DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

BIMO INSPECTION ASSIGNMENT - GENERAL INFORMATION

Memorandum of IND - Initiated Good Laboratory Practice Inspection Assignment

Date: February 16, 2016

From: Charles R. Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

To: (b) (5)

Subject: Premarket Original BIMO Inspection Assignment

(b) (5)

Compliance Program: 7348.808 (GLP)
PAC Code: 48808 (CDER BIMO GLP)
Priority: (b) (5)
Operation Code: 12 (Domestic)

Application Number: IND (b) (4)
Product Name: (b) (4)

Sponsor: (b) (4)

Study/Protocol Number:

Application Number	Lovelace Study/Protocol Number
IND (b) (4)	(b) (4)

Inspection Due Date: (b) (5)
EIR Due Date:

Center Participation: (b) (5)
Joint Regulatory Agency Participation: (b) (5)

Establishment(s) for inspection	FEI Number	FACTS Number
Lovelace Respiratory Research Institute (LRRI) Bldg. 9217, Area Y Kirtland Air Force Base Albuquerque, NM 87115	1000066007	11618938

Reference ID: (b) (5)

Note	(b) (5)

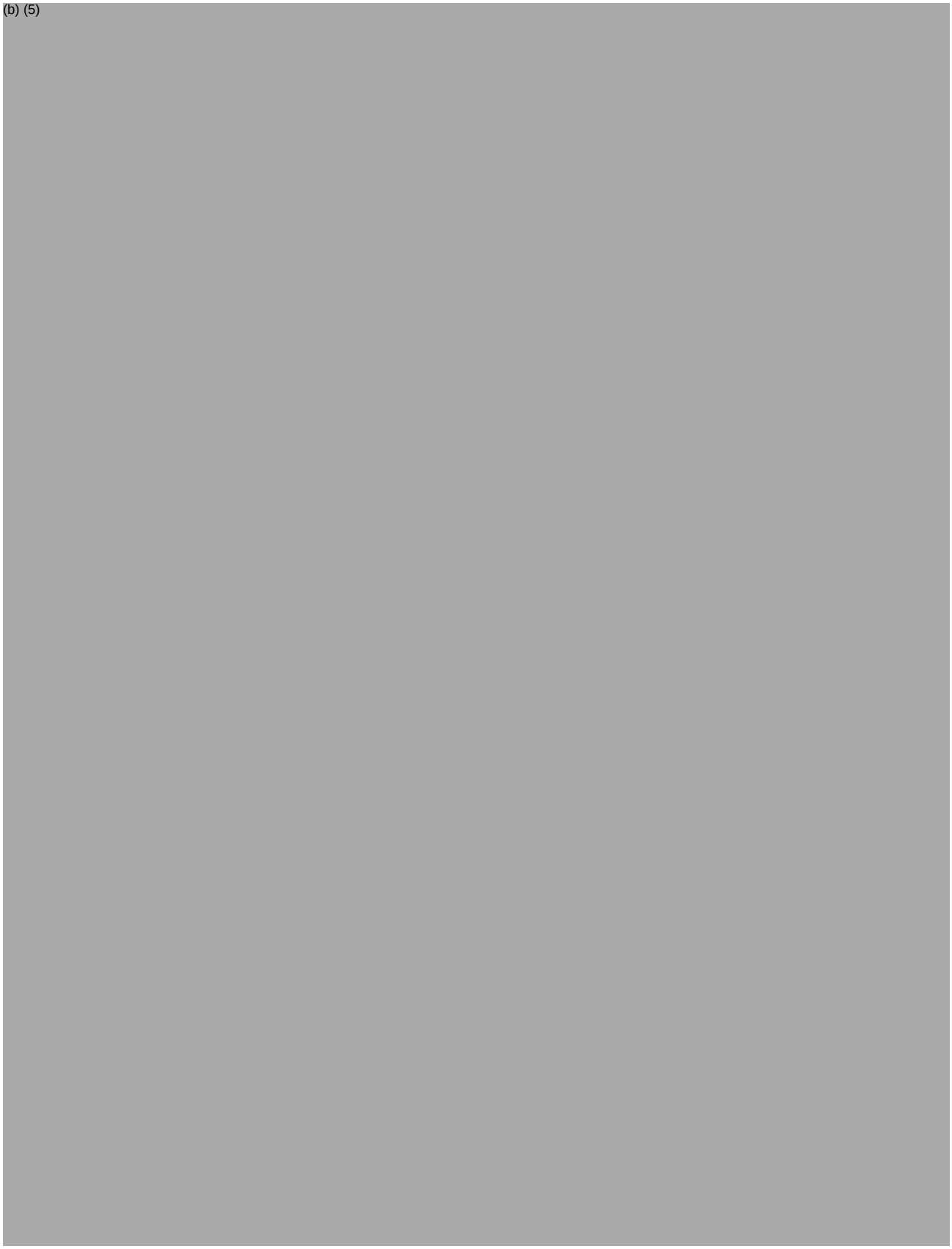
BACKGROUND INFORMATION

(b) (5)

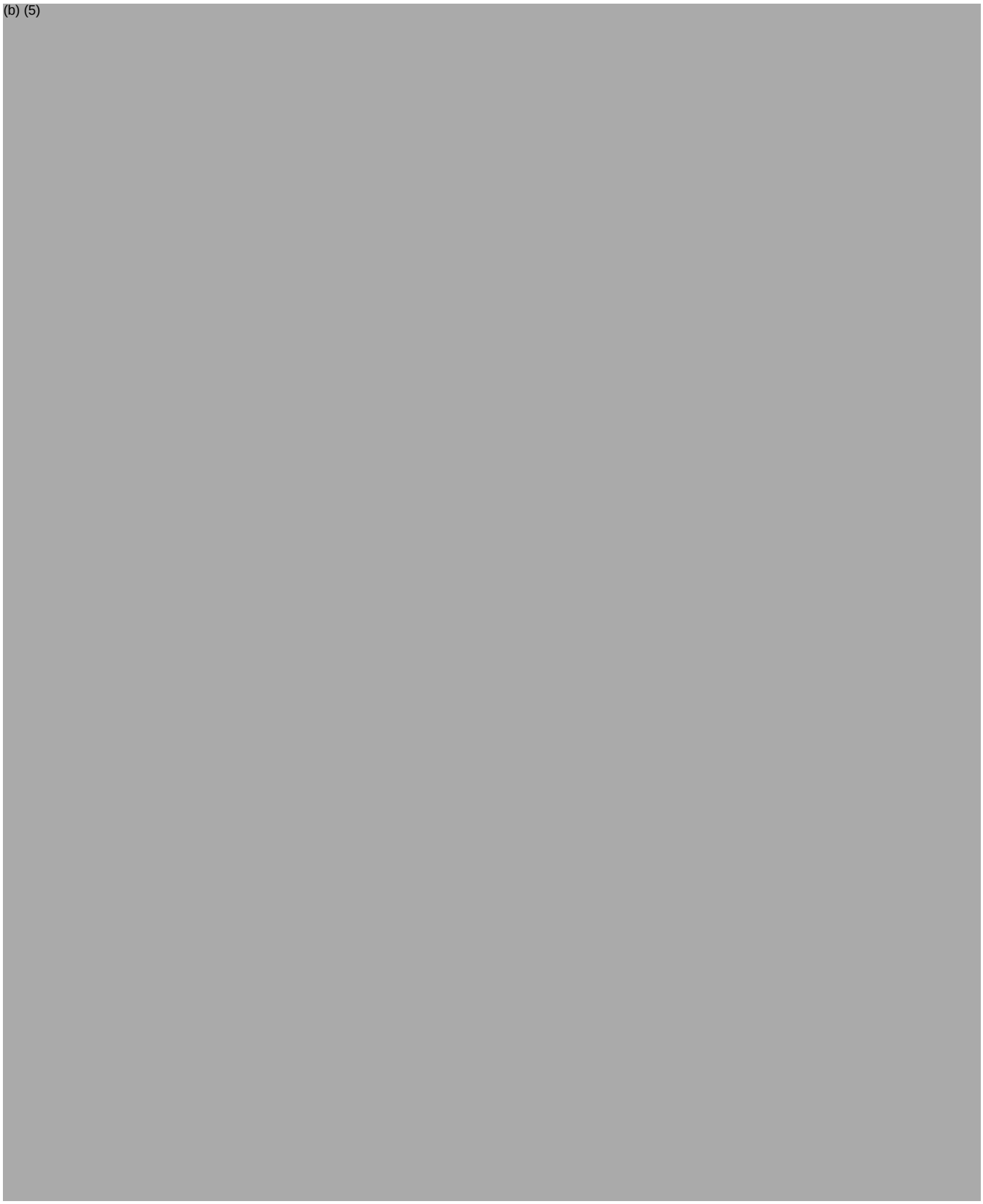
TESTING FACILITY: Lovelace Respiratory Research Institute (Lovelace, LRRI)
VISITOR ADDRESS: 2425 Ridgecrest Drive SE
Albuquerque, NM 87108
COURIER ADDRESS: Bldg. 9217, Area Y
Kirtland Air Force Base
Albuquerque, NM 87115
FEI: 1000066007

(b) (5)

(b) (5)



(b) (5)



Reference ID: (b) (5)

(b) (5)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ABHIJIT RAHA
02/16/2016

ZHOU CHEN
02/18/2016

CHARLES R BONAPACE
02/21/2016

Reference ID: (b) (5)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
PO Box 28057- Bldg 20, Denver Federal Center Denver, Colorado CO 80225 303-236-3000 Industry Information: www.fda.gov/oc/industry	10/31/16-11/4/16, 11/7/16-11/11/16
	FEI NUMBER 1000066007

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Dr. Robert W. Rubin, CEO/President

FIRM NAME	STREET ADDRESS
Lovelace Respiratory Research Institute	Bldg. 9217, Area Y, Kirkland Air Force Base
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Albuquerque, NM 87115	GLP Laboratory

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

1. The stability of each test or control article was not determined by the testing facility or by the sponsor before study initiation, or concomitantly according to written standard operating procedures which provide for periodic analysis of each batch. Specifically, validation #(b) (4) used to support the stability of test article (b) (4) demonstrates stability in stock solution ((b) (4) TA). Formulated dosage administered for study (b) (4) was (b) (4) and (b) (4).

2. The identity, strength, purity, composition, or other characteristics of each batch of test and control article have not been appropriately defined and documented. Validation #(b) (4) used to qualify analytical methods for characterization of test article (b) (4) was not performed for dose formulations equivalent to those utilized in Study (b) (4).

3. The study director did not have overall responsibility for the technical conduct of the study as well as for the interpretation, analysis, documentation and reporting of results, and does not represent the single point of study control. Specifically,

a. The study director for (b) (4) failed to assure test article characterization, and stability described within Section 5.2 of the final study report, as analyzed under validation #(b)(4), was performed in conformance with dose formulations equivalent to those used in the study.

b. Study ((b) (4)) related communications (internal and external), sufficient in detail to reconstruct the study, were not maintained by the study director, and subsequently archived as defined within SOP (b) (4) 1142,

Add Continuation Page

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	Theressa B. Smith -S	Theressa B. Smith, CSO	11/11/2016

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Maintenance of GLP Study Records and Documentation. Examples include (amendments; contributing scientist dialogue; sponsor communication).

4. The study director failed to assure that all raw data, documentation, protocols, specimens, and final reports were transferred to the archives during or at the close of the study. Specifically,

a. Protocol Section 9.0, Assignment to Study, states animals will be randomly sorted into cohorts using (b) (4) (b) (4). Randomization for animals in Cohort (b) (4) as performed in (b) (4), were not maintained for study (b) (4).

b. Study (b) (4) Procedure Checklist dated 07/10/2014 for study (b) (4) documents slides contaminants on plates from cohort (b) (4) were placed in Room (b) (4) (located in BSL-3 facility). These slides were not archived as a part of the study at the close of the study as defined within SOP (b) (4)-1081, Submission and Retention of GLP Study Records, Specimens and Samples.

c. The study director for (b) (4) was notified on 09/29/2014 images of contaminant and (b) (4) were placed in an electronic study file for viewing. These images were not archived with study data at the close of the study; nor an electronic file archived appropriately as defined within SOPs (b) (4)-1152, GLP Archive Facility Operation and Maintenance and (b) (4) 1081, Submission and Retention of GLP Study Records, Specimens and Samples.

5. Not all significant changes in established standard operating procedures were properly authorized in writing by management. Specifically,

a. A dose preparation form used to document the preparations used in study (b) (4) was incorporated into SSP (b) (4) Dose formulation preparation of (b) (4). Revisions to the form were made during Cohorts (b) (4) and (b) (4) were not in compliance with SOP (b) (4)-1185, Study Specific Procedures and fail to document appropriate

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		Theresa B. Smith, CSO	11/11/2016

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and approval by the Study Director.

b. Appropriate employee restrictions have not been applied such that revisions to forms published on (b) (4) are controlled and completed in compliance with LRRI Policy #62, Compliance Document Control and Use. Examples include: 1) Multiple versions of the form, Feed Rotation Documentation, used to identify animal feed were observed in use during the tour of the area on 11/2/2016. All versions were identified as "Rev. 07May10"; and 2) Multiple versions of the form, Archive Record Retrieval Request, were observed used for the retrieval of study records for study (b) (4). All versions were dated as "15Mar2016".

6. 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 was taken and documented. Specifically,

a. No training was documented for employee (b)(6) for (b) (4), protocol amendment #3, signed by the study director on 05/22/2014. This amendment was specific to Section 14.1 Cage Side and Clinical Observation Modification. Clinical observations were documented within (b) (4) for this employee for the following animals: (b) (4) (8/30/2014 and 09/18/2014); and (b) (4) (07/15/2014, 07/23/2014).

b. Employee (b)(6) failed to document training for (b) (4), protocol amendment #3, signed by the study director on 05/22/2014, prior to completion of tasks. This amendment was specific to Section 14.1 Cage Side and Clinical Observation Modification. Training is documented as being completed on 08/25/2014; however the employee completed clinical observation within (b) (4) on: 07/24/2014, 07/27/2014 ((b) (4)).

7. The quality assurance unit failed to review the final study report to assure that such report accurately described the methods and standard operating procedures, and that the reported results accurately reflected the raw data of the study. Specifically,

a. The sponsor's description of test article ((b) (4)) is documented as "(b) (4)" on the (b) (4)

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However, the test article is described as "(b) (4) " within (b) (4) final report.

b. The (b) (4) Chain of Custody Form for test article ((b) (4)) used in study (b) (4) document the material was received on 02/27/2014. The final report, signed by the SD on 10/23/2015, states the test article was received on 02/28/2014.

c. The (b) (4) Chain of Custody Form for control article (lot #(b) (4)) used in study (b) (4) documents the material was received on 04/22/3014. The final report, signed by the SD on 10/23/2015, states the control article was received on 04/23/2014.

8. The quality assurance unit did not monitor each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls were in conformance with FDA GLP regulations. Specifically,

a. Between April 2015 and October 2016, the firm failed to complete pest evaluations per SOP. Deviation signed on 06/20/2016 failed to accurately document this noncompliance. Specifically, 1) deviation signed on 10/27/2016 states the bait boxes were checked in August 2016; however no documentation exists for an assessment in this month.

b. SOP Deviations signed 6/20/2016 and 10/27/2016 document non compliance for evaluations and treatment of defined areas stated within (b) (4) -0569, Pest and Weed Control at LRRI (v 16-17) from October 2014- Jan 2016; Febrnary 2016 – April 2016; and July 2016. No appropriate corrective action has been implemented.

c. Pest control records for evaluations completed in May 2016, document bait station were filled at stations identified as (b) (4) and (b) (4) Additionally, a comment was recorded to state pest control was needed for building (b) (4) and (b) (4) . Subsequent (b) (4) evaluations completed in 06/2016, 09/2016 and 10/2016 do not document evaluation of these areas. A tour of these areas on 11/02/2016 confirmed the following: 1) presence of bait stations at (b) (4) and (b) (4); and 2) three damaged boxed (live trap and bait box) located around

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the building for (b) (4) and (b) (4). No deviation has been recorded.

9. Not all data entries were dated on the date of entry and signed or initialed by the person entering the data. Specifically, Media Preparation Logs fail to document the actual amounts of ingredients used in the preparation of the media. Preparation logs include the typed amount required to make the media.

10. The quality assurance unit failed to maintain a copy of a master schedule sheet that contained all required elements for all nonclinical laboratory studies conducted by the testing facility. Specifically, the most current version of the master scheduled provided during audit failed to include the test system for study (b) (4) documented as initiated on 08/28/2015. Archived copies of the master schedule maintained as required by SOP QAU-1182.7, Master Schedule. reviewed from May-October 2016 also fail to include this information

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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Albuquerque, NM 87115	GLP Laboratory

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

1. The stability of each test or control article was not determined by the testing facility or by the sponsor before study initiation, or concomitantly according to written standard operating procedures which provide for periodic analysis of each batch. Specifically, validation #(b) (4) used to qualify analytical methods for characterization of test article (b) (4) was not performed for dose formulations equivalent to those utilized in Study (b) (4).

2. The identity, strength, purity, composition, or other characteristics of each batch of test and control article have not been appropriately defined and documented. Specifically, validation #(b) (4) used to support the stability of test article (b) (4) demonstrates stability in stock solution ((b) (4) TA). Formulated dosage administered for study (b) (4) was (b) (4) and (b) (4).

3. The study director did not have overall responsibility for the technical conduct of the study as well as for the interpretation, analysis, documentation and reporting of results, and does not represent the single point of study control. Specifically,

a. The study director for (b) (4) failed to assure test article characterization, and stability described within Section 5.2 of the final study report, as analyzed under validation #(b) (4), was performed in conformance with dose formulations equivalent to those used in the study.

b. Study ((b) (4)) related communications (internal and external), sufficient in detail to reconstruct the study, were not maintained by the study director, and subsequently archived as defined within SOP (b) (4) 1142,

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Maintenance of GLP Study Records and Documentation. Examples include (amendments; contributing scientist dialogue; sponsor communication).

4. The study director failed to assure that all raw data, documentation, protocols, specimens, and final reports were transferred to the archives during or at the close of the study. Specifically,

a. Protocol Section 9.0, Assignment to Study, states animals will be randomly sorted into cohorts using (b) (4) (b) (4). Randomization for animals in Cohort (b) (4) as performed in (b) (4) were not maintained for study (b) (4).

b. Study (b) (4) Procedure Checklist dated 07/10/2014 for study (b) (4) documents slides contaminants on plates from cohort (b) (4) were placed in Room (b) (4) (located in BSL-3 facility). These slides were not archived as a part of the study at the close of the study as defined within SOP (b) (4)-1081, Submission and Retention of GLP Study Records, Specimens and Samples.

c. The study director for (b) (4) was notified on 09/29/2014 images of contaminant and (b) (4) were placed in an electronic study file for viewing. These images were not archived with study data at the close of the study; nor an electronic file archived appropriately as defined within SOPs (b) (4)-1152, GLP Archive Facility Operation and Maintenance and (b) (4) 1081, Submission and Retention of GLP Study Records, Specimens and Samples.

5. Not all significant changes in established standard operating procedures were properly authorized in writing by management. Specifically,

a. A dose preparation form used to document the preparations used in study (b) (4) was incorporated into SSP (b) (4), Dose formulation preparation of (b) (4). Revisions to the form were made during Cohorts (b) (4) and (b) (4) were not in compliance with SOP (b) (4)-1185, Study Specific Procedures and fail to document appropriate

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7. The quality assurance unit failed to review the final study report to assure that such report accurately described the methods and standard operating procedures, and that the reported results accurately reflected the raw data of the study. Specifically,

a. The sponsor's description of test article ((b) (4)) is documented as "(b) (4)" on the (b) (4)

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a. Between April 2015 and October 2016, the firm failed to complete pest evaluations per SOP. Deviation signed on 06/20/2016 failed to accurately document this noncompliance. Specifically, 1) deviation signed on 10/27/2016 states the bait boxes were checked in August 2016; however no documentation exists for an assessment in this month.

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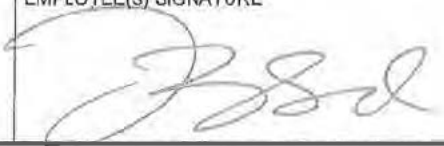
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Albuquerque, NM 87115	GLP Laborat●ry

the building for (b) (4) and (b) (4). No deviation has been recorded.

9. Not all data entries were dated on the date of entry and signed or initialed by the person entering the data. Specifically, Media Preparation Logs fail to document the actual amounts of ingredients used in the preparation of the media. Preparation logs include the typed amount required to make the media.

The quality assurance unit failed to maintain a copy of a master schedule sheet that contained all required elements for all nonclinical laboratory studies conducted by the testing facility. Specifically, the most current version of the master scheduled provided during audit failed to include the test system for study (b) (4) documented as initiated on 08/28/2●15. Archived copies of the master schedule maintained as required by SOP ●AU-1182.7, Master Schedule, reviewed from May-October 2016 also fail to include this information.

Add Continuation Page

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Theressa B Smith, CSO	11/10/2016

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."

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SUMMARY

This inspection of Lovelace Respiratory Research Institute, a non-clinical laboratory, was conducted per GLP Directed Inspection assignment from CDER (#11618938) and in accordance with the Nonclinical Laboratories Compliance Program (CP 7348.808). The inspection was limited in that it only focused on the review of the study, (b) (4) as identified within the assignment.

The firm was previously inspected 2/23/13 – 3/13/13. Form FDA 483 was issued to Dr. Robert W. Rubin, President/ CEO for the following observations: 1) study director failed to assure unforeseen circumstances that might affect the quality and integrity of the nonclinical laboratory study were noted when they occurred and corrective action taken and documented; 2) testing facility does not provide storage areas, as needed, for feed, bedding, supplies, and equipment; and 3) quality assurance unit failed to determine whether deviations from approved protocols or standard operating procedures had been made with proper authorization and documentation. Corrective actions were verified during the current inspection.

On 10/31/16, credentials were presented and FDA-482, Notice of Inspection provided to Jennifer S. Cleerdin, JD, Senior Director –Scientific Operations upon arrival to the inspection site. Inspectional areas covered include: facilities, operations, organization and personnel, equipment, test and control articles, the quality assurance unit, archives, and data audit for (b) (4). FDA- 483, Inspectional Observations was issued to Dr. Robert W. Rubin, President & CEO on 11/11/16 for the following observations: 1) the stability of each test or control article was not determined by the

testing facility or by the sponsor before study initiation, or concomitantly; 2) the identity, strength, purity, composition, or other characteristics of each batch of test and control article have not been appropriately defined and documented; 3) the study director did not have overall responsibility for the technical conduct of the study; 4) the study director failed to assure that all raw data, documentation, protocols, specimens, and final reports were transferred to the archives during or at the close of the study; 5) not all significant changes in established procedures were properly authorized; 6) 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 and documented; 7) the quality assurance unit failed to review the final study report to assure that such report accurately described the methods and standard operating procedures, and that the reported results accurately reflected the raw data of the study; 8) the quality assurance unit did not monitor each study to assure management conformance with GLP regulations; 9) not all data entries were dated on the date of entry, signed or initialed by the person entering the data; and 10) the quality assurance unit failed to maintain a copy of a master schedule sheet with all required elements for nonclinical laboratory studies.

No samples were collected and no refusals were encountered during the current inspection.

FMD-145 information and all post-inspectional correspondence should be addressed to Dr. Robert W. Rubin, President and CEO, 2425 Ridgecrest Drive SE, Albuquerque, NM 87108.

ADMINISTRATIVE DATA

Inspected firm:	Lovelace Respiratory Research Institute
Location:	Area Y, Building 9200, KAFB East Albuquerque, NM 87185
Phone:	505-845-1011
FAX:	-
Mailing address:	Kirtland Afb Po Box 5890 Albuquerque, NM 87115
Dates of inspection:	10/31/2016-11/4/2016 , 11/7/2016-11/11/2016
Days in the facility:	10
Participants:	**Theressa B Smith, Investigator**

Credentials were presented and FDA-482, Notice of Inspection issued to Jennifer S. Cleerdin, JD, Senior Director –Scientific Operations on 10/31/16. FDA-483 was issued to Dr. Robert W. Rubin, President & CEO on 11/11/16. The FDA-483 was amended, and re-issued on site.

HISTORY

Lovelace Respiratory Research Institute (LRRI) is a non-profit, private research institute. The lab was founded in 1947 in the State of New Mexico.

LRRI is a fully functional GLP and research facility that operates (b) (4) . LLRI currently performs a variety of research activities in the following areas: asthma, emphysema, lung cancer, inhalation toxicology, aerosol science, inhalation drug delivery, bronchitis, allergies, science service contracting, pulmonary fibrosis, pulmonary hypertension, infectious disease, radiation studies, chemical exposure research, clinical trials, specialized software for laboratory research, and neurobiological research. Ms. Cleerdin provided a presentation containing an overview of the firm's operations and areas of research, included as Exhibit 1.

LRRI conducts its research on two campuses. The north campus is located at 2425 Ridgecrest Dr. SE, Albuquerque. This (b) (4) square foot building houses the administrative offices as well as the Histopathology and Lovelace Scientific Resources (LSR). The south campus is located inside Kirtland Air Force Base and covers an area of (b) (4) square feet. This secured facility is where most of the research takes place. Animals such as dogs, rabbits, ferrets, rodents, and non human primates are housed in this facility. A facility diagram is enclosed as Exhibit 7.

Since the last inspection, the Analytical Department has been relocated within the facility. This infrastructure project began in 2014, and during the inspection equipment was still in the process of being moved and qualified.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Current organizational charts are attached as Exhibit 2. The following individuals answered questions and provided operational information including various records and documents.

Dr. Robert W. Rubin, President and CEO Dr. Rubin is the most responsible individual for the operations of this firm. He reports to the Board of Directors. He was only present during the closeout meeting and was issued the Form FDA 483.

Elizabeth Morrison, Quality Manager Ms. Morrision is responsible for ensuring the firm is in compliance with sponsor protocols and the regulations of multiple federal departments and agencies, managing the QA and QC departments. Ms. Morrison facilitated the inspection. She accompanied me during the physical inspection of the south campus, answered questions regarding firm operations, provided requested records for review and copies of the records as needed, and arranged for meetings with other key personnel. She has been in this position for approximately one year.

Jennifer S. Cleerdin, Senior Director – Scientific Operations In this role, Ms. Cleerdin, along with Mr. Jacob McDonald, VP –Applied Sciencs, serve as Test Facility Management. Responsibilities are divided such that Ms. Cleerdin provides oversight in regulatory, safety, training services, and project management. Ms. Cleerdin reports to Dr. Robert Rubin. Ms. Cleerdin has been in this position for approximately two years. Ms. Cleerdin worked with Ms. Morrison to facilitate the inspection.

Mr. William M. Mega, BS. Study Director Mr. Mega served as the study director for (b) (4) (b) (4) In this role, he was responsible for the overall technical conduct of the study as well as for the interpretation, analysis, documentation, and reporting of results. He represented the single point of study control. He has worked in this capacity with LRRI for approximately 10 years, and has experience working in GLP and non-GLP areas with mice, rats, rabbits, and primates. He also assists with BSL-3 training, and provides protocol training for study personnel. His CV is included as Exhibit 5. He reports to Melanie Doyle-Eisele, Life Sciences Director.

Dr. Philip Khuel, PhD, Director, Scientific Core Laboratories Dr. Khuel currently heads the division to include aerosol, analytical and bioanalytical chemistry, microbiology, and telemetry. During the conduct of (b) (4) , he was responsible for overseeing analytical work completed for assay validation, formulation, QC analysis, writing and final report reviews. His CV is included as Exhibit 3. He reports to Jacob McDonald, VP-Applied Sciences.

(b) (6), (b) (7)(C), BVSc, PhD, DipACVP (b) (6), (b) (7)(C) served as the pathologist for (b) (4) . He has worked at LRRI as a pathologist since (b) (6), (b) (7)(C) . (b) (6), (b) (7)(C) provided information regarding his involvement and responsibilities while working on (b) (4) . His CV is included as Exhibit 6. He reports to Dr. Andrew Cawthon, Director of Clinical Support.

Dr. Andrew Cawthon, PhD, Director of Clinical Support Dr. Cawthon serves as the Institute's Responsible Official and IACUC Chair. He manages the pathology, histology, clinical support, and comparative medicine departments at LRRI. He joined LRRI in 2014. Dr. Cawthon provided information regarding necropsy and IACUC procedures. In addition, Dr. Cawthon provided information regarding the blinding process for pathologist at LRRI specific to (b) (4) projects involving test article (b) (4) .

FIRM'S TRAINING PROGRAM

A thorough description of the firm's training system is reported in the 2012 EIR. No significant changes were noted during the current inspection.

During the inspection, training records were reviewed for select employees who worked on study (b) (4) . Observations are described within EIR Section Objectionable Conditions. Training records continue to be stored electronically within Training Manager.

MANUFACTURING/DESIGN OPERATIONS

The assignment (Attachment 1) requested Denver District complete a directed GLP inspection of:

- (b) (4)

  Study (b) (4)

- Sponsor: (b) (4)

Mr. William Mega, BS was assigned as the Study Director for this study. His CV is included as Exhibit 5.

The Final Report for Study (b) (4) was provided electronically by CDER along with the assignment prior to inspection. To aid in the review of this report, some records were printed for reference from the electronic records and are referenced as exhibits within the report.

Note: The firm requires evidence of TB skin test within (b)(4) months, and proof of immunization. Auditors should obtain and bring these documents as evidence for entry into the BSL 3 area. There was no tour of the BSL 3 areas utilized for this study, as recent TB skin testing was outside of this window.

Original signatures from the sponsor for protocol and amendments ((b) (4)) were not maintained by facility management. According to Section 6.1.1, General Records of (b) (4)-1142, Maintenance of GLP Study Records and Documentation, signed originals of protocols, amendments are maintained in the QA department until the study is archived. Approved copies are to be kept in the study records (Exhibits 16-18, pg 2). Ms. Cleerdin referenced SOP (b) (4) 1109, Preparation, Use and Approval of Study Protocols., Amendments and Deviation which states" in cases where logistical issues prevent 'wet signature' by the Sponsor in a timely manner, a PDF or fax approval from the Sponsor is acceptable. It is desirable that the original be sent from the Sponsor, if possible" (Exhibit 32, pg 4). Ms. Cleerdin was informed of the policy contradictions.

PROTOCOL SUMMARY & REVIEW

The primary objective of this study was (b) (4)

(b) (4) The majority of project personnel were blinded to the study groups.

Section 5.1, Blinding of the final reports states: "All study technicians administering test article, performing clinical observations, handling animals, necropsy personnel and pathologist were blinded. The Study Director, study coordinators and the telemetry coordinator were blinded". Moribund euthanasia calls were made by blinded personnel (Study Director). The study was unblinded after the conclusion of the (b) (4) cohort. Data captured within (b) (4) was unblinded on 10/1/14 (Exhibit 58, pg 1) . The original protocol provided little information regarding blinding for this study, only stating: " To control potential bias, technicians and scientists recording animal status, or dosing the animal will not be aware of treatment group allocation. *** The Study Director or designee will make decisions regarding the euthanasia of moribund animals and will be blinded to treatment groups" - see Protocol Section 9.0, Assignment to Study. Blinding for this study was clarified in Amendment #1 (signed by Study Director and Sponsor on 5/1/14) in Protocol Section 23.0 Appendix- Preserving the Blind (Exhibit 59, pgs 7-11). All personnel who were unblinded for this study were required to sign confidentiality agreements stating that they will not disclose or discuss test group information with study personnel who were blinded to the study. The section, *Necropsy and Pathology*, states "The pathologist will also be blinded until the completion of cohort (b)(4) of each study part. The pathologist will be unblinded at that time and then will perform his study analysis and report", see Exhibit 59, pg 11.

I asked Mr. Mega if the pathologist were blinded for this study. Mr. Mega stated he and the Sponsor had had many conversations regarding this, but the pathologist ((b) (6), (b) (7)(C)) was blinded for (b) (4) . However, Mr. Mega did not maintain any correspondence from the sponsor for this study (see Observation 3a). On 11/8/14, I interviewed (b) (6), (b) (7)(C) regarding his responsibilities for this study. He also stated he remembered being involved in many discussions regarding whether the pathologist would be blinded or unblinded for this study. I asked if he had any correspondence I could review; he replied "no". He stated he was unblinded for this study. Afterwards, I informed him of my prior discussion with Mr. Mega, and provided the Appendix for his review. *He then stated his role was exactly as stated in the protocol, and whatever Mr. Mega had told me.* Conversations with (b) (6), (b) (7)(C) regarding his responsibilities were contentious, and he was not forth coming in providing information.

On 09/30/2016, animal ID assignments for dosing groups for (b) (4) were provided to individuals designated to be blinded during the study, with the comment: "If for any reason you should not be un-blinded DO NOT open the attachments. Also please take care to not distribute beyond what is required" (Exhibit 19, pg 3). This communication was not forwarded by the Study Director, but by the dose formulation group manager. This communication was forwarded at the end of Cohort (b) (4) however, the protocol stipulated which individuals could be unblinded at this time point. Management was reminded the email should have been selective, and not sent to everyone. There is no record to ensure compliance that individuals ***did not*** open the file.

For each Cohort set of exposures, (b) (4) These logs were reviewed; no observations were noted. Observations were noted regarding media preparation logs used within the microbiology department were noted and further described within Observation 9a. The (b) (4) dose suspension was cultured for dosage and stability (b) (4) exposures by measuring (b) (4) and for purity using (b) (4) (b) (4) and (b) (4) Media preparation forms for (b) (4) state the media was prepared according to SOP (b) (4) Preparation of Microbiological Reagents and Media (Exhibit 47). The formulation within the SOP states that (b) (4) require (b) (4) and (b) (4) (Exhibit 46, pg 3). Media preparation forms for this study do not document either of these ingredients were used (see image included within Observation 9 and Exhibit 36, pg 1). (b) (6), (b) (7)(C) could not find documentation to support if the (b) (4) plates were / were not compromised in their ability to be read without the ingredients, but did state the organism was visible. The formulations list within this procedure was later revised (01Oct2014) and requirements for (b) (4) and (b) (4) removed (Exhibit 46, pg 4).

Incubators within the BSL 3 facility are continuously monitored; however, those located within the Microbiology (b) (4) are not. Only a (b) (4) reading is required for these incubators. Some media preparations for the study were completed in the (b) (4) For example, media preparation logs for incubator (b) (4) only document the temperature was taken at (b) (4) during a (b) (4) incubation (see Exhibit 36, pgs 7-9). Management was advised of the need to take multiple readings during the extended time period when manual recordings are required.

A review of the set-up & pre-exposure testing of the (b) (4) exposure system used for (b) (4) (b) (4) was completed. No observations were noted. However, an evaluation of LRRI (b) (4) applications by FDA Center personnel should be performed during the next EI. (b) (4) ABSL -3 Exposure data sheets were reviewed for each cohort, and data verified for all animals. The information from these data sheets are transcribed within (b) (4) tables for reporting and calculations. The audit determined the (b) (4) cells for some parameters ((b) (4) Output/Flow Rate, Main Exhaust Flow Rate, (b) (4) Control Flow Rate) have not been formatted to display all of the information "as found" on the corresponding study document (Exposure Data Sheet). The information within the (b) (4) table is rounded. The (b) (4) forms are QC'd; however, the discrepancies appear to have not been noted. For example,

Exposure Date	Animal	(b) (4) Output (L/min)/Flow Rate	(b) (4) Output (L/min)/ Flow Rate	(b) (4) Parameter Flow Rate (L/min)	(b) (4) Parameter Flow Rate (L/min)
		Raw Data	(b) (4)	Raw Data	(b) (4)
05/6/14	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
08/25/14					

Calculations were reported within Table 6, (b) (4) Summary Data of the (b) (4) Report (Exhibit 59, pg 16). However, differences were noted between the (b) (4) printed tables and the report. No tables within the study data were observed to contain the same information. Management reported the information was truncated when printed, but visible within the program. Examples include:

Exposure Date	Animal	Estimated (b) (4) Volume (L)	Estimated (b) (4) Volume (L)
		(b) (4)	Final report
05/6/14	(b) (4)	(b) (4)	(b) (4)
06/11/14			
08/25/14			

Note: See Exhibit 42 for exposure data from 5/6/14; Exhibit 43 for 7/11/14 exposure; and Exhibit 44 for 08/25/14.

All animals were (b) (4) to provide (b) (4) (b) (4). Pre-exposure telemetry data was captured during a (b) (4) day observation period immediately prior to (b) (4) exposure to develop baseline physiological measurements. Intermittent telemetry data was noted throughout the study for noted animals, but were appropriately documented through deviations. Study documents contained computer screen-shots of the telemetry data to document the trigger point for all animals except #(b) (4).

Test article accountability, and dose formulations were reviewed. Observations regarding dose formulations are discussed within Observation 5. Although two different dosage preparations (requiring (b) (4)) were made, at the onset of the study, employees recorded the amounts removed collectively onto the GLP Reagent, Test Control Article Use Form (Exhibit 46). As a result, multiple errors were made, and the amounts of TA recorded on form were observed as inaccurate in respect to the amount of TA documented as used on the Dose Formulations Preparation Form. Multiple errors were noted on the test article usage form that was corrected during later review of the forms. However, the first error was made on the first day of preparation (Exhibit 46, pg 1 & Exhibit 48, pgs 2-3).

Dispense Date	Dose (b) (4)	Dose (b) (4)	Total (b)(4)	GLP Test Article Use (b) (4)	Difference
5/7/2014	(b) (4)				

Employees did not begin to continuously record the individual weight for each formulation until late within Cohort (b) (4) although, some variability was still noted between employees (Exhibit 46, pgs 4-6). Management was encouraged to have employees record the specific amount as they are removed /used. The calculation error on 05/7/14 was not discovered following the QA audit specific for the test article (see Quality Assurance Statements). Re-calculations upon review of the forms were documented as completed in October 2015.

For up to (b) (4) days following challenge, clinical observations were performed at least (b) (4), with the exception of noted deviations. Observations were tailored to assess (b) (4), neurological symptoms, provoked and unprovoked behavior, food intake and body weight trends, appearance/posture, and gastrointestinal/urogenital abnormalities. These observations were recorded in (b) (4)

Water and feed analysis were not reviewed for this study, and should be covered during the next EI.

Animals reviewed for clinical observation and pathology include: (b) (4) (b) (4).

Clinical chemistry and hematology parameters were assayed pre-challenge, on Days (b) (4) (b) (4) and at (b) (4). On 7/72014, a blood smear slide was prepared for hematologic evaluation for animal #(b) (4) (Exhibit 45, pg 4). The laboratory received the sample on 7/7/14 (Exhibit 45, pg 1). However, the slide was mis-labeled as #(b) (4), also received and processed on 7/7/14 (Exhibit 45, pgs 1, 3-4). All slides prepared by the clinical pathology laboratory for this study were submitted to the facility archive on 10/13/2015, following a check of the inventory on 12/9/14 (Exhibits 45, pgs 2, 5). The archivist verified the slides using a Slide Inventory List on 10/20/15. No issues were noted, as the inventory list documents two (2) entries for #(b) (4) During the audit, I audited the archived slides for this study, and no slide labeled as #(b) (4) was found.

(b) (6), (b) (7)(C), Medical Technologist, was interviewed to discuss the verification process for slides prior to archival. She has worked in the area for 7 years. Upon her review, she confirmed which slide should have been identified as #(b) (4) by looking on the back of the slide. At the time of the study, employees who worked in the area labeled the back of the slide with the animal number in pencil. This process is no longer in practice. Additionally, she stated there is no second person verification completed of the inventory prior to archival submission.

Necropsy occurred for found dead animals, subsequent to euthanasia for animals found to be (b) (4) (b) (4) or (b) (4). Necropsy procedures were performed under the supervision of a veterinary pathologist by qualified necropsy technicians. Gross necropsy observations were recorded. Gross necropsy observations were recorded in (b) (4) (b) (6), (b) (7)(C) stated he was present for all necropsies completed for this animal. However, Dr. Andrew Cawthon, stated he doubted this was accurate, but that LRRI does have video feed available in the necropsy suite so that the pathologist may log in (if needed) for consult, when

requested by the necropsy staff as the pathologist staff is on call for moribund and found dead animals on (b) (4) and (b) (4) hours.

Various reports within (b) (4) were reviewed. The following observations were noted and discussed:

- Time stamps reported within the (b) (4) database were different (12 hour vs 24 hour) betweenreports. For example, Animal# (b) (4) –

1. Gross Pathology & Generalised Results Raw Data Prints reported the times using the 12 hour clock (Exhibit 4, pgs 5-12). For example, the time stamp for Tissue: Animal identification on 5/23/14 was recorded as "2:12"01 PM" (Exhibit 4, pg 5)
2. Clinical Observations Raw Data Print used the 24 hour clock (Exhibit 4, pgs 13-14). Time stamps for all clinical observations completed in the evening were documented as "19:40", see Day (b)(4) Observation week (b) (4) see Exhibit 4, pg 14

- Lock/ Un-lock Function for Pathology Module

Animal records reviewed for data collected and reported within the Pathology modules were all listed as "Unlocked", Exhibit 58, pg 7. Examples of this observation include animals: # (b) (4) #(b) (4) (Exhibit 58, pgs 8-10), #(b) (4) (Exhibit 4, pgs 5-8), and #(b) (4) (Exhibit 29, pgs 9-12). Staff on-site was not as knowledgeable regarding the lock features for the system. The (b) (4) User Guide was reviewed. According to this guide, to control multi user access to data, two approaches to locking are available within Pathology: 1) checking for locks once data has been entered, and 2) setting up locks before data entry commences. In the first example, it is assumed that no one else will enter or modify the data. Then prior to committing the data to the database, a check will be made to verify no data modification would have occurred. In the second example, it is assumed that another user will attempt to create/modify the data, so prior to the user attempting data entry, a lock is applied restricting other users from entering or changing the data, see Exhibit 58, pgs 4-5.

(b) (4) printed reports for Gross Pathology and Histo Pathology demonstrate continued recording within the system through February 2015 (see animals listed above). Study data within (b) (4), was not locked by the Study Director until 09/28/15 (Exhibit 58, pgs 2-3). According to management, there is no requirement the database by audited for changes prior to locking of the study. There is no current process / procedure regarding locking of the pathology data.

- Documentation of completed tasks within (b) (4)

During the inspection, I met with Ms. Kat Barrick, Necropsy Supervisor (current) to discuss departmental procedures and training. During earlier reviews of the (b) (4) system with Mr. (b) (6), (b) (7)(C), he located a report which identified the electronic signature for the role of each user completing a specific task. For animal (b) (4), a report entitled, *By Session* (b)(4) *Raw Data Print*, provided the electronic signatures for the personnel who completed the weighing of cultures taken at necropsy for this animal (Exhibit 4, pg 1). **User roles for this session completed for animal #(b) (4) (5/23/16) only document "Performed by"**. The report documents "Performed By" for two individuals, (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C).

Ms. Barrick (previously (b) (6), (b) (7)(C)) stated necropsy tasks involve (b) (4) people for safety reasons. However, in this example the individual tasks (proscector/recorder) were not captured accurately within the software.

(b) (4) allows users to sign as "Recorded by" and "Performed by". It is evident the individuals did not select the appropriate choice when signing the documented. However, (b) (6), (b) (7)(C) stated the department *always* uses a paper form to document the prosector and recorder for necropsy even when the electronic system is used. These forms were included within the study data, and noted many changes /corrections (Exhibit 4, pgs 3-4). For animal #(b) (4), (b) (6), (b) (7)(C) was listed as the prosector, and (b) (6), (b) (7)(C) as the recorder.

The practice of using the paper form still continues. Ms. Barrick provided the current form, entitled Job Assignment Record, recently revised on "03Nov2016" (Exhibit 4, pg 15). Facility management could not explain why the department was using the paper form instead of (b) (4). Several attempts were made to obtain this same electronic report for other animals but no one on-site knew how to generate/locate the specific report. (b)(6), (b) (7)(C) had left (b) (6), (b) (7)(C) and was not accessible for consult.

(b) (6), (b) (7)(C), System Implementation Coordinator serves as the Administrator for (b) (4) and was introduced as the most knowledgeable on-site person for assistance regarding my review of this system's audit trail. However, (b) (6), (b) (7)(C) was not able to be retrieving requested files for my review. Several questions were sent to (b) (4) (manufacturer) but no information and/or valuable assistance was received prior to close-out.

The firm plans to implement a new version of (b) (4) software. I asked they consider these observations during their upcoming validation.

QUALITY ASSURANCE

The QAU is governed by SOPs which were present and up-to-date. There was no indication the QAU did not operate separately and independent of the study personnel engaged in the conduct and direction of protocol (b) (4). Quality objectives for (b) (4) were defined within the Quality Assurance Project Plan (QAPP), see Exhibit 56. The plan detained all planned activities of the LRRI's QA unit and the Advanced QC unit. A lead QA auditor, (b) (6), (b) (7)(C), was assigned to assure QA activities defined within the QAPP were completed. Advanced QC review of in-process activities considered high-risk were identified (dose formulation) and required 100% QC verification prior to allowing the next step of the procedure to occur. Several concerns regarding the QC and QA of documents within (b) (4) were noted during the audit, and are described within EIR section Objectionable Conditions.

GLP training of employees is developed in-house, and authored by (b) (6), (b) (7)(C). A copy of the required training (rev 10Feb2015) was reviewed; no observations were noted. Following the review of the presentation, employees are required to answer questions on the information, and pass with an (b)(4)% score. The system randomly selects questions from the database so they are not

repeated year to year. GLP training was reviewed for (b) (4) study staff (during conduct of study and current). No significant observations were noted.
Requirements for the conduct of facility audits are included within QAU 1455, Internal Facility Inspections at LRRI. Evidence of these inspections performed in 2014-2016 was requested. Ms. Cleerdin stated facility inspections were not completed in 2014. Deviation of non-compliance was documented through a Non-Study Specfic Deviation Document signed by QA staff on 11/11/16 (Exhibit 57). In December 2015, the audit was completed by (b) (4)
Ms. Cleerdin stated these audits are conducted by contractors, and are changed (b) (4) to reduce bias.

During the audit, multiple errors were noted during the review of archive submission forms. Management was informed of the need to ensure a better QA audit of archival forms prior to the close / final submission of the study as required during the completion of the GLP Archive Submittal Preparation Checklist. The checklist for (b) (4) was signed by the QA auditor on 10/23/15 (Exhibit 23, pg 1). Errors observed included:

1. Submission form documents materials received in archive on 09/09/2015 were signed by the archivist as having been received on "09Sep2016" (Exhibit 23, pg 10). The year was incorrectly recorded on this entry.

2. Test article was submitted for archival on 10/05/2015. The location where the material is listed as stored states: "Rm (b) (4) Storage bottom self" (Exhibit 23, pg 6). During the audit, I toured this room to verify the retention of the test archival. The designated space for test article archive at LRRI is Room (b) (4)

3. The Archivist failed to sign to date the submission document which documents the return of notebook (b) (4) (study (b) (4)) back to archive (Exhibit 23, pg 12). According to the form, the notebook was retrieved from archives on 10/08/2015.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC)

LRRI has an on-site IACUC. The current roster is included as Exhibit 52, pg 1. The *LRRI IACUC Manual* outlines the responsibilities of the IACUC and details the specific operating guidelines which must be followed (Exhibit 54). The chair of the IACUC holds a (b) (4) term and general members are assigned for at least (b) (4) but typically participate for longer terms. Since the last inspection, the committee has implemented the Animal-related incident Report (ARIR), see Exhibit 54, pg 11. These reports are generated to capture incidents related to facility animals, which may/may not be study related, or defined as an adverse event which have been helpful with monitoring /awareness efforts within the facility. For example, the incidence of (b) (4) observed within the (b) (4) was reported as an ARIR. Dr. Cawthon stated multiple factors attribute to (b) (4) to include (b) (4) and (b) (4) of animals. Animal injuries or illnesses unrelated to approved procedures and being treated by the clinical veterinaries are generally not reported, unless they are reflective of system issues or negligence. Dr. Cawthon stated that previously the committee would become aware of this type of issue through reported AEs. Each ARIR is assigned

an IACUC investigator(s) to gather information and investigate the incident. Root cause analysis and corrective action are performed, as appropriate.

Initial approval of protocols must be obtained before the animals are ordered and brought into the study through Full Committee Review at a convened meeting, or Designated Member Review. The IACUC requires an (b) (4) review of all protocols involving animals as well as a (b) (4) protocol renewal. Amendments to protocols must also be reviewed by the IACUC prior to implementation. The initial application / approval for (b) (4) was dated as 10/22/13. An amendment was subsequently approved on 10/29/13 to change the Study Director to Mr. William Mega. These documents are included as Exhibit 53. Additional amendments associated with this protocol were reviewed. IACUC meeting minutes from 9/07/16 (last meeting), and the meeting for the initial approval of (b) (4) (10/16/13) are included as Exhibit 52, pgs 2-8.

ASSIGNMENT QUESTIONS

1. *What percentage of Lovelace's total workload is subject to part 58? What percentage of Lovelace's GLP workload is related to human drugs?*

(b) (4) percent of LRRI workload is estimated to be subject to part 58. Management stated (b) (4)% of the GLP workload is related to human drugs.

2. *Does Lovelace outsource any study phases, e.g., analysis of dosing formulations and histopathological evaluations? Document how QAU oversight is assured for the outsourced phases. Does the final report identify the facility(ies) that conducted the outsourced phases? Please collect and exhibit in the EIR a list of all firms Lovelace used for the outsourced phases.*

Occasionally the firm will outsource some segments of studies such as pathology and analytical portions. The QAU is responsible for determining the need to outsource and they are governed by an SOP. If possible, LRRI will perform all aspects of the study in-house. For (b) (4), 1) bioanalytical evaluation was completed by (b) (4), 2) pharmacokinetics was evaluated by (b) (4) and serology testing to evaluate antibody titers was completed by (b) (4). All facilities were identified within the final report.

LRRI QAU may delegate inspection and audit responsibilities to an alternate testing facility's QAU or perform this function through off-site inspection and audits. Responsibilities would be documented within the Quality Assurance Project Plan. QA audit oversight for these outside laboratories used in (b) (4) was completed by the facility themselves.

SOP (b) (4) 1451, Conduct of Multi-Site Studies defines the roles and responsible related to studies that may have portion of the studies conducted by the sponsor or other facilities designated by the sponsor or when LRRI subcontractors portions of a study to another facility. LRRI requires qualification of test sites, through a Quality Questionnaire for GLP Compliance, and facility inspection if deemed required. Vendor qualification for products, materials, services or equipment

required to meet quality standard of LRRI for studies conducted under GLP is described within SOP QAU1827, Vendor Qualification for Products, Services, or Equipment Used on Studies at LRRI. Pre-Risk Assessments are required prior to contracting of these services, which are evaluated by LRRI QAU to determine if vendor qualification is required. Assessments may include a Vendor Qualification Questionnaire, and/or site visit inspection. Once a vendor has been approved, the vendor's qualification status must be re-evaluated every (b) (4). A list of approved vendors is included as Exhibit 55.

3. *Did the study director sign and date protocol amendments on or before the day when procedures were actually changed?*

Yes, no observations were noted.

4. *Were the results of test article characterization and dosing formulation analyses reported to the study director and included in the final report of each in-life study audited?*

Deficiencies were noted regarding test article characterization and dose formulation analysis. These findings were cited within FDA-483, Observations 1-3.

5. *Were signed and dated contributing scientists' reports attached to the final report?*

Yes, no issues were noted.

6. *Have deficiencies from the March 2012 inspection been corrected? Have the corrective actions prevented recurrence of the deficiencies?*

The firm was last inspected in March 2013. Only corrections from the last inspected were verified, see EIR section Voluntary Corrections.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483

1. **The stability of each test or control article was not determined by the testing facility or by the sponsor before study initiation, or concomitantly according to written standard operating procedures which provide for periodic analysis of each batch. Specifically, validation #(b) (4) used to support the stability of test article (b) (4) demonstrates stability in stock solution ((b) (4) TA). Formulated dosage administered for study (b) (4) was (b) (4) and (b) (4) .**

2. **The identity, strength, purity, composition, or other characteristics of each batch of test and control article have not been appropriately defined and documented. Specifically, Validation #(b) (4) used to qualify analytical methods for characterization of test article (b) (4) was not performed for dose formulations equivalent to those utilized in Study (b) (4) .**

Protocol section 5.1, Test Article stated the TA will be characterized by the sponsor or sponsor contracted laboratory. The sponsor will ensure that documentation on the identity (supplier/manufacturer) batch number and/or lot number, strength, purity and stability for the TA are provided for inclusion in the Final Report.

Section 5.2.1, of the final report stated that test article was supplied by the sponsor and was considered characterized by manufacturer-provided documentation, included within Appendix L of the report (Exhibit 59, pg 15). The COA provided reference to summary analytical and stability data. Section 5.4, Analysis of the Test and Control Article Formulations (within the final report) references the use of a validated assay procedure, (b) (4) Analytical Method Qualification used in the analysis of the dose formulations. Requirements are described within SOP (b) (4)-1158, Validation of Analytical Methods (Exhibit 15). Dr. Dr. Philip Kuehl confirmed the work completed in this qualification was performed as the characterization for the (b) (4) projects involving test article (b) (4).

According to Lovelace management, this study was not the first project completed on behalf of (b) (4) using this test article. The analytical method qualification report for (b) (4) was approved by Dr. Kuehl on 03/27/2013. The report, included as Exhibit 13, was completed in association with (b) (4) protocol #(b) (4), the precursor study. The retrieval of the report for (b) (4) for review was not expedient, as it was not archived with either study. Protocol (b) (4) was approved on 05/08/2013 (Exhibit 14, pg 4).

Dose solution preparations specifications noted within (b) (4) were (Exhibit 14, pgs 1-3):

1. Dose of (b) (4)
2. Dose of (b) (4)
3. (b) (4) for (b) (4) formulation prior to dosing (e.g. (b) (4))
4. Vehicle used was (b) (4) formulated by the manufacturer

In comparison, dose solution preparation specfication noted within (b) (4) were (Exhibit 59, pgs 1-3):

1. Dose of (b) (4)
2. Dose of (b) (4)
3. (b) (4) for (b) (4) formulation prior to dosing(e.g. (b) (4))
4. Vehicle used was (b) (4) formulated by the manufacturer

The following exceptions were noted within (b) (4) (Exhibit 13):

1. (b) (4) solution for (b) (4)
2. (b) (4) solution for (b) (4)
3. (b) (4) solution for (b) (4)
4. No (b) (4) was performed of any formulations prior to testing (also see notebook worksheets, Exhibit 13, pgs 23-24)
5. Vehicle used was made in-house, using (b) (4) preparation (also see notebook worksheets, Exhibit 13, pgs 23-24, 26)

6. Stability of a single stock solution ((b) (4)) was assessed concomitantly at (b) (4) , and (b) (4) after formulation. (also see notebook worksheet, Exhibit 13, pg 25)

Review of this qualification noted in-equivalency for (b) (4) as well. Concentrations for testing did not span the range of the expected concentrations in the study. In addition, solution stability was not assessed for all dose formulations or in the equivalent solution. The Final Report Audit for (b) (4) was signed by QA on 5/17/13, and final approval by the Program Director on 5/21/13 (Exhibit 13, pg 21).

Mr. Mega was asked if he had reviewed this validation at any time prior to, or during the course of the study. He stated he had not. He indicated that he was aware prior studies and associated analysis had been performed on the test article, but made not inquiries to review the associated reports.

Management was informed of the need to assure prior characterization of test article performed at the site should be verified by the study director, and QA to assure no changes have resulted throughout the course of a project. After review of the qualification report by Dr. Kuehl, he confirmed the work performed was not adequate to support (b) (4) and (b) (4) , and stated the firm would repeat the analysis as corrective action.

3. The study director did not have overall responsibility for the technical conduct of the study as well as for the interpretation, analysis, documentation and reporting of results, and does not represent the single point of study control. Specifically,

a. The Study Director for (b) (4) failed to assure test article characterization, and stability described within Section 5.2 of the final study report, as analyzed under validation #(b) (4) , was performed in conformance with dose formulations equivalent to those used in the study.

See discussion within Observation 1.

b. Study ((b) (4)) related communications (internal and external), sufficient in detail to reconstruct the study, were not maintained by the Study Director, and subsequently archived as defined within *SOP* (b) (4) *1142, Maintenance of GLP Study Records and Documentation.* Examples include (amendments; contributing scientist dialogue; sponsor communication).

SOP (b)(4) 1142, Maintenance of GLP Study Records and Documentation provide requires for maintaining a GLP compliant study file by the Study Director. Section 6.1.6, Correspondence states all study related communications, internal and external, shall be maintained in the study file. The procedure further states, at a minimum, technical data, memoranda, FAX transmission from the sponsor or contract laboratories regarding information about the study; email records; and phone logs (Exhibit 16-18, pg 4). Although the procedure has been revised (v.7-v.9) throughout the time period (study start to archive), this section has remained unchanged.

The correspondence file/section submitted by the Study Director only contained three (3) documents.

- Email dated 6/16/14: email from (b) (4) to Mr. Mega regarding the review of the un-blinded data by the sponsor. Sponsor provided information to proceed with Cohort (b) (4) Exhibit 19, pg 1).
- Email dated 08/12/14: email from (b) (4) to Mr. Mega confirming the sites ability to proceed with Cohort (b) (4) The sponsor also asked who should receive the randomization schedule for Cohort (b) (4) Exhibit 19, pg 2).

- Email dated 09/30/14: Email from Dr. Philip Kuehl to Mr. Mega providing the animal assignments to staff personnel to unblind the study (Exhibit 19, pg 3)

The protocol for (b) (4) was signed by Mr. Mega on 4/15/14. No communications were submitted by the Study Director providing any communications for the study until 06/06/14. Nine (9) amendments are associated with this protocol. No communications were found between the sponsor, management and Mr. Mega in their regard. Section 6.1.2, Study Protocol Approval of SOP (b) (4) -1109, Preparation, Use and Approval of Study Protocols, Amendments and Deviations states that any correspondence (including email) substantiating the sponsor's approval of the protocol should be included in the study file (Exhibit 32, pg 4). Additionally, no communications were found within the study file in regards to changes regarding the blinding of study personnel (see previous discussion in Protocol Summary).

I asked Mr. Mega to check if he had additional correspondence which was not submitted. He informed me that his computer had crashed since the study, and he no longer had any emails associated with this study.

Mr. Mega disagreed with the observation regarding requirements to maintain all communications regarding the study. I reiterated that at a minimum, key correspondence should be maintained by him, and then submitted at the close of the study. During the review of study data submitted from the microbiology, necropsy and chemistry departments, additional correspondence was observed to have been submitted by area managers indicating their contact with Mr. Mega about the progress of the study. I pointed out this same information should have been submitted by him. Additionally, I stated that at a minimum, he did not comply with SOP (b)(4) 1142 in regards to this documentation.

4. **The study director failed to assure that all raw data, documentation, protocols, specimens, and final reports were transferred to the archives during or at the close of the study. Specifically,**

a. **Protocol Section 9.0, Assignment to Study, states animals will be randomly sorted into cohorts using (b) (4) . Randomization for animals in Cohort (b) (4) as performed in (b) (4) were not maintained for study (b) (4) .**

Randomization as described within protocol section 9.0 included the following (Exhibit 59, pgs 4-6):

- Animals will be randomly sorted into cohorts using (b) (4) (b) (4) Animals will be placed into test group based on (b) (4) group designations.

- Upon completion of all required screening/baseline assessments, eligible (b) (4) were registered in the (b) (4) by the investigator or authorized staff for randomization.

- (b) (4) were centrally randomized to (b) (4) using a randomization schedule generated by (b) (4) (b) (4) animals were to be randomized in each randomized of the (b) (4) cohorts. Randomization was stratified by (b) (4) (b) (4) randomization allocation ratio within (b) (4).

Randomization records observed within the study data demonstrate:

- On 02/25/14, (b) (4) animals for Cohort (b) (4) were randomized for (b) (4) and (b) (4) animals were randomized for Cohort (b) (4), for the application of the (b) (4). (b) (4) additional animals were randomized as extras, (Exhibit 20, pg 1).

- At the start of Cohort (b) (4) animals were randomized for this cohort, and (b) (4) animals were designated as spares which were designated to move to Cohort (b) (4) This randomization was performed on 03/27/14, (Exhibit 20, pg 2).

No records were maintained as evidence the randomization for Cohorts (b) (4) were performed. During the audit, I spoke with (b) (6), (b) (7)(C), QA who served as the Study Coordinator for Cohort (b) (4) regarding this observation. He stated he remembered completing the (b) (4) randomization documen for Cohort (b) (4) The lack of documentation was discussed with Mr. Mega who stated he did have these docume at the time the study was conducted. He provided an (b) (4) sheet (not in study file), listing all of the animals within each cohort, and an additional document within reported the animals selected for Cohort (b) (4) (Exhibit 20, pgs 3-4). Mr. Mega also provided the randomization completed for Cohort (b) (4) (Exhibit 20, pg 5). Although, Mr. Mega provided these additional documents, I explained the information was insufficient to support the randomization was performed as stated per the protocol. The documents should have been retained by the Study Director, and submitted with the study documents at archive. Management was also notified the missing records should have been discovered during the audit by the QA.

b. Study (b) (4) Procedure Checklist dated 07/10/2014 for study (b) (4) documents slides contaminants on plates from cohort (b) (4) were placed in Room (b) (4) (located in BSL-3 facility). These slides were not archived as a part of th tudy at the close of the study as defined within *SOP (b) (4)-1081, Submission and Retention of GLP Study Records, Specimens and Samples.*

c.* The Study Director for (b) (4) was notified on 09/29/2014 images of contaminant and (b) (4) (b) (4) were placed in an electronic study file for viewing. These images were not archived with study data at the close of the study; nor an electronic file archived appropriately as defined within SOPs (b) (4)-1152, *GLP Archive Facility Operation and Maintenance and* (b) (4) *1081, Submission and Retention of GLP Study Records, Specimens and Samples.

Protocol section 14.4.3, Whole Blood for Quantitative and/or Qualitative Bacteriology, states samples will be tested for quantitative and qualitative bacteriology just prior to (b) (4) (b) (4) and at scheduled study (b) (4) and at

(b) (4) . For qualitative analysis , whole blood (target volume (b) (4) ml) was collected for (b) (4) and (b) (4) samples. Blood cultures were sub-cultured to (b) (4) (b) (4) and (b) (4) to verify positive cultures (colony morphology and/or (b) (4)). SSP (b) (4) Procedures was written to direct to describe this process while working in the ABSL-3 facility.

Correspondence files, submitted by the microbiology department, indicated representative photos and (b) (4) of contaminants were associated with (b) (4) . [Note: None of this correspondence was submitted within files submitted by the Study Director]. For example,

- Email from Mr. Mega to (b) (4) staff (8/7/14)- email sent as reminder to collect representative (b) (4) samples from animal (b) (4) and any (b) (4) animals because of the need to (b) (4) . Also, staff was asked to collect representative contaminates if found (b) (4) plates as it was anticipated the sponsor will want to characterize (Exhibit 22, pg 4).

- Email from (b) (6), (b) (7)(C) to Mr. Mega (08/12/14 – email ask for clarification regarding the need for microbiology to take representative photos and complete (b) (4) for contaminants found (b) (4) plates. Mr. Mega was informed that micro would continue to keep the contaminants, and discard only after direction from him and the department supervisor (Exhibit 22, pg 4)

- Email from (b) (6), (b) (7)(C) to Mr. Mega and (b) (6), (b) (7)(C) (9/25/14) – email provides an update regarding the contaminants found on the (b) (4) plates for (b) (4) animals. Employee asks Mr. Mega if he would like photos of any of the contaminants. Email from Mr. Mega to (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C) (9/25/14) – In response, Mr. Mega informs (b) (6), (b) (7)(C) to take picture and gave permission for discard. See Exhibit 22, pg 5 for all communications.

- Email from (b) (6), (b) (7)(C) to Mr. Mega (9/29/14) – email provides an update regarding the contaminants found on (b) (4) plates for (b) (4) animals. Employee asks Mr. Mega if the laboratory should proceed with (b) (4) of the contaminants. In response (9/29/14), Mr. Mega responded "Yes***". See Exhibit 22, pg 6 for all communications.

- Email from (b) (6), (b) (7)(C) to Mr. Mega (9/29/14) – Mr. Mega was notified the contaminant images and (b) (4) from (b) (4) were placed in the electronic study file for viewing. He was also notified that all contaminant and stage plates from (b) (4) on 8/25/14 were discarded. A link to the file was included (Exhibit 22, pg 7).

Additionally, (b) (4) Procedure Checklists were maintained within the study files for work completed for the following:

1) (b) (4) of contaminants observed on plates from Cohort (b) (4) and all (b) (4) plates as requested by the Study Director on 06/10/14. The storage location of the slides was documented as Room (b) (4). (Exhibit 22, pg 1)

2) (b) (4) completed for Cohort (b)(4) on 09/16/14 and 09/29/14. The storage location of the slides was documented as Room (b) (4) however, pictures were taken and maintained in the electronic study folder. (Exhibit 22, ps 2-3)

I requested the firm show me the electronic study files containing the images. A copy of the directory and pictures of each file are included as Exhibit 22, pgs 8-16.

The submission of (b) (4) study data to the LRRI archives was completed over an extended time period, beginning on 9/9/15. A GLP Archive Submittal Preparation Checklist is used to ensure that all materials are archived at the close of a study. The form is used by the archivist to verify the presence /receipt of listed materials. The form must be signed by the Study Director, and audited by a member of QA. This form was signed by Mr. Mega, and (b) (6), (b) (7)(C) (QA Auditor) on 10/23/15 (Exhibit 23, pg 1). The form indicates that all electronic media for (b) (4) were archived.

Section 6.1.3, Tissues, Blocks and Slides of SOP (b) (4)-1142 states these items must be submitted in advance or before the final report is signed and must be accompanied by a detailed inventory (Exhibits 16-18, pg 4). Section 6.1.1, Archive of Electronic Data Generated on Systems that Do Not Have a Validated Archive Function of SOP (b) (4) 1081, Submission and Retention of GLP Study Records, Specimens and Samples, states the original raw data and metadata is copied from the secured data acquisition system to a dedicated data server. Verification of the documents, as noted by signature on the screen capture printouts are maintained in the study data file (Exhibit 21, pg 4). No printouts of the directory were found within the study file; and the data was never transferred to an approved storage media (e.g. CD/DVD) for submission to the archive.

Multiple errors were noted on the archive submission forms included / completed for this study (See Discussion with Management)

During the final meeting, I indicated the Study Director must ensure that all electronic data is archived appropriately. In this case, Mr. Mega was aware of the files, as documented in the correspondence between him and the laboratory. Additionally, I informed management the QA audit of the final study file at archive was inadequate. These missing files should have been discovered at some point of the audits completed. QA was asked to review their processes to ensure electronic servers are reviewed / captured in their archival audit.

5. Not all significant changes in established standard operating procedures were properly authorized in writing by management. Specifically, ***

a. A dose preparation form used to document the preparations used in study (b) (4) was incorporated into *SSP* (b) (4), *Dose formulation preparation of* (b) (4). Revisions to the form made during Cohorts (b) (4) and (b) (4) were not in compliance with *SOP* (b) (4)*-1185, Study Specific Procedures* and fail to document appropriate review and approval by the Study Director.

Formulation instructions, as described within Protocol Section 5.1, Test Article, were defined within SSP (b) (4), Dose Formulation Preparation for (b) (4) (Exhibit 37). The SSP was prepared by (b) (6), (b) (7)(C), Chemist and approved by Mr. Mega on 05/05/14. A Dose

Formulation Preparation Form was included within this procedure as Appendix A (Exhibit 37, pgs 5-8). The approved form, utilized during Cohort [redacted] on 05/07/14 ([redacted] preparation), is included as Exhibit 48.

SOP [redacted]-1185, Study Specific Procedures provides guidance regarding the preparation, approval, use and maintenance of LRRI study-specific procedures (SSPs). Section 6.3, Review and Approval states the author must submit the procedure to the Study Director for approval. Once the Study Director approves the procedure, the SPP will be submitted to QAU so it can be updated to a status of "approved" in Training Manager (Exhibit 41, pg 3). General considerations for SSPs state that all must be signed dated and approved the Study Director prior to performance of the procedure. The Study Director and/or designee is responsible for disseminating the procedure to the study team for review prior to use on study (Exhibit 41, pgs 1-2). Study personnel are responsible for following the SSPs and documenting their training (i.e. "read and understood") within the Training Manager database. As the study progressed, changes to the formulation preparation form were made without documented approval of the Study Director.

Minor changes noted with Cohort [redacted] included the following. An example of these changes is noted on the form for the batch prepared on 07/12/2014 included as Exhibit 49.

1. [redacted] Dose Preparation: Step [redacted]: added line requesting the transfer to microbiology be documented

2. [redacted] Dose Preparation: Step [redacted]: added line requesting the transfer to microbiology be documented

3. Removed documentation for "[redacted] Batch Disposed"

Significant changes noted with Cohort [redacted] included the following. An example of these changes is noted on forms used to prepare batches on 9/8/14 and 9/14/14 included as Exhibit 50 and 51, respectively.

1. [redacted] Dose Preparation: All formulations were [redacted]. For example, weight of [redacted] of test article. [redacted] was added at [redacted] was adjusted by adding [redacted]

2. [redacted] Dose Preparation: All formulations were [redacted]. For example, weight of [redacted] of test article. [redacted] was added at [redacted] was adjusted by adding [redacted]

3. Added requirement to provide document lot#, item number, expiry, and manufacturer name for [redacted] used to [redacted].

Note: General instructions stated the preparations should be made using a [redacted] *volumetric flask; however, the step* [redacted] *of each preparation instruction still stated to use a* [redacted] *volumetric flask.*

Dose formulations for changes in Cohort [redacted] were performed for solutions prepared beginning 09/08/14 (Exhibit 50). For this study, the firm utilized in-process QC checks for high risk

procedures requiring 100% observation of critical processes, and personal verification of the information prior to allowing the next step of the study procedure. The QC Checklist for dose preparation is included as Exhibit 38. Beginning on 09/8/14, these checklists were observed to have changed to indicate the new formulations, (b) (4) . The following errors were noted on the form: 1) A requirement to weigh (b) (4) test article for the (b) (4) dose preparation, and 2) a requirement to use (b) (4) for the (b) (4) for the (b) (4) preparation (Exhibit 38, pgs 1-9). These errors were corrected manually by the auditor.

I asked Ms. Morrison if she could provide any documentation regarding communication to the QC team members which would have prompted this change. In an email, dated 9/5/14, Mr. Mega notified the sponsor they did not have sufficient test article for (b) (4) days of prep, and asked if they could supply additional test article (Exhibit 38, pg 9). Later on the same day, Dr. Kuehl notified Mr. Mega of the approximate amount of remaining test article, and concerns regarding having sufficient amounts for the remaining animals on study. He offered they ask the sponsor for more, or revise the SSP/protocol to decrease the amount to be used for the remaining animals (Exhibit 38, pg 8). In a later response, Mr. Mega indicated he thought it would be feasible to make the additional (b) (4) if they had (b) (4) flasks. On 9/8/14, chemistry staff confirmed they had (b) (4) flask (Exhibit 38, pg 7). In an email from (b) (6), (b) (7)(C) (9/8/14), the employee indicates the changes to the SSP will be forwarded to Mr. Mega and Dr. Kuehl for approval (Exhibit 38, pg 7). The subsequent email from (b) (6), (b) (7)(C) included the worksheet (Preparation Form)- Exhibit 38, pg 7; however, no documented approvals of the SSP or this form were included with the study records.

Management was also notified that this key correspondence had not been maintained and submitted for archive by the Study Director. Ms. Cleerdin agreed the changes were not approved as required by (b) (4) -1185, and with the need to maintain key correspondence.

b. Appropriate employee restrictions have not been applied such that revisions to forms published on (b) (4) (b) (4) are controlled and completed in compliance with LRRI Policy #62, Compliance Document Control and Use. Examples include: Multiple versions of the form, Feed Rotation Documentation, used to identify animal feed were observed in use during the tour of the area on 11/2/2016. All versions were identified as "Rev. 07May10"; and 2) Multiple versions of the form, Archive Record Retrieval Request, were observed used for the retrieval of study records for study (b) (4) . All versions were dated as "15Mar2016".

LRRI Policy #602, Compliance Document Control and Use describes the mechanism and system to ensure compliance documents are maintained in a central location; changes are controlled, approved and documented prior to issue; that review are conducted according to set schedules; that changes and relevant revision status of documents are identifiable; that version and change records are audit ready; and current versions are available to employees as appropriate. Employees who have been granted access to controlled compliance documents are responsible for not making changes without going through proper channels, observing proper change control procedures (Exhibit40, pg 2). Study related and facility forms are managed by the Institute's Compliance Document Manager to ensure the forms are reviewed and revised in conjunction with the review and revision of the corresponding compliance document(s), (Exhibit 40, pg 3). The audit noted that employees within given department(s) have been making changes to forms in an effort to make improvements; changes

to the forms are not restricted; and employees are not requesting these updates through the appropriate change process.

- SOP (b) (4) 1294, Receipt, Storage and Disposition of Animal Feed and Bedding requires a sign must be placed on or above the feed to be used first. The signage must including the type of feed, milling; receipt; and expiration dates (Exhibit 39, pg 2). Employees who work in the area are to use the form template on available on (b) (4) During the walk through of the warehouse area, I observed multiple signs (3) with different formats and /or color, being used to identify feed. All signs (Feed Rotation Documentation) were dated as "Rev 07May10", see Exhibit 39, pgs 4-6 . One of the documents had designations to record 1) Use First or 2) Use Last (Exhibit 39, pg 4). Mr. Romero stated variable color differences were due to lack of paper when the documents were printed. A stack of green colored forms was observed on a shelf in the corner of the warehouse area.

- The Archive Record Retrieval Request forms completed on 05/09/16 and 10/31/16 were different. On the form completed in May, the archivist hand wrote ""& Re-archived" to the line formatted as "Archived by:" (Exhibit 23, pg 8). When the form was completed in October, two (2) additional lines were added: "Retrieved by", and "Re-archived by" (Exhibit 23, pg 7). Prior to this time, no line existed for "Retrieved by". Additionally, the font was changed. Change Authority for this document is listed as "Archivist". (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) was the Archivist in May 2016 and departed recently. The form completed in October was completed by (b) (6), (b) (7)(C), who recently took over the position. She stated she had not made the form changes. It was assumed that (b) (6), (b) (7)(C) made the changes, but did not go through proper channels as required by the policy.

6. 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 was taken and documented. Specifically, ***

a. **No training was documented for employee (b) (6) for (b) (4) , protocol amendment #3, signed by the study director on 05/22/2014. This amendment was specific to Section 14.1 Cage Side and Clinical Observation Modification. Clinical observations were documented within (b) (4) for this employee for the following animals: (b) (4) (8/30/2014 and 09/18/2014); and (b) (4) (07/15/2014, 07/23/2014).**

b. **Employee (b) (6) failed to document training for (b) (4) protocol amendment #3, signed by the study director on /22/2014, prior to completion of tasks. This amendment was specific to Section 14.1 Cage Side and Clinical Observation Modification. Training is documented as being completed on 08/25/2014; however the employee completed clinical observation within (b) (4) on: 07/24/2014, 07/27/2014 ((b) (4)).**

Training records were random selected for audit of study personnel who completed tasks within Necropsy, Clinical Observations, Telemetry, Formulations, Advanced Quality Control. Prior to study start, Mr. Mega provided training for designated personnel (see (b) (4) presentation included as Exhibit 25). For the study, SSP (Study Specific Procedures) were written to further describe processes required within the study. Training records noted that all study personnel did not have documented evidence of their review of updated protocol amendments. According to Ms.

Cleerdin, departmental supervisors decide if an amendment is applicable, and if so, then study employees are notified of the need to review the update. However, SOP (b) (4) 1151, Maintenance of Personnel Training and Experience Records states Study Directors are responsible for informing LRRI study personnel of SOP, SSP, and other training required for a specific study and ensuring all personnel assigned to their studies document that they have read and understood all applicable training items prior to being work on the study (Exhibits 24 & 60, pg 2). Employees self-enter information within have been read and understood into Training Manager database.

Protocol #3 was signed by Mr. Mega on 5/22/14. The amendment modified portions of Section 14.1, Cage side and Clinical Observations. The section was updated to allow the Study Director to perform additional observation, if deemed necessary for animal welfare and study related endpoints. Clinical observations were updated to state they would be recorded *at* (b) (4) on Days (b) (4) (b) (4) (Exhibit 59, pgs 12-14).

(b) (4) print-outs for clinical observations noted that employees (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C) completed these job tasks.

- No training was documented on the Training Manager print out for (b) (6), (b) (7)(C) for protocol #3 (Exhibit 26). (b) (4) records indicate the employee continued to work in this area of the study as documented through observations complete for animals 1) # (b) (4) (8/30/2014 and 09/18/2014); and2) # (b) (4) (07/15/2014, 07/23/2014).
- Training records for employee (b) (6) documents he 'read and understood" Protocol #3 on 8/25/14 (Exhibit 27, pg 3). However, the employees completed clinical observations of animals after the protocol was amended, and continued through the end of the study. Examples were noted for animal # (b) (4) 07/24/2014, 07/27/2014 (Exhibit TBS).

Print-outs of the clinical observations recorded within (b) (4) are included as Exhibit 28 ((b) (4)) and Exhibit 29 ((b) (4), pgs 1-8).

During the final meeting, I stated the training records showed each department manager had different requirements for their employees. For example, some training records documented employees were required to read all (b) (4) amendments; whereas others only had training for a few of the protocol amendments (specific to work area). However, the Study Director must assure this training has been completed. Failure to review this information could compromise the study.

7. **The quality assurance unit failed to review the final study report to assure that such report accurately described the methods and standard operating procedures, and that the reported results accurately reflected the raw data of the study. Specifically,**

a. **The sponsor's description of test article ((b) (4)) is documented as "(b) (4) " on the (b) (4) Chain of Custody Form received with the material on 02/27/2014. However, the test article is described as "(b) (4) " within (b) (4) final report.**

b. **The (b) (4) Chain of Custody Form for test article (b) (4) used in study (b) (4) document the material was received on 02/27/2014. The final report, signed by the SD on 10/23/2015, states the test article was received on 02/28/2014.**

c. The (b) (4) Chain of Custody Form for control article (lot #(b) (4)) used in study (b) (4) documents the material was received on 04/22/3014. The final report, signed by the SD on 10/2.3/2015, states the control article was received on 04/23/2014.

Information reported within Section 5.2.1, Test Article of the final report was noted as discrepant when compared to study data. The final report describes the test article as an "(b) (4) received on February 28, 2014" (Exhibit 59, pg 15). The (b) (4) Chain of Custody Form for Material Shipped to LRRI from (b) (4) describes the test article ((b) (4)) as sold, (b) (4) (Exhibit 31, pg 1). The material was signed as received at LRRI on 02/27/14 (Exhibit 31, pg 1).

As required by Section 6.4.1, Material Receipt of SOP (b) (4) -1426, Secure Material Storage Room ((b) (4) and (b) (4)) Controlled Access and Usage, materials are given an LRRI (b) (4) assigned from the (b) (4) Database, and labeled appropriately (Exhibit 30, pg 4). An (b) (4) and (b) (4) Receipt Documentation Form is completed and signed/dated for each material received that is assigned this number (Exhibit 30, pg 4). However, the form for (b) (4) described the color as "(b) (4) " (Exhibit 31, pg 2). Email notification of material receipt confirmation is required to be sent to all applicable personnel, to minimally include the Study Director (Exhibit 30, pg 4). Any discrepancies between the materials received and associated paperwork (i.e. shipping paperwork, COA) should be included in the notification. The notification of the receipt for (b) (4) describes the material as "(b) (4) ***", and documents the receipt date as "28Feb2014" in the Subject line (Exhibit 31, pg 3).

Ms. Cleerdin stated the employee may have determined the color as (b) (4) through visual observation. The test article was received in (b) (4) colored bottle, which could have attributed to the inaccurate description.

(b) (4) shipments of control article ((b) (4)) were received for use in the audited study. The (b) (4) Chain of Custody Form for Material Shipped to LRRI documents the facility received lot#(b) (4) on 04/22/14. (Exhibit 31, pg 4). On 4/23/14, the (b) (4) was assigned and the (b) (4) Receipt Documentation completed (Exhibit 31, pg 5). However, section 5.2.2., Control Article stated "the control article, a clear, colorless solution, was received on April 14 or 23, 2014 ***" (Exhibit 59, pg 15)

However, this was not identified and/or corrected in the final report. The Quality Assurance Statement for (b) (4) documents the final report audit was completed on 08/18/15, and signed by the Study Director and Management on 08/18/15. However, additional audits specific to the test article were completed on 10/5/15 (test article retention archive) and 10/20/15 (test article note book). During the audit, corrections were made to include: 1) the (b) (4) and (b) (4) Receipt Documentation states "the chain of custody indicated the color is (b) (4) . (b) (4) 08Oct2015"; and 2) the email confirmation states: "the chain of custody indicated the color is (b) (4) . Added in review. (b) (4) 08Oct2015", see Exhibit 31, pgs 1-3. It does not appear verification was performed on the final report, to determine if the error(s) were unique to the study records only.

8. The quality assurance unit did not monitor each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls were in conformance with FDA GLP regulations. Specifically,

a. **Between April 2015 and October 2016, the firm failed to complete pest evaluations per SOP. Deviation signed on 06/ 2016 failed to accurately document this noncompliance. Specifically, 1) deviation signed on 10/27/2016 states the bait boxes were checked in August 2016; however no documentation exists for an assessment in this month.**

b. **SOP Deviations signed 20 Jun 2016, and 27 Oct 2016 document non compliance for evaluations and treatment of defined areas stated within (b) (4)-0569, Pest and Weed Control at LRRI (v 16-17) from October 2014- Jan 2016; February 2016 – April 2016; and July 2016. No appropriate corrective action has been implemented.**

c. **Pest control records for evaluations completed in May 2016, document bait station were filled at stations identified as (b) (4) and (b) (4) Additionally, a comment was recorded to state pest control was needed for building (b) (4) and (b) (4) . Subsequent (b) (4) evaluations completed in 06/2016, 09/2016 and 10/2016 do not document evaluation of these areas. A tour of these areas on 11/02/2016 confirmed the following: 1) presence of bait stations at (b) (4) and (b) (4) and 2) three damaged boxed (live trap and bait box) located around the building for (b) (4) and (b) (4) . No deviation has been recorded.**

SOP (b) (4)0569, Pest and Weed Control at LRRI, describes the program for controlling vermin and weeds at LRRI. Records were reviewed for the time period of April 2015 through October 2016. Procedures in effect during this period include (b) (4) 0569.16 (Effective11/6/13), and (b) (4)-0569.17 (effective 02/05/16), included as Exhibit 33 and Exhibit 34, respectively. Prior to April 2015, chemical control of pests with insecticide and rodenticides within the interior and exterior areas was a contracted service. However, the last service provided by contractor, (b) (4) , was performed on 04/8/15 (Exhibit 35, pg 1). Since this time, program responsibilities are now completed by Comparative Medicine Animal Resources staff. Mr. Issac Romero, Animal Resources Supervisor stated the department was not immediately notified the contractor was no longer performing these services. He stated (b) (4) did not return any calls that were made by the previous supervisor to come out to the facility. After this point, they began performing all of the duties as documented on the June 2015 Pest Control Chemical Treatment Documentation form (Exhibit 35, pgs 2-3).

The review of pest control records noted that between April 2015 and October 2016, pest evaluations have not been completed as defined within the procedure. (b) (4)-0569.16 required CMAR staff to check bait stations approximately every (b) (4) and refill as needed (Exhibit 33, pgs 1-2). Upon revision, (b) (4)-0569.17 required the bait station be checked approximately (b) (4) and refilled as needed (Exhibit 34, pgs 1-2). There is no documentation for (b) (4) monitoring of bait stations for time periods of the review (see Exhibit 35, pg 2). Mr. Issac Romero, Animal Resources Supervisor, stated the (b) (4) requirement was not completed as such because the procedure uses the word "approximately". Instead, staff completed these checks (b) (4) **[Note: The Pest Control Documentation form used to document these tasks are noted as "Rev 26 Mar 2014", and state "Bait stations are checked approximately (b) (4)". This requirement contradicts (b) (4)-056.16**], see Exhibit 35, pgs 2-8. Additionally, no pest control records for bait checks were

found for (b) (4) ; (b) (4) 2016.

Section 6.1.1, Areas Designated for Routine Use of Rodenticides provides a listing of areas on the outside perimeter of builds which require rodenticides in the form of (b 4 placed inside bait stations. As needed, additional bait stations should be placed in other areas which have noted activity and documented on the Pest Control Documentation form (Exhibits 33-34, pg 3). On 5/5/16, the employee who completed the bait check noted high activity for bait stations located at (b) (4) and (b) (4) In addition, the employee recorded the Bldg (b) (4) needed pest control (Exhibit 35, pg 4). Subsequent forms (July –October 2016) do not indicated that bait stations have been checked at buildings (b) (4) and (b) (4) (Exhibit 35, pgs 6-8). All evaluations have been completed by a different employee. Therefore, a discussion was held regarding how employees are notified of additional bait stations which are not pre-listed on the form. On 11/2/16, I walked the facility to look for the identified locations. I observed bait stations still located at (b) (4) and (b) (4) At building (b) (4) (b) (4) boxes were located around the building but were damaged. (b) (4) of the boxes were for interior use, and had broken glass; and the one (1) bait box was missing the top cover making it un-useful as well.

Mr. Romero confirmed that employees take a blank form, available from the (b) (4) to fill out as they walk the facility. Management was informed they will need to develop a way to ensure all employees are notified of the additional bait stations; and assure employees communicate with the supervisor so that equipment can be replaced as needed.

Section 6.1.2, (b) (4) Area of the procedure states the grassy area is treated approximately (b) (4) from May until September (both SOP versions), see Exhibits 33-34, pg 4. Between the time period April 2015 – October 21016, this area was documented as treated only on 2/28/16 (Exhibit 35, pg 5). Although the procedure stated "approximately (b) (4)", the form, Pest Control Chemical Treatment Documentation, states this area is treated approximately every (b) (4) during (b) (4) . Revisions of the forms observed used are dated "Rev 09Apr2013", see examples included as Exhibit 35, pgs 3, 5. Although the form was newly revised "Rev 28Jun2016", the requirements remain the same (Exhibit 35, pg 9).

An audit of the pest program was recently conducted and reviewed by the QA department in 2016. As a result, Mr. Romero prepared two deviations:

1) SOP Deviation (Exhibit 35, pg11) – At the south facility (audited site), the deviation captured the failure to document (b) (4) bait station checks from October 2014 through January 2016; and no (b) (4) bait station checks from February 2016 through April 2016. The supervisor at the time, provided corrective action stating the bait station checks were decreased as pest control was not needed as often so areas were being checked (b) (4) The deviation also stated contractor paperwork contained all of the information required so duplicate paperwork was not filled out. Additional findings of missing documentation for bait station checks were described for the north facility. The deviation was signed by QA on 6/20/16.

2) Non Study Specific Deviation Document (Exhibit 35, pg 10) – A subsequent deviation was reported for failure to complete (b) (4) bait station checks (b) (4) 2016 by Mr. Issac Romero on 10/27/16. As corrective action, he reported the SOP would be revised to state how often the checks would be performed. He further reported there was no impact as (b) (4) checks were completed in (b) (4) 2016 with no boxes being reported as having been re-filled. The deviation was signed by QA on 10/27/16.

QA was informed that the SOP deviation completed in June 2016 was approved by the QA reviewer without an adequate corrective action. The deviation provided information to indicate this department had not been in compliance with the SOP for greater than 1 year. At minimum, employees should have been re-trained on procedural expectations. In addition, non-compliance within the department has continued, as evidence by a second deviation. Although the corrective action states the SOP will be revised; requirements for completing these checks are already provided in the procedure. QA was also informed the information reported by Mr. Romero was inaccurate – 1) June 2016: (b) (4) bait boxes were documented as re-filled (Exhibit 35, pg 6); and 2) no documentation was maintained as evidence that bait station checks were performed (b) (4) 2016. The audit of the records also failed to note any of the discrepancies between the forms and the approved SOP; and did not capture the additional issues noted within the observation. Management was informed of the need to require adequate corrective actions be implemented, and that QA further verify the information provided prior to signing off on deviations.

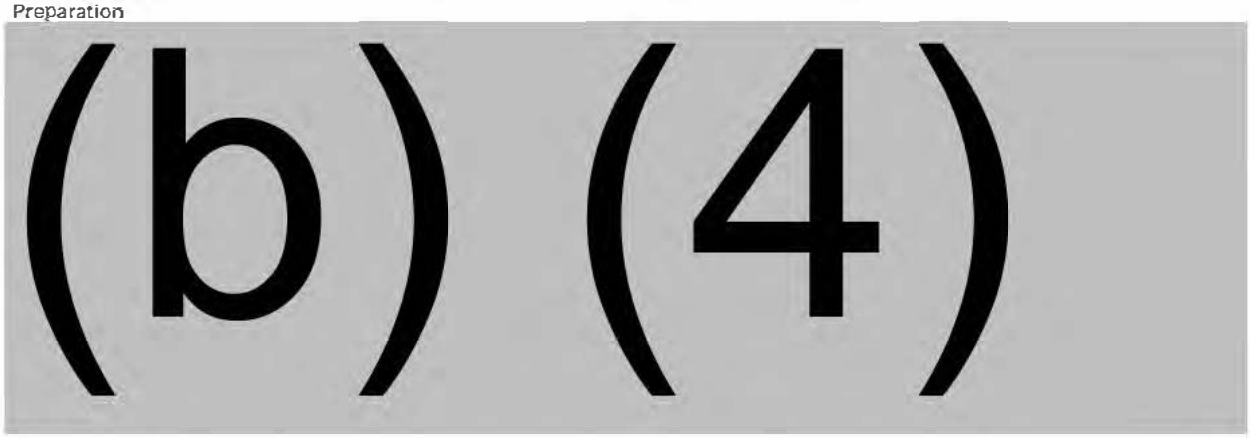
Following discovery and discussion of these observations, Ms. Cleerdin stated the firm would immediately implement (b) (4) verifications of the pest control records to ensure compliance within this department.

9. Not all data entries were dated on the date of entry and signed or initialed by the person entering the data. Specifically, Media Preparation Logs fail to document the actual amounts of ingredients used in the preparation of the media. Preparation logs include the typed amount required to make the media.

For (b) (4) media preparation logs were pre-formatted to provide the amount of ingredient for media according to the manufacturer's instructions or LRRI recipe. However, the forms did not require the employee to record the actual amount they used to make the media. An example of a formatted form is below. Additional examples are included as Exhibit 36.

Media Preparation Log (b) (4)

Preparation



Section 6.1. Media Preparation of (b) (4) Preparation of Microbiological Reagents and Media stated the amount measure must be within (b) (4) units of the weight specified (Exhibit 47, pg 1). Management was informed entries should be recorded directly; therefore, they should have included another column so the technician could record how much was actually weighed.

Additionally, errors were noted regarding incorrect information being recorded for the Manufacturer/Catalog # of ingredients used within a given media. This information was often pre-typed onto the form by the technician. Changes, if applicable, were not always documented. For example: (b) (4) (lot # (b) (4)) – the manufacture is listed as (b) (4) but the catalog # ((b) (4)) coincided with materials supplied by the manufacturer, (b) (4) (Exhibit 36, pg 2) as confirmed by (b) (6), (b) (7)(C). These errors were not noted during the QC review of the form, and/or QA audit of the data.

10. The quality assurance unit failed to maintain a copy of a master schedule sheet that contained all required elements for all nonclinical laboratory studies conducted by the testing facility. Specifically, the most current version of the master scheduled provided during audit failed to include the test system for study (b) (4) documented as initiated on 08/28/2015. Archived copies of the master schedule maintained as required by *SOP QAU-1182.7, Master Schedule*, reviewed from May-October 2016 also fail to include this information.

A random audit of the Master Schedule was performed to verify reported dates for regulated studies. SOP QAU-1182, Master Schedule requires the document be updated when there is a status change for a study or to add a new study. At least (b) (4) a hard copy of the Master Schedule in printed and archived (Exhibit 10, pg 2). The report template does include a requirement for "Test System" (Exhibit 10, pg 3). The missing information was observed on the current schedule provided for review. As a result, I requested the firm provided archived copies of the Master Schedule from May-October 2016, which also did not contain this information for (b) (4) (Exhibit 11). Although QAU-1182 does not require the print out be checked for completeness, management was encouraged to perform a review prior to archiving the (b) (4) lists. Without this review, information would remain outstanding and/or incorrect until a facility audit of the archive would reveal the deficiency.

GENERAL DISCUSSION WITH MANAGEMENT

A close-out meeting was held with management representatives on 11/11/16. FDA-483 was issued to Dr. Robert W. Rubin, President & CEO. Other personnel present include: Jennifer Cleerdin, Senior Director – Scientific Operations; Elizabeth Morrison, Quality Manager; (b) (6), (b) (7)(C), Quality Assurance Lead; William Mega, Study Director; Jake McDonald, Senior Scientist; Dr. Drew Cawthon, Director- Clinical Support; and Dr. Philip Kuehl, Director – Scientific Core Laboratories (Exhibit 9). During the discussion, it was noted that Observation 1 and 2 were incorrectly placed for the supporting citation. The FDA-483 was amended on site; all pages were hand signed due to the inability to record an electronic signature for the document. Available sanctions to the agency, should corrections not be made were explained. The firm promised to send a response to CDER contact and Denver District within 15 business days.

ADDITIONAL INFORMATION

Kirtland AFB and the south campus are secured sites. Government identification/credentials are needed to enter the air force base. NOTE: The main gate to Kirtland Air Force Base is located on Gibson Avenue east of the north campus. This gate should be used to gain entrance to the south campus.

VOLUNTARY CORRECTIONS

During the previous inspection (2013), the firm was cited for failure to document deviations when they occur. Following the inspection, the firm conducted training for employee, and changed SOP (b) (4) 1109, Preparation, Use and Approval of Study Protocols, Amendments and Deviations. The procedure now states that deviations must be recorded "as soon as possible after the deviation occurs. Documentation of the deviation is initiated on the deviation form as soon as possible even if the impact assessment may not be completed until a later date" (Exhibit 8). No evidence of repeat findings was noted for this study. Additionally, water was observed leaking from the ceiling of the warehouse area in which animal feed and bedding is housed. Ms. Cleerdin stated repair within the warehouse area had been completed; however, the site has not completed full roof resurfacing in the administrative areas.

EXHIBITS COLLECTED

Exhibit 1 LRRI Overview (b) (4) Presentation, 68 pages
Exhibit 2 Organizational Chart, 5 pages
Exhibit 3 CV Philip Kuehl, PhD, 11 pages
Exhibit 4 (b) (4) Example - Animal (b) (4), 15 pages
Exhibit 5 CV Willliam Mega, BS, 4 pages
Exhibit 6 CV (b) (6), (b) (7)(C) PhD, 12 pages
Exhibit 7 Facility Diagram, 1 page

Exhibit 8 Corrective Action 2013 EI, 2 pages
Exhibit 9 FDA Close-out Signature Log, 1 page
Exhibit 10 SOP QAU 1182, Master Schedule, 4 pages
Exhibit 11 Master Schedule, 6 pages
Exhibit 12 Master Schedule (Archived), 6 pages
Exhibit 13 (b) (4) Analytical Method Qualification Report, 26 pages
Exhibit 14 Protocol (b) (4), 4 pages
Exhibit 15 SOP (b) (4) 1158, Validation of Analytical Methods, 17 pages
Exhibit 16 SOP (b) (4) 1142.7 Maintenance of GLP Study Records and Documentation, 8 pages
Exhibit 17 SOP (b) (4) 1142.8, Maintenance of GLP Study Records and Documentation, 8 pages
Exhibit 18 SOP (b) (4) 1142.9 Maintenance of GLP Study Records and Documentation, 8 pages
Exhibit 19 Study Correspondence submitted by Study Director, 3 pages
Exhibit 20 Randomization (b) (4), 5 pages
Exhibit 21 SOP (b) (4) 1081 Submission and Retention of GLP Study Records, 12 pages
Exhibit 22 (b) (4) Documentation (b) (4) 16 pages
Exhibit 23 (b) (4) Archival Documents, 12 pages
Exhibit 24 SOP (b) (4) 1151, Maintenance of Personnel Training and Experience Records, 10 pages
Exhibit 25 (b) (4) Training given to study personnel, 20 pages
Exhibit 26 Training Records (b) (6), (b) (7)(C), 9 pages
Exhibit 27 Training Records [redacted], 5 pages
Exhibit 28 Clinical Observations Animal (b) (4) 9 pages
Exhibit 29 Clinical Observations Animal (b) (4) 12 pages
Exhibit 30 SOP (b) (4) 1246, Secure Material Storage Room & Usage, 4 pages
Exhibit 31 Test Article & Control Article Receipt, 5 pages
Exhibit 32 SOP (b) (4) 1109 Preparation, Use & Approval of Study Protocol 8 pages
Exhibit 33 SOP (b) (4) 0569.16 Pest& Weed Control at LRRI, 5 pages
Exhibit 34 SOP (b) (4) 0569.17 Pest Control at LRRI, 5 pages
Exhibit 35 Pest Records and Deviations, 11 pages
Exhibit 36 Media Preparation Records, 9 pages
Exhibit 37 SSP (b) (4), Dose Formulation Preparation, 8 pages
Exhibit 38 QC Checklist and emails for Dose preparation, 9 pages
Exhibit 39 SOP (b) (4) 1294.13 Receipt Storage Disposition of Feed and Bedding, 6 pages
Exhibit 40 LRRI Policy #62, Compliance Document Control and Use, 4 pages
Exhibit 41 SOP (b)(4) 1185.7, Study Specific Procedures, 4 pages
Exhibit 42 (b) (4) Exposure May 6 2014, 5 pages
Exhibit 43 (b) (4) Exposure July 11 2014, 5 pages
Exhibit 44 (b) (4) Exposure August 25 2014, 5 pages
Exhibit 45 Archival of Clinical Pathology and Observations, 5 pages
Exhibit 46 GLP Test Article Usage Form, 6 pages
Exhibit 47 SOP (b) (4) 1630, Preparation of Microbiological Reagents and Media, 7 pages
Exhibit 48 Dose formulation prep May 7 2014, 4 pages
Exhibit 49 Dose formulation prepared Jul 12 2014, 4 pages
Exhibit 50 Dose prep Sep 8 2014, 4 pages
Exhibit 51 Dose prep Sep 14 2014, 4 pages

Exhibit 52 IACUC Roster and Minutes, 8 pages
Exhibit 53 IACUC Initial Approval (b) (4) , 36 pages
Exhibit 54 LRRI IACUC Manual, 11 pages
Exhibit 55 Approved Vendor List, 9 pages
Exhibit 56 QAPP for (b) (4) , 10 pages
Exhibit 57 Deviation for Facility Audits, 1 page
Exhibit 58 (b) (4) Lock and Unblind, 10 pages
Exhibit 59 Protocol & Final Report Referenced Pages, 16 pages
Exhibit 60 (b) (4) 1142.11 Maintenance of Personnel Training Records, 10 pages

ATTACHMENTS

FDA-482, Notice of Inspection dated 10/31/16
FDA-483, Inspectional Observations dated 11/19/16
Amended FDA-483, Inspectional Observations dated 11/19/16
CDER Assignment # 11618938, dated 2/16/16, 7 pages

X Theressa B. Smith-S

Theressa B. Smith, CSO
Denver District Office

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

1. DISTRICT OFFICE ADDRESS & PHONE NO.
PO Box 25087 · 6th Ave & Kipling St
Denver, CO ~~80207~~ 80225-25087
303-236-3000

TO

2. NAME AND TITLE OF INDIVIDUAL
Jennifer S. Clearwater, JD, Sr. Dir. Scientific Operations

3. DATE
11/31/2016

4. FIRM NAME
Lovelace Respiratory Research Institute

5. HOUR
10:15 a.m.
p.m.

6. NUMBER AND STREET
Bldg 9217, Area Y, Kirtland Air Force Base

7. CITY AND STATE & ZIP CODE
Albuquerque, NM 87115

8. PHONE NO. & AREA CODE
505-348-9400

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetics Act [21 U.S.C. 374(a)][1] and/or Part F or G, Title III of the Public Health Service Act [42 U.S.C. 262-264][2]

As a small business that is subject to FDA regulation, you have the right to seek assistance from the U.S. Small Business Administration (SBA). This assistance includes a mechanism to address the enforcement actions of Federal agencies. SBA has a National Ombudsman's Office that receives comments from small businesses about Federal agency enforcement actions. If you wish to comment on the enforcement actions of FDA, CALL (888) 734-3247. The website address is www.sba.gov/ombudsman.

FDA has an Office of the Ombudsman that can directly assist small business with complaints or disputes about actions of the FDA. That office can be reached by calling (301) 796-8530 or by email at ombuds@oc.fda.gov.

For industry information, go to www.fda.gov/oc/industry.

9. SIGNATURE(S) *(Food and Drug Administration Employee(s))*	10. TYPE OR PRINT NAME(S) AND TITLE(S) *(FDA Employee(s))*
[signature]	Theresa B. Smith, CSO

[1] **Applicable portions of Section 704 and other Sections of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374] are quoted below:**

Sec. 704(a)(1) For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, tobacco products, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, tobacco products, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein. In the case of any person (excluding farms and restaurants) who manufactures, processes, packs, transports, distributes, holds, or imports foods, the inspection shall extend to all records and other information described in section 414, when the standard for records inspection under paragraph (1) or (2) of section 414(a) applies, subject to the limitations established in section 414(d). In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products are manufactured, processed, packed, or held, inspection shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products which are adulterated or misbranded within the meaning of this Act, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this Act, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this Act. No inspection authorized by the preceding sentence or by paragraph (3) shall extend to financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualifications of technical and professional personnel performing functions subject to this

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Act), and research data (other than data relating to new drugs, antibiotic drugs, devices, and tobacco products and subject to reporting and inspection under regulations lawfully issued pursuant to section 505 (i) or (k), section 519, section 520(g), or chapter IX and data relating to other drugs, devices, or tobacco products, which in the case of a new drug would be subject to reporting or inspection under lawful regulations issued pursuant to section 505(j)). A separate notice shall be given for each such inspection, but a notice shall not be required for each entry made during the period covered by the inspection. Each such inspection shall be commenced and completed with reasonable promptness.

Sec. 704. (a)(2) The provisions of the third sentence of paragraph (1) shall not apply to (A) pharmacies which maintain establishments in conformance with any applicable local laws regulating the practice of pharmacy and medicine and which are regularly engaged in dispensing prescription drugs or devices, upon prescriptions of practitioners licensed to administer such drugs or devices to patients under the care of such practitioners in the course of their professional practice, and which do not, either through a subsidiary or otherwise, manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail; (B) practitioners licensed by law to prescribe or administer drugs, or prescribe or use devices, as the case may be, and who manufacture, prepare, propagate, compound, or process drugs, or manufacture or process devices solely for use in the course of their professional practice; (C) persons who manufacture, prepare, propagate, compound, or process drugs, or manufacture or process devices solely for use in research, teaching, or chemical analysis and not for sale; (D) such other classes of persons as the Secretary may by regulation exempt from the application of this section upon a finding that inspection as applied to such classes of persons in accordance with this section is not necessary for the protection of the public health.

Sec. 704. (a)(3) An officer or employee making an inspection under paragraph (1) for purposes of enforcing the requirements of section 412 applicable to infant formulas shall be permitted, at all reasonable times, to have access to and to copy and verify any records (A) bearing on whether the infant formula manufactured or held in the facility inspected meets the requirements of section 412, or (B) required to be maintained under section 412.

Sec. 704(b) Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, tobacco product, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary.

Sec. 704. (c) If the officer or employee making any such inspection of a factory, warehouse, or other establishment has obtained any sample in the course of the inspection, upon completion of the inspection and prior to leaving the premises he shall give to the owner, operator, or agent in charge a receipt describing the samples obtained.

Sec. 704. (d) Whenever in the course of any such inspection of a factory or other establishment where food is manufactured, processed, or packed, the officer or employee making the inspection obtains a sample of any such food, and an analysis is made of such sample for the purpose of ascertaining whether such food consists in whole or in part of any filthy, putrid, or decomposed substance, or is otherwise unfit for food, a copy of the results of such analysis shall be furnished promptly to the owner, operator, or agent in charge.

Sec. 704(e) Every person required under section 519 or 520(g) to maintain records and every person who is in charge or custody of such records shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and to copy and verify, such records.

Section 704 (f)(1) An accredited person described in paragraph (3) shall maintain records documenting the training qualifications of the person and the employees of the person, the procedures used by the person for handling confidential information, the compensation arrangements made by the person, and the procedures used by the person to identify and avoid conflicts of interest. Upon the request of an officer or employee designated by the Secretary, the person shall permit the officer or employee, at all reasonable times, to have access to, to copy, and to verify, the records.

Section 512 (l)(1) In the case of any new animal drug for which an approval of an application filed pursuant to subsection (b) is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to experience, including experience with uses authorized under subsection (a)(4)(A), and other data or information, received or otherwise obtained by such applicant with respect to such drug, or with respect to animal feeds bearing or containing such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) or subsection (m)(4) of this section. Such regulation or order shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulation or order is applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this subsection to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

[2] Applicable sections of Parts F and G of Title III Public Health Service Act [42 U.S.C. 262-264] are quoted below:

Part F – Licensing – Biological Products and Clinical Laboratories and* * * * * *

Sec. 351(c) "Any officer, agent, or employee of the Department of Health and Human Services, authorized by the Secretary for the purpose, may during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation

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of any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid for sale, barter, or exchange in the District of Columbia, or to be sent, carried, or brought from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession."

Part F – * * * * * *Control of Radiation.

Sec. 360 A (a) "If the Secretary finds for good cause that the methods, tests, or programs related to electronic product radiation safety in a particular factory, warehouse, or establishment in which electronic products are manufactured or held, may not be adequate or reliable, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are thereafter authorized (1) to enter, at reasonable times any area in such factory, warehouse, or establishment in which the manufacturer's tests (or testing programs) required by section 358(h) are carried out, and (2) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, the facilities and procedures within such area which are related to electronic product radiation safety. Each such inspection shall be commenced and completed with reasonable promptness. In addition to other grounds upon which good cause may be found for purposes of this subsection, good cause will be considered to exist in any case where the manufacturer has introduced into commerce any electronic product which does not comply with an applicable standard prescribed under this subpart and with respect to which no exemption from the notification requirements has been granted by the Secretary under section 359(a)(2) or 359(e)."

(b) "Every manufacturer of electronic products shall establish and maintain such records (including testing records), make such reports, and provide such information, as the Secretary may reasonably require to enable him to determine whether such manufacturer has acted or is acting in compliance with this subpart and standards prescribed pursuant to this subpart and shall, upon request of an officer or employee duly designated by the Secretary, permit such officer or employee to inspect appropriate books, papers, records, and documents relevant to determining whether such manufacturer has acted or is acting in compliance with standards prescribed pursuant to section 359(a)."

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(f) "The Secretary may by regulation (1) require dealers and distributors of electronic products, to which there are applicable standards prescribed under this subpart and the retail prices of which is not less than $50, to furnish manufacturers of such products such information as may be necessary to identify and locate, for purposes of section 359, the first purchasers of such products for purposes other than resale, and (2) require manufacturers to preserve such information. Any regulation establishing a requirement pursuant to clause (1) of the preceding sentence shall (A) authorize such dealers and distributors to elect, in lieu of immediately furnishing such information to the manufacturer to hold and preserve such information until advised by the manufacturer or Secretary that such information is needed by the manufacturer for purposes of section 359, and (B) provide that the dealer or distributor shall, upon making such election, give prompt notice of such election (together with information identifying the notifier and the product) to the manufacturer and shall, when advised by the manufacturer or Secretary, of the need therefore for the purposes of Section 359, immediately furnish the manufacturer with the required information. If a dealer or distributor discontinues the dealing in or distribution of electronic products, he shall turn the information over to the manufacturer. Any manufacturer receiving information pursuant to this subsection concerning first purchasers of products for purposes other than resale shall treat it as confidential and may use it only if necessary for the purpose of notifying persons pursuant to section 359(a)."

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Sec. 360 B.(a) It shall be unlawful–

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(2) * * *

(3) "for any person to fail or to refuse to establish or maintain records required by this subpart or to permit access by the Secretary or any of his duly authorized representatives to, or the copying of, such records, or to permit entry or inspection, as required or pursuant to section 360A."

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Part G - Quarantine and Inspection

Sec. 361(a) "The Surgeon General, with the approval of the Secretary, is authorized to make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession. For purposes of carrying out and enforcing such regulations, the Surgeon General may provide for such inspection, fumigation, disinfection, sanitation, pest extermination, destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous infection to human beings, and other measures, as in his judgment may be necessary."