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

CBER-99-005

NOV 23 1998

WARNING LETTER

CERTIFIED MAIL - RETURN RECEIPT REQUESTED

Colman Casey, Ph.D.
Managing Director
Schering-Plough (Brinny) Co.
Innishannon
County Cork, Ireland

Dear Dr. Casey:

During an inspection of Schering-Plough (Brinny) Co., Innishannon, County Cork, Ireland, on July 20 to 24, 1998, FDA investigators documented violations of Sections 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and Title 21, Code of Federal Regulations (21 CFR), Part 211 as follows:

1. Failure to establish and follow appropriate written procedures designed to prevent objectionable microorganisms in drug products purporting to be sterile and to assure that such procedures include validation of any sterilization processes [21 CFR 211.113(b)] in that:
 - a. During sterile media fill operations, not all glass vials that are filled with growth media are incubated to detect microbiological growth. For example, following the initial inspection for defects, vials are inspected at several times during the 7 day incubation period for signs of growth and allowed to be culled if vials have a "damaged seal which has a definite impact on closure integrity."
 - b. Validation studies have not been completed to support the one week expiration period for sterile filtered isopropanol used routinely at room temperature in the aseptic production areas. In addition, the isopropanol containers are not monitored for microorganisms.
2. Failure to establish and/or follow control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing

variability in the characteristics of in-process material and the drug product, and to test and approve, or reject in-process material at the commencement or completion of significant stages of the production process [21 CFR 211.110]. For example, potency test results on in-process samples collected from the top of the vessel during mixing for lot 8-IOT-001 did not conform to the acceptance specification. However, the lot was not rejected and the data was used to support the validation study for the manufacture of Intron A (HSA Free) solution in compounding vessel

3. Failure to establish and/or follow adequate 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 and to assure that such procedures, including any changes, are reviewed and approved by the appropriate organizational units and reviewed and approved by quality control [21 CFR 211.100] in that:
 - a. Sampling procedures for Water for Injection specify the use of a sanitizing agent and sterile hoses; however, sanitizing agents and sterile hoses are not always used during normal manufacturing when Water for Injection is dispensed.
 - b. Written procedures which describe steps to be taken when personnel exceed the action limits for environmental monitoring are not always followed. For example, there was no evidence of retraining of aseptic operators in seven out of eight excursions occurring between August 1997 and June 1998.
 - c. Written procedures do not provide for Quality Compliance Group review and approval prior to the initiation of reprocessing.
 - d. Written procedures do not provide for the submission and approval of a supplement to the firm's Biologics License Application prior to release of drug product made from reprocessed or reworked drug substance.
 - e. Personnel participating in aseptic filling operations are not always trained in accordance with written training procedures 1409.90-03 "Microbial Monitoring of Personnel for Gowning Training and Media Fills" and 225.07-05 "Microbial Monitoring of Personnel for Gowning Training and Media Fills in

Neither this letter nor the list of inspectional observations is meant to be an all-inclusive list of deviations at your facility. It is your responsibility as management to ensure that your facility is in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act and all applicable regulations and standards. 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.

We acknowledge receipt of your responses dated August 18 and November 9, 1998, to the Form FDA 483 issued at the close of the inspection. We have reviewed the contents of your responses and we have several comments addressing the adequacy of some of your corrective actions. Our comments regarding corrective action are detailed below. The items correspond to the observations listed on the Form FDA 483:

Observation 2. - The August 18, 1998, response states that Intron A HSA free solution lot 8-IOC-001 and Intron A bulk drug substance batch 8-AVAW-212 have been "dispositioned by the MRB." Please provide a detailed explanation of the final disposition of this material, including the dates of the decisions by the Material Review Board.

Observation 4.b. - Your response is inadequate because it does not address the out-of-specification result in relation to the uniformity of the product. It is our view that "wording changes" and/or "improvement in the clarity of the discussion" in the validation report would not be sufficient to remedy this issue. If the purpose of the HPLC potency testing of the top, middle, and bottom samples is to evaluate the uniformity of the bulk product, perhaps a historical review of the data should be considered in order to reassess the acceptance specification of

Observation 5.a. - We have reviewed your response to observation 5.a. and the revised SOP 1430.12-02, "Purification Processes Reprocessing/Reworking." We are concerned about sections 2.0 and 3.0 of your revised SOP. Section 2.0.2. states,

Section 3.0 of your SOP states that a

It is our view that virtually all reworks, in the absence of a previously approved protocol, would constitute changes that have substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product pursuant to 21 CFR 601.12(b). In addition, no provision has been added to the SOP for submission of a supplement when a lot is reprocessed without a previously approved protocol.

Observation 8. - Your response is unacceptable because it proposes different methods of sampling for "critical" user points (where Water for Injection is added directly to the batch) and "other" user points (where Water for Injection is used to wash equipment or components). It is our view that Water for Injection should be sampled in exactly the same manner as it is used during production at all user drop points, regardless of the intended use or application.

Observation 17. - We disagree with your response to this observation. It is our view that surface monitoring of Class support areas such as compounding and component preparation should be performed periodically to indicate the adequacy of cleaning and sanitizing procedures as well as to detect contamination caused by personnel. We note that this view is articulated in the FDA's 1987 "Guideline on Sterile Drug Products Produced by Aseptic Processing," page 34. Please comment.

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Please submit in writing, within 15 working days of receipt of this letter, your responses to the violations identified in this letter. Corrective actions addressed in your letters may be referenced in your response to this letter as appropriate. Failure to promptly correct these deviations may result in regulatory action, such as seizure, injunction, license suspension and/or revocation, without further notice.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610. If you have any questions regarding this letter, please contact The Division of Case Management at (301) 827-6201.

Sincerely,



Jerome A. Donlon, M.D., Ph.D.
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

cc: Nicholas J. Pelliccione, Ph.D.
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