Bioanalytical 483 and Non-clinical 483
Summary of Bioanalytical and Non-clinical 483's

Subscription Date: Example

This is the date range of the subscription delivery. These are based upon the calendar quarter, i.e. 1st Quarter 2011

Explanation

This is an example of the type of deliverable you will receive about every three months. It contains the excerpted Form 483 observations. Note that the time of the inspection and the location of the facility are not disclosed. The intent is to provide you with the actual observations so over time you as a professional in the industry can understand the focus and direction of FDA inspections and enforcement. This should help inform your decisions about compliance in your own daily activities. The file is locked so you cannot print or extract text from the file. It is searchable by keyword and the observations have been entered into the sheet by related categories, based upon the 21 CFR part 58 requirements and bioanalytical activities.

Each deliverable will contain a brief synopsis of trends, important observations, or new observations. These are divided between Non-clinical and Bioanalytical.

Synopsis

Non-Clinical: The greatest number of observations are for the Study Director and their role as the person responsible for ensuring the protocol is followed and that deviations from the protocol and related SOP's are acknowledged, evaluated for impact on the study, and documented in the final report. There seems to be much more scrutiny of the role of the Study Director and expectation of full disclosure in study reports. Reinforcing this trend are observations for failure to follow the

protocol or amend it properly and the failure to relate these deviations in the final report. There is emphasis on ensuring that signed reports from contributing scientists are included in the study report.

Bioanalytical: The observations continue to emphasize the importance of using freshly prepared QC samples to control analytical runs evaluating stability samples (QC samples). Additionally, there are observations noting failure to have clearly established procedures (SOP's) for manual integration and sample reanalysis and reporting. There is emphasis on the long-standing issue of inadequacy of the analytical range based upon the measured concentrations of the study samples that are analyzed.

Reference	Observation	Comment
Personnel (58.029)		
21 CFR 58.029 (b)	The testing facility failed to maintain a current summary of training and experience and job description for each individual engaged in or supervising the conduct of the nonclinical laboratory study. Specifically, training records were incomplete for two individuals involved in dosing animals (of two reviewed) for study xxx conducted from 7/22/04 to 8/19/04. A. The record for employee no 6899 showed that training in swine oral gavage was initiated 2/2/04; however, the technician qualified to perform function section was not signed off by the instructor. B. The record for employee no 6838 showed that training in swine oral gavage was initiated 1/30/04 but not signed off by the instructor in the technician qualified section until 8/20/04, after study dosing.	Keeping training files and SOP training documents up to date can be a very time-consuming task. Annual reviews between supervisors and direct reports should check for missing entries and QA should review these for each study and perform an annual internal review to check for inadequacies.

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Testing Facility Management (58.031)		
21 CFR 58.031 (f)	Testing facility management failed to assure that all personnel clearly understood the functions they were to perform. Change in the storage condition for the test article utilized in study xxx was made without the approval of the study director. The change in the storage conditions for the test article utilized in study xxx was made after receiving direction from the group leader, not the study director nor has the study protocol amendment been written or approved by the study director.	When it is decided that a change must be made to some procedure (or storage condition, in this case) it needs to be documented and then reconciled against SOP's and the protocol to see if there is any problem.
Study Director (58.033)		
21 CFR 58.033 (a)	The study director failed to assure that the protocol, including any change, was approved and was followed. Study director failed to assure that the test article utilized in studies xxx were stored as required by the study protocol.	There is greater scrutiny of the role of Study Directors and the overall control they exhibit of the study.
21 CFR 58.033 (c)	The study director failed to assure that unforeseen circumstances that might affect the quality and integrity of the nonclinical laboratory study were noted when they occurred and corrective action taken, specifically, the study director failed to investigate bacterial contamination after the histopathology findings revealed bacteria in multiple organs and at the catheter/infusion sites for early death animals as well as animals that survived to terminal sacrifice. Although samples of dosing solutions were available for testing, the study director did not have them tested for bacterial contamination or investigate other possible sources of contamination.	There is greater scrutiny of the role of Study Directors and the overall control they exhibit of the study.
21 CFR 58.033 (c)	Not all deviations from standard operating procedures in a study were authorized by the study director and documented in the raw data. Specifically, in that the scale monitoring records for scales xxx and xxx used in study xxx were not reviewed within two weeks from the last data collected on the record, as required by SOP xxx for the following dates: (dates listed) Additionally, the xxx record with the last data entry of 9/27/02 is missing the initial date on the left side of the record and the time and date the reading was taken.	Some organizations are not very formal in how protocol and SOP deviations are documented and then acknowledged by the Study Director. There is greater scrutiny on how Study Directors manage and document these issues.

The observations are redacted by the FDA prior to delivery. Redacted material is denoted by "xxx" and can cover one word or whole sentences.

21 CFR 58.033 (c)	Not all deviations from standard operating procedures in a study were authorized by the study director and documented in the raw data. Specifically, for study xxx concerning receipt and return of test and control articles: On 8/5/04 additional control material (group 1) and additional test article material (group 4) were requested by the animal department. Although the two additional containers were recorded and released by the TMC department the additional receipt and later return of the two containers was not recorded. This was a deviation from SOP xxx.	While the observation addresses the Study Director not acknowledging and documenting the deviation, it appears that the underlying issue is the chain of custody documentation of study-critical materials.
21 CFR 58.033 (c)	The study director failed to assure that unforeseen circumstances that might affect the quality and integrity of the nonclinical laboratory study were noted when they occurred and corrective action taken, specifically, regarding study xxx according to the final report, during day 29, 168 hours post-dose bleed, animals numbers: xxx experienced significant trauma to their eyes during bleeding procedure. Animal xxx exhibited seizures following the bleeding procedure. The impact of these unexpected events was not assessed by the study director at the time of the occurrence, and there is no documentation o the corrective actions put in place to prevent a recurrence.	This comes from the requirement that the Study Director is the single point of control and interpretation for study data. Careful review of observations must be performed, since others may not recognize the significance or trends over time.
21 CFR 58.033 (c)	The study director failed to assure that unforeseen circumstances that might affect the quality and integrity of the nonclinical laboratory study were noted when they occurred and corrective action taken, specifically, regarding studies xxx according to the final report, animal xxx respectively suffered leg fractures due to struggling during dosing. The impact of these unexpected events was not assessed at the time of occurrence, and there is no documentation of corrective action put in place to prevent a recurrence.	This comes from the requirement that the Study Director is the single point of control and interpretation for study data. Careful review of observations must be performed, since others may not recognize the significance or trends over time.
21 CFR 58.033 (c)	The study director failed to assure that unforeseen circumstances that might affect the quality and integrity of the nonclinical laboratory study were noted when they occurred and corrective action taken, specifically, regarding study xxx on 9/22/07 a planned power interruption went longer than expected. The impact of this unexpected event was not assessed by the study director.	There is greater scrutiny of the role of Study Directors and the overall control they exhibit of the study

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Quality Assurance Unit (58.035)		
21 CFR 58.035 (b) (6)	The quality assurance unit failed to review the final study report to assure that each report accurately described the methods and standard operating procedures, and that the reported results accurately reflected the raw data of the study. The final report for study xxx inaccurately reported the storage conditions of the non-radio labeled test article.	This is a big load to lay on the QA group, since they are not the only ones responsible for reviewing the report. However, there should be adequate coverage between operations, study director, and QA so that all important information is reviewed at least once.
General (58.041)		
21 CFR 58.041	The testing facility is not of suitable size and construction to facilitate the proper conduct of nonclinical laboratory studies. Specifically, the limited access from the outside via the incoming receiving area was compromised in that the gap on the bottom of the overhead door and the regular door is sufficient for pest and insect intrusion. The door into the glassware washing room (119) was found to be open in the receiving area, where clean glassware was found on the bench top unprotected from possible contamination. Washing machine and dryer used to launder employee scrubs and laboratory coats were located adjacent to room 119.	One should always consider the flow of samples and animals through a facility and the ingress and egress of personnel when laying out workspaces. This should be periodically audited by the QA group.
Specimen and Data Storage Facilities (58.051)		
21 CFR 58.051	Space is not provided for archives, limited to access by authorized personnel only, for the storage and retrieval of all raw data and specimens from completed studies. Specifically, the key to the archives is kept in the drawer of an adjacent office which cannot be locked. This office is also located in close proximity to the waiting area.	Archives can be a room or a file cabinet – it just has to have limited access. Limited access means that the Archivist alone should control access to keys.

Equipment Design (58.061)		
21 CFR 58.061	Not all equipment used in the generation, measurement, or assessment of data is of the appropriate design and adequate capacity to function according to the protocol and is suitably located for operations, inspections, cleaning, and maintenance. Refrigerator's alarm system is inadequate in that it will not alarm until the temperature has reached below 0°C, freezing temperature for two hours. Study compounds, reagents, and/or retains may be kept in refrigerators. Furthermore, this facility utilized residential grade refrigerators which do not allow the firm to set temperatures accurately.	Adequate equipment should always be used, especially storage units. These should have industry- standard temperature monitoring and alarm capabilities.
Standard Operating Procedures (58.081)		
21 CFR 58.081 (a)	Not all significant changes in established standard operating procedures were properly authorized in writing by management, specifically, standard operating procedure xxx require a release of animal to study form to be completed for the animals in a study prior to initiation of the study. During the inspection it was discovered on 6/24/04 that no form and no evaluation had been completed for the 53 mice in study number xxx and the study was initiated on 6/23/04. The deviation was not authorized as of 6/24/04.	Hard to tell if this is an issue of failure to follow the procedure or unable to find the documentation. Possibly this is the wrong initial citation and should be citing the failure to follow established SOP's
Animal Care (58.090)		
21 CFR 58.090 (b)	Not all newly received animals from outside sources were isolated and their health status evaluated in accordance with acceptable veterinary medical practice, specifically, during the review of an on-going study number xxx which began on 6/23/04 it was found that no release of animal study form or document examination and evaluation of the 53 mice acquired for the study had been completed prior to beginning the study. Upon further review it was found that the examination and evaluation had not taken place prior to 6/24/04.	Hard to tell if this is an issue of failure to follow the procedure or unable to find the documentation.
21 CFR 58.090 (g)	Not all animal feed and water were analyzed periodically to ensure that expected contaminants were not present at levels above those specified in the protocol. Study number xxx or the firm's standard operating procedure does not specify the level of acceptable contaminant allowed in the animal water. Furthermore, water analysis conducted in December 2005 showed 8 cfu and pH was found to be below NJDEP and federal standards for four out of 8 analyses over the last two years. Also, there is no action plan for contamination levels as the firm does not have an established an acceptable contamination limits.	Most facilities just hold themselves to whatever the municipal water supplier provides as the drinking water requirements, and accept at face value the certificate of analysis provided by feed suppliers. However, it is still the

		responsibility of the facility management to review, interpret and then either accept or reject the results of these tests. Corrective action is required when they do not pass.
Conduct on Nonclinical Laboratory Study (58.130)		
21 CFR 58.130 (a)	Concerning study xxx the 44 beagle dogs received on 1/23/02 ranged in age between approximately 5 and 5.6 months old. Although the protocol specified that dogs should be at least 6 months old at receipt, a written protocol deviation or other evaluation was not prepared or noted in the final report. (However birthdates were included in the final report).	Protocols should be amended before the fact or a deviation documented after the fact.
21 CFR 58.130 (a)	Not all nonclinical laboratory studies were conducted in accordance with the protocol. Specifically, study xxx protocol states that the test article is to be stored at 17 to 27^{o}C, however the test article was placed into a freezer. Study xxx protocol states that the non-radio labeled test article is to be stored at room temperature. However, the shipments of the test article were placed in the freezer upon receipt. Study xxx the blood, urine, and feces samples collected during the conduct of the study were pooled when analyzed, however, this method was not specified in the study protocol.	Important information (or exceptions) should be established in the protocol, otherwise facility SOP's should dictate the appropriate action. All people involved in conduct of the study should have access to the protocol to ensure they follow the specific directions provided in the protocol.
Reporting of Nonclinical Laboratory Study Results (58.185)		
21 CFR 58.185 (a)	The final study report did not include a description of all circumstances that may have affected the quality or integrity of the data. Specifically, that in the final report for study xxx it was not discussed by the study director how the presence of the test article in the blood of control animals (not exposed to the test article) might have affected the interpretation of the study.	This points to the possible failure of the Study Director to review the bioanalytical results carefully before finalizing the report.

21 CFR 58.185 (a) (2)	The final report did not include the objectives and procedures stated in the approved protocol, including any changes in the original protocol. The final study report did not report the change in the storage conditions of the test article utilized in the study.	When the final report is written it must be reconciled against the protocol, all deviations to the protocol and relevant SOP's.
21 CFR 58.185 (a) (12)	The final study report did not include the signed and dated reports of each of the individual scientists or other professionals involved in the study. Specifically, the final report for study xxx did not include a separate and signed report from the pathologist.	This is a hot topic with the FDA. Even draft reports are being cited for having unsigned contributing scientist reports.
Bioanalytical - Validation		
Guidance for Industry Bioanalytical Method Validation (2001)	For bioanalytical study number xxx sponsor reference number xxx, failure to use freshly prepared calibration standards in the validation study for short-term matrix (freeze/thaw) stability and the processed-ample viability (sample processing stability) studies.	It is expected that freshly prepared calibrators must be used for quantitation and freshly prepared QC samples to determine if a batch is acceptable when running any stability (QC sample-based) evaluations.
Guidance for Industry Bioanalytical Method Validation (2001)	For study xxx a comparative bioavailability study of xxx tablets 10 mg under fasted conditions, observed the following: failure to compare the test article stability samples against freshly prepared standard and QC samples during a) long term stability verification, b) freeze/thaw stability verification, c) process samples stability, 3 days at room temperature stability.	It is expected that freshly prepared calibrators must be used for quantitation and freshly prepared QC samples to determine if a batch is acceptable when running any stability (QC sample-based) evaluations.
Test and Control Article Handling		
Guidance for Industry Bioanalytical Method Validation (2001)	For study xxx a comparative bioavailability study of xxx tablets 10 mg under fasted conditions, observed the following: failure to validate the expiration date and storage conditions for the assigned reference standard for xxx batch/lot number xxx.	It is hard to interpret this one except that if there is any reason to doubt the expiration date for reference material, then the laboratory will have to establish this for themselves.

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Bioanalytical – Sample Analysis		
Guidance for Industry Bioanalytical Method Validation (2001)	For study xxx a comparative bioavailability study of xxx tablets 10 mg under fasted conditions, observed the following: failure to maintain written SOP for the manual integration criteria	The bioanalytical laboratory must have an SOP that establishes the circumstances under which peak reintegration can be performed, how it will be done and documented.
Guidance for Industry Bioanalytical Method Validation (2001)	For study xxx a comparative bioavailability study of xxx tablets 10 mg under fasted conditions, observed the following: failure to maintain written SOP's that detail carryover acceptance criteria and the procedure for corrective action.	The bioanalytical laboratory must have an SOP that establishes the procedure for minimizing sample carryover, and how to address carryover or suspected carryover.
Guidance for Industry Bioanalytical Method Validation (2001)	During the review of project number xxx with study ID xxx protocol number xxx the following observation was made: Selection of QC levels was not appropriate in the QC's were at 3, 100, and 200 ng/mL whereas 100% of subject plasma xxx concentration were between 1-25 ng/mL and about 50% of subject plasma xxx concentration were between 10-70 ng/mL.	This relates to adequacy of range. The Crystal City 3 (2006) recommendations clearly establish the expectation that the range and QC levels will cover the actual study sample concentrations.
Guidance for Industry Bioanalytical Method Validation (2001)	No documentation of the justification for the subsequent manual reintegrations. The original results with automatic integration prior to manual reintegration cannot be confirmed. For example: a) Manual reintegration's in the electronic record were not consistently documented on the printed chromatograms in the study file, b) chromatograms with the original; integration before manual change were not maintained and the basis for the manual reintegration was not documented. Based on the electronic data, approximately 25% of the xxx QC's across the study were manually reintegrated., c) there were no established criteria for the manual reintegration of chromatograms, and d) handwritten additions to printed chromatograms regarding manual reintegration were not contemporaneous with study conduct. For example, chromatograms printed on January 24, 1997 had additions dated February 14, 1997.	Chromatogram reintegration should be defined in an SOP for the circumstances under which it occurs and how it will be performed. All reintegrations must be documented

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Bioanalytical – Sample Management		
Guidance for Industry Bioanalytical Method Validation (2001)	For study xxx a comparative bioavailability study of xxx tablets 10 mg under fasted conditions, observed the following: failure to maintain complete freezer entrance/activity logs such that samples removed/returned to the freezer can be tracked.	The facility must maintain adequate chain of custody of samples, including transfer to and from storage containers for processing. This is important as a mechanism for tracking the number of freeze/thaw cycles for individual samples.
Guidance for Industry Bioanalytical Method Validation (2001)	For study xxx a comparative bioavailability study of xxx tablets 10 mg under fasted conditions, observed the following: failure to maintain the shipping courier records for the receipt of plasma study samples, further the firm failed to maintain manual confirmation of verification by an individual that study samples were received by the firm on any day or the firm failed to use an electronic barcode system to verify the receipt of study samples by the firm.	Apparently there must be a robust system for the receipt of samples from courier including the collection and maintenance of the actual courier records.
Bioanalytical – Report		
Guidance for Industry Bioanalytical Method Validation (2001)	For bioanalytical study number xxx sponsor reference number xxx, failure to document all study data in the final bioanalytical report. Only four original samples from subject 1009 were reported in the table, analytical reassay summary, as being reassayed, because they were above the quantitation limit. However, at the sponsor's request, all samples from the duplicate sample set for this subject were additionally reassayed without being reported.	There is increased sensitivity to full disclosure of analytical results, regardless of the reason for reanalysis. The whole process must be tightly controlled: request for reanalysis, how it is performed, and how it is reported.
Guidance for Industry Bioanalytical Method Validation (2001)	For bioanalytical study number xxx sponsor reference number xxx, failure to be consistent with established, written SOP for accepting and reporting reassay results. - For subject 1042 the reassayed data were reported when the original data were confirmed.	The bioanalytical lab must have an SOP that clearly spells out the circumstances under which reassay can be performed, how they will be performed, and how they will be reported.

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