Four Lessons from MDS Montreal

Early in 2007 the FDA finally gave up hope that the contract bioanalytical testing facility, MDS Montreal, would be able to resolve the uncertainty associated with many of its bioanalytical methods used to support clinical studies between the years 2000 and 2004. The FDA placed the responsibility back onto the sponsors by directing them to take corrective action ranging in preference from repeating the affected studies to performing an extensive retrospective evaluation of the supporting bioanalytical method validation and analysis used to support the studies.

It is unfortunate that this situation came into being and much attention has been focused on the short-comings of the testing facility. However, the same detrimental outcome can occur at any testing facility during the conduct of any particular study. The sponsor is ultimately responsible for any of the work performed in association with their filings and there are four important lessons to be learned about how a sponsor manages its relationship with a contract facility performing bioanalytical testing and exercises due diligence in managing this work.

Vendor Qualification: Generally, pharmaceutical companies require that any new vendor be qualified prior to placement of work. The qualification procedure usually involves a member of the Quality Assurance or Compliance group going on site and reviewing the facilities procedures and systems. Often these auditors have no knowledge of bioanalytical testing and can only determine if procedures exist, not if the procedures are technically acceptable.

Lesson 1: As part of the vendor qualification process, a person should be included on the inspection team who is technically qualified to evaluate the procedures specifically related to bioanalysis. This person should be able to determine if the method validation procedures conform to current industry standards. This person should also be able to review method validations that the facility has developed for non-proprietary drugs, to determine how well they follow their own procedures in real-life applications.

Method Validation: The method validation is often viewed as an annoying activity that delays the actual activity of sample analysis. Many sponsors review the published validation report and leave it at that.

Lesson 2: The method validation should be thoroughly reviewed. A responsible person should inspect the study file and supporting data to evaluate the activity for compliance to the facilities SOP's and to ensure that it was performed in technically competent manner.

Sample Analysis: Sponsors are interested in the results of sample analysis in that these results are the quantitative end-product of the clinical study. The

sponsor usually has expectations about how these results will look and expends effort in evaluating them to determine if, as a group, they fit the expected profile or if there are individual results that fall outside of the expected ranges.

Lesson 3: The sponsor should care about how the method performs during the analysis of their samples. A responsible person should receive information from the laboratory during the course of study and coordinate with the facility as it evaluates the over-all performance of the method with respect to such things as batch failure, precision, accuracy, linearity, range, and carry-over. If any of these areas show degradation of performance over the course of the study, or fail to perform as originally validated, the responsible person should work with the lab to get resolution of the problem prior to the analysis of new samples.

Long-Term Stability, Sample Storage and Final Disposition: Often the sponsor losses interest in the bioanalytical method and even their own study samples once they have their results in hand. They often don't give thought to the final disposition of the method or making arrangements for the long-term storage of their samples in a way that would make future re-analysis possible.

Lesson 4: A method is not complete once the initial validation activities are finished, and often still not complete after the analysis of samples. There is long-term sample storage to be evaluated and sometimes information comes to light during the course of the drug development program that requires changes to the method such as adjustment of the range or the addition of metabolites to the assay. Based on specific clinical study requirements, additional concomitant medications may have to be evaluated. Samples should be stored in a safe and secure location along with quality control samples so that if future analysis is required the long-term storage can be adequately assessed.

What Should You Do?

Prospectively, you should implement the lessons described above for every new bioanalytical service provider and every time a new method is developed or used on your behalf.

Retrospectively, if your organization has performed clinical studies with a bioanalytical component that will be filed with the FDA, a qualified individual should perform an evaluation of the method validation and sample analysis. If the evaluation brings any deficiencies to light, take prompt action to ensure the problem is addressed or rectified. Ensure that all samples are adequately stored and that QC samples are stored with them.