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Pharma Services

March 26, 2001

Charles W. Sedgewick
District Director
Kansas City District
U.S. Food & Drug Administration
11630 West 80th Street
Lenexa, Kansas 66214-3338

Dear Mr. Sedgewick:

FDA Investigator George L. Van Wey, FDA Investigator Eric Nielsen, FDA Chemist LaTonya M. Mitchell, and FDA Pharmacologist Michael F. Skelly conducted a detailed inspection of multiple clinical trials and bioanalytical projects performed at MDS Pharma Services, Lincoln, Nebraska, and Phoenix, Arizona. The inspection began February 26, 2001 and concluded March 2, 2001. Three inspectional observations were listed on a Form FDA 483 issued at the conclusion of the inspection. During the wrap up meeting, we agreed to provide written responses to the inspectional observations.

Observation 1:

Reserve samples for the manufacturer and therefore were not available to FDA for sampling at this clinical site. Reserve samples for selected and retained at the clinical site (MDS Harris, Phoenix, AZ). were returned to were not

Response:

Through a misunderstanding of the applicable regulations, the reserve samples for these two studies, by agreement with the sponsor, were retained elsewhere and were not retained at the study site. The procedure that permitted this to happen was changed July 2000 and all required reserve or retention samples are being maintained. The sponsor has submitted an amendment to their IND clarifying how retention samples for the stated studies were handled and where they can be located.

Observation 2:

Software Problem Report # was written in response to a user-reported error in regression calculation in study. To date, there has been no final conclusion, resolution, correction, or evaluation of this error report. The extent and impact on data generated by the affected program, xpl_fit, has not been determined.

Charles W. Sedgewick

March 26, 2001

Page 2

Response:

The investigation of this error report was continued with renewed priority. The investigation shows that in the module `sserr` within the program `xpl_fit.c` a log of `-14.4575` were being taken. The C compiler accepted the log of `-14.4575` but produced an outrageous number, which could not be used in the statements following the log function and a high performance arithmetic trap was produced by the software. The error was reproducible whenever a log of a negative value was taken at this step and the error always produced a result easily recognized to be in error because it was far outside the normal or expected range.

It was determined the absolute value should have been taken prior to the log function. The use of absolute value in a log function was already included in other appropriate places within the software. When the program was changed to perform this function it executed on the curve in question without any errors. As an initial test, the data from the curve were compared to the data produced from a commercial package (Softmax Pro v.3.0) and the data was found to be equivalent. Additionally, the entire study data for this study have been generated by Softmax regression and sample concentrations from the affected program vs. Softmax will be compared side by side and with statistical analysis. The full statistical analysis will be completed by March 30, 2001.

A validation of the new change to the software will be performed. We will write a test plan, set up the acceptance criteria, execute the test plan and document this process. This validation will be completed by March 30, 2001 and if the software meets the acceptance criteria it will be implemented. Documentation will be retained as part of the validation documentation for the software package.

The second part of the observation was that the extent and impact on data generated by the affected program, `xpl_fit`, had not been determined. Because the reported error was found to be reproducible and in all instances resulted in values far outside the normal or expected range, the erroneous values were neither accepted nor used in the reported data.

Observation 3:

The information systems standard operating procedures for software problem Reporting are inadequate in that software problem reports are not resolved in a timely manner and software problem report summaries are not reviewed on a periodic basis.

Response:

The standard operating procedure for Software Problem Reporting (19.01.007) was modified and reissued on March 7, 2001 to require documented review of software problem reports by information systems supervisory personnel. Reviews will occur at one month intervals to ensure that problems are resolved in a timely manner. Documentation of SOP training for all associates responsible for compliance with the procedure is entered into the MDS Phanna Services training system.

Charles W. Sedgewick

March 26, 2001

Page 3

If possible, we request that this response be attached to the associated Form FDA 483 when copies of the Form FDA 483 are requested through the Freedom of Information Act or other sources.

We appreciate the opportunity this inspection offered to examine our procedures, as well as the courtesies extended to MDS Pharma Services associates.

Sincerely,



Herbert W. Smith

Senior Director, Quality Assurance

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