DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 26 2004

Certified Mail
Return Receipt Requested

Gilbert Godin, B.Eng., M.B.A.
Group Vice-President, Early Stage Development
MDS Pharma Services
2350 Cohen Street
Saint-Laurent (Montréal) Québec H4R 2N6 Canada

Dear Mr. Godin:

Between July 7 and 9, 2003, Allen F. Hall, Martin K. Yau, Ph.D., and Sriram Subramaniam, Ph.D., representing the Food and Drug Administration (FDA), inspected the following bioequivalence study conducted by your firm:

> Study[ ]"Comparative, Randomized, Single Dose, Four-Way Crossover, Fully-Replicated Bioavailability Study of[ ]and Schering (Claritin®) 10 mg Loratadine Tablets in Healthy Adult Males Under Fasting Conditions Following a 40mg Dose," performed for[ ]

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research, to ensure that the rights, safety, and welfare of the human subjects of the study have been protected, and to verify compliance with Title 21 of the Code of Federal Regulations (CFR), Part 320, Bioavailability and Bioequivalence Requirements.

At the conclusion of the inspection, our personnel presented and discussed with[ ]Ph.D. the items listed on Form FDA 483, Inspectional Observations. Following our review of the establishment inspection report and related documents, including the letter from Drs.[ ]and[ ]dated July 10, 2003, in response to the items listed on Form FDA 483, and the letter from[ ]Ph.D. dated October 2, 2003, we conclude that you failed to demonstrate that the analytical method used in this in vivo bioavailability study was accurate to measure the actual concentration of loratadine and its metabolite, descarboethoxyloratadine, achieved in the body, as required by 21 CFR 320.29(a).

Your analytical method for determining loratadine and descarboethoxyloratadine concentrations in subject plasma samples for this bioequivalence study used[

]

It is our understanding that during your analysis of plasma samples, it became apparent that at least 32 subject samples were contaminated because the samples contained unexpectedly high analyte concentrations. To assure accurate data when this occurred, you should have conducted a thorough and systematic evaluation to determine the extent and source of the contamination. Instead, you assumed that the contamination was limited to those samples with anomalous results. Based on this assumption, you selectively reassayed only the samples you assumed were affected, representing less than 1% of the total subject samples. We conclude that the limited steps you took to investigate and address the source of contamination failed to provide assurance of the accuracy of your analytical method as it was utilized in this study, as required by 21 CFR 320.29(a).

In your initial response to FDA Form 483 (letter dated July 10, 2003), you provided additional data and calculations that you claimed supported the validity of the original plasma sample analysis, notwithstanding the presence of contaminated samples. We note the following deficiencies in your analyses:

- You focused your analyses on the degree of contamination (i.e., the magnitude of the inaccuracy in the quality control (QC) samples) without fully addressing the extent of contamination (i.e., how many samples were contaminated). Your response failed to demonstrate any correlation between the accuracy of the QC results and the number of subject samples contaminated.
- You provided a statistical re-analysis that excluded the 9 subjects with recognized contamination. This re-analysis is not meaningful because you failed to demonstrate that the contamination was limited to those 9 subjects.
- You calculated that the QC error was only 6%. However, your calculation failed to characterize the overall performance of the assay in that at least 14 loratadine runs were rejected due to QC failure. Furthermore, the pharmacokinetic and statistical parameters you recalculated are irrelevant because your calculations were based on the unwarranted assumption that the 6% error in the accuracy of the QC results reflected the degree of contamination in all samples.
- You failed to provide any evidence to suggest that the degree of contamination was equivalent across subject samples. In fact, the data you submitted actually indicates that contamination was not equivalent because the original and repeat results for the selectively reassayed subject samples differed by a range of 2-fold to 133-fold.

Your subsequent response (letter dated October 2, 2003) described your post-FDA inspection efforts to evaluate the potential role of the [ ] in the contamination of plasma samples. This response included the results of the [ ] experiments you conducted using [ ] You indicated that your investigation did not identify the source of contamination and acknowledged that "there are numerous places where contamination might have occurred." You concluded "that it is extremely unlikely that cross well contamination in the instrument caused or contributed to the few random high concentrations observed" and that your initial assumption about the source of contamination "was erroneous." However,

notwithstanding your failure to identify the source of contamination, you maintained that your original data were "solid and valid."

In your October 2, 2003, response, you reconsidered your original position concerning the need to reassay samples, and concurred with the agency's position that all of the subject samples should have been reassayed. You subsequently re-analyzed the entirety of the subject samples, and the sponsor submitted this data to the agency on December 22, 2003. The agency conducted a follow-up inspection at your facility on February 9-13, 2004, to inspect the data from your reanalysis. Our audit found, among other things, that the data related to [redacted] experiments were missing. You claimed that these data could not be found.

As discussed above, your approach to investigating sources of contamination in bioequivalence studies is inadequate and has resulted in the submission of invalid data to the agency. You should have conducted a systematic and thorough evaluation to identify and correct the source of contamination when it was first observed. Our inspections indicate that your facility lacks adequate policies and procedures to address such contamination issues. The manner in which MDS Pharma investigated the contamination problem in this study causes FDA to have concerns with the validity of other bioequivalence data generated by MDS Pharma. Because of these concerns, the agency intends to determine on a case-by-case basis what additional steps may be necessary to assure the accuracy and validity of the analytical method for bioequivalence data generated by MDS Pharma in pending and future applications. Such steps could include, among other things, additional inspections, third-party audits, and rejection of data where circumstances warrant.

If you have questions or concerns about the issues raised in this letter, please reply to:

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Sincerely,

Joanne L Rhoads M.D.

Joanne L. Rhoads, M.D., MPH
Director
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