failure investigations are incomplete. For example:

   A. Twelve out of a total of 96 bottles from media lot # [redacted] remained after the sterility failure finding in October 2006. All 12 remaining bottles of media lot # [redacted] were discarded from production without subjecting the media to sterility testing to determine the extent of the contamination.

   B. The retain sample for filling of media lot # [redacted] was not tested for sterility.

   C. In 2005, six Rabies Vaccine [redacted] lots intended for use in Rabipur were found non-sterile, of which four were linked to contamination of media. Rabipur is non-US Rabies Vaccine. The same [redacted] and [redacted] are used for RabAvert (the US licensed vaccine) as for Rabipur. The failure investigation was closed in January 2006. Corrective actions were recommended and several were implemented, but final correction was not implemented until January 2007. From January 2006 to January 2007, two media lots, # [redacted] and # [redacted] were found to be contaminated and two RabAvert vaccine lots were linked to contamination of media lot # [redacted]

   D. As part of a failure investigation into inactivation failures, 21 Rabies Vaccine [redacted] lots that came in contact with media lot # [redacted] were re-tested for sterility prior to [redacted] of which one [redacted] lot [redacted] was found non-sterile upon retest. [redacted] rejected as part of the sterility failure investigation and lot # [redacted] was formulated into final filling lot # [redacted]

7. Your investigation of three rabies vaccine [redacted] batches which failed viable rabies virus testing after the virus inactivation process is incomplete. These lots (RabAvert [redacted] batch [redacted] RabAvert [redacted] batch [redacted] and RabAvert [redacted] batch [redacted] were rejected and your firm suspended production of rabies vaccine [redacted] in February 2007. Your investigations are incomplete in that they did not identify a root cause for the virus inactivation failures, and did not include an evaluation of the cleaning processes and procedures for product contacting equipment to determine if equipment cleaning is effective in preventing cross contamination of the inactivated batches.

CLEANING AND MAINTENANCE OF EQUIPMENT

8. Appropriate validation studies have not been conducted for critical processes. For example:

   A. SOP 102445, the cleaning procedure for the centrifuges used for [redacted] was revised May 14, 2004 to remove the requirement for [redacted] disinfection for [redacted] hours after each use/prior to cleaning.

Additionally, the cleaning procedure for inactivation [redacted] SOP 102448, was revised May 17, 2004 to remove the requirement for [redacted] after use/prior to cleaning if inactivation time and temperature requirements were met during the inactivation process. These new cleaning procedures were not validated to establish the impact of the changes on the cleaning process.

B. [redacted] used for mixing media and buffer solutions are Cleaned in Place (CIP'd) after use, then [redacted] for an undesignated time in Room [redacted] a class [redacted] area.

C. Report 402899, May 30, 2003, was provided as documentation to support the [redacted] day sterile [redacted] rabies [redacted] This study was conducted using a [redacted] Using this smaller [redacted] instead of the production size [redacted] has not been validated.

The deficiencies described in this letter are indicative of your quality control unit not fulfilling its responsibility to assure the identity, strength, quality, and purity of your components/in-process materials. Please describe in detail how Novartis Vaccines and Diagnostics will attain CGMP compliance with regard to bulk lot production and process controls and investigations. Please include in that description how Novartis Vaccines and Diagnostics will use all of the relevant information to conduct thorough investigations to ensure that adequate steps are taken to evaluate whether deviations impact product, and to implement effective corrective and preventive actions.

We acknowledge receipt of your written responses dated October 12, 2007 and November 9, 2007 which address the inspectional observations on the Form FDA 483 issued at the close of the inspection. Corrective actions addressed in your letter may be referenced in your response to this letter. Your response appears to address the individual FDA Form 483 items. However, we note that your response addresses these issues individually and not as part of a comprehensive corrective action plan.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deficiencies that may exist at your facility. It is your responsibility as management to assure that your establishment is in compliance with the provisions of the FD&C Act, PHS Act, and applicable federal 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 FDA initiating regulatory action without further notice. Such action may include license suspension and/or revocation.

Please notify us in writing, within 15 working days of receipt of this letter, of any additional steps you have taken or will take to correct the noted violations and to prevent their recurrence. Include any documentation necessary to show that correction has been

achieved. If corrective actions 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 me at the U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852. If you have any questions regarding this letter, please contact Robert A. Sausville, Director Division of Case Management, CBER at 301-827-6201.

Sincerely,

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Cc:

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