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MAR 12 1999

Food and Drug Administration  
Rockville MD 20857

WARNING LETTER

Certified Mail  
Return Receipt Requested

Reference No:99-HFD-340-0301

Howard Solomon  
Chief Executive Officer  
Forest Laboratories Inc.  
909 Third Avenue  
New York, NY 10022

Dear Mr. Solomon,

Your bioanalytical facility at Farmingdale, NY was inspected between October 5, 1998 and October 23, 1998 by investigators from FDA's New York District Office to review your firm's activities related to the conduct of bioequivalence studies. This inspection is a part of FDA's Bioresearch Monitoring program which is designed, in part, to validate clinical and analytical conduct of bioavailability and bioequivalence studies. This inspection covered the following bioequivalence studies:

- Study #
- Study # CIT-PK1-97-03-000 , NDA 20-822 (Citalopram)
- Study # R/1700/0004, ANDA 40-009 (Isosorbide Dinitrate)
- Studies # ANC-PK1-97-04-000 and # ANC-PK1-98-06-000 (Flunisolide)
- Studies # FLU-PK-03-000 and # R/5000/0001 (Rimantadine)

Following evaluation of the report of this inspection, we conclude that your firm has violated FDA regulation, 21 CFR 320.29a, in failing to assure the accuracy of the measured concentrations of the active drug ingredients and their metabolites in human biological matrices. We acknowledge your response to the Form FDA 483. Following an evaluation, we find that your response is not satisfactory.

Particularly, your procedure for estimating the accuracy of quality control (QC) samples based on the validated value is not accurate. Contrary to your response, the mean values of QCs estimated in the validation (i.e. validated values) only reflect the accuracy of the analytical method. The theoretical concentration of QC samples alone reflects the nominal value and should be used to set analytical run acceptance limits. For example, in Study \_\_\_\_\_ we found that the majority of QC data in several analytical runs had errors greater than \_\_\_\_\_ when QC accuracy was evaluated based on theoretical values. Consequently, the accuracy of subject data in such runs was overestimated. We also found that you exaggerated the performance of analytical methods involved by excluding unfavorable data. Contrary to your response, values outside

acceptance limits do not automatically qualify as outliers for precision analysis, unless there is an identifiable cause. It is imperative that such unfavorable data be included when evaluating the performance of analytical methods. The studies involving such violations are cited in the Form FDA 483 issued to you.

Your current practice of rejecting selected concentrations in the calibration curves solely for acceptance of QC data is not objective and is unacceptable. This practice allowed inclusion of unreliable subject data from analytical runs that should have been rejected in Studies CIT-PK1-97-03-000 and . The purpose of QC samples in an analytical run is to assure accuracy of the run. It is therefore imperative that your criteria for rejecting selected concentrations in the calibration curves be independent of QC acceptance. Analytical runs that do not meet the QC acceptance criteria should be rejected. The analytical runs involved are cited in the Form FDA 483 issued to you.

You failed to use the actual purity for analytical reference standards. You reported the standards to be 100% pure regardless of the actual purity. Therefore, the subject concentration data you reported were not accurate. Your response that certain reference standards can be assumed to be 100% pure when the actual purity is less than 100% cannot be accepted. The reported purity value should be used in your analysis. Likewise, your practice of assigning expiration dates to reference standards and stock solutions without supporting stability data needs to be reconsidered. The stability of reference standards should be assessed periodically or prior to use when the expiration date is unknown. Your revised standard operating procedure (SOP) for verifying the integrity and stability of chemical standards is not specific. Evaluation of stability of reference standards by comparing the slopes of calibration curves prepared using the same reference standards is not meaningful. The SOP has no provision for checking stability of stored stock solutions, although you use the same stock solutions for several studies. Furthermore, your allowance of degradation for stock solutions as per your SOP needs to be reconsidered. It is imperative that purity and stability of reference standards be adequately established and the actual purity be used, to assure that the measured concentrations of the drug and its metabolite(s) in human biological matrices are accurate. The studies involving such violations are cited in the Form FDA 483 issued to you.

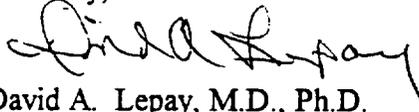
The above discussion of violations is not intended to be an all-inclusive list of deficiencies at your facility. You should take prompt action to correct these violations. If such action is not taken, we are prepared to recommend that studies conducted at your facilities be not accepted for review by the Agency. Failure to correct these violations may also result in regulatory action without further notice.

You should notify this office in writing, within fifteen (15) working days of receipt of this letter, with specific steps you have taken to correct these violations for your future studies.

If you have any questions concerning these matters, please contact:

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Associate Director, Bioequivalence  
Division of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
7250 Standish Place, Room 151  
Rockville, MD 20855  
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Sincerely,



David A. Lepay, M.D., Ph.D.  
Director  
Division of Scientific Investigations, HFD-340  
Office of Compliance  
Center for Drug Evaluation and Research