DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Via FedEx

AUG 3 1 2006

Stephen P. DeFalco
President and Chief Executive Officer
MDS Inc.
100 International Blvd.
Toronto, Ontario
M9W 6J6 Canada

Dear Mr. DeFalco:

Between March 6 and 24, 2006, Barbara J. Breithaupt, Sriram Subramaniam, Ph.D., Martin K. Yau, Ph.D., Michael F. Skelly, Ph.D., Nilufer M. Tampal, Ph.D., John A. Kadavil, Ph.D., and Jacqueline A. O'Shaughnessy, Ph.D., representing the Food and Drug Administration (FDA), conducted a follow up inspection of several bioequivalence studies performed by MDS Pharma Services (MDS) in Saint Laurent (Montréal), Québec Canada, including the following:

Study [ ]Tablets
Study [ ] Patch
Study [ ]Tablets

Also, between March 13 and 24, 2006, Ms. Breithaupt and Drs. Skelly and Tampal inspected several studies that measured plasma concentrations of the drug [ ]that MDS performed at its analytical laboratory in Blainville, Québec Canada, including the following:

Studies [ ]and [ ]Tablets

These inspections are a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research, to confirm that data intended for FDA submission is reliable for FDA regulatory decisions, and to verify compliance with Title 21 of the Code of Federal Regulations (CFR), Part 320, Bioavailability and Bioequivalence Requirements.

Previous FDA inspections of the MDS analytical facility in Saint Laurent found significant deficiencies that raised concerns about the validity of bioequivalence data generated by MDS. Specifically, on April 26, 2004, FDA issued to Gilbert Godin, Group Vice-President, Early Stage Development, correspondence citing MDS' failure to conduct a systematic and thorough

evaluation to identify and correct sources of contamination and implement adequate policies and procedures to address such contamination issues. The letter discussed FDA inspectional findings related to [ ] Study [ ] On December 21, 2004, FDA issued to Gilbert Godin, President and CEO, a second letter citing MDS' systemic failure to analyze and investigate anomalous testing results across multiple studies for multiple sponsors. The letter discussed FDA inspectional findings related to five [ ] studies for three sponsors [ ] and four [ ] studies sponsored by [ ] Because the identified deficiencies indicated a widespread problem in your analytical laboratory, FDA recommended that MDS review the validity of bioequivalence studies you conducted within the last five years. In response to FDA's letter, your senior management team met with FDA in February 2005 and MDS agreed to conduct a retrospective review of all bioequivalence studies conducted at the St. Laurent facility for the last five years (January 2000 through December 2004) and complete the review within one year. The original MDS plan to conduct the retrospective review was approved by MDS management in March 2005.

At the conclusion of the current inspections in Saint Laurent and Blainville, our personnel presented and discussed with Michael J. Butler, Ph.D. and Charles Grandmaison, respectively, the items listed on Form FDA 483, Inspectional Observations. The results of these inspections and our review of related documents lead us to conclude that you failed to demonstrate that your five year retrospective review is effective and capable of discriminating between valid and invalid study data and assure that the analytical methods used for *in vivo* bioavailability studies conducted in your facilities in Saint Laurent and Blainville could accurately measure the actual concentration of the active drug ingredient, or its active metabolite, achieved in the body, as required by 21 CFR 320.29(a). The details of these findings are listed below.

Five Year Retrospective Review (MDS Saint Laurent)

Our inspection found numerous significant deficiencies in your retrospective review, including the following:

- You provided incorrect information to FDA regarding the status of studies undergoing retrospective review. You misrepresented the study status and failed to report an accurate account of your progress to FDA. You informed FDA on January 26, 2006, that you closed the review of 225 studies. Our inspection found that this number was not accurate and that you repeatedly removed studies during the inspection from the list of closed studies without documented justification. You indicated during the March 2006 FDA inspection, that only 98 of [ ] studies under review were closed. Your response to the Form 483 dated April 21, 2006 indicates, contrary to the information you provided in January 2006 and during the inspection, that "none of the studies under review are closed." You state that MDS used the term "closed" differently on different occasions. These explanations are inconsistent and unacceptable. Your response dated April 21, 2006 stated that you believe you provided "an explanation of what the meaning of closed was" in your communications with FDA prior to FDA's March 2006 inspection. We have no documentation that supports your claim. Furthermore, your acknowledgement in

the April 21, 2006 response that there were "weaknesses in certain documentation and change control practices" regarding study status fails to provide FDA the necessary assurance that MDS is capable of completing a well-controlled and reliable retrospective review. You failed to close a single study by the end of the audit's one year period.

- You failed to appropriately include studies in the retrospective review. The review was to include the analytical portions of human bioequivalence studies performed at the MDS facility in Saint Laurent that were intended for FDA submission. Our inspection found that you excluded [ ]Study[ ]although the study was pivotal to the approval of the sponsor's generic drug application for[ ]tablets. Your claim that Study[ ]was excluded because of a clerical error, and your determination after FDA's March 2006 inspection that at least another nineteen studies were inappropriately excluded (MDS responses dated April 21, 2006, May 19, 2006, and June 9, 2006), further confirm the FDA position that your five year retrospective review is ineffective. It also demonstrates that you lacked appropriate procedures for the critical step in the retrospective review (i.e., the identification of studies intended for FDA submission). Also, please refer to the study-specific deficiencies for Study[ ]below.
- Management failed to approve revisions to the original review plan dated March 2005 and the user guides (audit tools for reviewers and supervisors) for the retrospective review study audits, as of the start of FDA's March 2006 inspection. Furthermore, MDS reviewers failed to document which version of the user guide was used for each study audit. Thus, there is no assurance that reviews were conducted in accordance with original or revised procedures.
- You failed to demonstrate that your retrospective review process was capable of identifying and evaluating significant issues that affect data validity. The following studies are examples:

[ ]Study[ ]<u>(MDS Saint Laurent)</u>

In addition to your failure to include Study[ ]in the retrospective review, our inspection of this study found that you failed to assure that the[ ]method was accurate when using additional[ ]procedures for sample processing. Although your written method allowed for[ ]you did not assess whether these processing procedures impacted assay accuracy. Our inspection found that your analysts failed to document when the additional procedures were used and that numerous subject samples were coded "lost in processing" and re-extracted because of[ ]blockage. In your response dated July 21, 2006, your retrospective review of Study[ ]conducted after FDA's March 2006 inspection, concluded that "there is no evidence that the use of[ ]and/or[ ] adversely affected data validity." However, you failed to support your conclusion with data generated by an experiment designed to evaluate the impact of the additional processing procedures. Furthermore, you stated that these procedures have been used "in many studies over many years." "Long term use" is not a sufficient assurance of assay accuracy. For these reasons, you have not demonstrated that the reported concentration results in Study[ ]are accurate.

[ ]Study[ ](MDS Saint Laurent)

Our inspection found that the pharmacokinetic profiles for some subjects had unexpected concentration results. For example, maximum concentrations (Cmax) of[ ]were followed by a sample with no measurable drug concentration or occurred at the first or last post-dose blood sampling time points. In addition to aberrant results at or near Cmax, there were anomalous concentrations at other time points in the pharmacokinetic (PK) profile. You failed to investigate the cause of these anomalous results, or reassay the affected samples. In your response dated June 9, 2006, your retrospective review of this study concluded that "considering the low frequency of occurrence across the entire study sample set as well as within the individual PK profile, these incongruent concentrations do not impact the overall accuracy and/or validity of the reported data." Contrary to your response, the frequency of occurrence is not a justification for accepting anomalous study results. Because of these unexplained anomalous results, we are concerned about the accuracy of the reported PK parameters (Cmax and AUC) for individual subjects based on your concentration results. Your failure to investigate anomalous results in this study is similar to previous FDA inspectional findings for numerous studies regarding[ ]and[ ]as discussed in the FDA letters to MDS dated April 26, 2004 and December 21, 2004.

[ ]Study[ ](MDS Saint Laurent)

Our inspection found that the Period I samples from Subject 19 had internal standard (IS) responses that were 5 to 6 times the average IS response of calibrators and quality controls. You did not adequately investigate the anomalous results or reassay the affected samples. Your retrospective review dated May 19, 2006 concluded that the abnormal IS response is "subject specific" and "not due to an analytical reason," providing no documentation to support your position. Contrary to your response, the IS response for Subject 19 in Period 1 fails to demonstrate subject specificity because the Period 2 samples for Subject 19 did not exhibit a similar abnormally high IS response. Also, since you failed to demonstrate that a similar aberrant response occurred upon reanalysis, you lack data to support your conclusions.

[ ]Study[ ](MDS Saint Laurent)

Our inspection found that you failed to identify the biased exclusion of individual calibration points from the standard curve in run 13. Recalculation of the standard curve in an unbiased manner during the inspection found that the run should have been rejected because the quality control (QC) samples did not meet the run acceptance criteria. Your retrospective review dated January 4, 2006 failed to identify the biased exclusion and failed to determine that the data from the run was not valid due to QC failure.

[ ]Studies[ ]and[ ](MDS Blainville)

FDA also inspected numerous studies for[ ]conducted at your Blainville facility. Our inspection found that your analytical method for[ ]is seriously flawed and is not

capable of reliably measuring [ ] concentrations in subject samples. Specifically, several studies for multiple sponsors (e.g., [ ] Study [ ] Studies [ ] Study [ ] Study [ ] had large inconsistencies between original and repeat results for incurred subject samples. The root cause investigation that you conducted about the anomalous data for [ ] Study [ ] found that your assay was not reproducible. For this study, more than 40% of the repeat results differed from the original results by approximately 20-275%. Although you discontinued use of the [ ] method in August 2005, you failed to inform study sponsors that the data you generated with this method was invalid until two months after the March 2006 FDA inspection. This extensive delay does not constitute timely or responsible reporting on the part of MDS. We also note that your reported [ ] plasma concentrations in these studies were significantly higher (three to twenty times) than those reported by other laboratories conducting similarly designed [ ] bioequivalence trials in healthy subjects. According to the MDS response dated May 23, 2006, you eventually informed eight study sponsors that your data for nineteen [ ] studies was not reliable.

These study-specific findings from FDA's March 2006 inspection are in addition to previous deficiencies found during FDA inspections in July 2003, February 2004, and September 2004. The previous inspections found that your analytical methods were not demonstrated to be accurate when utilized in the following ten bioequivalence studies:

Study [ ]		Tablets
Study [ ]		Tablets
Studies [ ]	and [ ]	Tablets
Studies [ ]	and [ ]	Tablets
Studies [ ]	and [ ]	Suspension
Studies [ ]	and [ ]	Tablets

In summary, the significant deficiencies regarding your five year retrospective review and failure to demonstrate the accuracy of your analytical methods in more than thirty studies for six different drugs confirm that there are widespread problems at your facilities in Saint Laurent and Blainville. Based on FDA's multiple inspections of these facilities (July 2003, February 2004, September 2004, March 2006) and our evaluation of numerous studies, we conclude that you failed to systematically investigate contamination and anomalous results, conduct an effective retrospective review, and demonstrate that your retrospective review is capable of discriminating between valid and invalid study data.

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

C.T. Viswanathan, Ph.D.
Associate Director, Bioequivalence
Chief, GLP & Bioequivalence Investigations Branch
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
7520 Standish Place, Room 116
Rockville, MD 20855

Sincerely,

Joseph P. Salewski

Joseph P. Salewski
Acting Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research