GLP Medical Device CRO Warning Letters: Two Companies' Perspectives and Learnings

Co-sponsored by GLPSS and MDSS
Agenda

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GLP Medical Device CRO Warning Letters, GLP interpretations

Presented by:
Barb Munch
Munch GLP Consulting, LLC
GLP Specialty Section, past chair
Disclaimer – I do not work for FDA, or represent the FDA.

Presenters are providing their own opinions.

It’s not unusual for a firm to perceive an observation differently from the FDA.

What we don’t have is the FDA perspective.

The bottom line for us all is the work we do directly impacts public health.
GLP Interpretations

- Limitations of Warning Letter reviews by other firms
- Be careful how Warning Letters are interpreted or applied
- Slides are my interpretations, not based on APS or NAMSA experiences
- FDA text in black, my thoughts in red
- Concepts presented once
GLP Interpretations

APS

1. Failure of the Study Director to fulfill responsibilities …
   a. …did not take corrective action for animal deaths and unexpected study findings…
   • SD to explain unforeseen circumstances to show they are in control of the study.
   b. …failed to ensure that the protocol was followed.
      i. …required evaluation of the activated clotting time (ACT) during the implant procedure every (b)(4) minutes. The ACT for several animals were not evaluated at least every (b)(4) minutes as required by the protocol.
      • This time was determined to be scientifically required and important enough to include in the protocol, but the protocol was not followed.
      • The difference in time was not documented as a deviation, nor was it identified by QC, QA, or SD.
1. Failure of the Study Director to fulfill responsibilities ... (cont)
   c. ...failed to ensure that all raw data, documentation, protocols, specimens, and final reports were transferred to the archives during or at the close of the study.

   • 58.3(p), Close of Study ”Study completion date means the date the final report is signed by the study director.”
APS

2. Failure of the Quality Assurance Unit (QAU) to fulfill responsibilities...
   a. For study (b)(4), the QAU did not identify that surgical technicians performed anesthesia of animals but failed to maintain the required tidal volume range. The animals were ventilated on average 38% higher than the maximum amount defined in the “(b)(4)” training provided by your firm’s veterinarian.

   - Text hard to interpret.
   - Had QAU been trained in this procedure?
APS

3. ...failure to ensure that water used for the animals was analyzed...
   b. The SOP titled “(b)(4)” required sampling from (b)(4) rooms and (b)(4) utility sink at the (b)(4) facility, the (b)(4) facility and the (b)(4) facility for (b)(4). Your firm failed to follow your SOP by not analyzing the water samples from the (b)(4) facility in 2016...
   • Failure to follow your water testing SOP was a deficiency noted during a previous FDA inspection which ended on (b)(4)...
   • Staff failed to follow SOP.
   • Repeated event, preventative action was not effective.
We also note that the water supply valves and the hot water heater were broken for an undetermined amount of time at the (b)(4) facility. The water supply valves were not inspected for two years and the hot water heater was not on a maintenance or inspection schedule. On March 19, 2018, hot water was observed to be unavailable in the facility’s animal rooms, restrooms or surgical sink outside of (b)(4)...

- Preventative maintenance on facility equipment.
- Appears to be newly identified issue.
1. Failure of the Study Director to fulfill his or her responsibilities...
   a. ...did not ensure that review and evaluation of clinical pathology data by the attending veterinarian was performed contemporaneous with data collection.
      • Not done in a timely manner; if data had shown impact to animals the SD could have taken action at that time.
   b. ...failed to ensure that the protocol was followed in regards to kidney sectioning, and blood and urine collection.
      ii. ...However, raw data shows that all terminal blood samples were collected...
      iii. ...the protocol states that (b)(4). However, raw data shows that (b)(4).
   • Staff failed to follow protocol.
   • Sampling error not identified or documented as deviation.
2. Failure to adequately identify study specimens
   b. Specimens were not identified by study, type, or date of collection for the following studies:.....

   • 58.130(c) Specimens shall be identified by test system, study, nature, and date of collection.
   • Assume ‘type’ = ‘nature’
GLP Interpretations

NAMSA

3. Failure to provide for orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens, and interim and final reports, and to have an archive index...

- FDA’s investigator observed that specimens were stored outside of your firm’s archives, in a tissue and supply closet.
  - Not under control of Archivist.
  - Firm does not have an index of materials retained in the on-site archives...
  - Index of study specific records (contents, e.g. clin path, necropsy), and archive index location (e.g. rack 1, shelf A).
  - SD reviews, signs/dates prior to transfer, Archivist confirms all records are present and complete.
NAMSA

4. Failure to adequately identify reagents and solutions used in the laboratory areas...
   • reagents and solutions in the laboratory area which lacked concentration, storage requirements, and expiration date. Additionally, this is also a requirement found in your firm’s SOP...

   • Provide evidence that expired reagents were not used on a GLP study.
   • Include reagent lot number and expiration date in study data or equipment records.

Closing reminders
GLP Medical Device CRO
Warning Letters,
Medical Device Learnings

Presented by:
Christy Hansen, RQAP-GLP
Hansen Quality Assurance Consulting, LLC
SQA Medical Device SS, vice chair
Disclaimer – I do not work for FDA, or represent the FDA.

Test and Control Article Retention - Regulation

- According to 21 CFR 58.105(d), For studies of more than 4 weeks’ duration, reserve samples from each batch of test and control articles shall be retained...

- The 1978 preambles outline the rationale for retention. “Maintaining a reserves sample is necessary to provide independent assurance that the test system was exposed to the test article as specified in the protocol.”
Test and Control Article Retention – Real Life Challenges

- Each article represents its own lot
- The article is a piece of capital equipment
- The sponsor cannot obtain enough control article (typically a competitors product)
Test and Control Article Retention – Solutions?

- During the 2019 SQA Annual Meeting, an FDA representative provided guidance on how to best handle the lack of retention in a GLP study.
  - Include the information in the protocol or, if discovered during the conduct of a study, amend the study to include the lack of retention.
  - A GLP deviation documented and impact assessed by the Study Director.
  - Include the lack of retention in the final report.

- It may also be beneficial to obtain and retain documentation from the sponsor that can help explain WHY there is a lack of retention articles.

- CAUTION! Even if these steps are performed, it is still non-compliant and it could result in a 483.
GLP Medical Device CRO Warning Letters, Responding to FDA: What Does FDA Expect?

Presenter:
Thomas Purdue, RQAP-GLP; GLP Compliance Analyst V, Boehringer Ingelheim Pharmaceuticals, Inc.
Responding to FDA: What Does FDA Expect?

- Disclaimer – I do not work for FDA, or represent the FDA.

The views expressed are those of the presenter, they do not necessarily reflect those of the FDA or Boehringer Ingelheim Pharmaceuticals, Inc., my previous employers, other employees, my wife, my siblings and their pets; none of which accepts any liability for the content of this presentation.

Lest we forget:

FDA inspections are enforcement actions. These inspections are performed to verify the quality and integrity of the data underlying GLP safety studies submitted to US government. FDA inspections test the claim of GLP compliance made in these regulatory submissions required under the FFD&C Act. These submissions are used in decisions that protect the lives of clinical patients and potentially more patients if approved.
Responding to FDA: What Does FDA Expect?
Responding to FDA: What Does FDA Expect?

- A written response to FDA allows the firm to:
- Provide details of how 483 observations have been or plan to be addressed.
- Provide Investigation/evaluation/analysis of what conditions/events led to those specific 483 observations.
- Add any additional information related to the scope of issues found:
  - short and or long term impact
  - Systemic or isolated nature
  - Impact to study or patient safety (if any)
Responding to FDA: What Does FDA Expect?

- Conduct comprehensive investigation into each observation
- Identify observation category and any trends
- Develop plans to remediate the observations – short term, long term & (if needed) process impact
- Provide documentation to FDA in your response
- Response should include effectiveness checks
Responding to FDA: What Does FDA Expect?

- If a Form FDA-483 is issued – Firms should respond in writing
  - Restate all observations as written in the form FDA-483
  - Provide an explanation – (you can indicate if you agree or disagree) however your response should express your understanding of the observation and your compliance analysis of why your planned response adequately addresses the observation and
  - how this response resolves/addresses any potential impact on current or ongoing GLP studies/processes
Responding to FDA: What Does FDA Expect?

• **If a Form FDA-483 is issued – Firms should respond in writing**
  - Describe any assessments you made and corrective actions taken with achievable timelines for implementation. These might include any study or facility deviations, SOP updates, investigations, training/retraining, etc.
  - Address the impact on the current study(s) cited and the SD action taken and (potentially) any other on-going and/or future studies
Responding to FDA: What Does FDA Expect?

- If there were no Form FDA-483 observations, but there are discussion items?
  - Consider impacts and corrective actions needed to mitigate further/future regulatory action (next inspection).
  - Strongly recommend a written response, as these items will be included in the Establishment Inspection Report (EIR) and are reviewed by other experts further up the line at FDA who may decide that discussion items are (in fact) departures from the regulations.
Responding to FDA: What Does FDA Expect?

- If were no Form FDA-483 observations, but there are discussion items?
  - Resolving “Discussion items” shows TFM’s commitment to study integrity and quality and...
  
  (FDA will follow-up on these items at the next inspection)
FDA 483 Observations can be avoided, how?
- By ensuring those personnel involved in GLP work fully understand the study protocol and GLP regulatory requirements related to their work; this baseline of knowledge is the minimum any firm should provide when conducting GLP studies.
Responding to FDA: What Does FDA Expect?

- Training
  - Make it effective for your staff – (have a measure of training effectiveness)
  - Most firms provide training and yet there are still violations – Why?
  - Yearly GLP training may not be enough; training tailored to the study requirements or study work attributes; in other words Training geared to the trainee’s job role/description
Responding to FDA: What Does FDA Expect?

So...
To Summarize: Responding to FDA

FDA: Response Checklist

- Include a commitment to compliance from the most responsible official = TFM
- Address each observation separately
- Note whether you agree or disagree and why [written justification; build a case]
- Provide both corrective (current study) and preventative (future studies) actions
- Provide both completed and planned actions (with timeline for completion)
To Summarize: Responding to FDA

FDA: Response Checklist

- Evaluate and discuss impact of changes on studies or processes
- Provide a method of verification or monitoring of the effectiveness of your current/proposed corrective action
- Submit documentation (evidence) [deviations, training, CA, updated SOPs]
- Submit a response within 15 working days; This can be a specific plan and timeline for completion (meet all timeline commitments)
• FDA-482 will list the geographical district office and phone number
• FDA Ombudsman
• Program Director, Deputy Program Director, Program Division Director
The ORA Ombudsman is dedicated to two primary objectives:

- Informally address concerns, complaints, and other issues that arise between ORA and stakeholders outside of the Agency, including industry, governmental organizations (federal, state, territorial, and tribal), and other members of the public; and
- Engage in outreach and education for these stakeholders and employees of ORA to enhance communication and transparency with stakeholders.

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GLP Medical Device CRO Warning Letters, Review by NAMSA & APS

Presented by:
Sean Cadaret – NAMSA, Regional Leader, Quality Operations, North American Laboratories
Emily Markuson – APS, Director, Process Improvement
Disclaimer – *We are presenting this information from the viewpoint of our companies, not the FDA*

Why are we doing this?
- Share experience with others in industry
- Training
- Share complete story of inspection process leading up to Warning Letter

Current Status:
- Both NAMSA and APS have received letters of acceptance for their proposed actions from the Warning Letters and are currently awaiting follow-up inspections
• General Inspection Experience
• 21 CFR 58 non-conformance findings
  • Test Article/Specimen Labeling
  • Training Evidence
  • Archiving
  • Study Director Responsibilities
• Other interesting findings
General Inspection Experience
NAMSA

- North American Science Associates (NAMSA)
  - November 1 to November 17, 2017
    - Form 483 issued with 3 observations
  - Prior inspections
    - August 2009, VAI
    - July 2012, VAI
- Unannounced “routine” BIMO Inspection for medical device GLP testing started in the late afternoon with a tour
  - Several days into the inspection, it was clear that it was more directed at a specific Sponsor’s study submission.
  - Should have more directly engaged the Sponsor at this point – possessed detailed knowledge of FDA concerns.
- One BIMO investigator
- Several days spent offsite with “at home” review of data
- Daily hours were usually 10 – 6, sometimes later.
American Preclinical Services (APS)
- March 19 to April 13, 2018
  - Form 483 issued with 4 observations
- Previous inspection
  - 2014, NAI
  - 2011, VAI
- Unannounced “routine” BIMO Inspection for medical device GLP testing started in the morning with opening meeting and a tour
- Two BIMO investigators
- Several days spent offsite with “desk” review of data
  - A few requests were made to have additional space available for calls unrelated to the inspection
- Daily hours were usually 9 a.m. – 4 p.m.
Both labs had some areas that were not in full compliance with the GLP regulations

- Several corrective actions were completed and evidence presented and accepted during the inspections
  - Those issues were still cited on the 483 in all cases
  - Revision of SOP (including training) for labeling and/or storage of reagents and solutions (NAMSA and APS)
  - Process was changed for animal identification on individual kennels versus the housing room during inspection (NAMSA and APS)
  - Not all areas had immediate availability of SOPs. Hard-copy books with all SOPs applicable to area were created and distributed (NAMSA).

Note: FDA has indicated that they will still cite observed deficiencies, even if they have been corrected prior to close of the inspections.
Both labs had observations for labeling

- Traceability of the labeling on the test article or specimen along with paperwork or file name wasn’t enough to meet labeling requirements
  - Interpretation of inspector was very black and white – either labeling was fully complete on the test article or specimen or it didn’t count
  - In particular – for specimens – 58.130(c) states:
    - Specimens shall be identified by test system, study, nature, and date of collection. This information shall be located on the specimen container or shall accompany the specimen in a manner that precludes error in the recording and storage of data.
    - Expectation: Specimens were directly labeled with all information (test system, study, nature, date of collection); otherwise, considered to be inadequately labeled.
Test Article and Specimen Labeling

- **APS – Test Articles**
  - Test and Control Articles used during extraction phase for biocompatibility were not in storage containers as they were work-in-progress
    - Expectation from inspector was to have labeling requirements per §58.105(c), including storage condition
    - During extraction, conditions and expiration dates are not the same as Test Article
    - Had 100% traceability with paperwork of what each test article was
  - Change made: Each extract vial now contains two labels, one with all of the requirements for a test or control article storage container and another label that indicates the extract conditions and expiration date.
Test Article and Specimen Labeling

- NAMSA - Specimens
  - Specimens were being processed for return to client
  - Slides and blocks were labeled with study number, animal ID, and block number (if applicable) and related paperwork provided 100% traceability for nature and date of collection
  - By SOP, the animal ID is directly correlated/defined to represent the animal type/test system

- Change made: Every specimen is now labeled with test system, study ID, animal ID, nature, storage conditions and date of collection and paperwork is not relied on. This can be difficult for some slides due to “real estate” needed for the full labeling.
Both labs had observations for lack of training evidence

- There is a perceived expectation to fully investigate observations, identify root causes, develop corrective actions and plan implementation of actions within the 15-day response period to the Form 483.
  - Both Warning Letters cited lack of *training evidence*
  - Challenging to fully complete investigation activities to the point where details about action plans can be shared with the FDA as part of the response within this timeframe, let alone *evidence* of training to those actions

- APS and NAMSA could have been more specific that training would occur for every revision made to every updated SOP.
  - It was implied but not always stated as separate actions:
    - Update SOP XYZ by Dec 1, 2020
    - Train all employees on SOP XYZ by Dec 14, 2020
Archiving

- NAMSA
  - Investigator expected to see a very particular style of index with full traceability of all records/specimens within the index (e.g., test article identification, test system, dates of study, nature of study, etc.)
  - Would not accept study-specific chain of custody forms to show accountability of slides/blocks, etc. for documentation of transfer to archives.
  - Method of Archival Indexing change:
    - Archive index is now more of an archive “inventory” with full (duplicative to study specimen) traceability of all specimens, records, etc., within the archives.
• APS
  • Test Article Retention
    • Instances of single lot builds
    • Control Articles can be difficult for clients to acquire, which can lead to multiple lots
    • Large capital equipment as Test Article (e.g. ablation generator)
      • Per §58.105(d), reserve samples from each batch of test and control articles shall be retained
  • Change made: Updated SOPs and created a new form and to list each lot of test and control article used on the study and its archive location. If known during protocol development that retention is not possible, recognized GLP non-conformance is included, along with a deviation in the study file and addressed in the final study report.
Archiving

• APS
  • “Extra” raw data inadvertently collected for a test system – EKG strip from defibrillator
    • Expectation of inspector was this should have been collected for all animals
    • Was not requirement of SOP or protocol
    • Retained because it was data generated on a GLP study
      • Did not have deviation in study data
Both labs had observations related to Study Director Responsibility

- 21 CFR 58 compliance issues:
  - that would not be considered significant non-conformances, and/or
  - were single occurrences of missed non-impactful deviations

- These issues were aggregated by the Investigator as a single non-compliance under §58.33 – Failure of the Study Director to fulfill his or her responsibilities.

- Therefore, it appeared that several unrelated minor non-conformances were considered to be a significant compliance issue.
Not All Observations Seemed to be Compliance Issues

- The general feeling from NAMSA and APS is that FDA has increased their own Scientific Review Expectations
- Scientific Reviewers input seemed to drive the inspection and ultimately the issuance of the Warning Letters
Not Compliance Issue?

- NAMSA – Baseline Clinical Pathology
  - The expectation is that any Clinical pathology collected for routine assessment needs to be reviewed contemporaneously upon receipt.
  - However protocols clearly indicated multiple sources of health assessment data and did not stake reliance on a single source.
  - Even if its well established and documented that data was not to be used as inclusion/exclusion study criteria.
Not Compliance Issue?

- APS
  - Reporting of Thromboembolism
    - Was addressed in four section of the Final Report
  - Study Director did not speculate on the cause of the thromboembolism
  - Observation presented in Form 483 was focused on the Activated Clotting Time (ACT) management during the procedure, not reporting of thromboembolism events
Each company held multiple follow up calls with FDA.

- NAMSA – CDRH was the lead agency
- APS – CDRH was the lead agency

In meetings, FDA staff were frequently unable to answer follow up questions without referencing “other staff” they needed to gather information from first.

- This lack of transparency led to a feeling of frustration in the process

Response process
As of this presentation, both NAMSA and APS have completed all corrective actions, have verified effectiveness and are awaiting re-inspection to close the status of the Warning Letter.
GLP Medical Device CRO Warning Letters, Q & A

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