U.S. FOOD & DRUG ADMINISTRATION

Inspection Assignment Memorandum

User Fee: (b) (5)
Surveillance: (b) (5)
Directed: (b) (5)

Application: Yes
Submission: Premarket Original

Entity: Good Laboratory Practice (GLP)
Date: 12/13/2016

From: Abhijit Raha, Ph.D.
Pharmacologist
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)

Preannounce: (b) (5)
Priority:
ORA Due Date:

Compliance Program: 7348.808 (GLP)
PAC Code: 48808
Operation Code: 12 Domestic

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

IND Sponsor: (b) (4)

Tx.Biomed.Res.Inst. Study Numbers: (b) (4)
Center Participation: (b) (5)
Joint Regulatory Agency Participation: (b) (5)

Establishment(s) for inspection	FEI Number	FACTS Number
Texas Biomedical Research Institute Department of Virology and Immunology 7620 NW Loop 410 San Antonio, TX 78227	1626181	11698225
Inspection History	9/29-30/2014: NAI	

Note	(b) (5) [redacted]

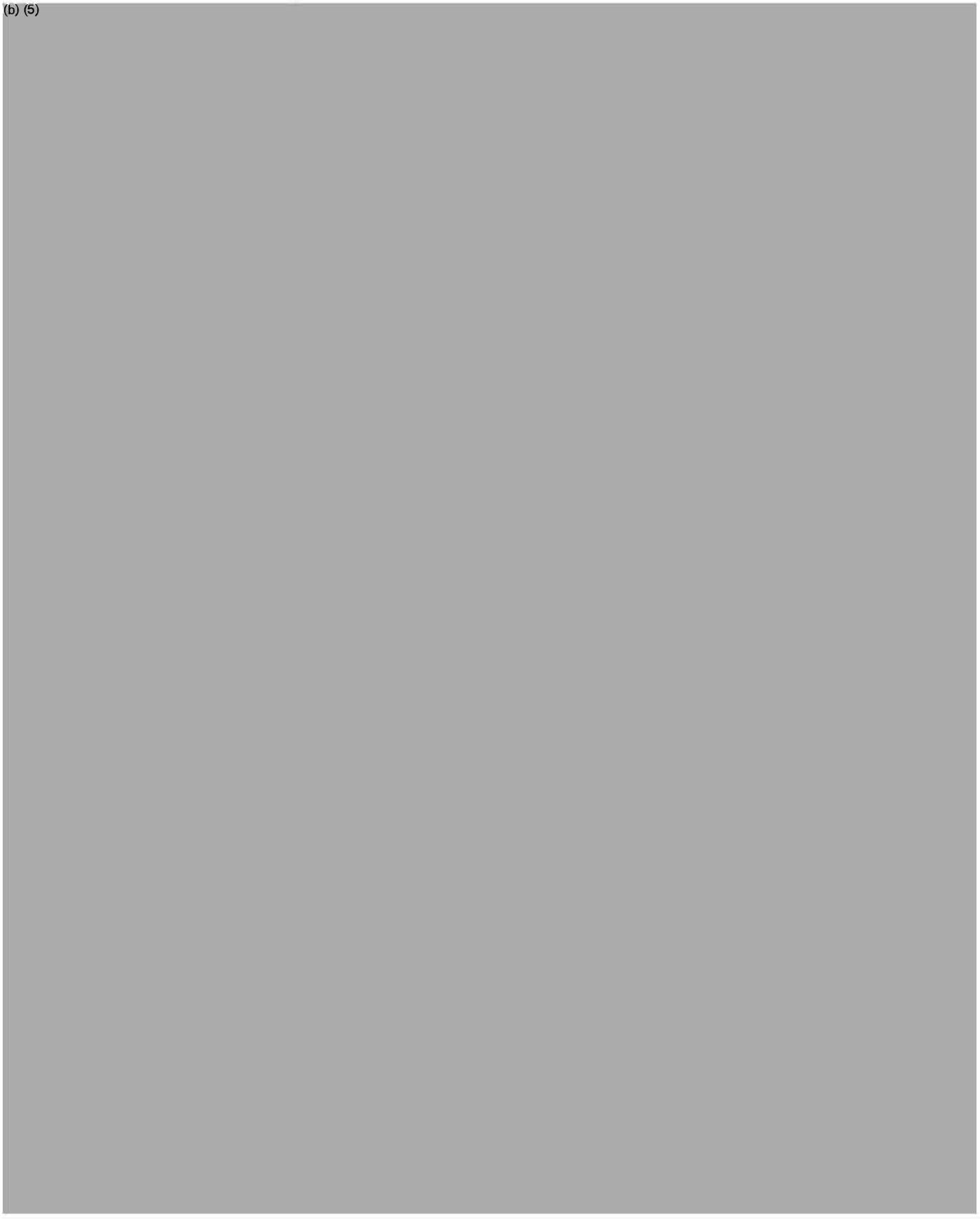
BACKGROUND INFORMATION

(b) (5)

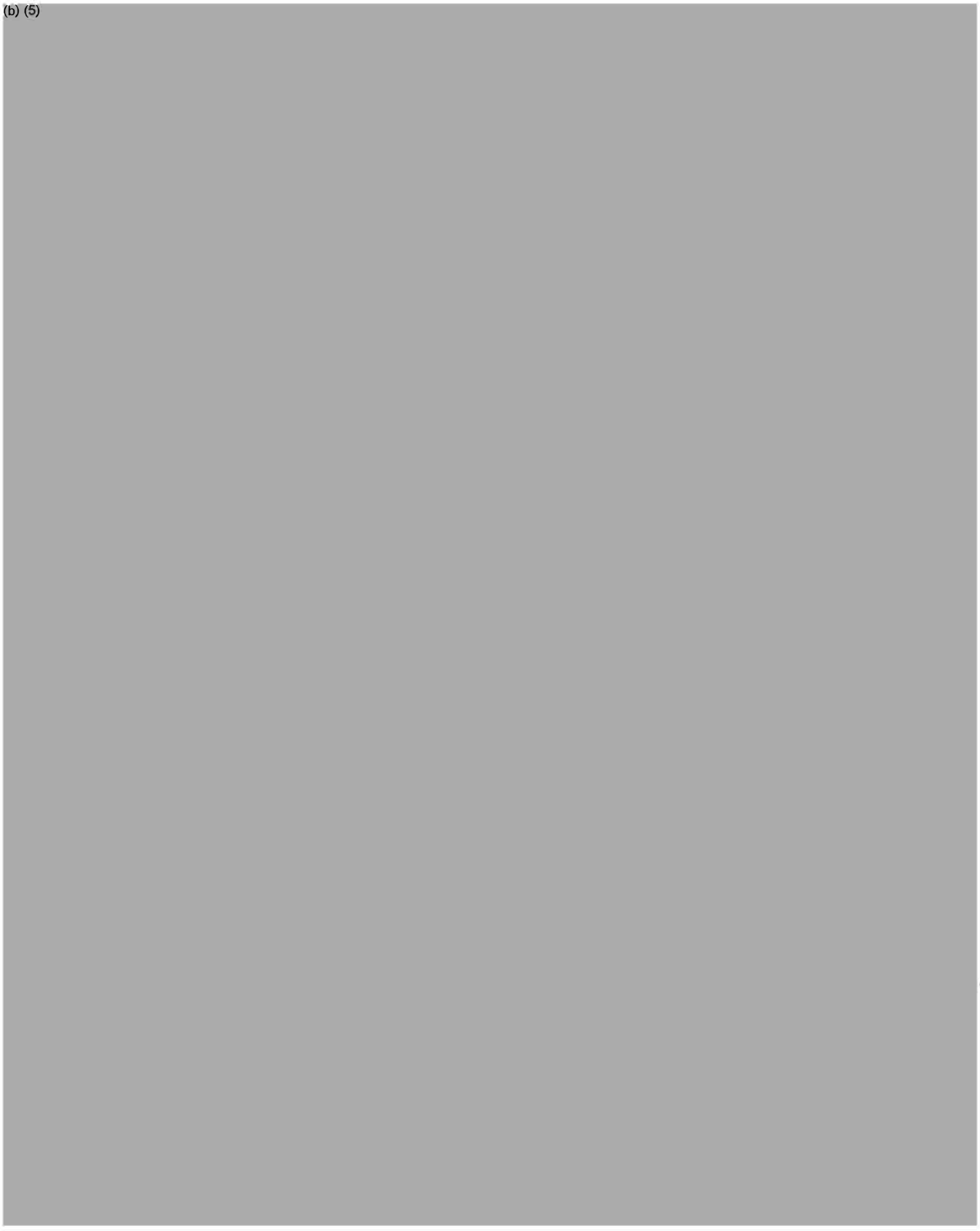
TESTING FACILITY: Texas Biomedical Research Institute
ADDRESS: Department of Virology and Immunology
7620 NW Loop 410
San Antonio, TX 78227
FEI: 1626181

(b) (5)

(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
12/13/2016

MARK J SEATON
12/13/2016

Reference ID: (b) (5)

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SUMMARY

Current inspection of this non-clinical laboratory was conducted pursuant to an assignment from the Division of New Drug Bioequivalence Evaluation (DNDBE), Office of Scientific Integrity and Surveillance (OSIS), CDER under FACTS# 11698225. The inspection was conducted under CP 7348.808, Non-Clinical Laboratories. NOTE: This was a limited inspection and did not cover all areas of this facility as they relate to non-clinical operations.

The previous inspection of this firm was classified as NAI.

Inspectional coverage was given to the non-clinical study (non-GLP) under Protocol No. (b) (4) entitled, (b) (4) ." The sponsor of this study was (b) (4) A copy of the signed, amended final report was collected and is included as **Exhibit MJS 1**. This was a non-GLP study conducted under the Animal Rule.

Prior to the inspection DNDBE made the decision not to cover (b) (4) ((b) (4)) during this inspection.

No objectionable conditions/practices were observed during this inspection. No FDA 483 was issued.

No samples were collected and no refusals were encountered.

ADMINISTRATIVE DATA

Inspected firm:	Texas Biomedical Research Institute
Location:	7620 Nw Loop 410 San Antonio, TX 78227-5301
Phone:	210-258-9400
FAX:	-210-670-3329
Mailing address:	7620 Nw Loop 410 San Antonio, TX 78227-5301
Dates of inspection:	11/27/2017-11/29/2017
Days in the facility:	3
Participants:	**Joel Martinez, Investigator** **Mark Seaton, Ph.D., DNDBE Regulatory Officer, OSIS, CDER** **Sabine Francke, DVM, PhD, Fellow IATP, Expert Regulatory Toxicologic Veterinary Review Pathologist, CFSAN**

Non-FDA Participants: None

At the initiation of the inspection I and Dr. Seaton presented credentials and issued an FDA 482, Notice of Inspection, to Robert A. Davey, PhD., Study Director.

NOTE: Dr. Francke did not carry FDA credentials; therefore, did not sign the FDA 482, Notice of Inspection. I informed Dr. Davey of Dr. Fancke's status and that she was primarily here to observe. Dr. Davey stated he understood. Dr. Davey did not present any objections.

Unless otherwise noted all EIR sections were written by JM.

HISTORY

The previous inspection of this firm conducted September 2014 was classified NAI.

Texas Biomedical Research continues to operate as a non-clinical laboratory. A copy of the firm's Master Schedule Sheet for GLP and non-GLP studies (under the Animal Rule) is attached as **Exhibit JM1**. Inspection revealed the firm has no active studies.

Any FDA correspondence should be addressed to Joanne Turner, Ph.D., Vice President for Research.

INTERSTATE (I.S.) COMMERCE

This non-clinical laboratory is not involved in any interstate commerce of FDA approved products.

JURISDICTION (PRODUCTS MANUFACTURED AND/OR DISTRIBUTED)

Data generated by this non-clinical laboratory can be used to support related FDA applications.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

James (Jamo) Rubin, M.D., is the Chairman for the Board of Trustees and Larry S. Schlesinger, M.D. is the President and CEO. A current organizational chart is attached as **Exhibit JM2 page 1**. Joanne Turner, Ph.D. is the Vice-President for Research. Dr. Turner answers to Dr. Schlesinger. Refer to **Exhibit JM2 page 2**. Luis Giavedoni, Ph.D., is the Interim Chair for the Department of Virology and Immunology who answers to Dr. Schlesinger. See **Exhibit JM2 pages 1 and 3**. All study directors within the Department of Virology and Immunology answer to Dr. Giavedoni. The Quality Assurance Unit answers to Dr. Turner. Refer to **Exhibit JM2 page 4**.

During the inspection we primarily met with:

- Ricardo Carrion, Ph.D.
- Robert Davey, Ph.D.
- Anthony Griffiths, Ph.D.

Other staff personnel were called upon by the aforementioned study directors to provide specific information in response to a query from the FDA inspection team.

FIRM'S TRAINING PROGRAM

This inspection included a review of employees which performed daily observations on the animals and analysts that performed the assays for (b) (4) (non-GLP). I reviewed training files for randomly selected employees that performed the daily observations and the two analysts that performed all assays. I did not reveal any objectionable conditions/practices with respect to training of employees.

MANUFACTURING/DESIGN OPERATIONS

Current inspection determined this non-clinical facility does have the proper organization, personnel, an established quality assurance unit, facilities, equipment and testing facility operations to conduct non-clinical studies. The firm has veterinarians on staff to provide animal care.

The firm does have the necessary staff for test and control of test articles.

The inspection focused on review of the firm's source records and data recorded and compared the data with the final clinical study report for the (b) (4) study.

The following was written by MJS:

My audit of animal records including Observation Forms, End Of Phase Packets, Worksheets, Bloodwork forms, Physical Exam records, Treatment sheets, and Animal Case Report forms. No issues were noted.

I audited treatment sheets and discussed test article preparation (i.e., filling syringes with the antibody cocktail or saline, as per protocol) with the study director. During my review of documents I found an apparent discrepancy in number of syringes prepared for animals on Day 5 versus Day 8. However, after discussion with the study director, it became apparent that the correct numbers of syringes were filled, per protocol. For example, a Group 3 animal that received 150 mg/kg of test article on Day 5 would not receive additional test article. To maintain the blind, those animals were to receive saline on days 8 and 11. However, the protocol did not require that contents of the same number of syringes be administered to every animal on each treatment day. Therefore, on Days 8 and 11 the animals in Group 3 were administered the amount of saline required to treat the animal with 50 mg/kg test article. The lack of consistency in the number of syringes administered on each treatment day may have had an impact on blinding.

I audited clinical observation sheets. Corrections made to the first page of clinical observation sheets were explained with comments on the second page. No issues were identified with the audited clinical observation sheets.

The study director was asked to describe supportive care given to both control and treated animals. According to the study director, no supportive care was given to animals in the (b) (4) facility.

Telemetry data was audited and was found to have many missing values. According to the study director there were several times during the study when the collection of telemetry data was interrupted. Sometimes the position of the animal prevented the collection of data and there was at least one time when telemetry data capture was interrupted by a power failure. According to the study director, telemetry data was collected at the request of (b) (4) and was not used as diagnostic tool when making decisions about the health of the animals. The table below from Telemetry report was corrected in the amended report (**Exhibit MJS1**).

Group	Implant ID	(b) (4) Group	Animal ID	Date/Time of Death (approximate)	Total Number Died in Each Group
(b) (4)					
	(b) (4)	No data	(b) (4)	No Telemetry Data	

*Animal (b) (4) in red font was removed from reporting due to the animal missing data/died during the baseline calculation

My audit of study records included a review of Veterinary Call Log records. I noted that the call log records were not contemporaneous. The records demonstrated that the veterinarian was called by technicians to discuss the health of several animals at the same time. The veterinarian apparently completed the call log for each animal at the end of the study rather than at the time of the call. According to test facility personnel, the Veterinary Call Log is no longer used. In current studies, calls to the veterinarian are documented in emails from the technician to the study director, with the veterinarian copied on the email.

The following was written by SF:

- I reviewed the gross pathology forms (pg. 459/641 of the NHP report) or pathology report forms to determine if animals dying prior to schedule death showed symptoms consistent with (b) (4) :

Animal number	Day of death	Date	Group	Necropsy findings consistent with (b) (4)
(b) (4)				

Result: All animals not surviving until day 28 of the study, showed 3 or more symptoms consistent of (b) (4) infection (b) (4) consisting of petechiation of the skin or mucous membranes; hemorrhage around organs such as the testes, the intestinal tract, or the nose; splenomegaly (enlarged spleen) or lymphadenopathy (diseased lymph nodes); and /or pale liver (hepatopathy).
I specifically verified that animal (b) (4) was sedated **because o**f a high clinical observation score related to (b) (4); the animal was very weak prior to sedation and succumbed while sedated.

- I verified the dates and times of death until necropsy. Most animals were necropsied within 30 minutes past euthanasia or death, with exception of animal (b) (4) which was euthanized at night (02.02 am), refrigerated and was necropsied 6 hrs later (08.17 am). I verified with the study director, that this procedure was in accordance with the respective SOP as the necropsy team is generally not available at night.

- I reviewed the CV of the consulted study pathologist (b) (6) with (b) (6) This pathologist was consulted based on his special expertise with hemorrhagic viral infections. The information contained in the CV deemed the pathologist sufficiently qualified.

- I reviewed selected slides (#1 injection side, 4 lymph node, 5 lung, 8 spleen, 9 liver) of 3 animals who died prematurely (b) (4) and of 1 survivor animal (b) (4), to generally verify the pathologist's diagnoses.

- I reviewed and verified the animal study numbers (b) (4) and corresponding histo-laboratory accession numbers (b) (4) no inconsistencies were found.

- I reviewed the histology paraffin blocks, corresponding paper work and corresponding slides; all matched up with the exception of animal (b) (4) who's accession number was missing a 0 on all blocks (labeled (b) (4) instead of (b) (4)).

- I also reviewed animal enrichment procedures as noted in appendix E daily clinical observation score sheets; we were informed that animals received a variety of food or behavioral enrichments such as ½ banana, grapes, biscuits or toys. the eating of the special food or utilization of the toy was then scored. The veterinary assistant explained that the '(b) (4) ' responsible for the (b) (4) enrichment during the acclimation phase has 'other' records, accounting for the discrepancy of being able to identify the type of enrichment that was given during the acclimation phase. All questions were ultimately resolved.

COMPLAINTS
There were no complaints in FACTS requiring follow-up.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483
We did not observe any objectionable conditions/practices. No FDA 483 was issued.

REFUSALS
No refusals were encountered during this inspection.

GENERAL DISCUSSION WITH MANAGEMENT

The following was written by SF

The study director discussed the study with the inspection team. Briefly, 4 groups of (b) (4) with 4-5 animals per group (n) were infected via intra muscular (i.m.) injection with (b) (4)) and then treated with the test compound, a monoclonal antibody cocktail (b) (4) at defined days post infection (p.i.) of the 28 day study period. We were informed that all study personnel was "blinded to treatment" with the exception of one principal investigator (Dr. Davey) who's laboratory prepared the viral and test compound syringes for intra muscular injection. Specifically,

(b) (4)

ADDITIONAL INFORMATION

Inspectional coverage was given to determine if this non-clinical facility was in compliance with its own standard operating procedures. Coverage was given to the following:

- Department: (b) (4)
  - Review Process for Ensuring Quality and Integrity of Research Data
  - (b) (4) Identification
  - (b) (4) Dose Administration and Injection Site Observation
  - Physical Examination of a (b) (4)
  - (b) (4) Husbandry in the Animal BioSafety Level 4 Biocontainment Laboratory
- Department: Virology and Immunology
  - Well Documented Study Process
  - Environmental Monitoring in the (b) (4) Laboratory
  - Environmental Monitoring in the Animal Biosafety Level 4 Laboratory Using (b) (4)
  - Performing Complete Blood Counts in (b) (4) and (b) (4) using an (b) (4)
  - Conventional (b) (4) assay for (b) (4)
  - (b) (4) method (b) (4) assay for (b) (4)
  - (b) (4) Assay
  - Drug Screening in Multi-Well Format
- Department: Quality Assurance Unit
  - QAU Inspections and Reports
  - Study Specific Audits
- Department: Environment, Health, and Safety
  - Water Testing: Compliance
  - Drinking Water Quality Testing

SAMPLES COLLECTED
No samples were collected during this inspection.

VOLUNTARY CORRECTIONS
There were no voluntary corrections to report.

EXHIBITS COLLECTED
1 Exhibit JM1 (Master Schedule Sheet), 2 pages
2 Exhibit JM2 (Organizational Charts), 5 pages
3 Exhibit mjs1 (Clinical Study Report), 938 pages

ATTACHMENTS
1 FDA 482, Notice of Inspection, 3 pages
2 Assignment MEMO, 6 pages

Joel Martinez -A
Digitally signed by Joel Martinez -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joel Martinez -A, 0.9.2342.19200300.100.1.1=1300025367
Date: 2018.02.23 12:38:50 -06'00'

Joel Martinez, Investigator

Mark J. Seaton -S
Digitally signed by Mark J. Seaton -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mark J. Seaton -S, 0.9.2342.19200300.100.1.1=1300154308
Date: 2018.02.23 11:25:17 -05'00'

Mark S. Seaton, Ph.D.

Sabine Francke-carroll -S
Digitally signed by Sabine Francke-carroll -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300162639, cn=Sabine Francke-carroll -S
Date: 2018.02.22 12:22:24 -05'00'

Sabine Francke, DVM, Ph.D.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

1. DISTRICT OFFICE ADDRESS & PHONE NO.
CBI HQ West
4040 N. Central Expwy. Suite 300
Dallas, TX. 75204
214-253-5200

TO

2. NAME AND TITLE OF INDIVIDUAL
Robert A. Davey, Ph.D., Study Director

3. DATE
11-27-17

4. FIRM NAME
TX. Biomedical Research Institute

5. HOUR
9:10 a.m.
— p.m.

6. NUMBER AND STREET
7620 NW Loop 410

7. CITY AND STATE & ZIP CODE
San Antonio, TX. 78227

8. PHONE NO. & AREA CODE
210 258-9826

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))*
Joel Martinez	Joel Martinez, Investigator
[illegible]	Mark S. Seaton, Regulatory Office

[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

(Continued on Reverse)

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

(Continued on Page 3)